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The Use of Nuclear Imaging for Cardiac Resynchronization Therapy

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Abstract Cardiac resynchronization therapy (CRT) has shown benefits in patients with end-stage heart failure, depressed left ventricular (LV) ejection fraction (≤ 35%), and prolonged QRS duration (≥ 120 ms). However, based on the conventional criteria, 20% to 40% of patients fail to respond to CRT. Studies have focused on important parameters for predicting CRT response, such as LV dyssynchrony, scar burden, LV lead position, and site of latest activation. Phase analysis allows nuclear cardiology modalities, such as gated blood-pool imaging and gated myocardial perfusion single photon emission computed tomography (GMPS), to assess LV dyssynchrony. Most importantly, GMPS with phase analysis has the potential of assessing LV dyssynchrony, scar burden, and site of late activation from a single acquisition, so that this technique may provide a one-stop shop for predicting CRT response. This article provides a summary on the role of nuclear cardiology in selecting patients for CRT, with emphasis on GMPS with phase analysis.

Keywords Phase analysis · Gated SPECT · Myocardial perfusion imaging · Cardiac resynchronization therapy

Introduction

Heart failure (HF) is widely prevalent (> 5 million cases) and rapidly growing (> 0.5 million new cases annually) in the United States [1]. Hospital discharges rose from approximately 400,000 in 1979 to over 1 million in 2004. Based on 44-year follow-up of the National Heart, Lung, and Blood Institute's Framingham Heart Study, 80% of men and 70% of women under 65 years of age who have HF will die within 8 years; in people diagnosed with HF, sudden cardiac death occurs at six to nine times the rate of the general population. The 2004 overall total death rate for HF was 52.0% [2]. In 2008, the estimated total cost of HF in the United States was $34.8 billion [2].

Cardiac resynchronization therapy (CRT), provided by multisite pacing of the right and left ventricles, showed benefits in patients with end-stage HF. The benefits include improved HF symptoms, exercise capacity, quality-of-life score, and left ventricular (LV) function [3-8], as well as mortality benefits, in patients with advanced drug-refractory HF [9, 10]. The American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines recommend CRT in patients with end-stage drug-refractory HF of New York Heart Association (NYHA) class III or IV severity, depressed left ventricular ejection fraction (LVEF; ≤ 35%), prolonged QRS duration (≥ 120 ms), and sinus rhythm as a class I indication with level of evidence A [11]. However, using these conventional criteria for selecting patients for CRT, 20% to 40% of patients fail to respond to CRT [6, 7, 12-15]. It was suggested that electrical dyssynchrony represented by prolonged QRS intervals is not necessarily related to mechanical dyssynchrony, which may explain why 20% to 40% of the patients in the above trials did not respond to CRT [16-18]. It is also possible that some patients who would have benefited from CRT were not included in the trials, such as patients with wide QRS complex who do not exhibit LV dyssynchrony and patients who have narrow QRS complex but who have LV dyssynchrony [17].

Echocardiography techniques, in particular two-dimensional echocardiography using color-coded tissue Doppler imaging

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(TDI), have been most widely used to measure LV dyssynchrony. These techniques have shown that LV mechanical dyssynchrony is an important predictor of response to CRT [13, 19, 20]. However, reliable TDI measurements require expertise to obtain reproducible results. Because of high intraobserver and interobserver variability, the PROSPECT (Predictors of Response to Cardiac Resynchronization Therapy) trial found that under "real-world" conditions the current available echocardiography techniques are not ready for routine practice to clinically predict CRT responses [21]. These results prompted the search for a more reproducible method of measuring LV dyssynchrony. Besides LV dyssynchrony, location and extent of viable or infarcted myocardium [22-24] and LV lead position [25, 26] were shown to be related to success of CRT.

Phase analysis allows nuclear cardiology modalities, such as gated blood-pool imaging and gated myocardial perfusion single photon emission computed tomography (SPECT; [GMPS]), to assess LV dyssynchrony. Phase analysis using GMPS (SyncTool, Emory University, Atlanta, GA) has evoked special interest because this technique has the potential for comprehensive assessment of multiple parameters (eg, LV dyssynchrony, myocardial scar burden and location, and site of latest activation) that influence response to CRT. This article provides a summary of the role of nuclear cardiology for selecting CRT candidates, with emphasis on GMPS with phase analysis.

