Background: Activation imaging with 3-dimensional speckle-tracking echocardiography (3D-STE) aims to visualize the time required for the onset of regional contraction from QRS onset. We hypothesized that the optimal setting of activation imaging was associated with electrical activation. This study was designed to determine an optimal setting of activation imaging with 3D-STE in comparison with that of a voltage mapping system and to assess the feasibility of this imaging method.

Methods and Results: We enrolled 7 patients who underwent electrical voltage mapping. Regional deformation was measured by area change ratio (ACR) with 3D-STE. Activation imaging data were obtained at 10%, 25%, 50%, and 100% of maximal ACR values as the threshold for onset of regional contraction. Duration of LV electrical intraventricular activation time (IVATelectrical) by voltage mapping and mechanical IVAT (IVATmechanical) by activation imaging was defined as the time difference between the first and latest endocardial activation sites. We obtained 21 data sets under various conduction patterns and pacing configurations. The strongest correlation between IVATmechanical and IVATelectrical was observed at 25% of maximal ACR values (IVATelectrical=0.47 * IVATmechanical+20, R=0.80, P<0.001). Concordance of the first and latest activated segments between activation imaging and voltage mapping was 90.5% at this setting (19 studies).

Conclusions: Activation imaging with 3D-STE may be a feasible noninvasive method of dyssynchrony imaging based on electromechanical coupling. (Circ J 2013; 77: 2481–2489)

Key Words: Activation imaging; Dyssynchrony; Speckle-tracking echocardiography; 3-dimensional echocardiography

Interventricular dyssynchrony has drawn attention as an important candidate of cardiac resynchronization therapy (CRT). However, the significance of mechanical dyssynchrony to predict CRT responders remains controversial. Based on the concept of CRT, electromechanical coupling-based dyssynchrony imaging may be useful in assessing intraventricular dyssynchrony. In the field of electrophysiology, the 3-dimensional (3D) noncontact mapping system (EnSite™ electro-anatomical system; St. Jude Medical, Minneapolis, MN, USA) and the 3D contact system (CARTO Mapping System; Biosense Webster, Diamond Bar, CA, USA) are clinically available for assessing propagation of electrical activation. However, the techniques required by these systems are clinically unfriendly because of their invasiveness. Recently, in vivo studies of electrical-mechanical coupling imaging with ultrasound techniques revealed a significant relation between electrical and mechanical activation. Speckle-tracking echocardiography (STE) to visualize regional myocardial deformation has been developed to assess LV dyssynchrony and is available in the clinical setting. In the present study, we proposed novel 3D-STE software to visualize mechanical activation (termed “activation imaging”). The concept of activation imaging is visualizing the onset of regional mechanical activation modeled after that of electrical mapping systems. Thus, based on the concept of electrical-mechanical coupling, this study was designed to determine an optimal setting of activation imaging that could reflect the onset of regional mechanical activation in comparison with that from 3D electrical voltage mapping systems.
Methods

Our study group comprised 7 patients who underwent catheter-based electrical voltage mapping (Table). The patient in case 1, who had idiopathic ventricular tachycardia, had no apparent underlying cardiac disease. The other 6 patients had nonischemic cardiomyopathy with severe LV dilatation and systolic dysfunction. The patient in case 3 was diagnosed as having cardiac sarcoidosis and showed an area of akinesis in the basal inferior wall. CRT was performed in 5 patients (cases 3–7), and in the remaining 2 patients with left bundle branch block (LBBB), catheter ablation therapy was performed for treatment of ventricular tachycardia. This study was approved by the local research ethics committee, and all patients gave their written informed consent.

Echocardiography

All patients were examined in the left lateral position. Baseline Doppler echocardiographic examinations were performed with an Artida™ ultrasound system (Toshiba Medical Systems Co, Tochigi, Japan). Standard echocardiographic examinations were performed using a multifrequency transducer. LV end-diastolic volume (LVEDV), end-systolic volume (LVESV), and ejection fraction (EF) were measured using a modified Simpson’s
method. For 3D-STE, full-volume R waves of ECG-gated 3D data sets were acquired from apical positions using a matrix array 2.5-MHz transducer. To obtain these data sets, 4 or 6 sectors were scanned and automatically integrated into a wide-angle (max. 90°×90 degrees) pyramidal data image covering the entire LV. Volume rate of each image was set at more than 20Hz. The data were stored and transferred to a computer for offline analysis. The images were analyzed with 3D Wall Motion Tracking software (Toshiba Medical Systems Co) in a manner reported previously.9,10

**Activation Imaging Based on Regional LV Deformation**

A novel activation imaging method was proposed to assess LV dyssynchrony. Activation imaging was visualized on the basis of deformation in regional endocardial surfaces. Regional deformation was measured by area change ratio (ACR), which is a deformation parameter obtained from the area tracking method by 3D-STE.10

Activation imaging concepts are as follows.

