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The performance of phase analysis of gated SPECT myocardial perfusion imaging in the presence of perfusion defects: A simulation study

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Abstract

Background—Phase analysis has been developed and validated to measure left-ventricular dyssynchrony from gated SPECT myocardial perfusion imaging. The purpose of this study is to evaluate its performance in regions with perfusion defects.

Methods—A special version of the eXtended CARDiac Torso digital phantom was developed to track B-spline points in each temporal frame. A region of 35 B-spline points in the inferior wall with normal and abnormal perfusion uptakes were simulated. Phase shifts were simulated in the same region, representing dyssynchronous contraction. Gated SPECT data were analyzed using a modified phase analysis algorithm, which tracked the same 35 B-spline points to calculate their phases.

Results—Phases and phase shifts measured in the B-spline points with perfusion uptake in the range of 50%–10% did not significantly differ from those measured in the same B-spline points with normal perfusion uptake.

Conclusion—Phase analysis can accurately measure phases in regions with abnormal perfusion uptake as low as 10% of the perfusion uptake in the normal regions, which corresponded to a regional signal-to-noise ratio (SNR) of 12.0 or greater. In 42 consecutive patients with myocardial infarction >20% of the left ventricle, only two patients had a SNR within the perfusion defects below that threshold.

Keywords

Myocardial perfusion imaging; gated SPECT; phase analysis; LV dyssynchrony

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Conflict of interest

Dr Faber, Dr Garcia, and Dr Chen 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.

INTRODUCTION

Cardiac resynchronization therapy (CRT) is a FDA-approved therapy indicated for patients with end-stage heart failure (HF), severe left ventricular (LV) dysfunction (LV ejection fraction $\leq 35\%$), and prolonged QRS duration (≥ 120 ms).^{1–4} Although CRT has been shown to improve the quality of life of recipients, there are still significant percentages (20–40%) of patients who do not respond favorably to CRT.^{2–4} A few of the emerging studies have suggested that LV mechanical dyssynchrony is an important predictor of response for patients undergoing CRT.^{5,6} As a result, many techniques have been developed to utilize common medical imaging modalities, such as echocardiography via tissue Doppler imaging (TDI)⁷ or strain imaging,⁸ magnetic resonance imaging,⁹ and gated blood-pool single photon emission computed tomography (SPECT) to measure LV mechanical dyssynchrony.^{10,11} Phase analysis is a technique that allows gated SPECT myocardial perfusion imaging (MPI) to measure LV mechanical dyssynchrony.¹² Moreover, it can integrate dyssynchrony assessment with myocardial scar assessment using data acquired from a single acquisition of gated SPECT MPI. Studies have shown that both regional dyssynchrony and regional scar are important for optimizing LV lead placement, which is an important factor related to CRT response.^{13,14}

Phase analysis is a count-based method that measures mechanical dyssynchrony using the linear relationship between variation of regional maximum counts and myocardial wall thickening during a cardiac cycle. A study by Galt et al.¹⁵ has shown that regional maximum counts are linearly proportional to myocardial wall thickening based on the partial volume effect. By fitting a continuous first-harmonic Fourier curve to the discrete regional maximum counts during the cardiac cycle, one can approximate the phase angle of the curve to represent onset of mechanical contraction of the region. Once a phase angle is obtained from each region, a phase distribution is formed for the assessment of LV (dys)synchrony. Phase analysis has been validated against TDI,^{16,17} and has been shown to predict patient response to CRT¹⁸ and identify optimal positions for CRT LV lead placement.¹⁴

Although phase analysis has shown promising clinical results, a question has been raised regarding its accuracy to measure phase information in regions of severe perfusion defect, where the true uptake counts are low. In such regions, signal-to-noise ratio (SNR) is low, i.e., the signal from true counts is not distinguishable from the erroneous counts from noise. Perfusion defects are common in patients suffering from HF with more than 60% of patients having ischemic etiology. A previous study by Cooke et al.¹⁹ has evaluated the accuracy of the count-based methodology for calculating systolic wall thickening (SWT) amplitude in regions of low count densities. That study showed that Fast Fourier Transform-derived SWT can be measured in regions of hypoperfusion as low as 5% of normal uptake. However, that study did not investigate the accuracy of the count-based methodology for calculating phase in relation to low count densities. The objective of this study is to evaluate the performance of phase analysis under varying degrees of hypoperfusion in synchronous and dyssynchronous ventricles using a digital phantom.