Gated Blood-Pool Imaging and Ventricular Dyssynchrony

Phase analysis was first introduced with planar gated blood-pool ventriculography for evaluating the contraction pattern of the left ventricle [27-32]. Planar gated blood-pool images are acquired from one left anterior oblique view in different time frames, ranging from 16 to 64 frames per cardiac cycle. Regions of interest (ROI) are drawn on the planar images for left and right ventricles to generate time-activity curves, representing the variation of the ventricular volumes over the cardiac cycle. These time-activity curves are characterized by amplitude (height or depth of fitted curve) and phase angle (timing of contraction of a particular region). The standard deviation of the phase angles of the pixels in each ventricular ROI represents intraventricular dyssynchrony. The difference between the means of the phase angles of both ventricular ROI represents interventricular dyssynchrony. Toussaint et al. [30] evaluated the value of intraventricular and interventricular dyssynchrony measured from gated blood-pool ventriculography in 34 patients with end-stage HF undergoing CRT. All patients underwent gated blood-pool ventriculography at baseline and 6-month follow-up. Improvement of interventricular and intraventricular dyssynchrony was observed after CRT. Moreover, the combination of a baseline LVEF greater than 15% with significant interventricular dyssynchrony were the best predictors for improvement in LV systolic function after 6 months of CRT.

The major limitations of gated blood-pool ventriculography are overlap between adjacent structures and poor anatomic localization. In gated blood-pool SPECT, similar principles of phase analysis are used for detecting intraventricular and interventricular dyssynchrony. The gated blood-pool SPECT data are analyzed in three dimensions, resulting in better separation of adjacent structures and superior localization compared with gated blood-pool ventriculography [33-35]. A study including 19 patients with idiopathic dilated cardiomyopathy showed correlations between the clinical outcomes and the presence or absence of interventricular and intraventricular dyssynchrony, as measured by phase analysis of gated blood-pool SPECT [36]. This study also showed the improvement of interventricular and intraventricular dyssynchrony for patients with HF after CRT [36].

Gated Myocardial Perfusion SPECT with Phase Analysis and LV Dyssynchrony

Technical Essentials

Figure 1 shows the phase analysis of GMPS. The input to this tool is the standard gated SPECT short-axis image. At first, regional maximal count detection is performed in three dimensions for each temporal frame. Based on the partial volume effect [37], the variation of the regional maximal counts is proportional to the regional wall thickening over the cardiac cycle. The linear relationship was demonstrated in a phantom study [38]. Then, the first-harmonic Fourier function is used to approximate the discrete sample points into a continuous wall-thickening curve. For each region, the wall-thickening curve provides a phase angle that represents the onset of mechanical contraction of the region. Once the phase angles of all regions (> 600 regions over the entire left ventricle) are obtained, a phase distribution is generated that provides information on the degree of mechanical dyssynchrony for the entire left ventricle. The phase distribution can be displayed in polar map and in a histogram, as shown in Fig. 1. For a normal subject, the entire left ventricle starts contraction almost at the same time, so that the phase polar map is uniform and the phase histogram is narrow and highly peaked. Five quantitative indices are automatically calculated from the phase distribution: peak phase (the peak of the phase histogram), phase standard deviation (the standard deviation of the phase distribution), histogram bandwidth (the range of 95% of the phase angles),

