Quantitative Assessment of Dyssynchrony Using ECG-Gated SPECT Myocardial Perfusion Imaging Prior to and Following Cardiac Resynchronization Therapy

Takehiko Keida, MD; Hiroshi Ohira, MD; Masaki Fujita, MD; Toshiya Chinen, MD;
Kentaro Nakamura, MD; Takahiro Kato, MD; Naoki Sakakibara, MD*;
Zenichi Ihara, PhD**; Mitsuaki Takami, MD**

Cardiac resynchronization therapy (CRT) assists patients with advanced heart failure (HF) by improving left ventricular (LV) dyssynchrony, but there are significant numbers of non-responders, 1 reason being that the QRS duration is used as the only surrogate determinant of mechanical dyssynchrony, so an effective indicator of LV dyssynchrony is required. The present patient, who had HF, underwent CRT and showed clinical improvement with marked LV reverse remodeling. The regional contraction timing in the LV was assessed with software developed in an application on ECG-gated SPECT myocardial perfusion imaging that depicts the time–volume relationship of the segmented ventricular myocardium and the dispersion of time to end-systole as an expression of dyssynchrony. It was reduced in this patient following CRT. Discordance of systole in regional myocardial segments may present as mechanical dyssynchrony in the LV and could be used as an alternative to QRS duration. Quantitative assessment of dyssynchrony may be possible using this novel method, but further evaluation of the methodology is required. (Circ J 2009; 73: 1550–1553)

Key Words: Cardiac resynchronization therapy; ECG-gated SPECT myocardial perfusion imaging; Intraventricular dyssynchrony

Cardiac resynchronization therapy (CRT) is considered to be effective in patients with moderate to advanced heart failure (HF) and ventricular dyssynchrony defined by a prolonged QRS duration, but there are reports that CRT does not improve the medical condition of approximately 30% of HF patients. The efficacy of CRT in HF is mainly based on the minimization of mechanical dyssynchrony in the left ventricle (LV) by biventricular pacing, in which case, the selection of patients according to the present indications for the therapy (ie, New York Heart Association (NYHA) functional class III or IV; unimproved symptoms despite optimal medical treatment; depressed LV ejection fraction (EF≤35%); QRS duration ≥130 ms) may be imprecise, because the evaluation of LV dyssynchrony is only assessed by 1 surrogate indicator, the QRS duration. Although a wide QRS complex signifying electromechanical delay has been associated with favorable prognosis in HF patients undergoing CRT, estimation of LV dyssynchrony by a simple measure on the ECG often leads to an inaccurate evaluation! The lack of correlation between the QRS duration and ventricular dyssynchrony demonstrates that the standard ECG measure is a reflection on the body surface of the total duration of ventricular activation and hence not a specific index of synchrony/dyssynchrony, which implies that complex and varied heterogeneous mechanical responses to electrical resynchronization exist among individuals. A more direct determinant of dysynchrony should be determined, using imaging techniques that detect minor regional and local change in mass that otherwise do not influence QRS morphology in a standard measurement, given its unsubstantial volume. Echocardiography is currently regarded as the tool for determining mechanical dyssynchrony, and therefore the eventual response to CRT; however, effective indices for the classification of patients with respect to the efficacy of CRT is not yet established. Phase analysis of ECG-gated SPECT myocardial perfusion imaging has been compared with other methods and shown promising results for clinical evaluation. It has been suggested that a measure based on the phase distribution of the onset of LV contraction in perfusion imaging would predict the response to CRT and should therefore demonstrate its applicability in the clinical setting. We used a software program called cardioGRAF® (FUJIFILM RI Pharma Co, Ltd, Tokyo, Japan) to process perfusion imaging data recorded with ECG-gated SPECT as a new, noninvasive method of analyzing LV dyssynchrony. The dispersion of regional systolic timing was studied and is proposed as an expression of LV dyssynchrony for evaluating the response to CRT.