MATERIALS AND METHODS

XCAT Phantom and Simulation

This study utilized the XCAT (eXtended Cardiac Torso) digital human phantom to simulate gated SPECT MPI data. The XCAT phantom uses non-uniform rational basis splines (NURBS) to mathematically define geometrical surfaces of the human anatomy.²⁰ NURBS is commonly used in computer graphics because it is a mathematical model that defines continuous surfaces and curves with great precision. Thus, the XCAT phantom is capable of simulating activity and attenuation distribution with high spatial and temporal resolutions.

For this simulation study, the XCAT phantom was modified so that myocardial thicknesses and perfusion levels could be manipulated for specific basis spline (B-spline) points on the left ventricle in each temporal frame. Figure 1 demonstrates how to use the modified XCAT phantom to simulate dyssynchrony and hypoperfusion at the same location. For this study, 35 B-spline points in the inferior wall were simulated with perfusion defects of 50%, 40%, 30%, 20%, 10%, and 5% of normal uptake. Phase shifts of $\pm 20^\circ$, $\pm 40^\circ$, and $\pm 60^\circ$ were inserted into the datasets with normal uptake, with the perfusion defects of 10%, and with 5% of normal uptake, respectively.

The activity and attenuation distributions produced by XCAT used in this study were generated as 512×512 matrices with 128 slices for 16 frames per cardiac cycle with cubic voxels of size 2.5 mm. From the activity and attenuations distributions, an analytic projector was used to generate a 64×64 matrix with 64 slices and 6.4 mm/pixel Tc-99 m gated SPECT data from the activity and attenuation distributions generated by XCAT. The analytic projector included major physical factors, such as distance-dependent collimator resolution, photon attenuation, and first-order Compton scatter.²¹ The gated SPECT images were scaled to a level where the LV counts were at a clinically relevant level. Finally, Poisson noise was added to the simulated gated SPECT projections to closely resemble noise seen in clinical images by means of the noise infusion method described in Cooke et al.¹⁹ The gated SPECT projections were reconstructed with OSEM, and the transaxial images were reoriented into gated short-axis (SA) images. The gated SA images were submitted to a modified phase analysis program, which tracked the same B-spline points on each temporal frame to calculate their phases as illustrated in Figure 2.

Characterization of the Simulated Datasets by SNR in Comparison to Patient Data

The SNR of the modified B-spline point region of interest (ROI) for the summation of the gated images were calculated using the following equation:

$$\text{SNR}_{\text{Defect}} = \frac{\mu_{\text{signal}}}{\sigma_{\text{background}}} \quad (1)$$

where μ_{signal} is the mean of the signals within the perfusion defect, and $\sigma_{\text{background}}$ is the standard deviation of the counts in the background.

For the simulation data, the signals within the perfusion defects were the counts of the 35 B-spline points in the summed gated SPECT images. The background counts were calculated from a manually defined ROI away from the compartments (heart, lung, and liver) with different simulated activities than the background.

Forty-two consecutive patients, who had gated SPECT MPI within 40 days post myocardial infarction with perfusion defect size $>20\%$ as assessed by the Emory Cardiac Toolbox (Emory University, Atlanta, GA), were enrolled. SNR was also calculated by Eq. 1. The signals within the perfusion defects were the counts of the regions in the summed perfusion polar map, which were below 50% of the maximal counts of the perfusion polar map. The background counts were calculated from a manually defined ROI in the patient body.

Statistical Analysis

The mean and standard deviation of the measured phases and phase shifts were computed from all datasets. For each defect level in the range of 50%-5%, the measured phases within the perfusion defects were compared with those measured from the same region of the normal dataset using paired *t*-test. A *P* value less than .05 determined at what reduction of counts or SNR the phase analysis algorithm broke down. Such analysis was also applied to

the comparison between the measured phase shifts within the perfusion defects (for defect levels of 10% and 5%) to those measured from the same region of the normal dataset.

