Review Article
Speckle tracking echocardiography: clinical applications in cardiac resynchronization therapy

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Abstract: Cardiac resynchronization therapy (CRT) is a proven therapy for selected patients with heart failure, it has been shown to improve symptoms and left ventricular (LV) function and prolong survival. Despite proven benefit of CRT, a significant proportion of patients fail to respond to CRT. Multiple factors contribute to the non-response such as patient selection and device implantation including LV lead placement. Speckle tracking echocardiography (STE) derived strain imaging offers detailed characterization of LV function and provides indices of mechanical dyssynchrony, in addition, STE systolic strain could be used to identify area of scar, therefore applications of STE-derived strain imaging in CRT warrant a closer inspection. This review considers and summarizes different indices of mechanical dyssynchrony generated by STE-derived strain imaging and their relevance in patient selection for CRT and their prognostic values in predicting response to CRT. This review further examines applications of STE-derived strain imaging in optimizing LV lead position by detecting site of latest mechanical activation and presence or absence of transmural scar in a particular segment.

Keywords: Speckle tracking echocardiography, cardiac resynchronization therapy, mechanical dyssynchrony, strain, scar, left ventricular

Introduction

Cardiac resynchronization therapy (CRT) is a proven therapy for selected patients with heart failure, which has been shown to improve symptoms and left ventricular (LV) function and prolong survival [1-3], therefore, both the American College of Cardiology/American Heart Association/Heart Rhythm Society and the European Society of Cardiology recommend CRT for patients with continuing symptoms of heart failure despite optimal therapy, QRS duration > 120 ms, ejection fraction < 35% and sinus rhythm [4-6]. The routine approach of CRT is to implant simultaneously, or near so, a pacemaker lead at the right ventricular apex and a second lead to the posterior-lateral left ventricle through the coronary sinus for biventricular pacing in order to correct cardiac dyssynchrony [4]. Correcting mechanical dyssynchrony within the LV (intraventricular dyssynchrony) is suggested as one of the key mechanisms of benefit from CRT, the mechanical dyssynchrony consists of a pattern of uncoordinated regional myocardial deformation with dispersion in time-to-peak thickening of myocardial segments and produces regions of early and late contraction, impairing LV performance. By pacing these segments of late activation, earlier mechanical activation of the regions is achieved via earlier electrical stimulation, thus resulting in a more synchronous LV contraction [7-10].

Despite proven benefit of CRT, a significant proportion of patients fail to respond to CRT [11]. Multiple factors contribute to the non-response such as patient selection and device implantation including LV lead placement. The current clinical guidelines use electrocardiographic QRS width as a selection criterion for mechanical dyssynchrony [4], however, measurement of the mechanical dyssynchrony by imaging methods, especially echocardiography, is suggested to be a better criterion than QRS duration in patient selection for CRT, because a subset of patients with QRS widening do not benefit from CRT [1, 12, 13]. Further current evidence suggests that LV lead position is optimum at the site of latest mechanical activation and away from areas of scar, achieving the optimal LV
lead position could maximize CRT response rate and gain a survival advantage [14-16].

Echocardiography is often the first and only imaging technique used to assess patients considered for CRT. Speckle tracking echocardiography (STE) derived strain imaging offers detailed characterization of LV function and provides indices of mechanical dyssynchrony. In addition, STE systolic strain could be used to identify area of scar [17], therefore roles of STE-derived strain imaging in CRT warrant a closer inspection. This review considers and summarizes different indices of mechanical dyssynchrony generated by STE-derived strain imaging and their relevance in patient selection for CRT and their prognostic values in predicting response to CRT. This review further examines applications of STE-derived strain imaging in optimizing LV lead position by determining sites of latest mechanical activation and presence or absence of scar in a particular segment.

