A Prospective Pilot Study to Evaluate the Relationship Between Acute Change in Left Ventricular Synchrony After Cardiac Resynchronization Therapy and Patient Outcome Using a Single-Injection Gated SPECT Protocol

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Background—There are ongoing efforts to optimize patient selection criteria for cardiac resynchronization therapy (CRT). In this regard, the relationship between acute change in left ventricular synchrony (LV) after CRT and patient outcome remains undefined.

Methods and Results—A novel protocol was designed to evaluate acute change in left LV synchrony after CRT using phase analysis of standard gated single-photon emission computed tomography (SPECT) myocardial perfusion imaging with a single injection of radiotracer and prospectively applied to 44 patients undergoing CRT. Immediately after CRT, 18 (41%), 11 (25%), and 15 (34%) patients had an improvement, no change, or a worsening in LV synchrony. An algorithm incorporating the presence of baseline dyssynchrony, myocardial scar burden, and lead concordance predicted acute improvement or no change in LV synchrony with 72% sensitivity, 93% specificity, 96% positive predictive value, and 64% negative predictive value and had 96% negative predictive value for acute deterioration in synchrony. Over a follow-up period of 9.6±6.8 months, patients who had an acute deterioration in synchrony after CRT had a higher composite event rate of death, heart failure hospitalizations, appropriate defibrillator discharges, and CRT device deactivation for worsening heart failure symptoms, compared with patients who had an improvement or no change [hazard ratio, 4.6 (1.3 to 16.0); log rank test; P=0.003].

Conclusions—In this single-center pilot study, phase analysis of gated SPECT was successfully used to predict acute change in LV synchrony and patient outcome after CRT. (Circ Cardiovasc Imaging, 2011;4:532-539.)

Key Words: cardiac resynchronization therapy ▪ dyssynchrony ▪ phase analysis ▪ single-photon emission computed tomography

Cardiac resynchronization therapy (CRT) with biventricular (BiV) pacing is recommended for heart failure (HF) patients with left ventricular ejection fraction (LVEF) ≤35%, New York Heart Association (NYHA) class III-IV symptoms refractory to medical therapy, and QRS duration ≥120 ms on the 12-lead surface ECG. Recent studies have further demonstrated benefit in patients with less severe symptoms. However, there is ongoing concern about the suboptimal response rate to CRT in patients selected by these criteria. Although an improvement in the response rate to CRT might be achieved by further refining current ECG criteria (for example, by excluding patients with non–left bundle-branch morphology), prior efforts to optimize patient selection for CRT by improving the characterization and quantification of LV mechanical synchrony have not resulted in any substantial improvements in clinical outcome. To some extent, these efforts have been hampered by the poor repeatability of the quantification of dyssynchrony by echocardiography. It is also noteworthy that most prior studies did not assess acute change in LV mechanical synchrony after CRT. Thus, in patients without a favorable clinical or echocardiographic response to CRT, the proportion in whom the therapy provided (BiV pacing) simply failed to improve the causative pathophysiology (LV dyssynchrony) remains unknown.

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A recently validated and highly repeatable approach to the assessment of LV dyssynchrony is phase analysis of gated single-photon emission computed tomography (gSPECT) myocardial perfusion images (MPI). In this study, we investigated the feasibility of a new radiation-sparing, single radiotracer dose SPECT imaging protocol to assess acute changes in LV synchrony after BiV pacing. Using this...
Study Protocol

Patients underwent de novo BiV pacemaker/ICD implantation or upgrade from a right ventricular (RV) pacemaker, using standard procedures of our institution.

