

## Editorial

# Are New Myocardial Tracking Systems of Three-Dimensional Strain a Reality in Daily Clinical Practice?

¿Los nuevos sistemas de seguimiento de la deformación tridimensional del miocardio son una realidad en la práctica clínica diaria?

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## INTRODUCTION

Echocardiography is the most commonly used diagnostic method for assessing left ventricular (LV) function in clinical cardiology. However, echocardiographic measurements are subjective, semiquantitative, and relatively insensitive when detecting subtle abnormalities in contractility. Furthermore, early detection of either global or regional LV dysfunction may be crucial to patient care by influencing therapy and establishing prognosis.<sup>1</sup> Accordingly, a great deal of effort has been concentrated in developing echocardiographic technology to objectively and reliably quantify LV function. The most widely used and validated technique for quantitative assessment of regional LV function has been tissue Doppler imaging. However, tissue Doppler is limited by Doppler angle of incidence. An exciting recent advance has been 3-dimensional (3D) myocardial tracking technology, using 3D speckle tracking strain.<sup>2–5</sup> This article will review the emerging work on 3D myocardial tracking, its strength, technical limitation, and potential for clinical applications now and for the future.

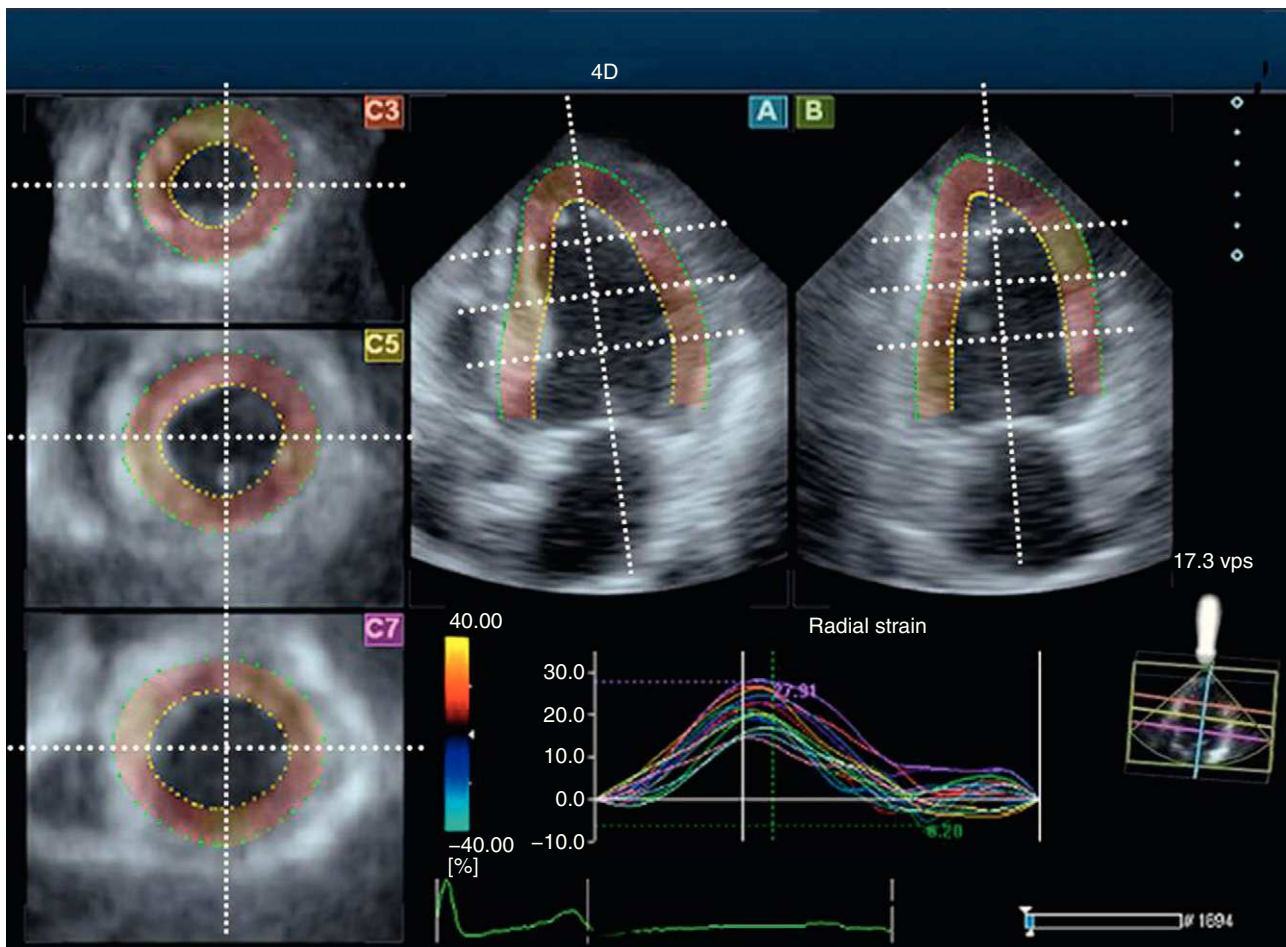
## TECHNICAL APPROACH TO 3D SPECKLE TRACKING STRAIN

