Original Article

Normal values of cardiac mechanical synchrony parameters using gated myocardial perfusion single-photon emission computed tomography: Impact of population and study protocol

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ABSTRACT

Purpose of the Study: Normal values of cardiac mechanical synchrony parameters in gated myocardial perfusion single-photon emission computed tomography (GMPS) are well established in literature from the Western population. The aim of the study is to establish normal values of mechanical synchrony with GMPS in Indian population and to find out whether it differs significantly from established values. **Procedure:** We retrospectively analyzed 1 day low-dose stress/high-dose rest GMPS studies of 120 patients (sixty males, 52 ± 11.7 years) with low pretest likelihood of coronary artery disease and having normal GMPS study. In GMPS, first-harmonic fast Fourier transform was used to extract a phase array using commercially available software. Phase standard deviation (PSD) and phase histogram bandwidth (PHB) were used to quantify cardiac mechanical dyssynchrony. **Results:** The values obtained were as follows, PSD: In men, 14.3 ± 4.7 (stress) and 8.9 ± 2.9 (rest), in women 11 ± 4 (stress) and 7.7 ± 2.7 (rest), and PHB: In men, 40.1 ± 11.9 (stress) and 30.6 ± 7.6 (rest), in women, 34.7 ± 12.6 (stress) and 25.3 ± 8.6 (rest). The value of PSD and PHB was significantly less in Indian population as compared with established values in literature. We also observed that synchrony indices derived from the low-dose stress studies are higher than high-dose rest studies. **Conclusions:** The value of synchrony parameters differs significantly according to population and methodology suggesting that specific population and methodology-based normal database for assessment of cardiac mechanical dyssynchrony should be established.

Keywords: Cardiac mechanical dyssynchrony, gated myocardial perfusion single-photon emission computed tomography, normal database, phase histogram bandwidth, phase standard deviation

INTRODUCTION

The assessment of left ventricular mechanical dyssynchrony (LVD) using phase analysis of gated myocardial perfusion single-photon emission computed tomography (SPECT) (MPS) was introduced in 2005, allowing for the simultaneous assessment of left ventricular (LV) perfusion, function, and mechanical dyssynchrony.[1] Phase analysis has shown excellent reproducibility and repeatability for assessing LVD.[2] Furthermore, compared to other imaging modalities such as echocardiography, magnetic resonance imaging, and equilibrium radionuclide angiography, phase analysis of MPS has shown several advantages such as simplicity, widespread availability, superior reproducibility, applicability to retrospective data, and ability to simultaneously assess myocardial scar location. LVD assessed by the GMPS has been recognized as an essential and additional criterion for response to cardiac resynchronization therapy (CRT) in heart failure patients.[3,4] Aljaroudi[5] outlined other potential clinical applications of LVD including prognostication and

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risk stratification of patients with ischemic,[6] nonischemic cardiomyopathy,[7] implantable defibrillators,[8] and end-stage renal disease.[9,10]

The normal database for cardiac mechanical dyssynchrony proposed by Chen *et al.* in 2005 is derived from the Western population.[1] It is important to determine whether these normal values are also applicable on the different ethnic groups and population. Therefore, the aim of the study was to establish normal values of mechanical synchrony with GMPS in Indian population both in rest and stress images and to find out whether it differs significantly from the established database.

PROCEDURE

Study population

This was a single center study performed at Cardiothoracic Centre at All India Institute of Medical Sciences, New Delhi. We retrospectively analyzed data of 120 patients who underwent Technetium-99 m (99 mTc) sestamibi GMPS for routine clinical indications between the period of January 2012 and December 2013. Studies of patients with low pretest likelihood of coronary artery disease, no known history of cardiac disease and normal sinus rhythm on electrocardiogram (ECG) and having QRS duration <120 ms were included in the study. All studies with normal perfusion at both stress and rest, normal-sized LV cavity, no regional wall motion abnormality, and LV ejection fraction (LVEF) >55% were considered normal by two experienced observers.

Gated myocardial perfusion single-photon emission computed tomography acquisition

All patients underwent 1 day stress–rest Gated SPECT myocardial perfusion imaging according to American Society of Nuclear Cardiology.[11] All patients underwent exercise stress according to Bruce protocol. Nearly 8–12 mCi (low dose) of 99 mTc sestamibi (hexakis-6 methoxyisobutylisonitrile) was injected at peak stress. SPECT image acquisition was performed 15–30 min after exercise. For rest study image, acquisition was performed 45–60 min after intravenous injection of 24–30 mCi (high dose) of 99 mTc sestamibi. GMPS acquisition was performed on a dual head camera system (General Electric Medical System, Infinia, Hawkeye, Waukesha, WI, USA). Patients were positioned supine and limb leads placed for ECG gating. Both stress and rest-gated images were acquired using a 15% window centered over the 140 Kev photo peak of Tc99 m with parallel hole, low energy, high-resolution collimator. ECG-gated SPECT imaging was performed with eight frames per cardiac cycle, using a 100% beat acceptance window. Studies were acquired using step and shoot mode with the heads at an angle of 90° to each other. Sixty projection (30 steps, 3° steps) of 20 s/projection were acquired over 180° from 45 right anterior oblique position to −135 left posterior oblique position.

