



Published in final edited form as:

*J Nucl Cardiol.* 2011 August ; 18(4): 685–694. doi:10.1007/s12350-011-9392-x.

## SPECT myocardial perfusion imaging for the assessment of left ventricular mechanical dyssynchrony

Ji Chen, PhD<sup>a</sup>, Ernest V. Garcia, PhD<sup>a</sup>, Jeroen J. Bax, MD<sup>b</sup>, Ami E. Iskandrian, MD<sup>c</sup>, Salvador Borges-Neto, MD<sup>d</sup>, and Prem Soman, MD, PhD<sup>e</sup>

<sup>a</sup>Department of Radiology and Imaging Sciences, Emory University School of Medicine, Atlanta, GA <sup>b</sup>Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands <sup>c</sup>Division of Cardiology, University of Alabama at Birmingham, Birmingham, AL <sup>d</sup>Department of Radiology, Duke University Medical Center, Durham, NC <sup>e</sup>Cardiovascular Institute, University of Pittsburgh Medical Center, Pittsburgh, PA

### Abstract

Phase analysis of gated single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) is an evolving technique for measuring LV mechanical dyssynchrony. Since its inception in 2005, it has undergone considerable technical development and clinical evaluation. This article reviews the background, the technical and clinical characteristics, and evolving clinical applications of phase analysis of gated SPECT MPI in patients requiring cardiac resynchronization therapy or implantable cardioverter defibrillator therapy and in assessing LV diastolic dyssynchrony.

### Keywords

Myocardial perfusion imaging; SPECT; left ventricular function; heart failure; phase analysis; left ventricular dyssynchrony

## INTRODUCTION

Gated single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) is widely used in patient care for the detection of myocardial ischemia, serial testing in response to therapy, risk stratification, infarct sizing, and viability assessment. The presence of automated methods for measuring ischemic or scar burden and left ventricular (LV) ejection fraction (EF) have been major attractions although not always fully utilized. The automated methods have been implemented into several commercial software packages,<sup>1–5</sup> which have enhanced standardization and improved reproducibility.

In 2005, the assessment of LV mechanical dyssynchrony using phase analysis of gated SPECT MPI was introduced, allowing for the simultaneous assessment of LV perfusion, function, and mechanical dyssynchrony.<sup>6</sup> LV mechanical dyssynchrony has been shown to play an important role in the pathophysiology of heart failure (HF). Phase analysis could potentially expand the applicability of SPECT MPI to the large HF population. There are other methods to assess LV mechanical dyssynchrony, such as echocardiography,<sup>7,8</sup>

magnetic resonance imaging,<sup>9</sup> and planar and tomographic radionuclide ventriculography.<sup>10,11</sup> Two recent review papers addressed these methods<sup>12,13</sup> and they will not be further discussed here. Compared to other imaging modalities, phase analysis of SPECT MPI has shown several advantages such as simplicity, widespread availability, superior reproducibility, applicability to retrospective data, and ability to simultaneously assess myocardial scar location and severity for optimizing cardiac resynchronization therapy (CRT) in HF patients.

From its inception in 2005, phase analysis has undergone considerable technical development and clinical evaluation (Figure 1). This article reviews the background, the technical and clinical characteristics, and evolving clinical applications in patients requiring CRT or implantable cardioverter defibrillator (ICD) therapy and in assessing LV diastolic dyssynchrony.

