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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-dyssynchrony (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 dyssynchrony before CRT was significantly associated with serious unfavorable events. The 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 dyssynchrony 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 dataset [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 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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References

[1] Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL, Ellestad M, Trupp RJ, Underwood J, Pickering F, Truex C, McAtee P, Messenger J; MIRACLE Study Group. Multicenter InSync Randomized Clinical Evaluation. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002; 346: 1845-1853.

[2] St John Sutton MG, Plappert T, Abraham WT, Smith AL, DeLurgio DB, Leon AR, Loh E, Kocovic DZ, Fisher WG, Ellestad M, Messenger J, Kruger K, Hilpisch KE, Hill MR; Multicenter InSync Randomized Clinical Evaluation (MIRACLE) Study Group. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. Circulation 2003; 107: 1985-1990.

[3] Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L; Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005; 352: 1539-1549.

[4] Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA 3rd, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Buller CE, Creager MA, Ettinger SM, Faxon DP, Halperin JL, Hiratzka LF, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura RA, Ornato JP, Page RL, Riegel B, Tarkington LG, Yancy CW;

American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee toRevise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices); American Association for Thoracic Surgery; Society of Thoracic Surgeons. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices): developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. Circulation 2008; 117: e350-e408.

[5] Hunt SA, Abraham WT, Chin MH. 2009 Focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults. A Report of the American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation. J Am Coll Cardiol 2009; 53: e1-e90.

[6] Dickstein K, Vardas PE, Auricchio A. 2010 Focused Update of ESC Guidelines on device therapy in heart failure: an update of the 2008 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure and the 2007 ESC guidelines for cardiac and resynchronization therapy. Developed with the special contribution of the Heart Failure Association and the European Heart Rhythm Association. Eur Heart J 2010; 31: 2677-2687.

[7] Vardas PE, Auricchio A, Blanc JJ, Daubert JC, Drexler H, Ector H, Gasparini M, Linde C, Morgado FB, Oto A, Sutton R, Trusz-Gluza M; European Society of Cardiology; European Heart Rhythm Association. Guidelines for cardiac pacing and cardiac resynchronization therapy: the task force for cardiac pacing and cardiac resynchronization therapy of the european society of cardiology. Developed in collaboration with the European Heart Rhythm Association. Eur Heart J 2007; 28: 2256-2295.

[8] Aiba T, Hesketh GG, Barth AS, Liu T, Daya S, Chakir K, Dimaano VL, Abraham TP, O'Rourke B, Akar FG, Kass DA, Tomaselli GF. Electrophysiological consequences of dyssynchronous heart failure and its restoration by resynchronization therapy. Circulation 2009; 119: 1220-1230.

[9] Kass DA. Pathobiology of cardiac dyssynchrony and resynchronization. Heart Rhythm 2009; 6: 1660-1665.

[10] Gorcsan J 3rd, Yu CM, Sanderson JE. Ventricular resynchronization is the principle mechanism of benefit with cardiac resynchronization therapy. Heart Fail Rev 2012; 17: 737-746.

[11] Cunningham D, Charles R, Cunningham M. Cardiac Rhythm Management: UK National Clinical Audit 2010. Available at http://www.angliacn.nhs.uk/assets/doc/pdf/Workstreams/Cardiac/Reports/Cardiac-Rehab/Reports/National%20Report%20 2010%20draft.pdf. Accessed November 20, 2013.

[12] Bax JJ, Bleeker GB, Marwick TH, Molhoek SG, Boersma E, Steendijk P, van der Wall EE, Schalij MJ. Left ventricular dyssynchrony predicts response and prognosis after cardiac resynchronization therapy. J Am Coll Cardiol 2004; 44: 1834-1840.

[13] Gorcsan J III, Oyenuga O, Habib PJ, Tanaka H, Adelstein EC, Hara H, McNamara DM, Saba S. Relationship of echocardiographic dyssynchrony to long-term survival after cardiac resynchronization therapy. Circulation 2010; 122: 1910-1918.

