# Analysis of temporal delay in myocardial deformation throughout the cardiac cycle: Utility for selecting candidates for cardiac resynchronization therapy

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**BACKGROUND** Analysis of myocardial strain using two-dimensional (2D) echocardiography to assess left ventricular (LV) mechanical dyssynchrony by measuring time differences in peak systolic strains from opposing LV walls has been proposed. However, peak systolic strain may be difficult to identify.

**OBJECTIVE** The purpose of this study was to evaluate (1) LV dyssynchrony by assessing the overlap among strain traces of the LV walls throughout the cardiac cycle and (2) its usefulness in identifying responders to cardiac resynchronization therapy (CRT).

**METHODS** Fifty patients with heart failure and LV systolic dysfunction undergoing CRT were studied with 2D echocardiography at baseline and 6-month follow-up. Myocardial radial strain and circumferential strain were analyzed using commercially available software. The resulting strain traces were postprocessed with a mathematical script.

**RESULTS** Quantification of LV dyssynchrony was expressed as an index of temporal overlap from the analyzed traces. Responders to CRT were defined by ≥15% reduction of LV end-systolic volume at 6-month follow-up. Responders to CRT had higher LV dyssynchrony in both radial strain and circumferential strain analysis. A cutoff time overlap ≥7% for radial strain (area under the curve 0.79) and ≥8.5% for circumferential strain (area under the curve 0.66) identified responders to CRT.

**CONCLUSION** Quantifying the temporal superposition of LV wall deformations with a computed algorithm allows measurement of LV intraventricular dyssynchrony throughout the cardiac cycle. The derived index is useful in stratifying the probability of response to CRT.

**KEYWORDS** Cross-correlation; Delay index; Dyssynchrony; Resynchronization; Strain

**ABBREVIATIONS** **2D** = two-dimensional; **CRT** = cardiac resynchronization therapy; **LV** = left ventricle; **LVEF** = left ventricular ejection fraction; **NYHA** = New York Heart Association; **LBBB** = left bundle branch block; **RBBB** = right bundle branch block

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## Introduction

Cardiac resynchronization therapy (CRT) improves symptoms and reduces mortality in heart failure patients. The final objective of CRT is restoration of synchronous mechanical contraction of the left ventricle (LV), if possible, thereby improving LV stroke volume. Evaluation of mechanical dyssynchrony by cardiac imaging has been postulated as a more accurate marker of response to CRT than QRS duration.[1] Intensive research has focused on the detection of intraventricular dyssynchrony before CRT implantation to improve the rate of response.[2,3] The most frequently used techniques for evaluating dyssynchrony by cardiac imaging rely on time differences between systolic peaks of either myocardial velocities or strains.[4–6] Both can be derived from tissue Doppler imaging or two-dimensional (2D) speckle tracking echocardiography (2D strain).[7,8] The advantage of newer 2D strain technique over tissue Doppler imaging is the independence of the angle of incidence. We propose a new index based on speckle tracking strain imaging for quantifying LV dyssynchrony. The index characterizes the temporal superposition of segmental myocardial strain traces throughout the cardiac cycle on the circumferential and radial axes. Evaluating all deformation traces avoids the need to identify peak values. To validate this novel approach, we aimed to assess the usefulness of the index in predicting response to CRT and how that index is modified after CRT.

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## Methods

### Patient population

The present study included 10 healthy volunteers and 50 heart failure patients undergoing CRT implantation. The study protocol was approved by our hospital's ethics committee, and written informed consent was obtained from all patients according to the World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects.

### Healthy volunteers

Ten subjects (age 35 ± 10 years) without any heart disease or remarkable medical history (mean left ventricular ejection fraction [LVEF] 66% ± 4%, QRS duration <120 ms) were chosen as a healthy control group. These healthy volunteers were recruited from a population group with a normal echocardiographic examination, which was indicated to rule out cardiac disease in a routine check-up study.