The fundamental approach of speckle tracking echocardiography is to utilize routine gray-scale digital images to track stable patterns of speckles, frame-to-frame. To determine strain, a region of interest is placed on the myocardial walls to calculate the typical components of strain, including radial, circumferential, longitudinal, transverse, and rotational strain. Speckle tracking was first developed to be applied to 2-dimensional (2D) echocardiographic images, with a major advantage being that it can calculate myocardial strain independent of angle of incidence.<sup>6</sup> Several clinical applications for 2D speckle tracking have been introduced to quantify global and regional LV function.

Although 2D speckle tracking approaches are clinically useful, they are restricted to the assessment of LV function in a single plane. Moreover, each segment must be evaluated sequentially and, thus, is subject to beat-to-beat variability. A more recent quantitative approach is a newly developed 3D speckle tracking echocardiography system. Perez de Isla et al. showed that a new 3D wall motion tracking system was a new and faster tool for myocardial strain assessment when compared with 2D wall motion tracking.<sup>5</sup> An important advance that made this possible was the 3D echocardiographic matrix array transducer to acquire a pyramidal 3D data set, which is essential to the 3D speckle tracking system. Subsequent analysis of the acquired 3D data provides more detailed information than was previously possible. The 3D speckle tracking system used a pyramidal volume from a full-volume dataset requiring 4 smaller wedge-shaped subvolumes from 4 consecutive cardiac cycles during a breath hold, which were combined to provide the larger pyramidal volume. Data are typically acquired from the apical window during breath hold and a relatively stable relative risk interval to minimize translation artifacts among the 4 acquired subvolumes. A stable image is of great importance for successful 3D acquisition. Gain settings also need to be adjusted to optimize endocardial and epicardial definition. For LV applications, a wide sector was used to include the entire LV volume. The 3D datasets can be then displayed in 5 different 2D cross-sections that can be modified interactively (Fig. 1). These tomographic planes include the apical 4-chamber view, apical 2-chamber view, and the 3 standard short-axis views, and serve as reference images to allow precise placement of the region of interest (ROI). Using this convention, maximal long-axis dimensions were adjusted to obtain the true apex. First, the orientation of the long axis of the 4- and 2-chamber views is determined by positioning the main axis line to pass near the center of the LV cavity. Next, 3 standard short-axis planes are defined by positioning the lines in the 2 apical views at each level perpendicular to the long axis of the left ventricle. The ROI is traced in a counterclockwise direction on the endocardium starting from the right hand mitral annulus at end-diastole in the 2 apical views using a point-and-click approach, with special care taken to adjust tracking of all endocardial segments. A second, larger region of interest is then automatically generated and manually adjusted

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**Figure 1.** Examples of images generated from a 3-dimensional myocardial tracking system from a control subject utilizing a pyramidal 3-dimensional dataset with corresponding 2-dimensional reference images: (A) apical 4-chamber view, (B) 2-chamber view, (C3) apical left ventricular short-axis view, (C5) mid-left ventricular short-axis view, and (C7) basal left ventricular short-axis view with 16 segmental time-strain curves.

near the epicardium in the 2 apical views. The software automatically divided the left ventricle into 16 standard segments based on the recommendation of the American Society of Echocardiography<sup>1</sup> and generated corresponding time-strain curves from each segment (Fig. 2). The region of interest was fine-tuned by visual assessment during the cine-loop play feature to ensure that all wall regions were included throughout the cardiac cycle. The 3D movies of regional strain were generated with color coding of strain. Several 3D applications are possible, including 3D LV volumes, wire mesh, and polar or bull's-eye plots. One of the most successful applications is 3D radial strain with thickening or positive radial strain color-coded as orange-yellow, and thinning or negative radial strain color-coded as blue.