Speckle tracking is a post-processing computer algorithm that uses the routine grayscale digital images. Briefly, discrete speckle patterns are present in routine grayscale digital images of the myocardium. Within a user-defined region of interest placed on the myocardial wall, the image-processing algorithm automatically subdivides regions into blocks of pixels that track stable patterns of speckles. Subsequent frames are then automatically analyzed by searching for new location of the speckle patterns within each of the blocks. Velocity vectors can then be calculated using the spatial and temporal data generated by the tissue movement information represented by the location shift of these acoustic markers from frame to frame. Temporal changes in these stable speckle patterns are identified as moving farther apart or closer together and create a series of regional strain vectors. Since the strain information is not dependent on the Doppler angle of incidence like tissue Doppler imaging (TDI) strain, more strain analyses are possible, including longitudinal, circumferential, radial, and rotational strain analysis [4, 14, 18].

**STE-derived strain image, patient selection for CRT and prognosis of response to CRT**

Mechanical dyssynchrony as a means to predict response to CRT has always been of interest because about 1/3 of the patient do not show demonstrable benefit using standard clinical selection criteria [1, 3]. Interest in quantification of LV dyssynchrony by strain imaging has continued, and tissue Doppler imaging (TDI) was utilized first in various studies. However, its application was limited by its inability to differentiate active from passive motion and that TDI of longitudinal strain is greatly affected by the Doppler angle of incidence which poses as a major limitation for enlarged spherical left ventricles commonly seen in the CRT patients [12, 19-21].

STE-derived strain information is not dependent on the Doppler angle of incidence such as tissue Doppler imaging (TDI) strain, therefore more strain analyses are possible, including longitudinal, circumferential, radial, and rotational strain analysis, and has been suggested to be superior to TDI strain in quantifying LV dyssynchrony [4, 14, 18]. Four different speckle tracking dyssynchrony approaches have been considered, they are radial strain (myocardial thickening) and circumferential strain (myocardial shortening) assessed from short-axis view, and longitudinal strain (myocardial shortening) and transverse strain (myocardial thickening) assessed from apical view [18].

**Dyssynchrony assessed by speckle tracking radial strain**

It was first reported by Suffoletto et al. that speckle tracking radial strain-quantified-dysynchrony (defined as the time difference in peak antero-septum to posterior wall strain ≥ 130 ms) was associated with ejection fraction (EF) response to CRT [22]. Subsequent study found that combining both TDI longitudinal velocity opposing wall delay and speckle tracking radial strain showed additive value in predicting response to CRT [23]. The STAR (Speckle Tracking and Resynchronization) study was the first prospective, multicenter study on association of speckle tracking strain dyssynchrony and EF response and long-term survival after CRT [24]. It showed that speckle tracking short-axis radial strain and transverse strain from apical views were associated with favorable EF response to CRT and long-term outcome, while longitudinal and circumferential strains were less sensitive in detecting dyssynchrony; and that a lack of baseline radial or transverse dysynchrony before CRT was significantly associated with serious unfavorable events. The
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Association of dyssynchrony by speckle tracking radial strain with long-term outcome was also reported by Gorcsan et al. in another study of 229 patients wherein a lack of dyssynchrony by radial strain was associated with unfavorable outcome in patients with shorter QRS duration of 120-150 ms [13]. Delgado et al. later reported that lack of dyssynchrony by speckle tracking radial strain was associated with death or heart failure hospitalization in CRT patients with ischemic heart disease [16].

Recently Tatsumi et al. suggested that combining assessment of baseline radial strain dys-synchrony index (SDI) (representing average of the energy wasted due to LV dyssynchrony) that expressed both LV dyssynchrony and residual myocardial contractility, and of acute reduction in this index may have clinical application for predicting favorable response to CRT [25, 26]. This finding is consistent with the finding of Imanishi et al. that reported that the combined assessment of baseline LV dyssynchrony using speckle tracking radial strain and its acute improvement after CRT produced a more accurate prediction of long-term outcome after CRT [27].

Furthermore, Wang et al. assessed the value of acute re-coordination derived from speckle-tracking echocardiography for predicting response to CRT, wherein the acute re-coordination after CRT was indexed by an acute reduction in radial dis-coordination index (RDI), defined as the ratio of average myocardial thinning to thickening during the ejection phase. They found that the acute LV re-coordination was a good predictor of CRT response at 6-month follow up [28]. This same group further evaluated predictive value of a baseline speckle tracking strain rate imaging-derived LV dis-coordination index (stretch/shortening or thinning/thickening during ejection) for CRT response, wherein the LV dis-coordination index was calculated from radial, circumferential and longitudinal deformation using STE strain rate imaging, and it concluded that a mid-ventricular radial dis-coordination index could predict reverse modeling at 6 months after CRT and survival of patients receiving CRT [29].

