

## Determination of normal ranges of regional and global phase parameters using gated myocardial perfusion imaging with Cedars-Sinai's QGS software

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### ABSTRACT

**Introduction:** Myocardial perfusion imaging using gated SPECT and phase analysis is an effective tool in evaluation of mechanical dyssynchrony. The purpose of this study was to determine the normal ranges of global and regional phase parameters.

**Methods:** A total of 100 patients with normal resting and stress electrocardiograms, low pretest likelihood for coronary artery disease and a normal gated MPI study were recruited in the study. All of the patients underwent a standard 2-day stress/rest gated MPI study according to standard protocols. The reconstructed images were further analyzed by Cedar-Sinai's quantitative gated SPECT. Left ventricular phase indices were provided both globally and regionally for both genders and the normal interquartile range of these parameters were defined.

**Results:** Normal ranges of global and wall-based regional phase parameters are presented both in unisex and in gender-specific formats. Both global ( $P < 0.001$ ) and major LV regional phase parameters ( $P < 0.05$ ) are found to be significantly different between the two genders with a significant positive association between end-diastolic volume with phase global indices ( $P < 0.01$ ). There is also more synchronized phase distribution in phase analysis results of post-exercise gated MPI as compared to the phase analysis of the same patients at resting state.

**Conclusion:** Normal ranges of phase indices are defined in this article by using Cedar-Sinai's QGS software. As normal ranges of phase dyssynchrony parameters are gender-specific and are related to LV volume, stress or resting state and stress type, the need for careful incorporation of these data is indicated in interpretation of phase studies.

**Key words:** Myocardial perfusion gated SPECT; Myocardial perfusion imaging; Left ventricular dyssynchrony; Phase analysis

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## INTRODUCTION

Heart failure (HF) is a common clinical issue in public health with an estimated prevalence of 10% in the elderly and a one-year mortality risk of approximately 30% [1, 2]. Implication of appropriate pharmacologic therapies and cardiac resynchronization therapy (CRT) can improve outcomes and mortality of HF patients [3, 4]. It has been shown that left ventricular (LV) mechanical dyssynchrony plays an essential role in the pathophysiology of HF [5]. Various imaging modalities have been introduced for the assessment of LV dyssynchrony, including echocardiography [6], magnetic resonance imaging [7] and gated single photon emission computerized tomography (SPECT) myocardial perfusion imaging (MPI) [8, 9], among which the latter one has the advantage of simplicity, extensive availability, superior reproducibility and ability to concurrent assessment of myocardial scar for optimizing CRT in HF patients [5]. SPECT MPI could also be advantageous in patients in whom echocardiography might generate suboptimal results, such as obese patients, critically ill or those who've received recent chest surgery [10]. Various software packages are commercially available for evaluation of ventricular synchrony such as Emory cardiac toolbox (ECTb) and Cedars-Sinai's quantitative gated SPECT (QGS) [11, 12]. The goal of this study is to determine the normal ranges of regional and global phase parameters using gated MPI with Cedars-Sinai's QGS software.

## METHODS

### Patients

The total study population consisted of a prospective cohort of 100 patients who were referred to our department in 2016 for MPI study on account of clinical indication and had normal resting and stress electrocardiograms (ECG), low pretest likelihood (<15%) for coronary artery disease (CAD) according to age, sex, symptoms and CAD risk factors on the basis of CAD consortium calculator [13, 14] and a normal myocardial perfusion and function on the basis of gated MPI study. A normal myocardial perfusion was defined as summed stress score (SSS) of less than 4 along with absence of elevated lung to heart uptake ratio ( $LHR \geq 0.4$ ) or transient ischemic dilation ( $TID \geq 1.1$  for exercise stress and  $TID \geq 1.15$  for Dipyridamole stress MPI) and a normal myocardial function was described as global LV ejection fraction (EF) of  $\geq 50\%$  as well as summed motion score (SMS) and summed thickening score (STS) of zero [15].