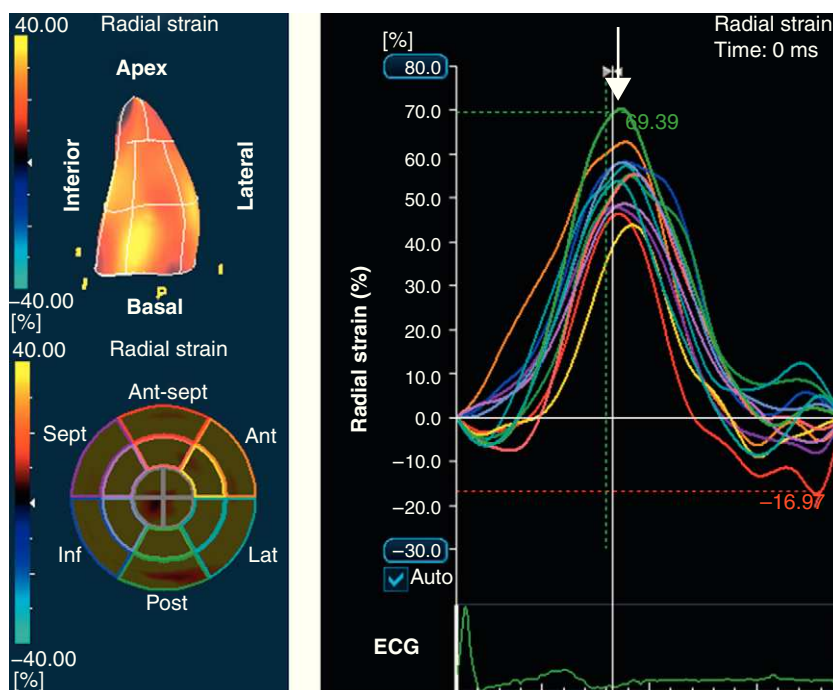
#### APPLICATIONS OF 3D SPECKLE TRACKING STRAIN FOR VENTRICULAR VOLUMES

It is widely known that 2D echocardiographic techniques, including 2D speckle tracking strain used for LV volume quantification, are often affected by foreshortened apical views and geometric assumptions. Furthermore, the 2D methodology lacks the ability to track motion occurring in and out of plane,

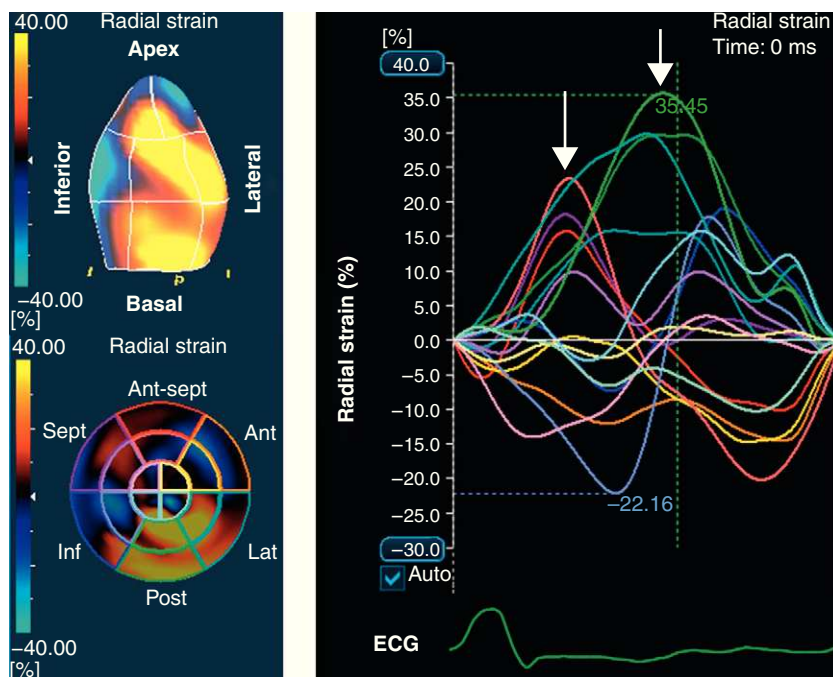
which may result in inaccurate representations of true mechanical function and noise, which may interfere with tracking. Nesser et al<sup>2</sup> evaluated the accuracy of LV volumes by means of 3D speckle tracking strain side by side with 2D speckle tracking strain using cardiac magnetic resonance as a reference.<sup>2</sup> They observed that the measurements by 3D speckle tracking strain showed higher correlation with cardiac magnetic resonance ( $r=0.85$  for end-diastolic volume and  $r=0.92$  for end-systolic volume), smaller biases ( $-16$  ml for end-diastolic volume and  $-1$  ml for end-systolic volume), and narrower limits of agreement (37 ml for end-diastolic volume and 28 ml for end-systolic volume). Importantly, 3D speckle tracking strain showed lower inter- and intra-observer variability (11%–14% and 12%–13%) than 2D speckle tracking strain (16%–17% and 12%–16%, respectively). These important data illustrate the accuracy of the 3D system, and its superiority over routine 2D echocardiographic approaches.