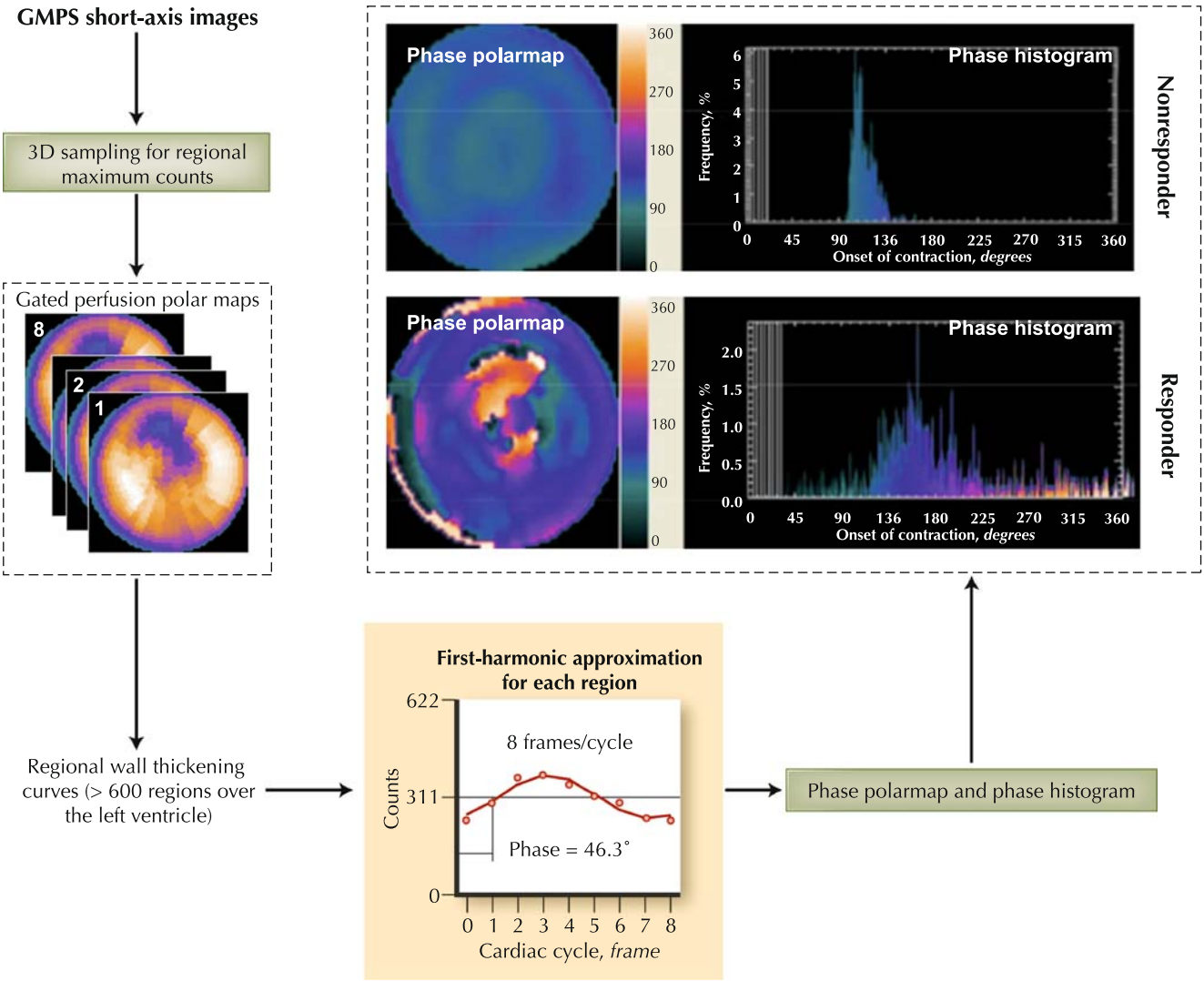

Fig. 1 Phase analysis of gated myocardial perfusion single photon emission computed tomography (GMPS) images. The inputs to phase analysis are the standard GMPS short-axis images. Three-dimensional (3D) sampling is performed on each temporal frame to detect the regional maximum counts. The variation of regional maximum counts over the cardiac cycle is proportional to wall thickening of the region. The points shown in the plots are the regional wall-thickening data. The first-harmonic Fourier function is used to approximate the wall-thickening data (*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 a polar map or in a histogram. Two examples are shown in this figure (a nonresponder and a responder to cardiac resynchronization therapy [CRT]). Both patients had New York Heart Association (NYHA) class III, depressed left ventricular (LV) ejection fraction (< 35%), and prolonged QRS duration (> 120 ms). LV dyssynchrony was not present in the nonresponder, but present in the responder. Six months after CRT, the nonresponder deteriorated in NYHA class from III to IV, whereas the responder improved from class III to II

skewness (positive skewness means that the phase histogram is skewed to the right), and kurtosis (peakedness of the phase histogram) [39]. Among the five indices, histogram bandwidth and phase standard deviation (standard deviation of the phase distribution) are well studied for assessing LV dyssynchrony.

