Correlation of Left Ventricular Eccentricity Index with Other Scintigraphic Parameters on Gated Myocardial Perfusion Single Photon Emission Computed Tomography

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ABSTRACT

BACKGROUND: *Left ventricular (LV) eccentricity index (EI) is a measure of the LV shape obtained with a commonly used quantitative software for myocardial perfusion scintigraphy (MPS). However, there are limited studies evaluating its correlation with other MPS parameters, for which this study was done.* **METHODOLOGY:** *All patients who underwent ^{99m}Tc-sestamibi stress MPS from 2013 to 2015 were screened. A total of 353 patients, 228 (65%) males and 125 (35%) females, met the inclusion criteria. One hundred twenty-nine (37%) underwent exercise stress while 224 (63%) were given dipyridamole. Spearman's rho correlation was used to determine the correlation of rest and post-stress EI with the other study variables.* **RESULTS:** *Among males, rest EI showed negative correlation with summed stress score (SSS) (r_S = −0.182, p < 0.005), transient ischemic dilatation (TID) (r_S = −0.172, p = 0.009), rest LV end-diastolic volume (EDV) (r_S = −0.291, p < 0.001), rest LV end-systolic volume (ESV) (r_S = −0.316, p < 0.001), post-stress LVEDV (r_S = −0.278, p < 0.001), and post-stress LVESV (r_S = -0.331, p < 0.001). There was positive correlation with rest LV ejection fraction (EF) (r_S = 0.297, p < 0.001) and post-stress LVEF (r_S = 0.336, p < 0.001). No significant relationship with any of the MPS parameters was observed among females. For both exercise and dipyridamole groups, EI exhibited negative correlation with SSS, and rest and stress LVESV; and positive correlation with rest and post-stress LVEF. Significant relationship with rest and stress LVEDV was only observed in the dipyridamole group.* **CONCLUSIONS:** *This study shows that EI is correlated with most, if not all, of the MPS parameters with different levels of association depending on the patient's sex and the type of stress employed. More spherical LV is correlated with more severe perfusion defects, larger LV cavity volumes and poorer LV systolic function.*

Keywords: *left ventricular shape, eccentricity index, myocardial perfusion scintigraphy*

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INTRODUCTION

Myocardial perfusion scintigraphy (MPS) is a valuable noninvasive tool for the evaluation of cardiac diseases among a broad spectrum of patients (1,2). Its clinical indications include diagnosis of coronary artery disease (CAD), assessment of the impact of coronary artery stenosis on regional perfusion, differentiation of viable ischemic myocardium from scar, risk assessment and stratification, and monitoring of treatment effect (2,3). Aside from determining the extent, severity and location of perfu ion defects, additional scintigraphic findings that have prognostic value can be obtained (1,4,5). These include transient ischemic dilatation (TID), thallium-201 lung uptake, left ventricular (LV) cavity volumes, and LV ejection fraction (LVEF) (1,4,5). The ability of MPS to provide simultaneous assessment of LV perfusion and function is possible with the development of electrocardiographic (ECG)-gating and the use of dedicated cardiac softwares for automatic segmentation, analysis and quantification (4-6).

The LV configuration can also be evaluated in MPS studies (4,6). Eccentricity index (EI), which reflects the LV shape, is routinely calculated with commonly available quantitative software for cardiac single photon emission computed tomography (SPECT) (6). Numerous studies have been conducted on LV architecture during remodeling, with few literatures exploring its shape. In addition, two-dimensional echocardiogram was mostly used in these studies. There are limited literatures on LV shape determined by cardiac SPECT. A study by Gimelli et al. (7) in 2016 evaluated the interaction of EI with LV functional and structural parameters on MPS obtained using a gamma camera with Cadmium-Zinc-Telluride (CZT) detectors. It was found that abnormal EI was correlated with a more impaired myocardial perfusion, LVEF, and LV end-diastolic volume (LVEDV) (7).

Although EI is also routinely generated by the software available in our institution, the lack of studies on its clinical utility precludes its inclusion in our official MPS reports. The aim of this study is to determine the correlation of EI, as a measure of LV shape, with the other parameters obtained with cardiac SPECT that are indicators of adverse outcome and prognosis. These include severity of perfusion defects, LV cavity volumes, and LV systolic function. The interaction of EI with these measures will provide a clue on the possible utility of EI as an additional parameter to prognosticate patients undergoing MPS.