In patients who consented to participate in the study, the defibrillator function was tested, but the LV pacing lead was left inactive at the time of implantation; the RV lead was activated in pacemaker-dependent patients. The next day, after injection of 30 mCi of Tc-99m sestamibi, a 12-lead ECG, and resting gSPECT were performed before and 30 minutes after activation of CRT. Thus, the pre- and post-CRT gSPECT were acquired with a single injection of Tc-99m sestamibi (Figure 1). SPECT images were acquired on a dual-headed gamma scintillation camera (Philips Medical Systems, Milpitas, CA), using standard parameters for MPI (20% acceptance window around 140 keV energy peak, 180° orbit, 32 steps with 25 seconds of data acquisition per step, 16-bin gating, iterative reconstruction using a maximum likelihood expectation maximization algorithm, Butterworth filter with cutoff of 0.66 and order of 0.5).

Phase analysis of gSPECT has been previously described. Briefly, a Fourier transformation is performed on the 16-frame time-activity curve of each myocardial sample to derive the first harmonic function. Because the increase in count activity of a myocardial voxel during the cardiac cycle is linearly related to myocardial thickening (partial volume effect), the first harmonic function represents a continuous thickening curve of the myocardial sample. The temporal onset of mechanical contraction (OMC) during the cardiac cycle of each myocardial sample is considered to be the phase of the inflection point of the thickening curve on a horizontal line representing the average myocardial count over a cardiac cycle (Figure 2A). The OMC phase information from the >600 LV myocardial samples collected is used to generate a phase distribution, which is displayed in histogram and polar map formats (Figure 2B). The phase histogram displays the OMC for all LV myocardial samples collected on the y-axis against phase/time of one cardiac cycle on the x-axis. The phase polar map is a standard bull’s-eye representation of the LV displaying the temporal dispersion of regional OMC using a color-coded scheme. Previously validated measures of LV dyssynchrony include the histogram bandwidth (HBW), which encompasses the range of phases during which 95% of the myocardium initiates OMC, and phase standard deviation (PSD), which is the standard deviation of the phase distributions. Prior studies have established 5° as the smallest difference in phase between 2 events that can be detected by this approach. Because the cardiac cycle is represented as 360°, this translates into a temporal resolution of 1/64th of a cycle.

Methods

Patients

All patients scheduled for BiV pacemaker with implantable cardioverter-defibrillator (ICD) implantation (de novo implant or upgrade from right ventricular pacemaker) were approached for study participation. Patients with atrial fibrillation and an intact ativoventricular node were excluded from participation. All other consecutive, consenting patients were included until the target recruitment of 50 patients who completed the protocol was reached.

Figure 1. Protocol for the serial assessment of changes in left ventricular (LV) mechanical synchrony after cardiac resynchronization therapy (CRT) by phase analysis of gated single-photon emission computed tomography (SPECT) using a single injection of radiotracer.

Figure 2. A, Example of a time-activity curve for a single myocardial sample volume generated by 16-bin gating. The data points (J) are then fitted to a continuous curve, using a Fourier transform. Based on the partial volume effect, this time-activity curve represents the thickening curve of this particular myocardial sample during a cardiac cycle. The point at which the continuous thickening curve intersects with the average density of this voxel (horizontal line) is considered the onset of mechanical contraction (OMC) for this region. The software computes the OMC for all left ventricular (LV) myocardial samples collected (>600) and then displays the composite result as a phase histogram and phase polarmap (B). The phase histogram shows the percentage of myocardium contracting (y-axis) at each point in the cardiac cycle (x-axis). The phase polarmap is a bull’s-eye representation of the LV, showing the sequence of mechanical activation, using a color-coded scheme. This is an example of synchronous LV contraction with a narrow and highly peaked histogram and a uniform color on the phase polarmap.
Predicting Acute Response to CRT

An algorithm incorporating parameters known to influence outcome of CRT was prospectively applied to predict acute change in synchrony after CRT. These parameters consisted of (1) the presence of significant baseline dysynchrony defined as PSD and HBW > 2 SD above published normal limits, (2) scar burden <40% of the LV myocardium, and (3) lead concordance, defined as LV lead position in the segment of latest activation or an adjacent segment, based on the phase polar map. Prior work from our group has demonstrated a low response rate to CRT if ≥40% of the myocardium is scar. LV lead position in or adjacent to the area of latest activation has previously been shown to be associated with LV reverse remodeling. An improvement in LV synchrony was predicted to occur if all of the above criteria were fulfilled. A significant change in synchrony was defined by applying Z-scores to limits of variability derived prospectively from serial SPECT imaging in patients who fulfilled conventional clinical criteria for CRT but did not get a BiV pacemaker in between the 2 SPECT studies. These limits of variability have been previously published by our group.