Patients with valvular heart disease (as proved by patient's echocardiographic study within a one-month period before the MPI), history of prior sternotomy or myocardial infarction, atrial fibrillation or multiple premature ventricular contractions (PVC) were not included in the study.

### Image acquisition

Each patient underwent a standard 2-day stress/rest protocol. All of the patients received a weight-based adjusted standard dose of  $99mTc$ -Sestamibi (8-12 mCi) in each phase of the study. The patients were stressed by either exercise or dipyridamole administration on the basis of the standard protocols [16]. Acquisitions were initiated 45-60 minutes after completion of pharmacologic stress test with dipyridamole or at resting state and 15 minutes after completion of exercise stress test, using a dual-detector SPECT/CT camera (Symbia T2, Siemens Medical Systems) with low-energy high-resolution collimators, 90-degree detector configuration and a non-circular body contoured 180 degree acquisition arc from right anterior oblique to left posterior oblique. Each phase of gated MPI SPECT study was performed in step-and-shoot mode with a zoom factor of 1.4, a matrix size of 64x64 (Pixel size, 6.6 mm) and 64 projections, 25 seconds per projection and 16-frame fixed temporal resolution forward-backward gating per R-R interval, using a fixed acceptance window of 30%. The energy window was set to 20% centered over the 140-keV photopeak, accepting gamma rays of 126 to 154 keV. The patients' ECG were monitored through the acquisitions to make sure that the sinus rhythm is maintained during the imaging.

### Image processing

The rotating raw images of all the participants were assessed visually and those with low-count density, motion artifact or interfering subdiaphragmatic or extracardiac activity were excluded [17, 18]. Reconstruction of the projection images was performed by filtered backprojection using postreconstruction Butterworth filtering (cutoff frequency, 0.4; order, 5). No attenuation or scatter correction was applied. The reconstructed images were further analyzed by Cedar-Sinai's quantitative gated SPECT (QGS) in order to provide left ventricular phase indices on the basis of the software predefined algorithm [19].

Once processing has been completed, global whole-ventricle and regional wall-based LV synchrony parameters were derived for both resting state and poststress MPI studies, including phase histogram bandwidth (the width of the histogram that includes 95% of the samples)(PHB), phase standard deviation (the standard deviation of the phase distribution) (PSD) and entropy (defined by summation of  $[f_i * \log(f_i)] / \text{Log}(n)$ ), in which  $f$  and  $n$  are frequency in the  $i_{th}$  bin and number of bins, respectively) [5, 11]. As computing the endocardial and epicardial surfaces is the critical step for accurate phase analysis in QGS, the accuracy of all region of interests (ROIs) were evaluated visually [20].

### Statistical analysis

The one-sample Kolmogorov-Smirnov test was used to assess whether continuous variables were normally distributed. Data were described as median (interquartile range). Synchrony parameters were compared between the two genders by Mann-Whitney U test and between the stress and resting state phases by Wilcoxon signed-rank test. Multivariate analysis was performed by quartile regression modules. Statistical analysis was performed by SPSS software (IBM SPSS Statistics for Windows, version 22.0. IBM Inc. Armonk, NY) and Stata 14 for windows (Stata Inc. Texas, USA). A P value of less than 0.05 was considered statistically significant.

## RESULTS

### Patients

Of the total 100 subjects who were recruited in the study, 56 (56%) were male and 44 (44%) were female. The patient characteristics are presented in Table 1.

### Phase analysis result and sex difference

The global whole-ventricle and regional wall-based LV synchrony parameters, including PHB, PSD and entropy at resting state are presented in an overall format for both genders in Table 2 and in a gender-specific format in Table 3.

As it is shown in Table 3, there is a significant difference between the median of phase parameters of males and females, both globally and regionally for major LV walls except for apex.

**Table 1:** Characteristics of study population.

Male (%)	56/100 (56)
Age (y)	48.4 ± 9.7
BMI (kg/m <sup>2</sup> )	29.7 ± 5.2
LV EF (%)	74.4 ± 8.7
LV EDV (ml)	66.3 ± 18.9
LV ESV (ml)	20.5 ± 15.4

LV = Left ventricle; EDV = End-diastolic volume; ESV = End-systolic volume; Statistics are numbers (%) or mean standard deviation.