## TECHNICAL CONSIDERATIONS

### Basic Principles

Phase analysis is based on the partial volume effect, which states that LV regional maximal counts in SPECT MPI images are nearly proportional to the myocardial wall thickness of the same region.<sup>14</sup> This linear relationship indicates that the variation of regional maximal counts over the cardiac cycle represents myocardial wall thickening of the same region. Phase analysis approximates such variation with Fourier harmonic functions to measure the onset of mechanical contraction (OMC). Figure 2 illustrates the processing steps of phase analysis. The input is a gated SPECT MPI short-axis image. Every temporal frame of this image is searched in 3D to obtain regional maximal counts. These 3D samples can be displayed as gated polar maps as shown in Figure 2. Once the regional samples obtained from all temporal frames, the variation of the regional maximal counts over the cardiac cycle is obtained. Then, the first-harmonic Fourier function is used to approximate the regional wall thickening curve to calculate a regional phase, which is related to the time interval when the region starts to contract, presumably OMC. Repeating the Fourier analysis over the left ventricle, an OMC phase distribution is obtained and submitted to quantitative assessment of its uniformity or heterogeneity, i.e., a measure of LV mechanical synchrony or dyssynchrony. Phase standard deviation (the standard deviation of the OMC phase distribution) (PSD) and phase histogram bandwidth (the width of the histogram band including 95% of the 3D samples) (PHB) are two quantitative indices to assess LV global mechanical dyssynchrony. Normal limits for these indices have been generated from gated SPECT MPI studies of 45 male and 45 female normal subjects.<sup>10</sup>

### Temporal Resolution

Since gated SPECT MPI studies are usually acquired as 8 or 16 frames per cardiac cycle, these data are perceived to have low temporal resolution. It is important to note that phase analysis uses continuous Fourier harmonic functions to approximate the discrete wall thickening samples. As shown in Figure 2, the phase difference between 8 and 16 frames/cycle is very small— $0.5^\circ$  ( $360^\circ$  corresponding to one cardiac cycle) demonstrating that Fourier harmonic approximation improves the temporal resolution of the phase measurement. A simulation study based on a digital phantom has shown that in common clinical settings ( $\geq 10$  counts per myocardial pixel) phase analysis can detect phase delays using gated SPECT MPI data acquired with 8 or 16 frames/cycle as well as though it is acquired using 64 frames/cycle but processed without Fourier analysis.<sup>15</sup> This study indicated that the temporal resolution of phase analysis is equivalent to 1/64th cardiac cycle, when there are enough counts.

## Reproducibility, Repeatability, and Robustness

Phase analysis is largely automatic, and has been shown to have high reproducibility (the variation of a measurement by a single operator in different times or by different operators) and high repeatability (the variation of successive measurements). The intra-observer and inter-observer reproducibility of phase analysis has been evaluated in a study using 10 consecutive subjects with LV dysfunction (LVEF  $\leq$  35%) and 10 normal controls.<sup>16</sup> For PSD and PHB, intra-observer correlation coefficients were 1.00 and 1.00, and inter-observer correlation coefficients were 0.99 and 0.99. The high reproducibility of phase analysis makes it very promising in prediction of CRT response, since the Predictors of Response to CRT (PROSPECT) trial showed that echocardiographic techniques yielded modest accuracy to predict CRT response because of the limited reproducibility.<sup>17</sup> The repeatability of phase analysis has been evaluated in a study using 30 HF patients, who met the standard criteria of CRT.<sup>18</sup> These patients underwent two serial gated SPECT MPI scans with a single injection of Tc-99 sestamibi and 30 minutes apart. PSD and PHB were highly correlated between the serial scans ( $r > 0.95$ ). The coefficients of variability in these parameters between the serial scans were very small ( $< 10\%$ ). The high repeatability of phase analysis makes it very promising in assessment of acute and long-term CRT outcomes using serial SPECT MPI scans. Furthermore, the robustness of phase analysis has been shown in multiple studies.<sup>19–21</sup> The LV dyssynchrony parameters measured by phase analysis have been shown to be independent from the type of camera used,<sup>19</sup> the type of image reconstruction,<sup>20</sup> or the clinically relevant tracer doses.<sup>21</sup>

## Validation Against Echocardiography

PSD and PHB given by phase analysis of gated SPECT MPI have been compared to LV mechanical dyssynchrony parameters given by echocardiography. In a study of 75 patients undergoing CRT, phase analysis showed excellent correlation with 2D echocardiography (PSD:  $r = 0.80$ ,  $P < .0001$ ; PHB:  $r = 0.89$ ,  $P < .0001$ ).<sup>22</sup> Phase analysis has also shown good correlation with 3D echocardiography for assessment of LV mechanical dyssynchrony.<sup>23</sup> In 40 consecutive HF patients, good agreement was found between standard deviation of time-to-peak systolic velocity (Ts-SD) on 3D echocardiography and PSD ( $r = 0.74$ ,  $P < .0001$ ) and PHB ( $r = 0.77$ ,  $P < .0001$ ). Patients with substantial LV mechanical dyssynchrony (Ts-SD  $\geq 33$  ms) on 3D echocardiography showed significantly higher PSD ( $55.3 \pm 13.6^\circ$  vs  $25.1 \pm 7.6^\circ$ ,  $P < .0001$ ) and PHB ( $186 \pm 52^\circ$  vs  $74 \pm 24^\circ$ ,  $P < .0001$ ) as compared to patients without substantial LV mechanical dyssynchrony (Ts-SD  $< 33$  ms).