MATERIALS AND METHODS

This study was conducted in compliance with the ethical principles set forth in the Declaration of Helsinki, and was duly reviewed and approved by the Philippine Heart Center Institutional Ethics Review Board (PHC IERB). It was deemed eligible for a waiver of written informed consent.

Study Design

This is a cross-sectional analytical study.

Study Population, Setting, and Time Frame

All patients who were referred for exercise or dipyridamole ^{99m}Tc-sestamibi MPS to the Nuclear Medicine Division of Philippine Heart Center from 2013 to 2015 were included in this study. Technically suboptimal scans, patients who achieved sub-maximal exercise, and patients with significant arrhythmia were excluded. A minimum of 53 patients were required on 0.43 correlation coefficient of LV EI and summed stress score (SSS) (7), level of significance of 0.05, and 90% power.

Data Collection

The records of the patients who met the inclusion criteria were retrieved from the Division's database. Relevant data such as patient demographics, clinical characteristics, and risk factors for cardiovascular diseases such as hypertension, diabetes, dyslipidemia and smoking were recorded in a data acquisition form. Pertinent scintigraphic variables such as EI, SSS, TID, LVEDV, LV end-systolic volume (ESV), and LVEF were tabulated.

Patient Preparation

All patients were advised to discontinue beta blockers, calcium channel blockers and caffeine intake 24 hours prior; and fast and hold intake of nitrates 4 hours before the schedule. One-day rest-stress protocol using ^{99m}Tc-sestamibi was done.

Stress Protocol

The type of stress employed (exercise or dipyridamole) and the treadmill exercise protocol (Bruce, modified Bruce, or NIH) used were upon the attending physician's discretion.

1. For treadmill exercise stress, the radiopharmaceutical was administered upon reaching ≥ 85% of the predicted maximum heart rate or once an indication for termination of exercise testing was observed.
2. For dipyridamole, it was infused at 0.56 mg/kg over 4 minutes. The radiopharmaceutical was given at the 8th minute of the procedure.

Image Acquisition Protocol and Processing

All studies were performed using the Philips Forte dual-head gamma camera with the patient on supine position after intravenous injection of ^{99m}Tc-sestamibi with approximate activity of 333 MBq and 999 MBq at rest and post-stress, respectively. Images were obtained by non-circular 180-degree acquisition for 32 projections at 25 seconds per projection at rest and 20 seconds per projection at post-stress. A 64 x 64 image matrix with a zoom factor of 1.48 was used with a 20% energy window centered at the 140 keV photopeak of ^{99m}Tc. Gated SPECT was performed, obtaining 8 frames per cycle. No attenuation or scatter correction was employed. Additional prone imaging was done as necessary.

Projection datasets were filtered, reconstructed and reoriented using an automated processing software, AutoSPECT®. AutoQuant® was used for myocardial SPECT analysis and quantitation. The following study variables were generated by the software:

1. EI - a measure of the elongation of the LV. It is calculated from the major axis and the minor axes of the ellipsoid that best fit the mid-myocardial surface, using the formula: $EI = [1 - (R_x R_y / R_z^2)]^{0.5}$;
2. SSS - the summation of the stress visual scores in a 17-segment model, indicating the severity of the perfusion defect;
3. TID - LV cavity appearing larger on post-stress images than on images obtained at rest [computed using the formula: (LV chamber volume at stress) / (LV chamber volume at rest)];
4. LVEDV - the amount of blood in the left ventricle (in mL) just prior to contraction;
5. LVESV - the amount of blood in the LV (in mL) at which contraction of a cardiac cycle chamber occurs and blood is expelled; and
6. LVEF - a measure of the ability of the LV to expel blood (calculated using the formula: LVEF = (LVEDV - LVESV)/LVEDV x 100%)

Statistical analysis

Descriptive statistics was used to summarize the demographic and clinical characteristics of the patients. Frequency and proportion was used for categorical variables, median and interquartile range (IQR) for non-normally distributed continuous variables, and mean and standard deviation (SD) for normally distributed continuous variables. Spearman's rho was used to determine the correlation between two non-normally distributed variables. Shapiro-Wilk was used to test the normality of the continuous variables. Missing variables were neither replaced nor estimated. Null hypotheses were rejected at $\alpha = 0.05$ (level of significance). STATA 13.1 was used for data analysis.