### Phase analysis result and stress type difference

We found a significant difference in PHB, PSD and entropy between stress and resting states in patients who performed stress test with exercise as it is shown in Table 4. However, no significant difference was found in patients who underwent pharmacologic stress test with dipyridamole as compared to resting state. Furthermore, there is a significant difference in entropy and PSD on the basis of the stress type (P

value of 0.03 and 0.042, respectively) whereas no such a difference was found in PHB (P=0.412).

### Multivariate regression analysis

Multivariate analysis was performed to investigate the adjusted associations between age, gender and EDV with global indices of phase analysis at resting state. As it is shown in Table 5, after adjustment, only EDV was found to have significant positive association with global indices (P<0.01).

## DISCUSSION

Our study evaluates global whole ventricle and regional wall-based phase parameters in a normal population of referred patients with low likelihood of CAD, normal baseline and stress ECG and normal MPI study without known heart disease in whom synchronous myocardial contraction is expected. To the best of our knowledge, this study is one of the few studies that define normal range of global whole ventricle and the first study which defines regional wall-based phase parameters.

Analysis of LV contractile phase has been used for decades to evaluate LV dyssynchrony, beginning with equilibrium multiple gated blood pool scintigraphy in early days [21] to SPECT MPI in recent years. Today, various software programs are available, from which global and regional phase parameters can be derived [11]. We analyzed all SPECT MPI studies by Cedars-Sinai QGS software, by which global and regional phase measurements are derived from automatically created myocardial surfaces on a count-based algorithm [22]. Furthermore, it has been proposed that several factors might potentially influence phase distribution including gender, total accumulated count, radionuclide injection dose, stress or resting state and the amount of frames per cardiac cycle [23]. In order to lessen the impact of the aforementioned factors, we followed the standard procedure of MPI and the obtained images were meticulously quality controlled.

We also evaluated phase parameters in each gender, which shows a significant difference in both global and regional phase parameters of major LV walls as a result of different LV volumes. There is also difference in global whole ventricle phase parameters between our population and previously presented American population whereas it is partially similar to Japanese population [11, 19].

As phase parameters are related to LV volume, this difference seems to be related to different mean LV volume of different population, prompting population- and gender-specific definition of normal range for these parameters.

**Table 2:** Overall global and regional synchrony phase parameters at resting state.

	Whole LV	Apex	Lateral	Inferior	Septum	Anterior
<b>PHB</b>	30 (24-36)	12 (12-18)	24 (18-30)	21 (18-30)	16 (18-24)	24 (18-30)
<b>PSD</b>	6.3 (4.9-8.5)	2.9 (2.2-3.1)	5.8 (4.2-8.8)	5.1 (3.9-7.3)	4.6 (3.2-6.5)	5.5 (4.1-8.3)
<b>Entropy</b>	34 (27-40)	16 (11-18)	30 (23.2-38.7)	28 (22-34.7)	26 (19-32)	30 (23-36.7)

Data presented as median (interquartile range); PHB and PSD in degrees and entropy in percent; PHB = phase histogram bandwidth; PSD = phase standard deviation.