## CLINICAL CHARACTERISTICS OF LV DYSSYNCHRONY BY PHASE ANALYSIS

### Relations with Other Physiological Parameters

LV mechanical dyssynchrony measured by phase analysis has been shown to differentiate normal controls and patients with left bundle branch block, right bundle branch block, ventricular paced rhythm, or LV dysfunction (all  $P < .001$ ), who were expected to have various degrees of LV dyssynchrony.<sup>24</sup> In addition to the above conduction and functional abnormalities, other factors have been shown to affect LV mechanical dyssynchrony. A study including 125 patients with LVEF  $< 35\%$  showed that patients with perfusion abnormalities or prolonged QRS durations have higher degrees of mechanical dyssynchrony.<sup>25</sup> It also showed that there were moderate correlations ( $r < 0.5$ ) between QRS duration and phase analysis indices of mechanical dyssynchrony, which was consistent with the finding using echocardiography.<sup>26</sup> A recent study including 20 patients with reversible perfusion defects involving  $> 10\%$  of the LV myocardium and 20 normal subjects showed that there was no significant change from rest to stress in PSD and PHB between the two

groups.<sup>21</sup> It also found that there was no correlation between the size of the reversible perfusion defect and the change in PSD or PHB. Although the presence of a large reversible perfusion defect did not alter the LV dyssynchrony parameters by phase analysis in that study, it must be noted that the stress scans using Tc-99m tracers are acquired 1 hour post-stress, therefore, the LV dyssynchrony parameters derived from the post-stress gated SPECT data represent resting function. Whether ischemia can affect LV mechanical dyssynchrony at peak or early post-stress needs further investigation. Another study including 140 patients with end-stage renal disease and 133 subjects with normal renal function divided the control and ESRD groups into tertiles based on heart rate and showed that there were no significant correlations between the LV dyssynchrony parameters by phase analysis and heart rate in either groups.<sup>27</sup> This study suggested that the measurement of LV dyssynchrony by phase analysis is not affected by heart rate within the examined range (48 to 113 beats/minute,  $75 \pm 13$ ), since the phase analysis algorithm normalized the RR cycle using  $360^\circ$ .

### Prevalence in Various Patient Populations

The prevalence of LV mechanical dyssynchrony, assessed by phase analysis of SPECT MPI, has been evaluated in multiple patient populations. A study including 260 patients with LVEF < 35% showed that the prevalence rates of significant LV dyssynchrony (defined as PSD >  $43^\circ$ , which was shown predictive of CRT response<sup>28</sup>) were 52% in the entire population, 71% in the subgroup of patients with wide QRS duration (>120 ms), and 39% in the subgroup of patients with narrow QRS duration (<120 ms).<sup>29</sup> In another study with 93 consecutive patients with LVEF between 35% and 50%, significant LV mechanical dyssynchrony (defined as PSD >  $43^\circ$ ) was present in 65% of the patients with QRS > 120 ms (N = 20), and 29% of the patients with QRS < 120 ms (N = 73).<sup>30</sup> The high prevalence rates of LV mechanical dyssynchrony in patients with mild-to-moderate LV dysfunction and/or narrow QRS indicates that there may be a population of patients, who are not currently indicated for CRT, but can potentially benefit from CRT. It must be noted that “significant LV dyssynchrony” in these prevalence studies was defined as PSD >  $43^\circ$ , which was shown predictive of CRT response.<sup>28</sup> However, this might not be true as it pertains to a very specific group of patients. Later studies found that PSD and PHB greater than the mean plus 2 standard deviations derived from normal controls was abnormal, and hence reflected LV mechanical dyssynchrony,<sup>31</sup> and that patients with abnormal synchrony could respond to CRT.<sup>32</sup>