[14] Ypenburg C, Sieders A, Bleeker GB, Holman ER, van der Wall EE, Schalij MJ, Bax JJ. Myocardial contractile reserve predicts improvement in left ventricular function after cardiac resynchronization therapy. Am Heart J 2007; 154: 1160-1165.

[15] Ypenburg C, van Bommel RJ, Delgado V, Mollema SA, Bleeker GB, Boersma E, Schalij MJ, Bax JJ. Optimal left ventricular lead position predicts reverse remodeling and survival after cardiac resynchronization therapy. J Am Coll Cardiol 2008; 52: 1402-1409.

[16] Delgado V, van Bommel RJ, Bertini M, Borleffs CJ, Marsan NA, Arnold CT, Nucifora G, van de Veire NR, Ypenburg C, Boersma E, Holman ER, Schalij MJ, Bax JJ. Relative merits of left ventricular dyssynchrony, left ventricular lead position, and myocardial scar to predict long-term survival of ischemic heart failure patients undergoing cardiac resynchronization therapy. Circulation 2011; 123: 70-78.

[17] Becker M, Hoffmann R, Kühl HP, Grawe H, Katoh M, Kramann R, Bücker A, Hanrath P, Heussen N. Analysis of myocardial deformation based on ultrasonic pixel tracking to determine transmurality in chronic myocardial infarction. Eur Heart J 2006; 27: 2560-2566.

[18] Gorcsan J, Tanaka H. Echocardiographic assessment of myocardial strain. J Am Coll Cardiol 2011; 58: 1401-1413.

[19] Yu CM, Chau E, Sanderson JE, Fan K, Tang MO, Fung WH, Lin H, Kong SL, Lam YM, Hill MR, Lau

CP. Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. Circulation 2002; 105: 438-445.

[20] Gorcsan J 3rd, Kanzaki H, Bazaz R, Dohi K, Schwartzman D. Usefulness of echocardiographic tissue synchronization imaging to predict acute response to cardiac resynchronization therapy. Am J Cardiol 2004; 93: 1178-1181.

[21] Yu CM, Gorcsan J 3rd, Bleeker GB, Zhang Q, Schalij MJ, Suffoletto MS, Fung JW, Schwartzman D, Chan YS, Tanabe M, Bax JJ. Usefulness of tissue Doppler velocity and strain dyssynchrony for predicting left ventricular reverse remodeling response after cardiac resynchronization therapy. Am J Cardiol 2007; 100: 1263-1270.

[22] Suffoletto MS, Dohi K, Cannesson M, Saba S, Gorcsan J 3rd. Novel speckle-tracking radial strain from routine black-and-white echocardiographic images to quantify dyssynchrony and predict response to cardiac resynchronization therapy. Circulation 2006; 113: 960-968.

[23] Gorcsan J 3rd, Tanabe M, Bleeker GB, Suffoletto MS, Thomas NC, Saba S, Tops LF, Schalij MJ, Bax JJ. Combined longitudinal and radial dyssynchrony predicts ventricular response after resynchronization therapy. J Am Coll Cardiol 2007; 50: 1476-1483.

[24] Tanaka H, Nesser HJ, Buck T, Oyenuga O, Jánosi RA, Winter S, Saba S, Gorcsan J 3rd. Dyssynchrony by speckletracking echocardiography and response to cardiac resynchronization therapy: results of the Speckle Tracking and Resynchronization (STAR) study. Eur Heart J 2010; 31: 1690-1700.

[25] Tatsumi K, Tanaka H, Matsumoto K, Kaneko A, Tsuji T, Ryo K, Fukuda Y, Norisada K, Onishi T, Yoshida A, Kawai H, Hirata K. Relation between strain dyssynchrony index determined by comprehensive assessment using speckle-tracking imaging and long-term outcome after cardiac resynchronization therapy for patients with heart failure. Am J Cardiol 2012; 109: 1187-1193.