### Patients undergoing CRT

Fifty patients (age 67 ± 7 years old) with LV dysfunction (mean LVEF 26% ± 7%) undergoing CRT implantation were studied. Patients were selected for CRT according to currently accepted guidelines[9] as follows: heart failure patients in New York Heart Association (NYHA) functional class III to IV, LVEF <35%, and wide QRS complex (>120 ms) on surface ECG. Clinical and echocardiographic baseline characteristics are listed in Table 1.

### Echocardiography

The study protocol included a comprehensive transthoracic echocardiogram. Patients and healthy volunteers were scanned using a commercially available system (Vivid 7, General Electric, Milwaukee, WI, USA). Patient scans were performed before CRT activation (OFF) and at 6-month follow-up. On each scan, LV volumes and LVEF were calculated from standard four- and two-chamber apical views by Simpson method.[10] Short-axis 2D images of the LV were optimized to obtain a frame rate greater than 40 frames per second.

**Table 1** Clinical and echocardiographic baseline characteristics of the cardiac resynchronization therapy group

| | Baseline |
|---|---|
| Age (years) | 67 ± 7 |
| Male | 36 (72) |
| Ischemic etiology | 15 (30) |
| QRS width (ms) | 177 ± 22 |
| Left bundle branch block | 34 (68) |
| Right bundle branch block | 7 (14) |
| Right ventricle paced | 9 (18) |
| Six-minute walking test (m) | 238 ± 163 |
| Minnesota quality-of-life test | 46 ± 36 |
| New York Heart Association functional class | |
| III | 42 (84) |
| IV | 8 (16) |
| LV end-diastolic volume (mL) | 216 ± 66 |
| LV end-systolic volume (mL) | 162 ± 61 |
| LV ejection fraction (%) | 26 ± 7 |

Values are given as number (%) or mean ± SD.
LV = left ventricular.

### Two-dimensional or speckle tracking strain

Circumferential and radial 2D strain of the LV were measured in the parasternal short-axis view at the level of the papillary muscles using commercially available software (EchoPac version 7.0.1, General Electric). Radial strain measures the thickening and thinning of myocardium, whereas circumferential strain measures the shortening and lengthening along the curvature of the LV. Special care was taken to avoid oblique views from midlevel short-axis images and to obtain images with the most circular geometry possible. For the analysis, endocardial contours were traced manually at the end-systolic frame, and the software automatically displayed the entire myocardial wall of a region of interest. The speckles within the myocardium were tracked automatically, frame by frame, allowing the operator to validate the tracking and adjust the region of interest if needed. LV myocardium was divided into six segments: septum, anterior, anteroseptum, lateral, posterior and inferior. Radial and circumferential time–strain traces were obtained for all segments and exported for mathematical analysis.

LV dyssynchrony was evaluated by three different methods based on 2D strain analysis: (1) a dyssynchrony index (delay index) based on temporal superposition of all six LV segments in a short-axis view at the midpapillary muscle level—for this purpose we use a customized software that evaluates the temporal superposition of different traces; (2) measurement of the time difference between peak systolic strain of the anteroseptal and posterior LV walls[5]; and (3) measurement of the time difference between peak systolic strain of the first and last LV segments to reach the maximum strain.[6] The three parameters then were analyzed for their ability to predict CRT response.

At 6-month follow-up, a second echocardiogram was obtained for patients undergoing CRT. Response to CRT was considered LV end-systolic volume decrease ≥15% at 6-month follow-up.[11]

### Assessment of LV dyssynchrony: Calculation of the delay index

A cross-correlation function was applied to develop this novel method of LV dyssynchrony assessment. Cross-correlation is commonly used in signal processing and yields the time delay between analyzed traces.

Cross-correlation was calculated by using Equation 1, and the degree of similarity between two signals was measured:

$$R_{xy}(\tau) = \int_{-\infty}^{\infty} x(t)y(t-\tau)dt \tag{1}$$

where x(t) and y(t) = time-dependent sequences, and $\tau$ = shifting value over the time limits.[12] Therefore, the closer $R_{xy}$ is to 1, the more superposition exists between