End Point and Follow-Up

The primary end point was a composite of HF hospitalizations, death, appropriate defibrillator discharges (physician verified by device-stored intracardiac electrocardiograms), and BiV device deactivation for worsening HF symptoms. Prior data have shown a relationship between LV dyssynchrony assessed by phase analysis and appropriate defibrillator discharge. Follow-up data were obtained by review of the medical records at the University of Pittsburgh Medical Center and the Social Security Death Index.

Data Analysis

Baseline patient characteristics are represented as mean±SD or number. Measured dyssynchrony parameters include PSD and HBW. The presence of baseline dysynchrony was defined as 2 SD above the mean normal published values (for men, HBW >62.2 and SD >24.4, and for women, HBW >49.8 and SD >22.2). Z-scores for the change in synchrony after activation of the CRT device were based on prior data showing that with serial imaging there is a measurement variability of 0.58±5.11° for phase SD and 2.03±13.77° for HBW. Improvement and deterioration in synchrony were defined as a Z-score of <−1.28 and >1.28, respectively, since these values represent the 10th and 90th percentiles of the expected distribution of change. Unchanged synchrony was defined as a z score between −1.28 and 1.28. Kaplan-Meier analysis
was performed for outcome data with patients censored after the first event. The log rank test was used to compare survival curves and hazard ratios were calculated. Probability values of <0.05 are considered significant.

## Results

### Baseline Characteristics

A total of 63 patients were recruited into the study. Of these, 13 patients did not complete the protocol because of technical reasons precluding a successful BiV implant (n=13 patients did not complete the protocol because of technical reasons). Table 1 presents the baseline characteristics of the cohort.

### Predicting Acute Response to CRT

Of the 22 (50%) patients who met all 3 criteria (predicted acute responders), only 1 (4.5%) patient had an acute deterioration in synchrony, whereas 21 (95.5%) patients had either an improvement or no significant change. Of the 22 (50%) patients who were predicted acute nonresponders, 8 (36%) had an improvement or no change in synchrony, whereas 14 (64%) patients had a deterioration. Thus, our predictive algorithm had a 72% sensitivity, 93% specificity, 96% positive predictive value (PPV), and 64% negative predictive value (NPV) for the prediction of acute improvement or no change in LV synchrony immediately after CRT (Figure 6 and Table 2). Conversely, the performance of the algorithm for prediction of acute deterioration was sensitivity, 93%; specificity, 72%; PPV, 64%; and NPV, 96%.

### Relationship Between Acute Change in LV Synchrony After CRT and Patient Outcome

Average follow-up was 9.6±6.8 months (median=7.5 months, 25th percentile=4.0 months, and 75th percentile=11.9 months).
censored after the first event. Follow-up was 95% complete at study termination, which was 22.9 months after enrollment of the first patient. One patient was lost to follow-up after he moved residence, and another was excluded after his LV lead became dislodged 1 month after implantation, and no revision was performed. Of the remaining 42 patients, 13 (31%) patients met a primary end point: 3 deaths, 4 HF hospitalizations, 5 defibrillator discharges, and 1 BiV deactivation due to worsening of HF symptoms (Table 2). There was a significant association between acute change in synchrony after CRT and subsequent clinical outcome. Patients who had an acute deterioration in synchrony had a higher event rate (57%) than patients who had acute improvement or no change in synchrony (18%, Table 2). Kaplan-Meier survival analysis (Figure 7) demonstrated worse event-free survival in patients who had an acute deterioration in LV synchrony after CRT [hazard ratio, 4.6 (1.3 to 16.0); *P*=0.003]. There was no difference in event-free survival probability between patients who had an acute improvement in LV synchrony after CRT and those who remained unchanged [hazard ratio, 0.62 (0.09 to 4.4); *P*=0.67]. When ICD discharge was excluded from the composite end point, this did not substantially change the results [2 patients with ICD discharge as the first event were subsequently hospitalized; thus, 7% (2/28) of patients with acute improvement or no change versus 57% (8/14) of patients with acute worsening in dyssynchrony after CRT met the end point [hazard ratio, 9.5 (2.5 to 37.1); *P*=0.0004)].