Therefore dyssynchrony assessed by speckle tracking radial strain, as well as its variation, has become a promising parameter for selecting patients for CRT and predicting response to CRT.

Other speckle tracking indices of LV dyssynchrony and markers for response to CRT

Other speckle tracking indices of LV dyssynchrony or markers for response to CRT have been suggested. D'Andrea et al. reported that global longitudinal strain was different in CRT responders and non-responders and thus was an excellent independent predictor of response to CRT [30]. Further, Iwano et al. reported that the strain rate dispersion index (SRDI) (defined as the average of segmental peak systolic strain rates minus global peak systolic strain rate in the longitudinal, circumferential and radial directions), an index of LV contractility loss because of mechanical dyssynchrony could be a good predictor for CRT response [31, 32]. In addition, Ito et al. used STE to investigate whether the extent of pre-CRP septal flash (SF), an early inward/outward motion of the ventricular septum, was associated with LV functional recovery after CRT, and they found that a large number of presystolic ventricular flash (PSVF) (defined if there is a peak in the radial strain curve in the pre-ejection period)-positive segments before CRT predicts fair LV functional recovery after CRT [33].

Three dimension (3D) speckle tracking strain

3D STE is a newer speckle tracking approach to quantify LV dyssynchrony [34, 35], it overcomes the inherent limitation of the two-dimensional (2D) STE as the heart moves in and out of the thin incident imaging plane during a heart cycle, and thus 3D STE may be more accurate in tracking the speckle throughout the cardiac cycle [36]. Unlike 2D STE, 3D STE could perform a combined assessment of longitudinal and circumferential strain (area strain). Compared to 2D STE, 3D STE has the obvious advantage of saving time by assessing all strain and rotation parameters from a single 3D data-set [36]. Various studies have shown that 3D STE was superior to 2D STE in assess LV mechanical dyssynchrony [37, 38]. A recent meta-analysis of left ventricular dyssynchrony assessment and prediction of response to CRT using 3D STE showed that systolic dyssynchrony index derived from the 3D STE had good accuracy to predict CRT response and concluded that 3D STE was a reliable tool to assess LV
dyssynchrony and could have value for accurate prediction of response to CRT [39]. Further, only 3D STE, but not 2D STE, could assess LV global peak twist, whose improvement is one of the mechanisms for the long-term effect of CRT and is correlated to torsion delay index [40]. However, 3D STE still has its disadvantage, that is, it depends on the quality of 2D images used for acquisition [36]. 3D STE is still pretty new and has not yet been fully validated, more studies are needed to further explore its application in assessing LV dyssynchrony, patient selection and prediction of response to CRT.

**STE-derived strain imaging and LV lead position optimization**

Current evidence suggests that LV lead position is optimum at the site of latest mechanical activation and away from areas of scar, achieving the optimal LV lead position could maximize CRT response rate and gain a survival advantage [14, 16, 41].

**Site of latest mechanical activation**

It is suggested by the current evidence that the LV lead should be placed at the site of the latest mechanical activation [42, 43], theoretically, positioning the LV lead at the latest segment allows maximum resynchronization, generates the most efficient ejection and thus achieves greatest gain in systolic function. Various studies have consistently shown that compared with discordant LV lead position, concordant LV lead placement with the site of latest activation led to greater clinical benefit, improved LV performance and survival [15, 42]. The Speckle Tracking Assisted Resynchronization Therapy for Electrode Region (STARTER) study and others showed that STE-derived mechanical activation patterns allows identification of sites of latest activation which could guide the concordant placement of the LV lead with the latest segments, wherein the concordant placement of the LV lead resulted in more responders to CRT and improved patient outcome [43-45].

