Combined assessment of left ventricular dyssynchrony and contractility by speckled tracking strain imaging: A novel index for predicting responders to cardiac resynchronization therapy

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BACKGROUND Mechanical dyssynchrony is an important factor in the response to cardiac resynchronization therapy (CRT). However, no echocardiographic measure can improve prediction of case selection for CRT.

OBJECTIVE The purpose of this study was to assess the efficacy of a newly combined echocardiographic index for ventricular dyssynchrony and contractility using speckled tracking strain analysis to predict responders to CRT.

METHODS Forty-seven patients with severe heart failure in New York Heart Association functional class III/IV, left ventricular ejection fraction ≤35%, and QRS duration ≥130 ms were included in the study. Echocardiography was performed, and a novel index (i-Index), the product of radial dyssynchrony and radial strain, was calculated. Responder to CRT was defined as a patient with a ≥15% decrease in left ventricular end-systolic volume at 6-month follow-up.

RESULTS Thirty-two patients (68%) were classified as responders. The i-Index was significantly higher in responders than in nonresponders (3,450 ± 1180 vs 1,481 ± 841, P <.001). The area under receiver operator characteristic curve was 0.92 for the i-Index, which was better than the index of radial dyssynchrony only (0.74). A cutoff value of i-Index >2,000 predicted responders with 94% sensitivity and 80% specificity. The index using only radial dyssynchrony had 81% sensitivity and 53% specificity. Furthermore, i-Index decreased in responders (1,985 ± 1261, P <.001) but not in nonresponders (1,684 ± 866, P = .48).

CONCLUSION Our findings suggest that a novel combined index by radial strain echocardiography might be a predictor of response to CRT. The value of this novel echocardiographic index requires further assessment in larger studies.

KEYWORDS Cardiac resynchronization therapy; Dyssynchrony; Echocardiography; Heart failure; Myocardial contractility; Pacemaker; Responder

ABBREVIATIONS **CRT** = cardiac resynchronization therapy; **EF** = ejection fraction; **LV** = left ventricular; **LVEDV** = left ventricular end-diastolic volume; **LVESV** = left ventricular end-systolic volume; **NYHA** = New York Heart Association; **RD** = radial dyssynchrony; **RS** = radial strain; **SDt** = standard deviation of time to peak systolic strain of six LV segments; **SPWMD** = septal–posterior wall-motion delay; **Ts-SD** = standard deviation of time from QRS to peak systolic velocity in ejection phase for 12 left ventricular segments

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Introduction

Cardiac resynchronization therapy (CRT) is a new therapeutic modality for improving symptoms, cardiac function, and prognosis in patients with severe heart failure.[1–3] Randomized clinical trials have demonstrated that the majority of patients receive benefit from CRT; however, at the same time, approximately 30% of patients are nonresponders to CRT.[1,4,5] Although the criteria for inclusion in randomized clinical trials were New York Heart Association (NYHA) functional class, cardiac ejection fraction (EF), and ECG QRS complex, several studies have suggested that indices of mechanical dyssynchrony by cardiac imaging are superior for predicting responder to CRT compared with ECG QRS duration. Therefore, assessment of left ventricular (LV) dyssynchrony by echocardiography has been emphasized as a predictive marker.[6–15] However, in the Predictors of Response to CRT (PROSPECT) trial, no single echocardiographic measure of dyssynchrony was recommended to improve patient selection for CRT beyond current guidelines.[16] These echocardiographic measures can evaluate the existence and site of dyssynchrony but cannot evaluate the existence of scar or local myocardial contractility, particularly in patients with ischemia.

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A novel method of speckle tracking radial strain imaging can evaluate dyssynchrony[15] and quantify myocardial systolic function and viability.[17,18] Accordingly, we propose a novel index (i-Index), which includes both LV dyssynchrony and contractility. The objective of this study was to test the hypotheses that a novel combined assessment of LV dyssynchrony and contractility by radial strain imaging can identify responders to CRT from among patients with echocardiographic dyssynchrony.