## EVOLVING CLINICAL APPLICATIONS OF PHASE ANALYSIS

### Optimizing Patient Selection for CRT

CRT has shown benefits in patients with HF such as improved HF symptoms, exercise capacity, quality of life, and LV function, and prognosis.<sup>33–40</sup> CRT is recommended in HF patients with New York Heart Association (NYHA) class III-IV symptoms refractory to medical therapy, LVEF  $\leq 35\%$ , and sinus rhythm with QRS  $\geq 120$  ms.<sup>41</sup> However, when chosen for CRT based on these conventional criteria, according to clinical endpoints up to one third of the patients did not show response to CRT,<sup>36,37</sup> and according to echocardiographic endpoints even higher non-response rates have been reported.<sup>42–45</sup> Thus, there is considerable interest in optimizing patient selection for this expensive therapy.

**The echocardiographic approach**—One mandatory parameter for optimizing CRT found by echocardiography was LV mechanical dyssynchrony, which has been shown to predict response to CRT.<sup>46,47</sup> Another important issue related to CRT response is the position of the LV pacing lead. One study using echocardiography with speckle tracking analysis showed that pacing at the site of latest mechanical activation resulted in superior echocardiographic response after 6 months of CRT and better prognosis during long-term

follow-up, as compared to pacing outside the site of latest mechanical activation.<sup>48</sup> Another study using echocardiography and cardiac MRI showed that CRT resulted in clinical and echocardiographic nonresponse when there was myocardial scar in the lateral or inferolateral wall, the most commonly used position of the LV pacing lead.<sup>49</sup> These studies suggest that LV mechanical dyssynchrony, site of latest mechanical activation, and myocardial scar are important parameters related to CRT response.

It must be noted that reliable echocardiographic measurements require expertise to obtain consistent and reproducible results. Due to high intra-observer and inter-observer variability, the results from the PROSPECT trial demonstrated modest accuracy to predict response to CRT, due to limited reproducibility of echocardiographic measurements.<sup>19</sup> In addition, to integrate the assessment of LV mechanical dyssynchrony, site of latest mechanical activation, and myocardial scar for optimizing CRT, echocardiography has to combine with another imaging modality.

**The comprehensive phase analysis approach**—The LV mechanical dyssynchrony parameters measured by phase analysis have been shown to predict response to CRT in a study with 42 HF patients having CRT.<sup>28</sup> Based on the improvement of  $\geq 1$  NYHA functional class at 6 months follow-up, 30 patients were classified as responders and the other 12 patients as non-responders. Both PSD ( $56.3 \pm 19.9^\circ$  vs  $37.1 \pm 14.4^\circ$ ,  $P < .01$ ) and PHB ( $175 \pm 63^\circ$  vs  $117 \pm 51^\circ$ ,  $P < .01$ ) were significant higher in the responders as compared to the non-responders. The optimal cutoff values of PSD ( $43^\circ$ ) and PHB ( $135^\circ$ ) for predicting CRT response were derived by receiver operating characteristic curve analysis. With these optimal cutoff values, phase analysis showed sensitivity/specificity values of 70% and 74%, respectively, in predicting clinical response to CRT.

A new development on phase analysis has been done to quantify regional mechanical activation. A 7-segment model is used to divide the phase polar map into apex, anterior, lateral, inferolateral, inferior, septal, and anteroseptal regions as shown in Figure 3. The six regions other than the apex divide the mid-basal left ventricle evenly, and the mean phases of the six regions are compared. The region with the largest mean phase is the site of latest mechanical activation. In a study with 90 HF patients having CRT, 52 patients had a concordant LV pacing lead position with the site of latest mechanical activation determined by phase analysis, whereas the other 38 patients had a discordant LV pacing lead position.<sup>50</sup> At 6 months follow-up, patients with a concordant LV lead position showed significant improvement in LVEF and reduction in LVESV ( $P < .05$ ), whereas with a discordant LV lead position showed no significant improvement in these echocardiographic endpoints. Noteworthy, the new phase analysis tool has been shown to be highly reproducible in identifying site of latest mechanical activation. Using a randomly selected subset of the patients ( $N = 30$ ) in,<sup>50</sup> a high intraobserver ( $\kappa = 0.96$ , total agreement of 93%) and interobserver reproducibility ( $\kappa = 0.92$ , total agreement of 87%) for the identification of the site of latest mechanical activation was observed.