Case Report

Data Acquisition and Analysis With cardioGRAF

Regional contraction timing in LV was computed and visualized with the cardioGRAF software, which processes imaging data acquired by ECG-gated myocardial perfusion SPECT as described previously. The LV is divided into
progressive symptom of dyspnea on exertion and was hospitalized repeatedly for HF. Despite optimal medical therapy including spironolactone (25 mg/day), carvedilol (2.5 mg/day), and furosemide (80 mg/day), his sustained HF symptoms corresponded to NYHA class III with confirmed episodes of non-sustained ventricular tachycardia. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers were not administered because the patient had previously shown intolerance of those drugs. CRT with an implantable defibrillator (CRT-D; InSync III Marquis Model 7279, Medtronic Inc, Minneapolis, MN, USA) was proposed. The LV lead (Attain Model 4193, Medtronic Inc) was positioned at the LV posterior lateral vein, ensuring perfusion in the lateral region was preserved (Figure 1). The clinical findings pre- and post-implantation are shown in Table 1. At 6 months post-implantation, the systolic blood pressure, +dP/dt max, QRS duration, NYHA functional classification, BNP, and 6-min walk distance all showed major improvement. The +dP/dt max, which was calculated using the radial arterial pressure, was increased by 50%; the QRS duration shortened from prior to CRT, and the cardiothoracic ratio decreased from 60% to 52%. The pre- and post-implantation parameters measured with cardioGRAF and by echocardiography are shown in Table 2. The LV end-systolic volume (LVESV) decreased 16.8% after implantation, LVEF improved, and the septal-to-posterior wall motion delay derived from M-mode echocardiography decreased from 175 to 122 ms. The patient was considered to be a responder to CRT based on these results.

We evaluated the regional contraction timing in the LV using cardioGRAF. The software displays pre- and at 6 months following CRT are shown in Figure 2. The time–volume curves of the volume segments had a disorganized pattern prior to CRT (Figure 2a); time-to-end systole was inconstant among the volume segments and the instant of end-systole was dispersed over more than 400 ms. The SDI value was 16.8. Following CRT (Figure 2b), the time–volume curves aligned in a coherent manner and the peaks of contraction concentrated in a narrower time zone; in 12

17 volume segments and the regional wall motion and change in myocardial wall thickening of each segment are estimated. The variation in volume over time is measured for each segment, where the onset of a cardiac rhythm is triggered on the peak of the R-wave, and the instant of end-systole is detected using the zero-crossing detection on the first-derivative of the time-volume curve (ie, contraction velocity). Among the zero-crossing points on the contraction velocity, the instant coinciding with the minimal volume on the time–volume curve is estimated as the time of end-systole. End-systole of the entire LV is estimated as the instant at which the sum of all segments is minimal.

**Quantitative Assessment of LV Dyssynchrony**

The systolic dyssynchrony index (SDI) is defined as:

\[
SDI = \frac{\sigma_t}{\text{RR}} \times 100
\]  
where \(\sigma_t\) is the standard deviation of time to contraction (time from the onset of the beat to end-systole) of all 17 segments, and \(\text{RR}\) is the RR interval. This index is similar to those used in color-coded tissue Doppler imaging, such as the standard deviation of time-to-peak systolic velocity in the ventricular segments (Ts-SD), in that the spread of contraction timing in the LV segments is used as the indicator of dyssynchrony. The same principle is used in gated myocardial perfusion SPECT imaging to represent the onset of mechanical contraction (ie, first-harmonic phase of the wall thickening curve in respect to regional segments). The proposed SDI also takes into account the independent contribution of the contraction of each volume segment, while normalizing with the RR interval (eq. 1). Moreover, it is precise because it uses a zero-crossing detection for the estimation of the instant of end-systole.

The patient was a 71-year-old man with a history of anterior myocardial infarction. Hypoperfusion affecting the anteroseptal LV was observed (Figure 1) and he subsequently developed advanced AV block requiring implantation of a single-chamber VDD pacemaker with the pacing lead positioned in the right ventricular (RV) apex. Following implantation, the cardiac rhythm of the patient depended totally on the pacemaker. He began to gradually develop

Figure 1. Bull’s eye image that aids identification of hypoperfused areas in myocardial perfusion SPECT.