Predicting Patient Outcome After CRT From the Baseline SPECT

Of the 44 patients who underwent BiV implantation, 22 were predicted to have an acute improvement in synchrony, based on the baseline SPECT. There were more events in patients who were predicted to be acute nonresponders (43%) compared with patients who were predicted to be acute responders (19%). Kaplan-Meier analysis (Figure 8) showed higher event-free survival after CRT in patients who were predicted to be acute responders, based on the baseline SPECT [hazard ratio, 2.9 (0.98 to 9.79); *P*=0.06].

Clinical Perspective

There are ongoing efforts to optimize the selection of heart failure patients for CRT. We applied phase analysis of
gSPECT, using a novel single-injection protocol to prospectively measure LV synchrony before and immediately after clinically indicated BiV pacemaker implantation. Patients who had deteriorated LV synchrony acutely had worse outcome, defined as a composite of cardiac death, heart failure hospitalization, appropriate ICD discharge, and deactivation of BiV pacing for worsening symptoms. Furthermore, the acute response to CRT was accurately predicted using baseline gSPECT-derived information on the presence of LV dyssynchrony, global and regional LV scar, and LV lead concordance with delayed mechanical activation.

**Discussion**

This study identified several new findings. First, it establishes the feasibility of performing serial pre- and post-CRT gSPECT imaging with a single injection of radiotracer, thus minimizing the radiation dose to the patient. Although this protocol has limited applicability to routine clinical practice, it can be used effectively in future clinical trials to explore the effect of CRT on dyssynchrony. The data correlating baseline SPECT parameters to CRT outcome, if confirmed in larger, multicenter studies, could be used to improve patient selection for CRT. Recent multicenter trials have revealed the poor repeatability of echocardiographic measures of LV dyssynchrony. Phase analysis of gSPECT has been shown to have excellent repeatability in single-center studies, attributable to the automated nature of its processing. However, this must be confirmed in multicenter studies.

Second, this is the first prospective study to report the prevalence of acute worsening in LV dyssynchrony after CRT in...
patients selected on the basis of current criteria. Furthermore, these data suggest that an acute worsening of LV synchrony after CRT is associated with adverse patient outcome. Despite numerous published multicenter and single-center studies evaluating the effects of CRT on patient outcome, there is a paucity of data on the relationship between acute response of LV synchrony to CRT and subsequent clinical outcome. In a single-center study of 100 heart failure patients with standard indications for CRT, Bleeker et al determined the relationship between the immediate effects of CRT on LV mechanical synchrony (acute response) and the occurrence of ≥10% reduction in end-systolic volume at 6 months (sustained response).21 Dyssynchrony was defined by phase analysis, indicating that the acute assessment provides accurate information about sustained changes in LV synchrony after CRT. In this study, <10% of patients had a deterioration in synchrony after CRT and the relationship between such a deterioration and outcome was not systematically reported. Our findings that patients with an acute deterioration in LV synchrony after CRT have a worse clinical outcome has potentially important clinical implications and sets the stage for a randomized trial comparing a CRT-on versus CRT-off strategy in such patients.