Methods

Study population

Forty-seven consecutive patients who underwent CRT were included in the study. Selection criteria used for CRT in this study were (1) drug-refractory severe heart failure in NYHA functional class III or IV, (2) depressed LVEF ($\leq$35%), and (3) wide QRS complex ($\geq$130 ms). No patients had atrial fibrillation. All patients received a CRT device with or without automatic defibrillator function and were fully examined by echocardiography before CRT implantation and 6 months after CRT. All patients received optimal drug treatment, including angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, and spironolactone, if tolerated.

Device implantation and optimization

The LV lead was placed on the posterior or lateral wall through the coronary sinus in all patients. The right atrial and ventricular leads were positioned in the right atrial appendage and right ventricular mid or apical septum. The procedure for implantation of the right ventricular lead consisted of advancing the lead out the pulmonary artery, withdrawing the lead until it dropped below the pulmonic valve, and then advancing the lead into the midventricular or apical septum with the use of stylet. Proper right ventricular lead was confirmed by fluoroscopy. The leads were connected to CRT devices (InSync III or Concerto, Medtronic, Inc., Minneapolis, MN, USA). Atrioventricular interval and interventricular delay were optimized to maximize the left ventricular outflow tract velocity–time integral by echocardiography within 1 week after device implantation.

Echocardiography

All echocardiographic studies were performed using a commercially available system (Vivid 7, GE Healthcare, Milwaukee, WI, USA). Patients were examined before and 6 months after CRT implantation. Echocardiographic data were obtained in the apical (two-chamber and four-chamber) and parasternal (short-axis and long-axis) views using a 1.5- to 4.0-MHz transducer at depths of 12 to 16 cm. Standard M-mode, gray-scale two-dimensional, and tissue Doppler images were obtained during breath-hold and stored in cineloop format from three consecutive beats. Pulsed-wave Doppler of the LV and right ventricular outflow tract also was recorded. LV end-diastolic diameter and LV end-systolic diameter were measured from M-mode echocardiography of the parasternal long-axis view. Left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and EF were assessed by biplane Simpson's rule. Septal–posterior wall-motion delay (SPWMD)[6] and standard deviation of time from QRS to peak systolic velocity in ejection phase for 12 left ventricular segments (Ts-SD)[7,9] were calculated before and after CRT, and other conventional echocardiographic predictors also were calculated, if needed, before CRT.

Speckle tracking strain analysis

Standard two-dimensional gray-scale images were acquired in the parasternal short-axis view at the papillary muscle level and analyzed using the software for speckle tracking strain echocardiography (EchoPAC 6.0, GE Healthcare). A minimum rate of 50 Hz was required for reliable operation of this program, and images were recorded with frame rates of 50 to 80 Hz in this study (63.6 $\pm$ 4.8 Hz). This custom acoustic software tracks movement of stable acoustic patterns, called *speckles,* in myocardial tissues. Tracking occurs frame by frame throughout the cardiac cycle. Myocardial radial thickening was represented as a positive value. The short-axis image was then divided into six standard segments with corresponding time–strain curves from each segment. After these echocardiographic measurements were recorded by operators, all strain measurements were performed by a single observer blinded to the clinical and echocardiographic information without two-dimensional images used for strain analysis. For discriminating dyssynchrony indices from strain images, several parameters were obtained from the time–strain curves: maximal time difference of peak systolic strain among six LV segments [radial dyssynchrony (RD)], standard deviation of time to peak systolic strain of six LV segments (SDt), and mean radial thickening of six LV segments [radial strain (RS); Figure 1]. To add assessment of contractility to dyssynchrony, we calculated a novel index (i-Index), which is the product of SDt and RS.

Definition of responders to CRT

Responders to CRT were defined as patients displaying a $\geq$15% reduction in LVESV at 6-month follow-up after implantation.

Statistical analysis

Continuous variables are expressed as mean $\pm$ SD and compared using two-tailed Student t-test for paired and unpaired data. Categorical data are expressed as number and percentage and compared using Chi-square test. Linear regression analysis was performed to assess the relationship between LVESV and baseline dyssynchrony indices. The extent of baseline LV dyssynchrony needed to predict response to CRT was determined by receiver operator characteristic curve analysis. The variables that were significant in univariate analysis were used in logistic regression analysis to determine independent predictors of evolution. $P < .05$ was considered significant.