The phase analysis tool is largely automatic. Intraobserver and interobserver reproducibility of this technique have been evaluated in a study using 10 consecutive subjects with LV dysfunction (LVEF≤35%) and 10 normal control subjects [40••]. For phase standard deviation and histogram bandwidth, intraobserver correlation coefficients were both 1.00, and interobserver correlation coefficients were both 0.99. The superior reproducibility of phase analysis is an advantage over echocardiography that may improve prediction of CRT response.

GMPS studies are often perceived to have a low temporal resolution, as the data are usually acquired using 8 to 16 frames per cardiac cycle. Because the discrete points of regional maximum counts are transformed into the continuous wall-thickening curves by the first-harmonic Fourier approximation, the actual temporal resolution of the

phase analysis technique is greatly enhanced. A phantom simulation study demonstrated that with image quality achieved during routine clinical GMPS (≥ 10 counts/pixel), the phase analysis tool was able to detect a minimum phase delay of 5.6°, representing 1/64 of a cardiac cycle [41••].

Clinical Validations

GMPS with phase analysis was evaluated in a study comparing consecutive patients with LV dysfunction (LVEF<40%; n=120), left bundle branch block (n=33), right bundle branch block (n=19), ventricular paced rhythms (n=23), and normal control subjects (n=157) to demonstrate its feasibility to detect LV dyssynchrony [42]. Phase standard deviation and histogram bandwidths were significantly different between the patient cohorts and the normal control subjects. Another study including 125 consecutive patients with LVEF less than 35% showed that patients with prolonged QRS duration, on average, had significantly more LV dyssynchrony than patients without prolonged QRS duration [43]. However, the correlation between QRS duration and phase analysis results (phase standard deviation and histogram bandwidth) was weak. This finding confirmed that electrical dyssynchrony is not necessarily related to mechanical dyssynchrony, as was also suggested by an echocardiography study [44].

Henneman et al. [45••] reported on the agreement between GMPS and two-dimensional echocardiography using TDI for the detection of LV dyssynchrony in 75 patients undergoing CRT. Good correlations were found between LV dyssynchrony measured with TDI and histogram bandwidth (r=0.89, P<0.0001) and phase standard deviation (r=0.80, P<0.0001) measured with GMPS. GMPS with phase analysis has also shown good correlation with three-dimensional (3D) echocardiography for assessing LV dyssynchrony [46, 47]. In 40 consecutive patients with HF, good agreement was found between standard deviation of time-to-peak systolic velocity (Ts-SD) on 3D echocardiography and histogram bandwidth (r=0.77, P< 0.0001) and phase standard deviation (r=0.74, P<0.0001) measured with phase analysis of GMPS. Patients with substantial LV dyssynchrony (Ts-SD≥33 ms) on 3D echocardiography showed significantly higher histogram bandwidth (186°±52° vs 74°±24°; P<0.0001) and phase standard deviation (55.3°±13.6° vs 25.1°±7.6°; P<0.0001) compared to patients without substantial LV dyssynchrony (Ts-SD<33 ms).

Henneman et al. [48••] evaluated whether GMPS with phase analysis can predict clinical response after 6 months of CRT in 42 patients with end-stage HF. Based on the improvement of ≥ one NYHA functional class, 30 patients were classified as responders and the other 12 patients as nonresponders. Both histogram bandwidth (175°±63° vs 117°±51°; P<0.01) and phase standard deviation (56.3°± 19.9° vs 37.1°±14.4°; P<0.01) were significant higher in responders compared with nonresponders. Moreover, the optimal cutoff values of histogram bandwidth (135°) and phase standard deviation (43°) for predicting CRT response were derived by receiver operating characteristic curve analysis. With these optimal cutoff values, GMPS with phase analysis showed sensitivity/specificity values of 70% and 74%, respectively, in predicting clinical response to CRT. Figure 1 shows an example of phase analysis in a nonresponder and a responder to CRT. Both patients had NYHA functional class III, depressed LVEF (< 35%), and prolonged QRS duration (> 120 ms). LV dyssynchrony as measured by GMPS with phase analysis was not present in the nonresponder, but present in the responder. Six months after CRT, the nonresponder deteriorated in NYHA functional class from III to IV, whereas the responder improved from class III to II.

Phase analysis was recently implemented in the Quantitative Gated SPECT (Cedars Sinai Medical Center, Los Angeles, CA) software. Preliminary results for predicting CRT responses are similar to those detailed above [49, 50].