#### APPLICATIONS OF 3D SPECKLE TRACKING STRAIN FOR DYSSYNCHRONY

One of the most promising applications of 3D speckle tracking strain is for myocardial tracking to determine abnormalities in



**Figure 2.** Images of color-coded 3-dimensional left ventricular displays (top left) and bull's-eye plot images (bottom left) with corresponding time-to-strain curves from 16 left ventricular sites (right) from a normal control subject. The strain curves demonstrate synchronous time-to-peak-strain curves represented by homogenous coloring at end-systole (arrow). Ant, anterior; Ant-sept, anterior-septum; ECG, electrocardiogram; Inf, inferior; Lat, lateral; Post, posterior; Sept, septal.

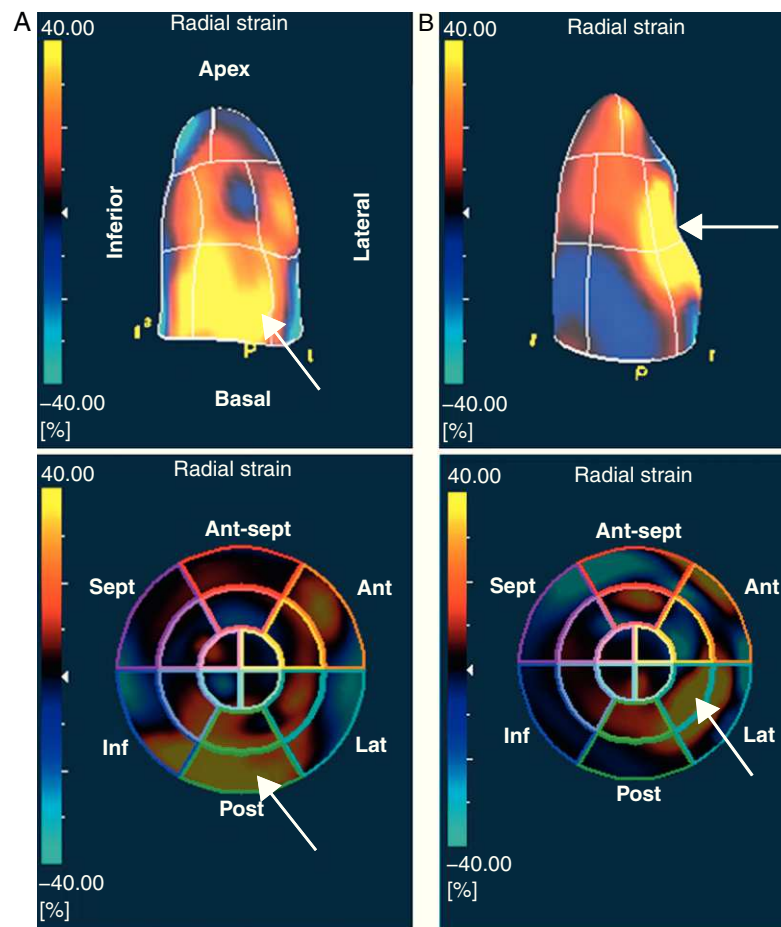


**Figure 3.** An example of a color-coded 3-dimensional left ventricular display (top left) and bull's-eye plot image (bottom left) and corresponding time-to-strain curves from 16 left ventricular sites (right) from a patient with heart failure and left bundle branch block. The strain data demonstrate dyssynchronous time-to-peak-strain curves represented by heterogeneous coloring at end-systole, with early peak strain in septal segments and delayed peak strain in posterior lateral segments (arrows). Ant, anterior; Ant-sept, anterior-septum; ECG, electrocardiogram; Inf, inferior; Lat, lateral; Post, posterior; Sept, septal.