RESULTS

Table 1 shows the phases of the 35 B-spline points with normal and abnormal perfusion uptakes. The phases with perfusion defects of 50%-10% did not significantly differ from those with normal uptake. However, once perfusion defect reached a severity of 5% of normal uptake, it resulted in significantly different phases from those with normal uptake ($P < .05$). The lowest SNR for the 10% uptake activity was determined to be 12.0. Once the SNR dropped below 12.0, the noise significantly affected phase analysis and resulted in inconsistent phase measurement.

Comparisons of the t -tests between the measured phase shifts in the 35 B-spline points with normal uptake to those with 10% of the normal uptake are shown in Table 2. The measured phase shifts did not significantly differ between the two datasets. The correlation coefficients between the measured and simulated phase shifts were 0.997 and 0.996 for the normal images and 10% uptake level images, respectively. The SNRs for 10% uptake activity were consistently above 12.0.

Table 3 compares the measured phase shifts in the inferior B-spline points with normal uptake, to those with 5% of the normal uptake. The measured phase shifts significantly differed between the two datasets, when the measured SNR was below 12.0.

The sizes of the perfusion defects of the 42 patients were $34.3 \pm 8.9\%$ as assessed by the Emory Cardiac Toolbox (Emory University, Atlanta, GA) using a 50% (of the maximal perfusion) cutoff. The SNR within the perfusion defects of the 42 patients was 28.1 ± 14.2 . Only two patients had SNR below 12.0.

DISCUSSION

This study used the XCAT digital phantom and a modified phase analysis algorithm to characterize the performance of phase analysis in perfusion defects. The phase analysis algorithm accurately measured phases and phase shifts in perfusion defects with as low as 10% of normal perfusion uptake. Such defect level corresponded to a SNR of 12.0 or greater within the defect region. For the dataset with perfusion defects with 5% of normal uptake activity, which corresponded to a regional SNR below 12.0, the phases and phase shifts measured from the perfusion defects were significantly different than those measured from normal perfusion uptake. This study indicated that a regional SNR of 12.0 was an important condition for the phase analysis algorithm to accurately measure phases in the region.

More than half of the patients suffering from HF are also diagnosed with some level of ischemia or infarction, which can cause a regional reduction in myocardial perfusion uptake. As a count-based method, phase analysis is reliant on the myocardial count intensities. Thus, questions regarding phase analysis' accuracy to measure LV mechanical dyssynchrony within regions of low perfusion uptake have been raised. More specifically, what level of perfusion defect will cause phase analysis to measure inaccurate phases? A previous study by Cooke et al.¹⁹ have shown that the count-based method did work accurately when measuring SWT amplitude in low count intensities, but did not address whether phase measurements were affected. This study specifically determines the lower limit of perfusion uptake before loss of accuracy in phase measurement. According to the XCAT simulation, a regional SNR of 12.0 or greater was an important condition for the phase analysis algorithm to accurately measure phases in the region. Furthermore, this study included 42 consecutive patients with myocardial infarction greater than 20% of the left ventricle and showed only

two of them had a SNR within the defect region below 12.0. This study validated previous studies, which have examined the utility of phase analysis with patients with ischemia or infarction.^{14,16–18,22}

The findings of this study also brought to light the necessity of quality control program for phase analysis. Mainly, the quality control program can determine whether the SNR in a patient scan is higher than the threshold for reliability. If the SNR of a patient scan falls below the threshold, then the phase analysis parameters derived from the scan should be interpreted with caution, and such patient may not use the nuclear phase parameters for the assessment of dyssynchrony and suitability for CRT.

In cases of low SNR, the phase analysis algorithm would be unable to accurately measure phases because of the errors in the first-harmonic approximation. In order to reduce the standard deviation of the background or increase SNR, one must reduce the noise in the gated SPECT data. A noise reduction algorithm has been developed to improve SNR in gated SPECT images.²³ The effect of noise reduction on phase analysis will be a subject of a future study. Furthermore, how the impact of noise on the regional phases and phase shifts translates to global dyssynchrony parameters, such as phase standard deviation and histogram bandwidth, remains to be investigated as well.