Gated myocardial perfusion single processing

GMPS studies were processed by two nuclear medicine physicians (AM, HS) using commercially available cardiac software "SyncTool™" (Emory Cardiac Toolbox, Emory University, Atlanta, GA, USA) on a Xeleris Workstation (GE Medical Systems; Waukesha, WI, USA).

Image processing

SPECT nongated projection images were reviewed in cine mode in all cases to assess patient movement, sources of potential attenuation artifacts and gastric activity. The raw images (both gated and nongated data sets) were then prefiltered with a butterworth filter. The resulting transaxial image slices were reoriented to generate short axis, vertical long axis, and horizontal long axis images, using vendor provided software. For the assessment of cardiac dyssynchrony, each gated study was processed using cardiac software "SyncTool™" (Emory Cardiac Toolbox, Emory University, Atlanta, GA, USA). First-harmonic fast Fourier transform was used to extract a phase array (three-dimensional regional phases). The two parameters used to assess cardiac dyssynchrony:

1. Phase standard deviation (PSD), which was the SD of the phase distribution
2. Phase histogram bandwidth (PHB), which included 95% of the elements in the phase distribution.

Statistical analysis

Continuous data were expressed as mean ± SD compared using the paired and unpaired Student's *t*-test or Wilcoxon rank test as appropriate. Categorical data were expressed as number and percentage. $P < 0.05$ was considered statistically significant. Statistical analysis was performed using the statistical software packages SPSS 17 (SPSS Inc., Chicago, Illinois, USA) and MedCalc 11.3 (MedCalc Software, Mariakerke, Belgium).

RESULTS

Patient characteristics

One hundred and twenty patients (sixty males, sixty females) were included in the study. Mean age was 52 ± 11.7 years (median 51; range 25–75). Mean LVEF on stress and rest was 62.9 ± 4% and 62.9 ± 3.9%, respectively ($P = 0.45$).

Phase analysis results

The values of PSD and PHB derived are given in Table 1 [Figure 1]. Significant differences between synchrony parameters were noted between men and women both on stress (PSD: 14.3 ± 4.7 vs. 11 ± 4, $P = 0.0001$ and PHB: 40.1 ± 11.9 vs. 34.7 ± 12.6, respectively, $P = 0.007$) and on rest studies (PSD: 8.9 ± 2.9 vs. 7.7 ± 2.7, $P = 0.009$ and PHB: 30.6 ± 7.6 vs. 25.3 ± 8.6, respectively, $P = 0.0001$). Furthermore, significant differences between synchrony parameters noted between stress and rest both in men (PSD: 14.3 ± 4.7 vs. 8.9 ± 2.9, $P < 0.0001$ and PHB: 40.1 ± 11.9 vs. 30.6 ± 7.6, $P < 0.0001$) and in women (PSD: 11 ± 4 vs. 7.7 ± 2.7, $P < 0.0001$ and PHB: 34.7 ± 12.6 vs. 25.3 ± 8.6, $P < 0.0001$).

Values of PHD and PHB greater than mean + 2 SD of normal parameters were taken as cutoff values for the presence of dyssynchrony [Table 2].

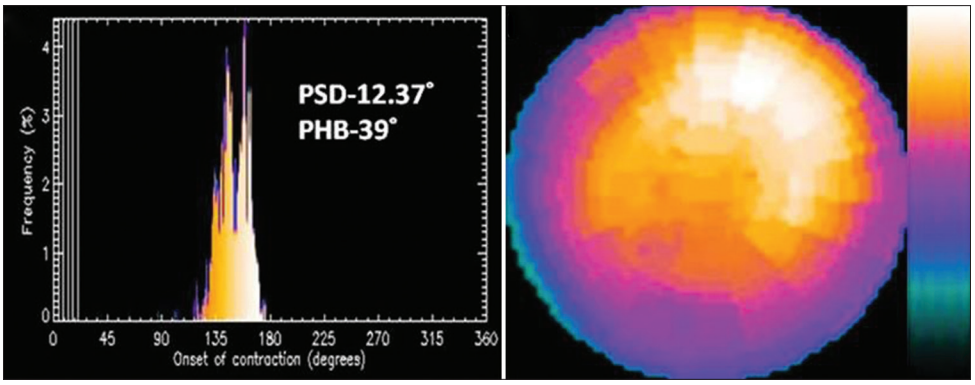

Figure 1: The phase image, phase histogram, and quantified synchrony parameters in a normal subject