From a practical standpoint, the most important finding of this pilot study was the demonstration of the potential utility of phase analysis of gSPECT for the selection of patients for CRT. Our data, which need to be confirmed in larger, multicenter studies, suggest that symptomatic heart failure patients with EF ≤35%, who have baseline dyssynchrony as defined by phase analysis, <40% scar burden, and a concordant lead position are more likely (96%) to benefit from CRT. The chances of a worsening in LV synchrony after CRT are higher (64%) when these criteria are not met. In addition to its excellent repeatability, another advantage of SPECT is the ability to comprehensively assess multiple parameters that potentially impact on response to CRT. Several studies have shown that the extent and location of myocardial scar impacts on CRT outcome. Specifically, myocardial scar involving ≥40% of the LV myocardium has been shown to predict lack of response to CRT.11 Other studies have shown strong correlation between the extent of scar and CRT outcome.14,22,23 In addition, scar in the posterolateral wall also predicts a low response rate after CRT.24 The position of the LV lead in relation to regional delay in myocardial contraction and location of scar also has been shown to predict the response to CRT. The posterolateral LV wall is usually the most delayed in HF patients,25 and the LV pacing lead position has been shown to be an independent predictor of CRT outcome. Previous studies have shown that LV pacing at a suboptimal site could result in worsening of LV dyssynchrony and that phase analysis of SPECT can be used to determine the optimal position the LV lead.15 In a recent publication, Delago et al demonstrated that the presence of LV dyssynchrony, as determined by radial strain analysis by 2D echo speckle tracking, and the LV lead position in relation to the delay in regional mechanical activation and scar have incremental prognostic value in HF patients undergoing CRT.26

The inclusion of appropriate ICD discharge in the composite end point is justified by recent data showing an association with LV dyssynchrony.18 Furthermore, when ICD discharge was excluded from the composite end point, this did not substantially change the results.

Study Limitations
This was a small, single-center study designed to explore the feasibility of a novel approach to dyssynchrony assessment and was primarily intended to collect preliminary data for a larger trial. We included patients who received de novo biventricular pacemakers and also those who were upgraded from an RV pacemaker, thus introducing some heterogeneity into the study population. Given the initial study objective of demonstrating protocol feasibility, we did not perform follow-up SPECT to correlate changes in LV volume and function with clinical outcome. However, the use of clinical endpoints rather than LV functional data to define CRT response should be considered a strength of this study, because defining CRT response based on small changes in LV volumes or ejection fraction as measured by serial echocardiography can result in poor reproducibility of study results, as shown in prior multicenter trials.20 We also did not prospectively collect data on improvement in quality of life or functional status, which are important practical objectives of CRT. A technical limitation of the gSPECT approach is that patients with conditions that produce heart rate variability, such as atrial fibrillation or intermittent pacing, are unsuitable because of potential gating artifacts.

Conclusions
In this single-center pilot study, phase analysis of gSPECT was successfully used to predict acute change in LV synchrony and patient outcome after CRT. Patients with deterioration in LV synchrony after CRT had worse outcomes compared with those who had an acute improvement or no change in LV synchrony.

Sources of Funding
This study was funded by a Nuclear Cardiology Foundation grant from the American Society of Nuclear Cardiology (PI: Dr Soman).

Disclosures
Dr Saba received modest research support from Medtronic, Boston Scientific, and St Jude Medical and has a consultant agreement with Spectranetics and St Jude Medical. Dr Soman has a consultant agreement with GE Healthcare and Astellas. Drs Chen and Garcia receive royalties from the sale of the Emory Cardiac Toolbox with SyncTool. The terms of this arrangement have been reviewed and approved by Emory University in accordance with its conflict-of-interest practice. The research in phase analysis is supported in part by a NIH/NHLBI-funded research project (1R01HL094438, PI: Dr Chen).
References


CLINICAL PERSPECTIVE

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_Circ Cardiovasc Imaging_. 2011;4:532-539; originally published online July 19, 2011; doi: 10.1161/CIRCIMAGING.111.965459

_Circulation: Cardiovascular Imaging_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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