RESULTS

A total of 353 patients, consisting of 228 (65%) males and 125 females (35%), were included in this study. One hundred twenty-nine (37%) underwent treadmill exercise stress, while 224 (63%) underwent dipyridamole MPS. Pertinent patient demographics, clinical data, and scintigraphic findings were summarized in Table 1.

Both rest and post-stress EI were shown to have statistically significant correlation with all of the MPS parameters included as study variables (Table 2). EI has positive correlation with rest and post-stress LVEF, and negative correlation with SSS, TID, rest LVEDV, rest LVESV, post-stress LVEDV, and post-stress LVESV. When compared with rest EI, post-stress EI appeared to have a better strength of association with SSS and TID.

Correlation of EI at rest with MPS parameters based on sex

Using the rest EI values, correlation with MPS parameters was determined separately for males and females (Table 3). Among male subjects, there was

Table 1. Characteristics of the patients

Age	58 ± 12 years
Sex	
Male	65
Female	35
Height (m) [mean ± SD]	1.64 ± 0.08
Weight (kg) [mean ± SD]	69.7 ±14.00
BMI (kg/m^2) [mean ± SD]	25.86 ± 4.26
Co-morbidities	
Hypertension	73%
Diabetes mellitus	37%
Dyslipidemia	55%
Myocardial infarction	11%
Smoking status	
Non-smoker	78%
Smoker	5%
Pack-years [median (IQR)]	30 (15–44)
Previous smoker	17
Pack-years [median (IQR)]	15 (7.5–25.0)
Years quit in smoking [median (IQR)]	6 (1.0–23.5)
Scintigraphic parameters	
Rest EI [median (IQR)]	0.81 (0.80–0.83)
Stress EI [median (IQR)]	0.82 (0.79–0.84)
Summed Stress Score [median (IQR)]	0 (0–7)
Normal	67.14
Mild	9.92
Moderate	5.95
Severe	17.00
TID Index [median (IQR)]	0.98 (0.89–1.06)
Rest	
LVEDV [median (IQR)]	92 (70–119)
LVESV [median (IQR)]	38 (24–63)
LVEF [median (IQR)]	58 (45–66)
Post-stress	
LVEDV [median (IQR)]	92 (68–119)
LVESV [median (IQR)]	37 (22–66)
LVEF [median (IQR)]	60 (46–67)

SD = standard deviation, IQR = interquartile range, BMI = body mass index, TID Index = transient ischemic dilatation index, LVEDV = left ventricular end-diastolic volume, LVESV = left ventricular end-systolic volume, LVEF = left ventricular ejection fraction

Table 2. Correlation of rest and post-stress eccentricity index with other myocardial perfusion scintigraphy (MPS) parameters

MPS Parameters	Rest EI		Post-stress EI	
	r	p	r	p
SSS	−0.151	0.004	−0.246	< 0.001
TID	−0.111	0.037	−0.215	<0.001
Rest				
LVEDV	−0.156	0.003	−0.123	0.021
LVESV	−0.168	0.002	−0.144	0.007
LVEF	0.159	0.003	0.148	0.005
Post-stress				
LVEDV	−0.147	0.005	−0.152	0.004
LVESV	−0.182	< 0.001	−0.176	< 0.001
LVEF	0.185	< 0.001	0.174	0.001

SSS = summed stress score, TID = transient ischemic dilatation, LVEDV = left ventricular end-diastolic volume, LVESV = left ventricular end-systolic volume, LVEF = left ventricular ejection fraction

Table 3. Correlation of eccentricity index at rest with other myocardial perfusion scintigraphy (MPS) parameters based on sex