regional mechanical activation known as dyssynchrony, which appears to be important for pacing therapy in heart failure (HF). Although the PROSPECT (Predictors of Responders to Cardiac Resynchronization Therapy) study has suggested that echocardiographic dyssynchrony did not have enough predictive strength to replace routine selection criteria for cardiac resynchronization therapy (CRT),<sup>7</sup> several recent reports document the usefulness of dyssynchrony by 2D speckle tracking radial strain as an important marker associated with long-term survival after CRT<sup>6,8–13</sup>. Suffoletto et al<sup>6</sup> first reported the utility of speckle tracking radial strain for quantifying dyssynchrony associated with the ejection fraction (EF) response to CRT. They demonstrated that baseline speckle tracking radial dyssynchrony, defined as a time difference in peak anteroseptum to posterior wall strain  $\geq 130$  ms, predicted immediate response to CRT ( $<24$  h) with 91% sensitivity and 75% specificity, and mid-term response to CRT ( $8 \pm 5$  months after CRT) with 89% sensitivity and 83% specificity. Furthermore, the STAR study (Speckle Tracking and Resynchronization) was a prospective multicenter study to assess the utility of radial, circumferential, transverse, and longitudinal speckle tracking strain for predicting response to CRT and important long-term outcome events after CRT.<sup>10</sup> This study demonstrated that patients who lacked dyssynchrony before CRT, as determined by either the 2D radial or transverse

speckle tracking strain approach, had serious unfavorable clinical events 3 times more frequently than those with significant baseline dyssynchrony. Furthermore, lack of dyssynchrony before CRT, as determined by the combined use of 2D radial and transverse speckle tracking strains, was associated with implantation of an LV assist device, heart transplant, or death in approximately 50% of patients, in contrast to these unfavorable events occurring in 11% to 13% of patients if baseline 2D radial or transverse speckle tracking dyssynchrony were present.

These important observations using 2D speckle tracking strain to predict important outcome events following CRT have strongly supported the association of speckle tracking dyssynchrony and response to CRT. The newer and theoretically superior approach is 3D speckle tracking because 2D speckle tracking is restricted to the measurement of dyssynchrony in a single plane, which may lack sensitivity to determine precise patterns of dyssynchrony. Since LV dyssynchrony in reality is a 3D phenomenon, 3D speckle tracking strain provides a unique and powerful tool for the evaluation of LV dyssynchrony.<sup>3,4</sup> Tanaka et al. have reported that 3D speckle tracking radial dyssynchrony was successfully quantified from all 16 LV sites as maximal opposing wall delay in time-to-peak strain and standard deviation of time-to-peak strain in 64 subjects (54 HF patients with wide QRS and 10 normal subjects).<sup>3</sup> We showed that



**Figure 4.** Color-coded 3-dimensional speckle tracking radial strain maps from 2 different HF patients with left bundle branch block. Patient A has the site of latest mechanical activation in the mid-posterior segment (arrow). In contrast the Patient B has the site of latest mechanical activation in the mid-lateral segment (arrow). Ant, anterior; Ant-sept, anterior-septum; Inf, inferior; Lat, lateral; Post, posterior; Sept, septal.