[26] Tatsumi K, Tanaka H, Matsumoto K, Miyoshi T, Hiraishi M, Tsuji T, Kaneko A, Ryo K, Fukuda Y, Norisada K, Onishi T, Yoshida A, Kawai H, Hirata K. Combined baseline strain dyssynchrony index and its acute reduction predicts mid-term left ventricular reverse remodeling and long-Term outcome after cardiac resynchronization therapy. Echocardiography 2013; 31: 464-73.

[27] Imanishi J, Tanaka H, Matsumoto K, Tatsumi K, Miyoshi T, Hiraishi M, Kaneko A, Ryo K, Fukuda Y, Yoshida A, Yokoyama M, Kawai H, Hirata K. Utility of combined assessment of baseline dyssynchrony and its acute improvement to predict long-term outcomes after cardiac resynchronization therapy. Am J Cardiol 2012; 110: 1814-1819.

[28] Wang CL, Wu CT, Yeh YH, Wu LS, Chang CJ, Ho WJ, Hsu LA, Luqman N, Kuo CT. Recoordination rather than resynchronization predicts reverse remodeling after cardiac resynchronization therapy. J Am Soc Echocardiogr 2010; 23: 611-620.

[29] Wang CL, Powell BD, Redfield MM, Miyazaki C, Fine NM, Olson LJ, Cha YM, Espinosa RE, Hayes DL, Hodge DO, Lin G, Friedman PA, Oh JK. Left ventricular discoordination index measured by speckle tracking strain rate imaging predicts reverse remodelling and survival after cardiac resynchronization therapy. Eur J Heart Fail 2012; 14: 517-525.

[30] D'Andrea A, Caso P, Scarafile R, Riegler L, Salerno G, Castaldo F, Gravino R, Cocchia R, Del Viscovo L, Limongelli G, Di Salvo G, Ascione L, Iengo R, Cuomo S, Santangelo L, Calabrò R. Effects of global longitudinal strain and total scar burden on response to cardiac resynchronization therapy in patients with ischaemic dilated cardiomyopathy. Eur J Heart Fail 2009; 11: 58-67.

[31] Iwano H, Yamada S, Watanabe M, Mitsuyama H, Nishino H, Yokoyama S, Kaga S, Nishida M, Yokoshiki H, Onozuka H, Mikami T, Tsutsui H. Novel strain rate index of contractility loss caused by mechanical dyssynchrony. A predictor of response to cardiac resynchronization therapy. Circ J 2011; 75: 2167-2175.

[32] Iwano H, Yamada S, Watanabe M, Mitsuyama H, Mizukami K, Nishino H, Yokoyama S, Kaga S, Okada K, Nishida M, Yokoshiki H, Mikami T, Tsutsui H. Strain rate dispersion index can predict changes in left ventricular volume and adverse cardiac events following cardiac resynchronization therapy. Circ J 2013; 77: 2757-2765.

[33] Ito T, Kizawa S, Nogi S, Shimamoto S, Yokoyama K, Ishizaka N. Association between presystolic ventricular flash and left ventricular functional recovery after cardiac resynchronization therapy. Echocardiography 2014; 31: 149-154.

[34] Tanaka H, Hara H, Adelstein EC, Schwartzman D, Saba S, Gorcsan J 3rd. Comparative mechanical activation mapping of RV pacing to LBBB by 2D and 3D speckle tracking and association with response to resynchronization therapy. JACC Cardiovasc Imaging 2010; 3: 461-471.