**Visualization of the Onset of Regional Mechanical Activation**

The activation imaging method aims to quantify the time from onset of QRS to onset of regional deformation in the 16 LV segments, but not the timing of maximum deformation corresponding to the maximum ACR value. To visualize the timing of regional activation, if a regional ACR value exceeded a threshold value in each regional area, then the area was delineated with a color corresponding to an activation imaging value on the polar map image (Figure 1). The parameter representing the time to onset of regional activation was named “AI (ms)”. Intraventricular mechanical activation time was quantified as the time difference from the minimum AI to the maximum AI in the 16 LV segments (mechanical intraventricular activation time: IVAT mechanical), and LV dyssynchrony was assessed by the standard deviation of AI in the 16 segments (AI-SD).

**Initiation Phase Selection for STE Analysis**

As a novel function of the present system, the initial phase for ACR calculations can be changed after a full-volume R-wave of ECG-gated 3D data sets is obtained. Initial phases for ACR calculations in all studies were set at the onset of the QRS. In the current system, the R-wave was automatically selected at the time of data acquisition, so the initial frame for ACR calculation was manually moved to the QRS onset, which was determined from the ECG waveform on the echocardiography system. In some studies, because the onset of the QRS was obscured by complex conduction disturbance, it was visually determined with the greatest of care. With this change, we referred early septal motion in LBBB cases, which often occurred before the R-wave.11,12

![Figure 2](image-url)
CRT Procedure
CRT devices were implanted transvenously in all patients. After performing retrograde coronary venography, we selected a lateral or posterolateral cardiac vein as the target branch of the coronary sinus to stimulate the latest activation site. If attempts to access these veins were impossible because of an unusual anatomy preventing access to the coronary sinus or which resulted in poor sensing, phrenic nerve stimulation, or pacing failure, the middle cardiac vein was considered as an alternative branch. In some patients, CRT with triple-site pacing was performed by our original procedure reported previously.

Reproducibility
Two studies in each case (14 studies overall) were selected at random for the assessment of the intra- and interobserver variabilities of AI in the 16 LV segments and IVATmechanical measurements. To test intraobserver variability, a single observer (Y.S.) analyzed the data twice on occasions separated by an interval of 1 month. To test interobserver variability, a second observer analyzed the data without knowledge of the first observer’s measurements. Reproducibility was assessed as the mean percent error (absolute difference divided by the mean of...
Activation Imaging by 3D-STE

Statistical Analysis

Results are expressed as the mean value±SD. Correlations between 2 variables were evaluated by Pearson’s rank correlation coefficient. The significance of the difference between the segments was tested by 1-way analysis of variance (ANOVA). When a significant difference was detected, significance was tested by Scheffé’s post-hoc test. A P-value <0.05 was considered to indicate statistical significance. All calculations were performed with SPSS ver. 20 (SPSS Inc, Chicago, IL, USA).

Results

Standard Doppler echocardiographic and 3D-STE images were obtained in all patients, and all procedures were performed without complications. The 21 studies in the 7 patients are summarized in the Table. In the patient with intermitted LBBB (case 1), 2 data sets were obtained under normal conduction and LBBB, respectively. In the patient with Wolff-Parkinson-White syndrome and dilated cardiomyopathy (case 2), the baseline ECG showed a LBBB pattern and echocardiography revealed typical LV dyssynchrony with septal flash. In this case, the ECG after ablation therapy showed a nonspecific ventricular conduction delay with QRS duration of 145 ms. Thus, 2 data sets were obtained at baseline and after ablation therapy. In patients undergoing CRT (cases 3–7), echocardiography and voltage mapping data sets were obtained under several configurations in each patient. In certain patients with CRT (cases 4, 6, and 7), a study was performed to identify the effect of CRT by triple-site pacing.13,14 Optimal STE analysis was available in 331 LV segments (98%, 15.8 segments/study).

Activation Imaging Study

A representative case (no. 5) is presented in Figure 2 and shows the significant differences in the activation imaging pattern based on the initial phase for STE analysis. A comparison of activation imaging between threshold values is shown in Figure 3. Correlations between IVAT<sub>mechanical</sub> and IVAT<sub>electrical</sub> in the 21 studies are shown in Figure 4. The strongest correlation was obtained at the threshold setting using 25% of maximum ACR values. At this setting, IVAT<sub>mechanical</sub> was significantly higher than IVAT<sub>electrical</sub> (142.5±24.8 ms vs. 76.1±31.2 ms, P<0.001). Concordance of the first activated segment between activation...
Figure 5. Correlations between electrical activation time and activation imaging (AI) values in regional segments.
**Figure 6.** Regional time differences between activation imaging (AI) values and onset of electrical activation.

**Figure 7.** Changes in activation imaging (AI) by cardiac resynchronization therapy (CRT). (Center) Baseline (Upper) activation imaging and that after CRT (Lower). (Left) 3-dimensional AI as seen from the direction of the septal wall (blue arrows on center panels) and as seen from the direction of the lateral wall (Right [orange arrows on center panels]). After CRT, free-wall AI values were shorter than those at baseline, and free walls were colored blue or green, which indicates resynchronization.
imaging using the 25% value and voltage mapping was 90.5% (19 studies) and that of the latest activated segments also was 90.5%. In contrast, in the setting with maximum ACR, correlations between IVAT\textsubscript{mechanical} and IVAT\textsubscript{electrical} were not significant.