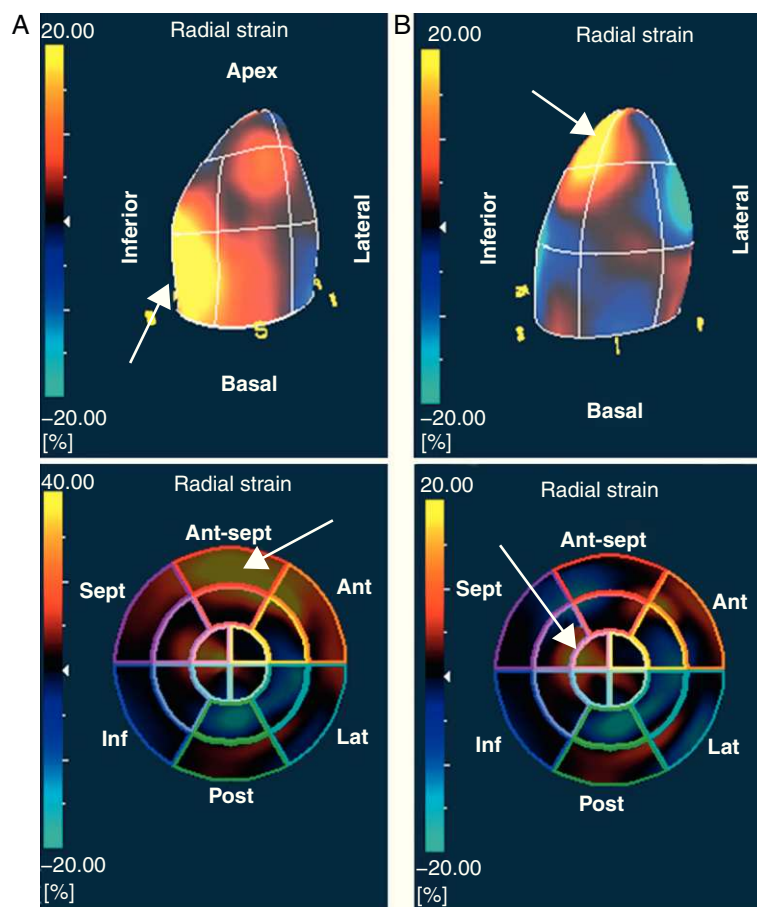


the maximum opposing wall delay and standard deviation were significantly correlated with anteroseptum to posterior wall delay by 2D speckle tracking radial strain ( $r=0.83$  and  $r=0.85$ , respectively, all  $P<.001$ ). An example appears in Fig. 3 showing a color-coded 3D LV display and bull's-eye plot image and corresponding time-to-strain curves from 16 LV sites from a patient with HF and left bundle branch block (LBBB), demonstrating dyssynchronous time-to-peak-strain curves represented by heterogeneous coloring at end-systole, with early peak strain in septal segments and delayed peak strain in posterior lateral segments. Dyssynchrony by 3D speckle tracking is too new a method to prove superiority to the 2D speckle tracking approach because more time is needed to generate outcomes-based data, but there is a clear potential for the 3D speckle tracking information to be more accurate, and further studies are ongoing.

#### DETERMINATION OF SITE OF LATEST ACTIVATION FOR PACING THERAPY

An exciting potential application of 3D speckle tracking strain system is to map mechanical activation and to guide LV lead

positioning. Although the LV lead is routinely positioned in a posterior or lateral epicardial vein through the coronary sinus, several investigators have demonstrated that LV lead positioning at the site of latest mechanical activation by means of speckle tracking radial strain may result in a more complete resynchronization and favorably impact patient response to CRT.<sup>6,14</sup> Although determining the site of latest activation for CRT was first tested with a 2D speckle tracking method, the novel 3D speckle tracking echocardiography system has potential to improve dyssynchrony analysis by providing a more complete 3D mechanical activation map. The pattern of site of latest mechanical activation in HF patients with LBBB varies by individual (Fig. 4) and the timing of regional mechanical contraction is impossible to determine using the surface electrocardiogram. Tanaka et al. have recently demonstrated the prevalence of the site of latest mechanical activation in 54 HF patients with wide QRS using time-to-peak maximal 3D speckle tracking radial strain.<sup>3</sup> Furthermore, we showed utility to determine the site of earliest and latest mechanical activation from all 16 LV sites in CRT patients with intrinsic LBBB and right ventricular (RV) paced with time-to-peak maximal 3D speckle-tracking radial strain.<sup>4</sup> Slight differences in the site of earliest mechanical activation were observed in



**Figure 5.** Color-coded 3-dimensional speckle tracking radial strain maps from same patient with intrinsic left bundle branch block (A) and during right ventricular apical pacing (B). During right ventricular apical pacing, left bundle branch block patients had acute increases in baseline dyssynchrony (standard deviation from  $106\pm31$  ms to  $139\pm30$  ms), and right ventricular apical shifted the site of earliest activation from basal anterior-septum to apical-septum (arrow). Ant, anterior; Ant-sept, anterior-septum; Inf, inferior; Lat, lateral; Post, posterior; Sept, septal.

RV-paced patients, occurring more often from the apex (28% vs 6% of intrinsic LBBB patients,  $P<.05$ ) and inferior septum (55% vs 34% of intrinsic LBBB patients). The site of latest mechanical activation in intrinsic LBBB patients was similarly distributed to that in RV-paced patients. These studies combine to support imaging guided LV lead positioning as a potential advance for CRT, and especially 3D speckle tracking strain may have important clinical implications for the decision of transvenous or surgical epicardial LV lead positioning.