Since phase analysis can assess LV mechanical dyssynchrony and site of latest mechanical activation, and SPECT MPI has been established for assessment of myocardial scar, this imaging modality can provide a one-stop-shop for comprehensive evaluation of the three parameters for optimizing CRT. A comprehensive model has recently been established as follows: in currently indicated patients for CRT, CRT implantation should be considered for patients with baseline LV mechanical dyssynchrony and performed with the LV pacing lead placed in the site of latest mechanical activation with viable myocardium. This model is demonstrated in the patient examples in Figure 3. This model has been retrospectively evaluated using the patients in.<sup>50</sup> In the 52 patients classified as “concordant lead placement”, 7 of them had myocardial scar at the site of latest mechanical activation. Taking

this into account, 45 patients had an optimal LV lead position and the response rate in this group was >90%. This finding indicated that the comprehensive model has a high positive predictive value in predicting CRT response and can significantly improve CRT response rate if it is used to screen the patients currently indicated for CRT and to guide LV lead placement.

The comprehensive model has been evaluated prospectively using 44 patients from the University of Pittsburgh Medical Center. The preliminary results have been presented at the 2010 American Society of Nuclear Cardiology Annual Scientific Session, showing the comprehensive model has a very high positive predictive value (92%) in predicting acute CRT response, which has been shown to be related to long-term outcome.<sup>32</sup>

### Optimizing ICD Therapy

The relation between the degree of LV mechanical dyssynchrony measured by phase analysis of SPECT MPI and outcome in patients with ICD has been evaluated in 70 patients with ICD and LVEF < 40% by gated SPECT MPI performed within 6 weeks of the device implantation.<sup>51</sup> At 1 year, 8 patients died or had ICD shocks. The patients with events had significantly higher PSD than those without events ( $60 \pm 5$  vs  $50 \pm 21$ ,  $P = .002$ ). PHB was also higher in those with events ( $185 \pm 37$  vs  $154 \pm 75$ ,  $P = .07$ ). All patients with events had a PSD  $\geq 50$ , while none of the patients with a PSD < 50 ( $N = 26$ ) had an event ( $P = .02$ ). This study indicated that the severity of LV mechanical dyssynchrony by phase analysis in patients with LV dysfunction and ICD is associated with increased risk of death and appropriate ICD shock. This is a small, single-center, observational study. Its finding needs to be validated prospectively using a large patient population.

### Assessing LV Diastolic Dyssynchrony

All of the above “LV mechanical dyssynchrony” is measured in systole. A recent, novel development used multiple Fourier harmonic functions in phase analysis to approximate the variation of myocardial wall thickness in diastole (illustrated in Figure 4).<sup>52</sup> Similar to the calculation of OMC phase in systole, this technique calculates the onset of mechanical relaxation (OMR) as a measure of LV diastolic dyssynchrony. It has been shown that the diastolic dyssynchrony parameters measured by multi-harmonic phase analysis represented a new LV mechanism of regional function from gated SPECT MPI and showed higher prevalence rate than systolic dyssynchrony in 121 consecutive patients with end-stage renal disease.<sup>52</sup> The diastolic dyssynchrony parameters are being evaluated in patients with diastolic HF. The preliminary results have been presented at the 2011 American College of Cardiology Annual Scientific Session, showing that the diastolic dyssynchrony parameters measured by multi-harmonic phase analysis correlated well with NT-pro-BNP ( $r > 0.8$ ) and with echocardiography  $E/E'$  ratio ( $r > 0.5$ ) in 30 patients with diastolic HF.<sup>53</sup> More studies are needed to compare the diastolic dyssynchrony parameters measured by multi-harmonic phase analysis to other modalities and to establish their prognostic value in patients with HF.