<table>
<thead>
<tr>
<th>Table 1. Clinical Findings Pre- and Post-Implantation of CRT-D</th>
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<tbody>
<tr>
<td>Clinical finding</td>
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<td>---------------------------------------------------------------</td>
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<tr>
<td>Systolic blood pressure (mmHg)</td>
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<td>+dP/dt max (mmHg/s)</td>
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<td>QRS duration (ms)</td>
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<td>NYHA functional classification</td>
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<td>BNP (pg/ml)</td>
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<td>6-min walk distance (m)</td>
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CRT-D, cardiac resynchronization therapy with an implantable defibrillator; NYHA, New York Heart Association.

<table>
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<th>Table 2. Cardiac Function Measurements Prior to and Following CRT-D</th>
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<td>Measurement</td>
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<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>LVEDV (ml)</td>
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<tr>
<td>LVESV (ml)</td>
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<td>LVEF (%)</td>
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LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction. Other abbreviation see in Table 1.
(71%) of the 17 segments, time-to-end systole was observed within a 50-ms window. The total dispersion reduced to less than 250 ms. The contraction velocity curves showed similar coherence. The SDI decreased to 6.1.

**Discussion**

The case presented was of low LV function because of a prior anterior myocardial infarction and permanent RV pacing for advanced AV block that provoked LV dyssynchrony. It has been reported that RV apex pacing increases the risk of atrial fibrillation and HF\textsuperscript{18,19} The altered (ie, non-physiological) electrical propagation in the ventricular myocardium initiated by stimulation at the RV apex is suspected to be the cause of this patient’s worsening HF. Upgrading to CRT (ie, biventricular pacing) at that stage is reported to be efficacious\textsuperscript{20,21} which was the case for the present patient. Clinical manifestations, as well as hemodynamics, improved, and the markers of reverse remodeling in chronic LV HF, as reported by Yu et al\textsuperscript{22} were observed. This was a case of a clearly positive response to CRT.

A prospective evaluation of the indicators of amelioration is required in HF patients who are candidates for CRT. The indicators should represent the mechanical dyssyn-

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*Figure 2.* Display of cardioGRAF processing the ECG-gated myocardial perfusion SPECT data of the patient (a) prior to and (b) following cardiac resynchronization therapy. (Upper right panel) At both time points, the left ventricular myocardium is divided into 17 volume segments. (Upper left panel) Time–volume plots of the segments. The time 0 on the abscissa is triggered on the peak of the R-wave, which is not shown here. (Lower left panel) Derivative of the time–volume curves, which corresponds to the contraction velocity of the respective volume segment. The vertical dotted line on the time–volume plot is the instant of end-systole of each regional myocardial volume estimated by zero-crossing of contraction velocity and minimal volume.
chrony in LV that is responsible for the deteriorated hemodynamics. Although indices derived from tissue Doppler echocardiography have gained attention as potentially effective indicators, methods based on ultrasound have challenges in terms of the objectivity of the measurements and reproducibility of the results. Moreover, a or a combination of indices that are specific and useful has not been established. We report a HF patient whose symptoms improved after CRT, with marked reverse LV remodeling, in whom we evaluated the dispersion of contraction timing in the LV using a dedicated software program. By visual inspection, as well as by use of a novel index, time-to-end systole had a widely dispersed distribution in the 17 ventricular segments before the device was implanted, whereas the time-volume plots at 6 months post-implantation displayed a focused timing of end-systole and coherent contraction velocity curves. The proposed SDI, which is computed with the cardioGRAF program, showed an important change: a 2.75-fold smaller value was observed at the 6-month post-CRT evaluation compared with the pre-CRT value.

Analyses using ECG-gated myocardial perfusion SPECT imaging data have limited resolution in time and space, although the time resolution can be compensated by using higher harmonics in the Fourier approximation. In this study we used up to the 3rd harmonic with 16frames/cardiac cycle. The results from 1 patient suggest the potential advantage of cardioGRAF and the proposed SDI as an indicative measure of LV dyssynchrony in HF patients.

The pattern of regional contraction timing in the LV volume segments assessed by the cardioGRAF program using gated myocardial perfusion SPECT imaging data showed an important change at 6 months post-CRT in a HF patient with marked reverse LV remodeling and clinical improvement. The proposed SDI is a measure of dispersion of the local contraction timing and was reduced in the patient reported here, corresponding to the change observed by visual inspection. Assessment of the chronological alignment of contraction in local myocardial volume may be related to mechanical dyssynchrony in LV. Further evaluation of our methodology is required.

References