Table 1: Normal values of synchrony parameters on gated myocardial perfusion single-photon emission computed tomography

	Range	Mean	SD
PSD			
Men			
Stress	9.2-25.2	14.3	4.7
Rest	3.6-18.2	8.9	2.9
Women			
Stress	4.7-20.8	11	4
Rest	3.3-16.5	7.7	2.7
PHB			
Men			
Stress	23-72	40.1	11.9
Rest	20-54	30.6	7.6
Women			
Stress	16-70	34.7	12.6
Rest	12-52	25.3	8.6

PSD: Phase standard deviation, PHB: Phase histogram bandwidth, SD: Standard deviation

Table 2: Cutoff values for presence of dyssynchrony on gated myocardial perfusion single-photon emission computed tomography

	Value
PSD	
Men	
Stress	23.7
Rest	14.7
Women	
Stress	19
Rest	13.1
PHB	
Men	
Stress	63.9
Rest	45.8
Women	
Stress	59.9
Rest	42.5

PSD: Phase standard deviation, PHB: Phase histogram bandwidth

DISCUSSION

GMPS now has been widely used in assessment of myocardial dyssynchrony and prediction of response to CRT worldwide.[4] The normal database used for the assessment of cardiac mechanical dyssynchrony was first established by Chen *et al*. in 2005[1] [Table 3].

After that, few studies have published normal values of PSD and PHB in some control group obtained by gated SPECT.[2,12-15] However, interestingly, all these normal values obtained from different population were different [Table 4]. Prevalence of cardiovascular risk factors of control groups in these studies is different. Diabetes, hypertension, and dyslipidemia could potentially affect phase histogram values.[15] Furthermore, the selection criteria of control group and methodology in these studies were different. Trimble *et al*.[12] in their study included patients with atrial fibrillation in the control group. Whereas the normal database first proposed by Chen *et al*.[1] derived from a standard Tl-201/Tc-99 m sestamibi dual isotope rest/exercise protocol. These differences in the selection criteria of normal group and methodology could possibly explain different normal values of PSD and PHB obtained from different studies. All of these studies however performed on western population. Till date, no study has been performed to establish a normal database in the Asian population. Therefore, in our study, we attempt to establish normal database of PSD and PHB in Indian population. In our study, the normal values of PSD and PHB are significantly lower than the values proposed by Chen *et al*.[1] In contrast to our study, Chen *et al*. derived the normal values of synchrony from poststress Tc99 m sestamibi studies, whereas we have derived these values from rest studies. Effect of stress on synchrony parameters derived from Tc99 m sestamibi study is negligible due to delayed imaging poststress. Other potential factors that may affect PSD and PHB include tracer dose, temporal resolution, change in hemodynamics, LVEF, and ischemia.[16] Since in both the studies, high dose of tracer was used, so the effect of tracer dose is also negated. Therefore, the possible confounding factor which may explain the difference between synchrony parameters may be the difference in the body habitus of patient population and differences in the LV mass. Asian population usually have a lower body mass index (BMI) as compared to people in the western population.[17] The effect of BMI is of particular importance since patients with larger BMI will have more attenuation and fewer counts. Lesser is the counts per pixel; the higher is the noise and potential measurement

errors lead to higher PSD and PHB indices.[18] Furthermore, LV mass increases with increase in BMI.[19] Since phase analysis is a count-based technique, it could be influenced by count density, which presumably will be higher among those with a greater LV mass. Therefore, people with greater LV mass will have greater variation in count density throughout the cardiac cycle which will ultimately lead to larger PSD and PHB values. Thus, having lower PSD and PHB indices in Indian population having lower BMI in comparison to Western population is completely justified. However, in concordance with the findings of Chen *et al.*,[1] we have found higher values for both PSD and PHB in men as compared to women both in stress and rest which further confirms the dependence of phase analysis parameters on LV mass since males have greater LV mass as compared to females.

In our study, we also compared rest and stress derived dyssynchrony indices. Several investigators in the past compared the rest- and stress-derived dyssynchrony indices and conflicting data exist in the literature regarding the effect of stress on cardiac dyssynchrony parameters [Table 5].