## OTHER APPROACHES TO ASSESSING LV DYSSYNCHRONY BY SPECT MPI

All the above-referenced software developments were done at Emory University. Their evaluation and validation were done in collaboration with scientific and clinical collaborators worldwide. There are other approaches to assessing LV mechanical dyssynchrony by SPECT MPI. Van Krieking et al<sup>54</sup> reported a program to evaluate global and regional dyssynchrony parameters using Quantitative Gated SPECT (QGS) (Cedars Sinai Medical Center, Los Angeles, CA). The QGS global dyssynchrony parameters have shown to be correlated with tissue Doppler echocardiography dyssynchrony parameters and

to predict CRT response in 40 HF patients.<sup>55</sup> Takahashi et al<sup>56</sup> reported a “cardioGRAF” program that measured regional LV systolic/diastolic function and dyssynchrony. It has been shown using cardioGRAF that LV function correlated with wall motion synchrony,<sup>57</sup> and baseline LV dyssynchrony and resynchronization achieved by CRT in a case of a 63-year-old male with non-ischemic cardiomyopathy and QRS duration of 112 ms.<sup>58</sup>

## SUMMARY

Phase analysis of gated SPECT MPI is an evolving technique for measuring LV mechanical dyssynchrony. Its major clinical application is to optimize CRT in HF patients through a comprehensive evaluation of baseline LV mechanical dyssynchrony, site of latest mechanical activation, and myocardial scar. Phase analysis can assess these parameters with excellent reproducibility and repeatability, and can measure them from a single resting gated SPECT MPI scan. This technique has been evaluated in single-center prospective trials, and is ready to be validated in a multi-center, randomized, prospective clinical trial. Once it is validated, it can be a viable clinical approach to consistently predicting CRT response in HF patients. Other clinical applications of phase analysis such as optimizing ICD therapy and assessing LV diastolic dyssynchrony in HF patients have been shown in single-center observational studies with promising results. More research is needed to establish phase analysis in these areas.

## Acknowledgments

The authors thank Dr Maureen M. Henneman, Dr Mark J. Boogers, and colleagues at Leiden University Medical Center, Leiden, The Netherlands; Dr Wael AlJaroudi and colleagues at University of Alabama at Birmingham, Birmingham, AL and Cleveland Clinic, Cleveland, OH; Dr Mark A. Trimble and colleagues at Duke University Medical Center, Durham, NC; Dr Matti Friebling and colleagues at University of Pittsburgh Medical Center, Pittsburgh, PA; Dr Javed Butler and colleagues at Emory University, Atlanta, GA; Dr Dianfu Li and colleagues at Nanjing Medical University, Nanjing, Jiangsu, China; Dr Xianhe Lin and colleagues at Anhui Medical University, Hefei, Anhui, China; Dr Kenneth J. Nichols and colleagues at St. Francis Hospital, Roslyn, NA; Dr Jose C. Meneghetti and colleagues at University of Sao Paulo, Sao Paulo, Brazil; Dr Philipp A. Kaufmann and colleagues at University Hospital Zurich, Zurich, Switzerland; and many others, who have contributed to the area of assessment of LV mechanical dyssynchrony by phase analysis of SPECT MPI. Ji Chen and Ernest V. 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 Grant (1R01HL094438, PI: Ji Chen, PhD)