Predictors of CRT Response in Addition to LV Dyssynchrony

Myocardial Scar Burden and Location

The presence, location, and extent of myocardial scar from prior myocardial infarction have been shown to influence CRT response. Adelstein and Saba [24] studied the relationship between scar burden and CRT response. Fifty patients with end-stage drug-resistant HF and angiographically proven coronary artery disease were enrolled. At baseline, all patients had echocardiography and myocardial perfusion SPECT. Six months after CRT, all patients had echocardiography to evaluate cardiac reverse remodeling. CRT response was defined as a decrease of ≥ 15% in LV end-systolic volume from the pre-CRT to post-CRT echocardiography measurements. Among the 50 patients, 28 showed response to CRT and had lower perfusion defect score (18.8±11.3 vs 33.7±11.1; P<0.01) and scar density near the LV lead (0.70±0.91 vs 1.64±0.82; P<0.01) than the other 22 nonresponders. An inverse relationship was observed between global scar burden and absolute (r=-0.63, P<0.01) or relative (r=-0.53, P<0.01) increase in LVEF after 6 months post CRT. Moreover, the presence of myocardial scar tissue adjacent to the LV lead position was negatively correlated with increase in LVEF at 6 months post CRT. Similar results were reported by Ypenburg et al. [23] in 52 patients with ischemic HF and substantial LV dyssynchrony undergoing CRT.

Bleeker et al. [22] reported the relationship between the location and transmurality of myocardial scar and CRT response in 40 patients with moderate-to-severe HF, LVEF≤35%, prolonged QRS duration (> 120 ms), and coronary artery disease. Patients with transmural infarction adjacent to the LV lead position (mostly the posterolateral region) showed a significantly lower response rate to CRT compared to patients without transmural scar tissue adjacent to the LV lead position.

Site of Latest Activation

The benefits of CRT are primarily based on synchronization of the myocardial contraction pattern, resulting in an improvement of LV systolic function. One important issue that may influence CRT response is the relationship between LV lead position and the site of latest activation. The site of latest activation in the left ventricle can vary substantially, and patients with an LV lead positioned away from the site of latest activation had suboptimal or no response to CRT [25]. Ypenburg et al. [26] evaluated echocardiographic and clinical outcome after 6 months post CRT in a large cohort of patients with ischemic or dilated cardiomyopathy. A total of 153 (60%) patients had LV lead positioned at or adjacent to the site of latest activation based on chest radiographs. These patients showed a significant decrease in LV end-systolic and end-diastolic volumes along with an increase in LVEF after 6 months post CRT. The other 40% of the patients did not have concordant LV lead position and site of latest activation, and demonstrated no evident improvement in LV end-systolic and end-diastolic volumes and LVEF post CRT. This study also showed that mortality rate was significant lower in patients with concordant LV lead position and site of latest activation compared to patients without concordant LV lead position and site of latest activation at 24 months of follow-up (15% vs 21%, P=0.048).

GMPS with Phase Analysis: A Potential One-Stop Shop

Phase analysis is a mathematical algorithm that applies to conventional GMPS data and does not need additional acquisition. This characteristic allows integrated analysis of multiple predictors of CRT response from a single GMPS study. Currently, phase standard deviation and histogram bandwidth are validated as the quantitative indices of global LV dyssynchrony. Because GMPS with phase analysis produces a phase distribution containing more than 600 regions over the left ventricle, it is possible to measure regional contraction delays and detect the site of latest activation. Then, the viability of the detected site of latest activation can be analyzed using the same perfusion image, so that an optimal LV lead position for the patient may be derived. Therefore, conceptually, GMPS with phase analysis has the potential of providing a one-stop shop for predicting CRT response by assessing LV dyssynchrony, myocardial scar burden and location, and site of latest activation.

Conclusions

Nuclear cardiology modalities, such as gated blood-pool imaging and GMPS, are promising alternatives for measuring LV dyssynchrony and predicting CRT response. Most importantly, GMPS with phase analysis has the potential for assessing LV dyssynchrony, myocardial scar burden and location, and site of latest activation from a single GMPS acquisition. Integrated analysis of these parameters, once validated, can be a viable clinical approach to consistently and reproducibly predict CRT response in patients with HF.

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