The main limitation of this study was that it only evaluated the inferior region of the LV myocardium, although the phase analysis algorithm was expected to exhibit similar performance in other regions. Noise levels in the simulation were maintained at constant levels throughout the simulation process. One future direction is to characterize the phase analysis algorithm in varying degrees of noise, representing rapid acquisition as well as low-dose imaging.

CONCLUSION

Phase analysis is capable of measuring phases in regions with abnormal perfusion uptake as low as 10% of the perfusion uptake in the normal regions, which corresponded to a regional SNR of 12.0 or greater. In 42 consecutive patients with myocardial infarction >20% of the left ventricle, only two patients had a SNR within the perfusion defects below that threshold.

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Figure 1.

A B-spline points of XCAT that defined the LV. The counts of the B-spline points in the *red box* were reduced to simulate perfusion defects. **B** Simulated image where defect and dyssynchrony have been inserted along the same B-spline points in the inferior wall. **C** The wall thickening curve of one B-spline point from the *red box* before inserting dyssynchrony. **D** Wall thickening curves of the B-spline point before and after shifting to insert dyssynchrony.

Figure 2.

Modified phase analysis was used to measure dyssynchrony at exact B-spline points using the workflow illustrated above.

Table 1

Paired *t*-test for regions of varying perfusion activity compared to normal heart

% Uptake activity	Normal	50	40	30	20	10	5
Mean phase $\pm$ SD	103.2 $\pm$ 6.4	93.1 $\pm$ 8.1	95.9 $\pm$ 11.0	95.1 $\pm$ 9.8	98.0 $\pm$ 11.3	94.5 $\pm$ 11.3	123.3 $\pm$ 8.20
Average SNR	35.18	16.25	14.86	14.18	13.28	12.42	10.13
<i>P</i>	N/A	.96	.97	.43	.35	.37	<.01

P, pair *t* test results when comparing phases of the inferior B-spline points with normal uptake to those with abnormal uptake; *SNR*, signal-to-noise ratios of the inferior B-spline points

Table 2Paired *t*-test for regions of 10% uptake perfusion activity

LV phase shift	60	40	20	-20	-40	-60
Normal uptake						
Mean phase $\pm$ SD	55.7 $\pm$ 15.1	31.5 $\pm$ 15.7	23.7 $\pm$ 12.6	-20.7 $\pm$ 11.3	-37.9 $\pm$ 19.8	-59.4 $\pm$ 16.1
Average SNR	35.82	28.13	29.98	27.54	32.91	35.20
10% uptake						
Mean phase $\pm$ SD	57.6 $\pm$ 13.7	34.1 $\pm$ 16.7	24.7 $\pm$ 12.4	-24.5 $\pm$ 13.3	-34.3 $\pm$ 16.4	-56.9 $\pm$ 16.5
Average SNR	12.61	12.54	12.87	12.97	13.75	12.92
<i>P</i>	.17	.21	.18	.21	.15	.11

P, pair *t* test results when comparing phases of the inferior B-spline points with normal uptake to those with abnormal uptake; *SNR*, signal-to-noise ratios of the inferior B-spline points

Table 3Paired *t*-test for regions of 5% uptake perfusion activity

LV phase shift	60	40	20	-20	-40	-60
Normal uptake						
Mean phase $\pm$ SD	55.7 $\pm$ 15.1	31.5 $\pm$ 15.7	23.7 $\pm$ 12.6	-20.7 $\pm$ 11.3	-37.9 $\pm$ 19.8	59.4 $\pm$ 16.1
Average SNR	35.82	28.13	29.98	27.54	32.91	35.20
5% uptake						
Mean phase $\pm$ SD	75.8 $\pm$ 21.2	74.6 $\pm$ 17.3	79.5 $\pm$ 13.4	80.5 $\pm$ 9.9	82.3 $\pm$ 10.8	96.7 $\pm$ 11.6
Average SNR	12.47	10.16	10.46	9.52	8.14	8.36
<i>P</i>	.07	< .01	< .01	< .01	< .01	< .01

P, pair *t* test results when comparing phases of the inferior B-spline points with normal uptake to those with abnormal uptake; *SNR*, signal-to-noise ratios of the inferior B-spline points