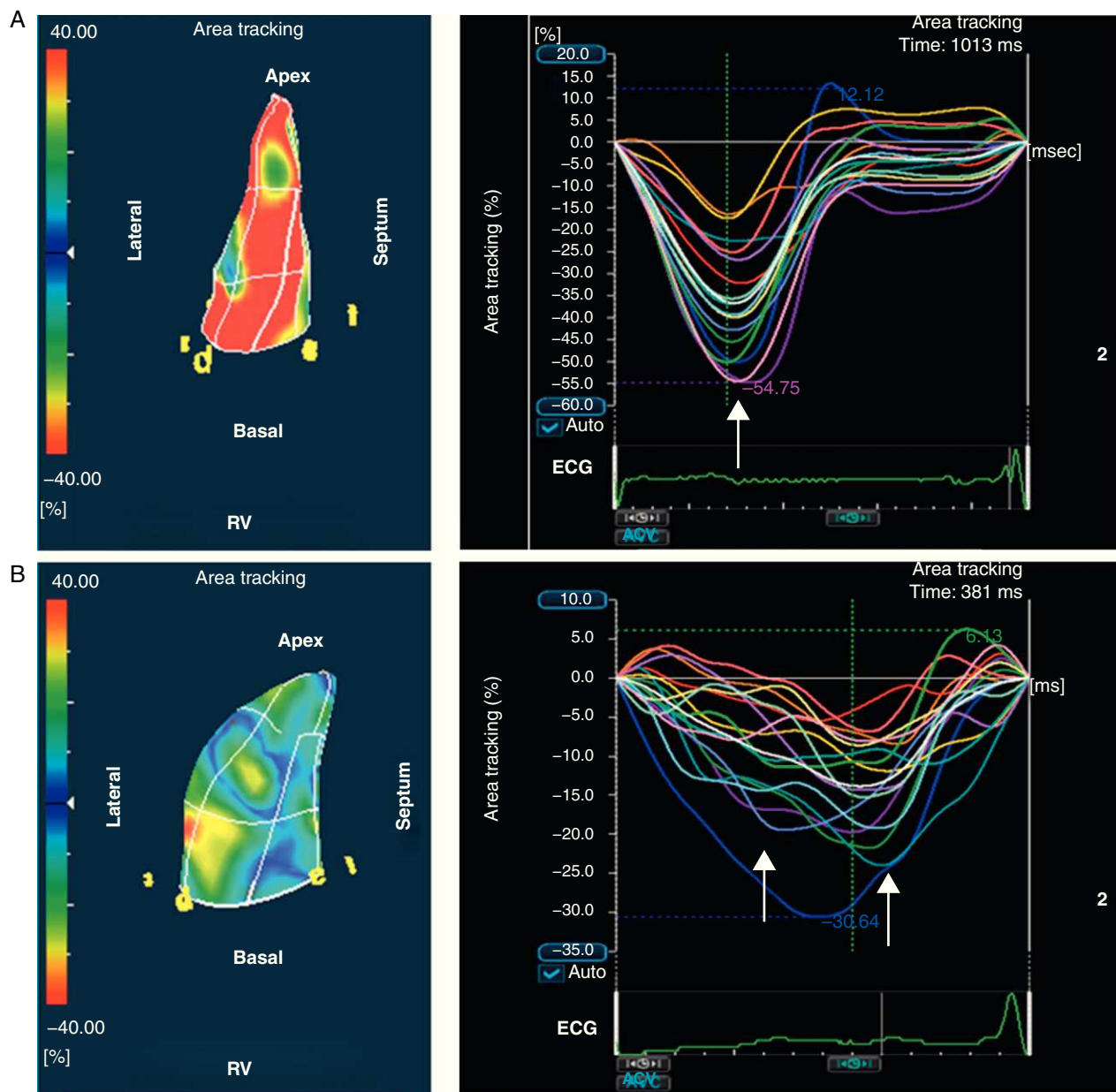
Interestingly, 3D speckle tracking strain also allows us to assess acute effects of RV apical pacing on LV function in HF patients with LBBB. During RV apical pacing, LBBB patients had acute increases in

baseline 3D speckle tracking dyssynchrony. Moreover, RV apical pacing shifted the site of earliest activation from typically basal septal to apical (Fig. 5).