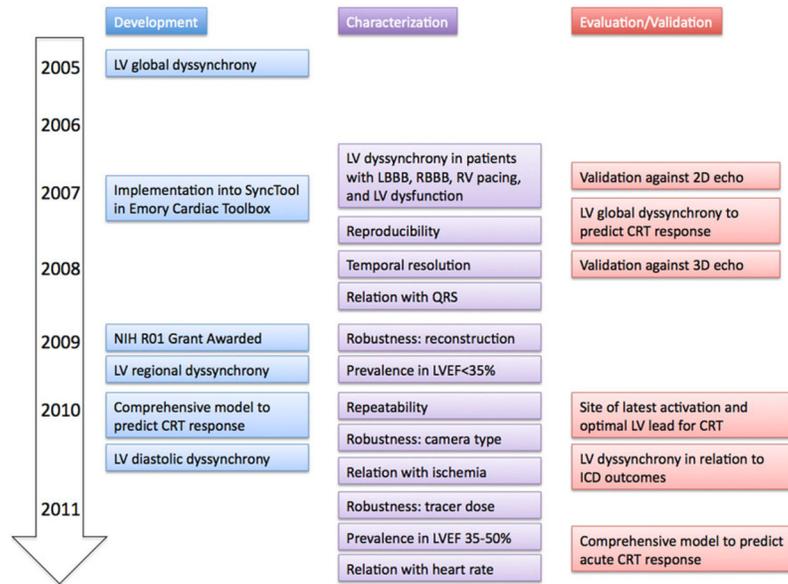
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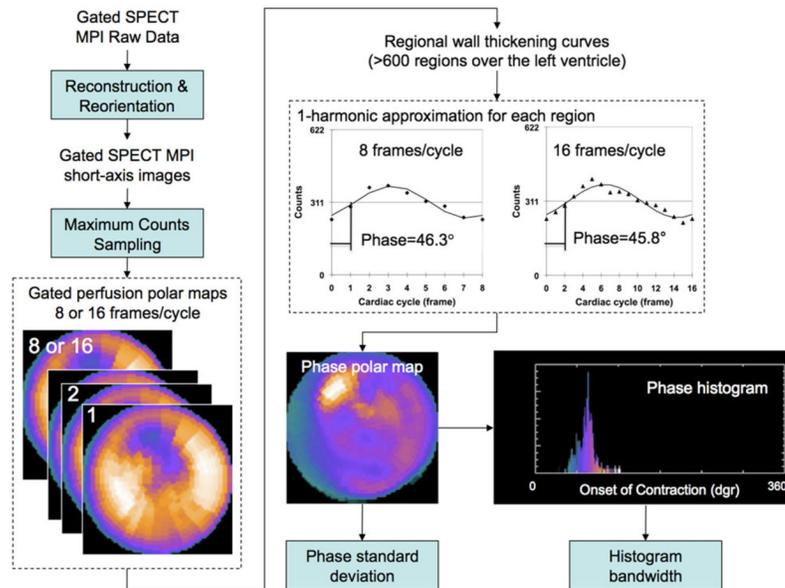
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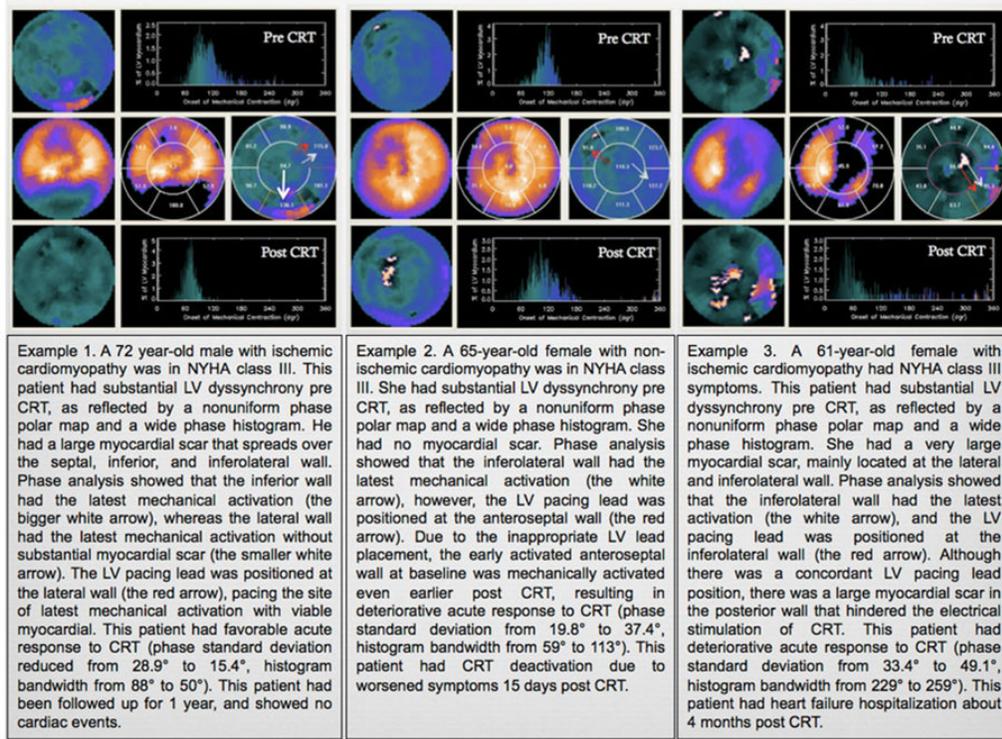