MPS Parameters	Male (n = 228)		Female (n = 125)	
	r	p	r	p
SSS	−0.151	0.004	−0.246	< 0.001
TID	−0.111	0.037	−0.215	<0.001
Rest				
LVEDV	−0.156	0.003	−0.123	0.021
LVESV	−0.168	0.002	−0.144	0.007
LVEF	0.159	0.003	0.148	0.005
Post-stress				
LVEDV	−0.147	0.005	−0.152	0.004
LVESV	−0.182	< 0.001	−0.176	< 0.001
LVEF	0.185	< 0.001	0.174	0.001

SSS = summed stress score, TID = transient ischemic dilatation, LVEDV = left ventricular end-diastolic volume, LVESV = left ventricular end-systolic volume, LVEF = left ventricular ejection fraction

better interaction of EI with all study variables (Figure 1). On the other hand, no statistically significant correlation of EI with other MPS parameters was seen in the female population.

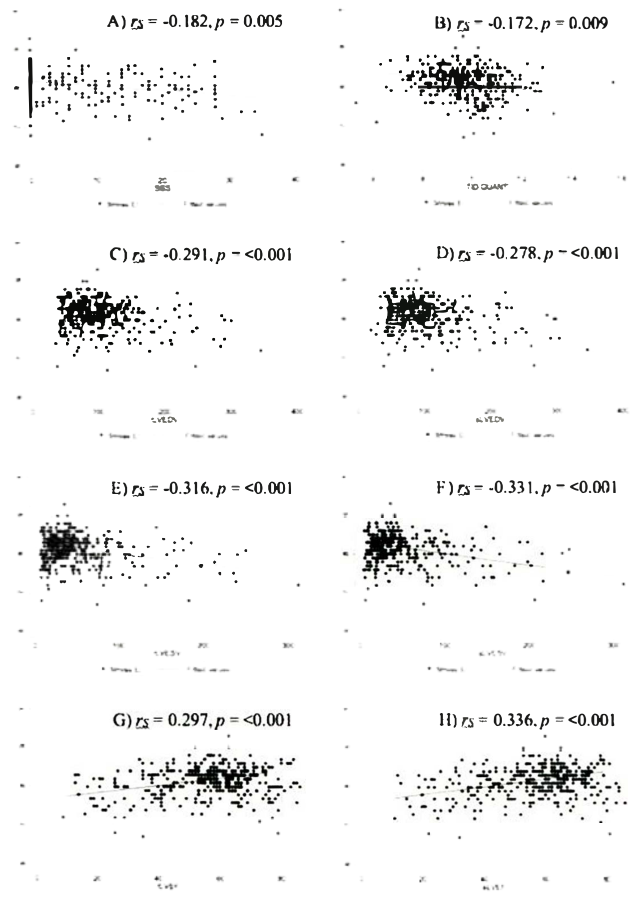

Figure 1. Correlation of eccentricity index (EI) at rest with A) summed stress scores (SSS), B) transient ischemic dilatation (TID), C) rest left ventricular end-diastolic volume (rLVEDV), D) post-stress left ventricular end-diastolic volume (sLVEDV), (E) rest left ventricular end-systolic volume (rLVESV), F) post-stress left ventricular end-systolic volume (sLVESV), G) rest left ventricular ejection fraction (rLVEF), and (H) post-stress left ventricular ejection fraction (sLVEF) among male subjects.

Correlation of EI at stress with MPS parameters

EI at stress was correlated with all MPS parameters with similar direction and strength of association to that of the EI at rest, except for SSS and TID, which