**Table 3:** Gender-Specific global and regional synchrony parameters (n=100).

Phase parameters		Male (n=56)	Female (n=44)	P value
<b>Global whole LV phase parameters</b>				
<b>Whole LV</b>	PHB	30 (24-32)	24 (18-28.5)	< 0.001
	PSD	7.8 (5.8-9.8)	5.2 (4.2-6.3)	< 0.001
	Entropy	38 (33-41)	29.5 (24.2-34.7)	< 0.001
<b>Regional wall-based phase parameters</b>				
<b>Apex</b>	PHB	12 (12-18)	12 (12-16)	0.425
	PSD	2.9 (2.2-3.4)	2.8 (2.2-3)	0.073
	Entropy	16 (11.2-19.7)	15 (11-17)	0.087
<b>Lateral</b>	PHB	30 (18-36)	18 (13.5-24)	< 0.001
	PSD	7(4.9-9.9)	4.7 (3.1-6.2)	< 0.001
	Entropy	33.5 (26-41)	27 (17-31)	< 0.001
<b>Inferior</b>	PHB	24 (18-30)	18 (18-24)	0.006
	PSD	5.9 (4.5-7.9)	4.3 (3.6-5.8)	0.001
	Entropy	31 (24.5-36.7)	25.5 (21.2-29)	0.002
<b>Septum</b>	PHB	24 (18-30)	18 (12-22.5)	< 0.001
	PSD	5.4 (4-9.8)	3.5 (3-4.8)	< 0.001
	Entropy	29.5 (24-40)	20.5 (17-28.7)	< 0.001
<b>Anterior</b>	PHB	27 (18-36)	18 (18-24)	< 0.001
	PSD	5.9 (5.2-9.7)	4.4 (3-6.1)	< 0.001
	Entropy	32.5 (27-41)	25 (17-32)	< 0.001

Data presented as median (interquartile range); PHB and PSD in degrees and entropy in percent; PHB = phase histogram bandwidth; PSD = phase standard deviation.

**Table 4:** Global synchrony phase parameters at stress and resting state

Phase parameter	Stress type	Stress	Rest	P value
<b>PHB</b>	Dipyridamole	24 (18-30)	30 (18-36)	0.200
	Exercise	24 (18-27)	30 (24-36)	<0.001
<b>PSD</b>	Dipyridamole	5.9 (4.6-7.8)	6.2 (4.5-7.9)	0.968
	Exercise	5.1 (4.2-6.5)	6.3 (4.9-8.8)	<0.001
<b>Entropy</b>	Dipyridamole	32 (28-37)	34 (27-39)	0.616
	Exercise	29 (25-32)	34 (27-40)	<0.001

Data presented as median (interquartile range); PHB and PSD in degrees and entropy in percent; PHB = phase histogram bandwidth; PSD = phase standard deviation.

**Table 5:** Multivariate regression analysis of factors influencing global phase parameters at resting state.

	Covariate	Coefficient ± Standard Error	P value
<b>PHB</b>	Age	0.086 ± 0.07	0.287
	Gender	-1.630 ± 2.59	0.530
	EDV	0.270 ± 0.06	<0.001
<b>PSD</b>	Age	-0.030 ± 0.02	0.093
	Gender	-0.220 ± 0.81	0.781
	EDV	0.088 ± 0.02	<0.001
<b>Entropy</b>	Age	0.071 ± 0.16	0.666
	Gender	-2.600 ± 1.62	0.114
	EDV	0.200 ± 0.40	<0.001

PHB = phase histogram bandwidth; PSD = phase standard deviation; EDV = End-diastolic volume

Moreover, we found that PHB, PSD and entropy are fairly similar for major LV walls (anterior, septal inferior and lateral walls). Nonetheless, phase parameters of apex were considerably different that may be explained by its smaller size and lower count accumulation at this region.

This study also showed that there is a significant different yet more synchronized phase distribution as described by narrower phase histogram with smaller PSD in phase analysis results of post-exercise gated MPI as compared to the phase analysis of the same patients at resting state. This finding is similar to the result of Li study, in which the homodynamic effect of exercise and shorter stress-to-acquisition interval were introduced as possible reasons for this finding [24]. In summary, based on the current study findings, the interpretation of phase analysis results should be cautiously performed considering the influence of LV volume, which may vary according to patient's gender or stress type.

### Study limitations

As phase parameters may differ among various software programs, the normal values that are presented in this article should not be considered as interchangeable with other software programs.

### CONCLUSION

The normal range of global and regional phase parameters of LV are presented in this article. As these parameters are affected by the LV volume, phase analysis of the gated SPECT MPI should be interpreted on the basis of a population- and gender-specific normal database.

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