## FUTURE PERSPECTIVE OF 3D SPECKLE TRACKING STRAIN

### Applications for Ischemic Disease

Since ischemic wall motion abnormalities are often associated with passive motion, such as passive expansion and recoil and tethering from adjacent segments, visual assessment of wall



**Figure 6.** (A) Color-coded 3-dimensional right ventricular display (left) and corresponding time-to-area-strain curves from 16 right ventricular sites (right) from a normal control subject, demonstrating synchronous time-to-peak-area-strain curves (arrow). (B) Color-coded 3-dimensional right ventricular display (left) and corresponding time-to-area-strain curves from 16 right ventricular sites (right) from a patient with severe pulmonary hypertension, demonstrating heterogeneous time-to-peak-area-strain curves (arrow) and lower peak-area strain. ACV, acute cerebral vascular disease; ECG, electrocardiogram; RV, right ventricle.

motion remains one of the most challenging determinations in routine clinical practice. Strain by speckle tracking imaging has the advantage to differentiate active contraction from passive motion, which may be a confounding variable in assessment of regional function in humans. Theoretically, 3D speckle tracking strain is a better tool to detect myocardial ischemic segments because it provides simultaneous comprehensive evaluation of 16 LV segments in a single beat. Recently, Seo et al. reported the utility of LV endocardial area change ratio by 3D speckle tracking (area strain), coupled with the factors of both longitudinal and circumferential strain, to assess acute myocardial ischemia induced by occlusion of mid-left ascending artery using an anesthetized sheep model.<sup>15</sup> They observed 3D speckle tracking area strain successfully distinguished changes in myocardial function induced by acute ischemia in both mid and apical anterior wall. Accordingly, 3D speckle tracking has great potential to more completely define regional LV mechanics in patients with ischemic heart disease.

### Applications of Three-Dimensional Strain for Right Ventricle

Precise assessment of RV function has remained clinically challenging because of the anatomical complexity of the right ventricle. The 2D approaches have been limited to tomographic imaging planes that offer an incomplete assessment of RV function in a 3D sense. Accordingly, there is great interest in the potential for 3D myocardial tracking systems to offer an advantage over 2D methodology for RV functional analysis. Although the definitive 3D speckle tracking software for the RV may be considered as being developed and currently a work in progress, initial attempts to assess RV function have yielded interesting observations. Figure 6 shows examples of RV endocardial area change ratio (area strain) in a normal subject and a patient with severe pulmonary hypertension (105 mmHg estimated systolic pulmonary artery pressure). A patient with severe pulmonary hypertension has lower peak-area strain value and heterogeneous time-to-peak-strain curves compared to a normal subject. Although the clinical meaning of these observations of RV mechanics has yet to be elucidated, this demonstrates the potential impact of this imaging technology. Future improvements in the software are anticipated to improve the tracking ability of the speckle tracking system for future RV functionality studies.

### Current Limitations of Three-Dimensional Speckle Tracking

A major limitation of the image acquisition for current 3D speckle tracking system is a relatively slow temporal resolution, with typical frame rates of 20 to 25 volumes/s. The sequential volume acquisition, which currently requires 4 sequential beats, is vulnerable to motion artifacts if the patient is unable to cooperate fully with a breath hold. These are practical limitations when considering the assessment of ischemic disease and stress echocardiography, where temporal resolution and breath holding become more challenging. Furthermore, the spatial resolution of 3D images and image quality is currently not as clear as comparable 2D imaging because of the technological demands required for 3D imaging. Despite these limitations, the initial experience of 3D speckle tracking systems has exceeded expectations because of the advantage that a 3D data set offers. We have seen hardware and software revisions in the recent past which have resulted in marked improvements in spatial resolution and 3D image quality. Technical advances in computer technology are anticipated for the near future that will likely result in further improvements in

both spatial and temporal resolution of 3D myocardial tracking approaches.

### CONCLUSIONS

New echocardiographic myocardial tracking systems utilizing 3D speckle tracking strain have emerged with a great deal of excitement and enthusiasm for future clinical applications. The 3D speckle tracking strain has provided a new insight to LV mechanics with potential applications including assessment of ischemic heart disease, dyssynchrony and pacing therapy, and RV function. Like many new technical advances, more time is needed to determine the precise role of 3D myocardial tracking in routine clinical practice. However, the initial experience of 3D speckle tracking has been so rewarding that a clear future role in patient care is anticipated.

### CONFLICTS OF INTEREST

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