[35] Tanaka H, Hara H, Saba S, Gorcsan J 3rd. Usefulness of three dimensional speckle tracking strain to quantify dyssynchrony and

the site of latest mechanical activation. Am J Cardiol 2010; 105: 235-242.
[36] Biswas M, Sudhakar S, Nanda NC, Buckberg G, Pradhan M, Roomi AU, Gorissen W, Houle H. Two- and three-dimensional speckle tracking echocardiography: clinical applications and future directions. Echocardiography 2013; 30: 88-105.
[37] Tanaka H, Tatsumi K, Matsumoto K, Kawai H, Hirata K. Emerging role of three-dimensional speckle tracking strain for accurate quantification of left ventricular dyssynchrony. Echocardiography 2013; 30: E292-E295.
[38] Thebault C, Donal E, Bernard A, Moreau O, Schnell F, Mabo P, Leclercq C. Real-time three-dimensional speckle tracking echocardiography: a novel technique to quantify global left ventricular mechanical dyssynchrony. Eur J Echocardiogr 2011; 12: 26-32.
[39] Kleijn SA, Aly MF, Knol DL, Terwee CB, Jansma EP, Abd El-Hady YA, Kandil HI, Sorour KA, van Rossum AC, Kamp O. A meta-analysis of left ventricular dyssynchrony assessment and prediction of response to cardiac resynchronization therapy by three-dimensional echocardiography. Eur Heart J Cardiovasc Imaging 2012; 13: 763-775.
[40] Lee Y, Mori N, Nakamura D, Yoshimura T, Taniike M, Makino N, Kato H, Egami Y, Shutta R, Tanouchi J, Yamada Y, Nishino M. New approach for rotational dyssynchrony using three-dimensional speckle tracking echocardiography. Echocardiography 2014; 31: 492-8.
[41] Ypenburg C, Schalij MJ, Bleeker GB, Steendijk P, Boersma E, Dibbets-Schneider P, Stokkel MP, van der Wall EE, Bax JJ. Impact of viability and scar tissue on response to cardiac resynchronization therapy in ischaemic heart failure patients. Eur Heart J 2007; 28: 33-41.
[42] Ansalone G, Giannantoni P, Ricci R, Trambaiolo P, Fedele F, Santini M. Doppler myocardial imaging to evaluate the effectiveness of pacing sites in patients receiving biventricular pacing. J Am Coll Cardiol 2002; 39: 489-499.
[43] Becker M, Kramann R, Franke A, Breithardt OA, Heussen N, Knackstedt C, Stellbrink C, Schauerte P, Kelm M, Hoffmann R. Impact of left ventricular lead position in cardiac resynchronization therapy on left ventricular remodelling. A circumferential strain analysis based on 2D echocardiography. Eur Heart J 2007; 28: 1211-1220.
[44] Kristiansen HM, Vollan G, Hovstad T, Keilegavlen H, Faerestrand S. The impact of left ventricular lead position on left ventricular reverse remodelling and improvement in mechanical dyssynchrony in cardiac resynchronization therapy. Eur Heart J Cardiovasc Imaging 2012; 13: 991-1000.
[45] Saba S, Marek J, Schwartzman D, Jain S, Adelstein E, White P, Oyenuga OA, Onishi T, Soman P, Gorcsan J 3rd. Echocardiography-guided left ventricular lead placement for cardiac resynchronization therapy: results of the Speckle Tracking Assisted Resynchronization Therapy for Electrode Region trial. Circ Heart Fail 2013; 6: 427-434.
[46] Molhoek SG, Bax JJ, Bleeker GB, Boersma E, van Erven L, Steendijk P, van der Wall EE, Schalij MJ. Comparison of response to cardiac resynchronization therapy in patients with sinus rhythm versus chronic atrial fibrillation. Am J Cardiol 2004; 94: 1506-1509.
[47] Shanks M, Delgado V, Ng AC, Auger D, Mooyaart EA, Bertini M, Marsan NA, van Bommel RJ, Holman ER, Poldermans D, Schalij MJ, Bax JJ. Clinical and echocardiographic predictors of nonresponse to cardiac resynchronization therapy. Am Heart J 2011; 16: 552-557.
[48] Bleeker GB, Schalij MJ, Van Der Wall EE, Bax JJ. Postero-lateral scar tissue resulting in non-response to cardiac resynchronization therapy. J Cardiovasc Electrophysiol 2006; 17: 899-901.
[49] Ypenburg C, Schalij MJ, Bleeker GB, Steendijk P, Boersma E, Dibbets-Schneider P, Stokkel MP, van der Wall EE, Bax JJ. Extent of viability to predict response to cardiac resynchronization therapy in ischemic heart failure patients. J Nucl Med 2006; 47: 1565-1570.
[50] Chalil S, Stegemann B, Muhyaldeen SA, Khadjooi K, Foley PW, Smith RE, Leyva F. Effect of posterolateral left ventricular scar on mortality and morbidity following cardiac resynchronization therapy. Pacing Clin Electrophysiol 2007; 30: 1201-1209.
[51] Khan FZ, Virdee MS, Read PA, Pugh PJ, O'Halloran D, Fahey M, Elsik M, Begley D, Fynn SP, Dutka DP. Effect of low-amplitude two-dimensional radial strain at left ventricular pacing sites on response to cardiac resynchronization therapy. J Am SocEchocardiogr 2010; 23: 1168-1176.
[52] Gjesdal O, Hopp E, Vartdal T, Lunde K, Helle-Valle T, Aakhus S, Smith HJ, Ihlen H, Edvardsen T. Global longitudinal strain measured by two-dimensional speckle tracking echocardiography is closely related to myocardial infarct size in chronic ischaemic heart disease. Clin Sci 2007; 113: 287-296.
[53] Roes SD, Mollema SA, Lamb HJ, van der Wall EE, de Roos A, Bax JJ. Validation of echocardiographic two-dimensional speckle tracking longitudinal strain imaging for viability assessment in patients with chronic ischemic left ventricular dysfunction and comparison with contrast-enhanced magnetic resonance imaging. Am J Cardiol 2009; 104: 312-317.