Table 3: Established normal cutoff values of dyssynchrony on gated myocardial perfusion single-photon emission computed tomography

	Range	Mean	SD	Cut-off
PSD				
Men	6.3-27.6	14.2	5.1	24.4
Women	5.1-31.4	11.8	5.2	22.2
PHB				
Men	22-81	38.7	11.8	62.3
Women	18-62	30.6	9.6	49.8

PSD: Phase standard deviation, PHB: Phase histogram bandwidth, SD: Standard deviation

Aljaroudi *et al.*[16] and Zhou *et al.*[21] used the same dose of radiopharmaceuticals for both rest and stress studies. Aljaroudi *et al.*[16] observed that stress-derived dyssynchrony indices are smaller in comparison to rest derived dyssynchrony index. Possible explanations put forward to explain these differences include poststress hyperemia and more synchronous cardiac contraction during peak stress. Poststress hyperemia usually leads to better counting statistics and thereby smaller dyssynchrony indices. In contrast, Zhou *et al.*[21] found no significant differences between stress-derived dyssynchrony indices using 2-day high-dose stress/rest sestamibi study. In Tc99 m sestamibi, poststress acquisition is performed after about 30–45 min, which would negate any effect of stress on the gated images derived synchrony parameters. Hence, delayed poststress imaging in sestamibi study could explain the findings observed by the Zhou *et al.*[21] In the studies where single day protocol was performed, higher dyssynchrony indices are noted in low-dose study as compared to high-dose studies.[20,22] Similar to these findings, we observed that low-dose stress images had significantly higher dyssynchrony indices as compared to high-dose rest images. We performed stress- and rest-gated imaging using same acquisition protocol, all the patients had normal perfusion both on stress and rest, and LVEF was comparable between stress- and rest-gated imaging. Hence, the only potential confounding factor in our study that could have resulted in different stress and rest synchrony values is the tracer dose. The effect of tracer dose is well known in assessment of cardiac mechanical dyssynchrony.[22] PSD and PHB indices derived from the low-dose study tend to be falsely higher in comparison of high-dose study. The lower signal to noise ratio is postulated to be one of the main reasons. Standard deviation of the count rate is proportional to the square root of the total counts, which is related to the

Table 4: Normal values proposed by different authors

Authors	Modalities	Definition of controls	Number of patients	PSD (degree)	PHB (degree)
Chen *et al.*[1]	Stress	No history of CAD, normal ECG, no coronary artery calcium	90	Female: 11.8±5.2 Male: 4.2±5.1	Female: 30.6±9.6 Male: 38.7±11.8
Trimble *et al.*[2]	Stress	No history of CAD, no LBBB and RBBB, no perfusion defects, EF >50%	157	15.7±11.8	42±28.4
Trimble *et al.*[12]	-	No history of CAD, QRS B 120 ms, no perfusion defects, EF >50%	50	8.6±2.9	27.9±8.9
Atchley *et al.*[13]	Stress	No history of CAD, normal myocardial perfusion imaging, EF >55%	75	8.8±3.1	28.7±9.3
Chen *et al.*[14]	Rest	No history of CAD, no LBBB, normal exercise ECG, normal EF (echo)	30	7.6±2	26.1±7
Romero-Farina *et al.*[15]	Rest	No history of CAD, normal ECG, no perfusion defects (peak heart rate ≥85%), EF ≥50%	150	12.2±4.9	36.5±12

CAD: Coronary artery disease, ECG: Electrocardiogram, EF: Ejection fraction, PSD: Phase standard deviation, PHB: Phase histogram bandwidth, LBBB: Left bundle branch block

Table 5: Effect of stress and rest on cardiac mechanical dyssynchrony parameters

Author	Modality	Number of patients	Rest PSD (degrees)	Stress SD (degrees)	Rest PHB (degrees)	Stress PHB (degrees)
Aljaroudi *et al.*[20]	Low dose stress/high dose rest sestamibi study	20	18±8	19±6	46±16	52±12
Aljaroudi *et al.*[16]	Gated 82-Rb PET	91	16.8±7.8	12.4±3.7	-	-
Zhou *et al.*[21]	2 day high dose stress/rest sestamibi study	60	9.3±1.9	9.3±2.0	29.5±5.7	28.5±5.9
Aljaroudi *et al.*[22]	Low dose rest/high dose stress tetrofosmin	54	12.2	7.9	-	-

PSD: Phase standard deviation, PHB: Phase histogram bandwidth

tracer dose. Hence, standard error of the count is inversely proportional to tracer dose.[18]

In our study, we have observed that the Indian population have significantly lower normal synchrony indices. Hence, the cutoff values for the presence of dyssynchrony (calculated as > mean + 2SD) will be significantly lower for the Indian population [Table 2] as compared to cutoff values established in the literature [Table 3].[1] This indicates that the normal values cannot be used interchangeably. Furthermore, synchrony indices differ significantly from one methodology to another methodology. Hence, the findings of this study suggest that a population-specific and methodology-specific normal database for assessment of cardiac mechanical dyssynchrony should be established.

The study has few limitations. It was a retrospective study. BMI which could be potential confounding factor could not be assessed due to retrospective nature of the study.

CONCLUSIONS

Cardiac mechanical dyssynchrony assessed by gated myocardial perfusion SPECT is influenced by the radiotracer and study protocol. Hence, centers using GMPS should have its normal database for assessment of cardiac mechanical dyssynchrony.

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Conflicts of interest
There are no conflicts of interest.

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