**Away from areas of scar**

Various studies support the notion that responses to CRT are directly related to extent of viability and are inversely correlated to the degree of scar [46, 47] and that positioning the LV pacing lead at a segment having transmural scar is associated with higher mortality and hospital admission for heart failure and reduced LV reverse remodeling [41, 48-51]. STE longitudinal segmental strain has been used to determine the transmural extent of the scar and to predict transmural scar [30, 52, 53]. Further Becker et al. showed that STE-derived epicardial circumferential strain could more accurate distinguish transmural scar from nontransmural scar than full-thickness circumferential strain [54], the same group further used speckle tracking to retrospectively indicate LV pacing lead position and identify the presence or absence of transmural scar in the LV paced segments using peak systolic circumferential strain and found that absence of transmural scar at the LV paced segments leads to significantly more favorable outcome at 12 month follow-up [55].

The ability of STE to identify transmural scar allows it to prospectively guide LV lead placement away from segment of scar. Khan et al. prospectively examined the impact of targeted LV lead placement on outcome of CRT and reported that placing the LV lead to the latest sites of contraction/activation and away from the scar guided by 2D STE radial strain imaging at the midmyocardial level yielded significantly improved response to CRT. In this study, optimum pacing site was pre-defined as the sites with latest mechanical activation and peak systolic strain > 9.8% indicating absence of transmural scar. This study showed that placing LV pacing lead at the predefined optimum site or adjacent segments was associated with increased response rate and clinical status and lower rates of combined death and heart failure-related hospitalization, while positioning the lead at an area of scar indicated by low amplitude radial strain was associated with increased mortality, death or hospitalization for heart failure [56].

Recently, the benefits associated with prospective multimodality imaging guided LV lead placement were studied. Bakos et al. evaluated the value of an integrated bullseye model for presenting data from cardiac computed tomography (CT) and magnetic resonance imagining (MRI) in combination with STE evaluation of segmental mechanical delay for guiding optimal LV pacing lead positioning in CRT in 39 patients, wherein the latest mechanical activation site was determined by speckle tracking
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radial strain, cardiac CT scan was used to anatomically evaluate coronary sinus and its branches and cardiac MRI was used to evaluate viability, the study showed that an optimal LV lead position could be suggested in almost all patients and therefore presenting data from echocardiography, cardiac CT, and MRI in a combined bullseye plot was a feasible approach for indicating the most appropriate site for LV lead placement [57]. Further, Sommer et al. is a randomized, prospective trial in a total of 192 patients targeting imaged guided LV lead positioning to the latest activated non-scarred myocardial region by combining information from STE, SPECT and cardiac CT, the result of this trial is still awaiting [58].

STE-derived strain imaging, LV mechanical dyssynchrony and scar

STE-derived strain imaging has allowed for integrated analysis of LV mechanical dyssynchrony and assessment of scar. Delgado et al. reported that the presence of LV dyssynchrony indicated by STE radial strain and LV pacing lead positioning relative to latest activation segment and scar had incremental prognostic value for long-term survival for patients receiving CRT [16]. Further indices representing an integrated assessment of both mechanical dyssynchrony and scar could be developed to predict response to CRT, for an example, Lim et al. developed a longitudinal strain delay index (SDI) that incorporates assessments of both segmental timings and contractility which predicted response to CRT [59].

Limitations

Lack of reproducibility of values obtained by 2D STE remains a major problem, though this problem is less severe compared to TDI. Therefore, before the results obtained by 2D STE are considered accurate, a thorough intra-and inter-observer variability testing shall be performed [60]. Further studies on STE have been limited to patient with sinus rhythm, and most of the clinical application of 2D and 3D STE need to be further confirmed in a large patient pool by different investigators.

Conclusions

Both 2D and 3D STE have becoming promising new tools for assessing regional and global cardiac function, especially mechanical dyssynchrony, and have clinical application in patient selection for CRT and predicting response to CRT. Further STE-derived stain imaging guided LV pacing lead placement at the latest mechanical activation site away from sites of scar produces favorable outcome. In summary, STE has become an important adjunct technique in CRT, although its wide application is still limited by low reproducibility and needs further confirmation.

Disclosure of conflict of interest

None.

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