[54] Becker M, Ocklenburg C, Altiok E, Füting A, Balzer J, Krombach G, Lysyansky M, Kühl H, Krings R, Kelm M, Hoffmann R. Impact of infarct transmurality on layer-specific impairment of myocardial function: a myocardial deformation imaging study. Eur Heart J 2009; 30: 1467-1476.

[55] Becker M, Zwicker C, Kaminski M, Napp A, Altiok E, Ocklenburg C, Friedman Z, Adam D, Schauerte P, Marx N, Hoffmann R. Dependency of cardiac resynchronization therapy on myocardial viability at the LV lead position. JACC Cardiovasc Imaging 2011; 4: 366-374.

[56] Khan FZ, Virdee MS, Palmer CR, Pugh PJ, O'Halloran D, Elsik M, Read PA, Begley D, Fynn SP, Dutka DP. Targeted left ventricular lead placement to guide cardiac resynchronization therapy: the TARGET study: a randomized, controlled trial. J Am Coll Cardiol 2012; 59: 1509-1518.

[57] Bakos Z, Markstad H, Ostenfeld E, Carlsson M, Roijer A, Borgquist R. Combined preoperative information using a bullseye plot from speckle tracking echocardiography, cardiac CT scan, and MRI scan: targeted left ventricular lead implantation in patients receiving cardiac resynchronization therapy. Eur Heart J Cardiovasc Imaging 2014; 15: 523-31.

[58] Sommer A, Kronborg MB, Poulsen SH, Böttcher M, Nørgaard BL, Bouchelouche K, Mortensen PT, Gerdes C, Nielsen JC. Empiric versus imaging guided left ventricular lead placement in cardiac resynchronization therapy (Imaging-CRT): study protocol for a randomized controlled trial. Trial 2013; 14: 113.

[59] Lim P, Donal E, Lafitte S, Derumeaux G, Habib G, Réant P, Thivolet S, Lellouche N, Grimm RA, Gueret P. Multicentre study using strain delay index for predicting response to cardiac resynchronization therapy (MUSIC study). Eur J Heart Fail 2011; 13: 984-991.

[60] Kleijn SA, Aly MFA, Terwee CB. Reliability of left ventricular volumes and function measurements using three dimensional speckle tracking echocardiography. Eur Heart J Cardiovasc Imaging 2012; 13: 159-168.