Correlations between regional electrical activation time and activation imaging are shown in Figure 5. The regression lines for the lateral and posterior walls are steeper than those for the septal wall. In addition, as shown in Figure 6, regional time differences between electrical activation and activation imaging were significantly larger in the lateral wall compared with those in the septal wall and apical wall.

**Alternation of Activation Imaging by CRT**
The activation image clearly revealed resynchronization after CRT, as shown in Figure 7 (case 3). Under biventricular pacing, IVAT\textsubscript{mechanical} and AI-SD were significantly decreased in comparison with the baseline setting (IVAT\textsubscript{mechanical}, 189±56 vs. 128±41 ms, P<0.001; AI-SD, 59±20 vs. 33±14 ms, P<0.001).

**Reproducibility**
Intra- and interobserver variabilities of AI and IVAT\textsubscript{mechanical} measurements were less than 10% (intraobserver variability: AI, 5.4±2.1%; IVAT\textsubscript{mechanical}, 7.1±4.0%, interobserver variability: AI, 7.1±4.3%; IVAT\textsubscript{mechanical}, 7.7±4.4%). There were no significant differences in intra- and interobserver variabilities of AI and IVAT\textsubscript{mechanical} measurements among the 16 LV segments.

**Discussion**
Activation imaging with 3D-STE could image the propagation patterns of the onset of mechanical activation, which were significantly related to those obtained from the voltage mapping systems.

The concept of our activation imaging method was visualizing the wavefront image of mechanical activation modeled after that of electrical mapping systems. Therefore, we tried to identify the setting that presents the onset of regional wall deformation most accurately in comparison with studies using 3D electrical voltage mapping systems.6–5 The present study’s results revealed that the setting of 25% of maximum ACR value was an optimal threshold, although it was an empirical threshold determined through comparison with electrical voltage imaging. In terms of ultrasonic engineering, the maximum deformation point that has the maximum ACR value is the most stable and feasible for assessing regional deformation. Therefore, we tried to determine the threshold based on the maximum ACR values. Because electrical voltage imaging as the validation method has higher spatiotemporal resolution than 3D-STE, the comparison studies confirmed the reliability of activation imaging for assessment of LV dyssynchrony.

**Stratification With Previous Dyssynchrony Imaging**
The crucial difference between activation imaging and previous STE methods is the surrogate point used to identify regional contraction. However, it has not been clear whether the maximum strain points actually reflect regional contraction timing.15 In addition, time-strain curves may have multiple peaks, as shown in Figure 2. Thus, which point should be selected? These unsolved issues around the definition of surrogate points have caused interindividual variations.

In the preset study, the 10% point, which was nearest the onset of shortening, showed weaker correlation with the electrical activation studies compared with the 25% point. We believe this is because the lower % point is unstable as a surrogate point. In the present study, the volume rate of each image was set at 20–30Hz. Accordingly, temporal resolutions were 30–50 ms in each frame, which may be inadequate to detect the onset of contractions. In addition, the lower signal-to-noise ratio of the current 3D STE system, because of its lower spatial resolution, might have caused the tracking error, which directly affects ACR calculations. In addition, the use of a % of maximum ACR caused differences between the electrical activation time and mechanical activation time among regional segments as shown in Figure 6, despite the significant relations in each segment (Figure 5). The differences were significantly larger in the lateral wall compared with those in the septal and apical segments. These results mean that delay of mechanical contraction was accentuated in areas of delayed electrical activation using our activation imaging system.

In some of our patients with LBBB, the initial frame for STE analysis was changed because of loss of early septal motion at the R-wave setting that triggered image acquisition (Figure 3). In the present system, the 3D-STE data set of 1 cardiac cycle is consisted by periodicity of each frame. The present system enables changing of the initial frame for STE analysis through periodic frame reconstitution. In patients with LBBB, early systolic septal wall motion, also called septal flash, are often observed.18–20 This slight motion has been noted as an important factor that induces LV dyssynchronization and has been reported as a significant predictor of CRT response. Therefore, this novel function could contribute to more accurate assessment of dyssynchrony compared with that provided by currently available systems.

**Study Limitations**
We validated activation imaging in this comparison study with electrical mapping in only 7 patients. However, this comparative study revealed that activation imaging could visualize electrical propagation patterns with clinically acceptable accuracy, and confirmed the reliability of activation imaging for assessment of LV dyssynchrony. In the near future, the ability of activation imaging to predict CRT responders must be assessed in large-scale prospective studies. In addition, the initial frame for ACR calculation was manually moved to the onset of the QRS. Therefore, this set-up method in the current system might have caused interindividual variations.
Conclusion

Activation imaging using 3D-STE appears to be a feasible and promising technique in assessing LV mechanical dyssynchrony from the viewpoint of propagation imaging of the wavefronts of activation.

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References