**Figure 1.** The advance of the field of assessment of LV mechanical dyssynchrony by phase analysis of gated SPECT MPI.

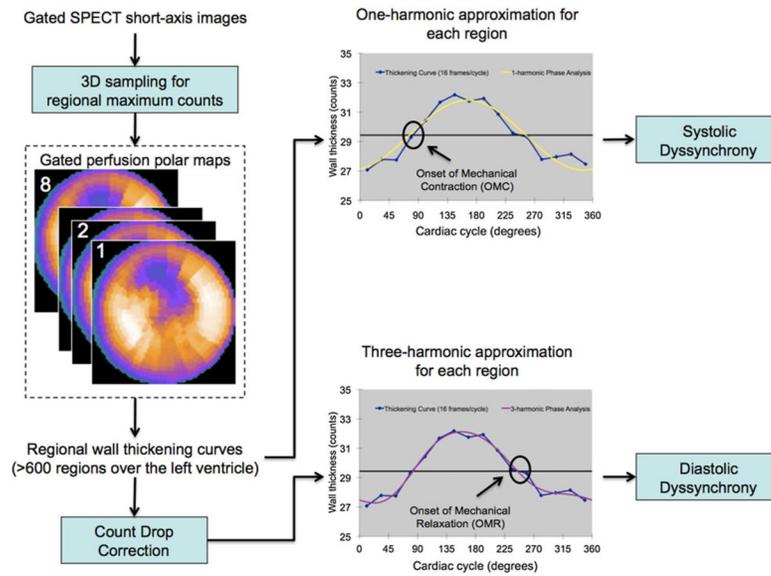


**Figure 2.**

Processing steps of phase analysis of gated SPECT MPI. The gated SPECT MPI data are reconstructed and reoriented to generate a gated short-axis image. 3D sampling is performed on each temporal frame of the gated short-axis image to detect regional maximum counts. The points shown in the plots are regional wall thickening data. The first harmonic Fourier function is used to approximate the wall thickening data (shown as the *solid line*) to calculate a phase angle for each region. Once the phase angles of all regions are obtained, a phase distribution is generated and displayed in polar map or in histogram. Note that the phase difference between 8 and 16 frame/cycle is very small— $0.5^\circ$  ( $360^\circ$  corresponding to one cardiac cycle) demonstrating that the first harmonic approximation improves the temporal resolution of the phase measurement. Also note that the phase polar map shows a significant phase delay (*bright region*) at the anterior and apical wall, where the perfusion polar maps shows a severe defect.



**Figure 3.** Patient examples of using the comprehensive phase analysis model to predict CRT response.



**Figure 4.**

Processing steps of the multi-harmonic phase analysis tool. Similar to those shown in Figure 2, the input was the standard gated SPECT short-axis image set. At first, regional maximal count detection was performed in 3D for each temporal frame to generate wall-thickening curves for over 600 LV regions. The wall-thickening curve for each region was approximated by the 1-harmonic function for systolic dyssynchrony and by the 3-harmonic function after a count drop correction for diastolic dyssynchrony. The count drop correction scaled every pixel in the last frame to make the total myocardial counts in the last frame equal to the total myocardial counts in the first frame. The phase angles derived by the systolic and diastolic approximation represented the onset of mechanical contraction (OMC) and onset of mechanical relaxation (OMR), respectively. Once the OMC and OMR phase angles of all regions were obtained, OMC and OMR phase distributions were generated that provided information on the degree of systolic and diastolic dyssynchrony for the entire LV, respectively.