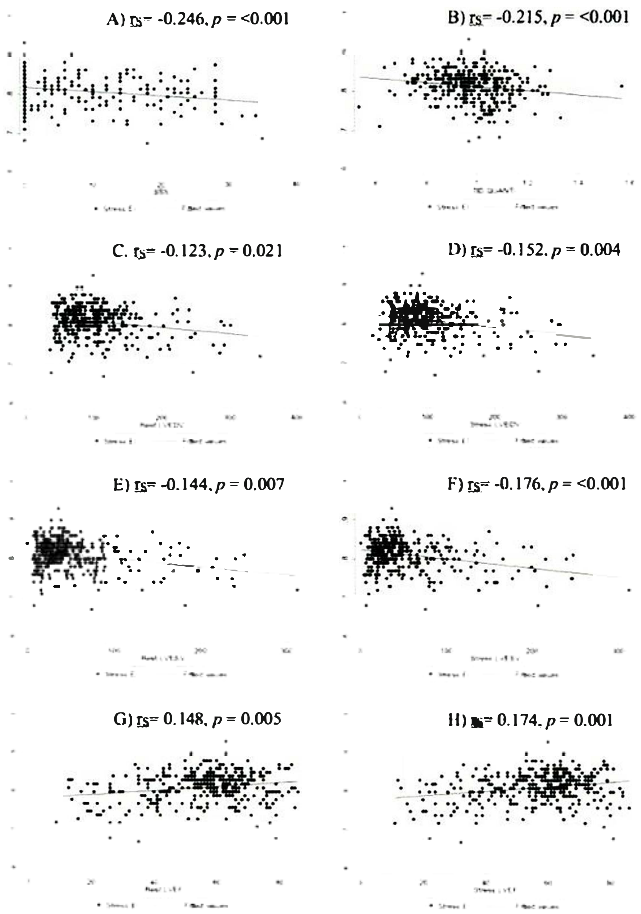

Figure 2. Correlation of eccentricity index (EI) post-stress with A) summed stress scores (SSS), B) transient ischemic dilatation (TID), C) rest left ventricular end-diastolic volume (LVEDV), D) post-stress LVEDV, (E) rest left ventricular end-systolic volume (LVESV), F) post-stress LVESV, G) rest left ventricular ejection fraction (LVEF), and (H) post-stress LVEF.

had better correlation with post-stress EI (Figure 2). Determination of the correlation of post-stress EI was done separately for patients who underwent exercise and pharmacologic stress test (Table 4). Among patients who underwent treadmill stress test, an inverse correlation was seen with SSS, rest LVESV and post-stress LVESV. There was direct correlation with both LVEF at rest and post-stress. No statistically significant relationship with TID, and LVEDV at rest and post-stress was observed. Post-

Table 4. Correlation of post-stress eccentricity index with other myocardial perfusion scintigraphy (MPS) parameters based on type of stress

MPS Parameters	Exercise (n = 129)		Dipyridamole (n = 224)	
	r	*p*	r	*p*
SSS	−0.252	0.004	−0.234	< 0.001
TID	−0.099	0.265	−0.120	0.073
Rest				
LVEDV	−0.156	0.078	−0.152	0.023
LVESV	−0.174	0.049	−0.152	0.023
LVEF	0.192	0.029	0.152	0.022
Post-stress				
LVEDV	−0.154	0.081	−0.161	0.015
LVESV	−0.190	0.030	−0.172	0.009
LVEF	0.204	0.020	0.171	0.010

SSS = summed stress score, TID = transient ischemic dilatation, LVEDV = left ventricular end-diastolic volume, LVESV = left ventricular end-systolic volume, LVEF = left ventricular ejection fraction

dipyridamole EI was correlated with all scintigraphic parameters, except for TID.

DISCUSSION

This study shows that EI is correlated with most, if not all, of the MPS parameters with different levels of association depending on the patient's sex and the type of stress employed. The direction of relationship of EI with these parameters is similar. More spherical LV is correlated with more severe perfusion defects, larger LV cavity volumes and poorer LV systolic function.

The normal LV cavity is elliptical in shape (8). Ventricular remodelling is a compensatory hypertrophy and dilatation to maintain cardiac output, and involves changes in chamber dimensions, wall thickness, and shape (9). This is a dynamic process triggered by an imbalance between myocardial wall stress and the normal restraining forces exerted by the collagen matrix (9). This leads to a cascade of events that ultimately result in progressive LV dilatation (9). Since the material properties of the myocardium and the distending stress within the ventricular chamber determine its configuration, changes in LV shape may ensue (10).

Studies have shown that during LV remodelling, there is disproportionately increased short-axis diameter relative to the long axis, causing the LV shape to change from an ellipse to a sphere (9,11). Eccentricity in mathematics is a parameter to measure how much a conic section deviates from being circular (12). The value can vary from 0 to 1, with 0 being a sphere and 1 being a line (6). Determination of LV EI using AutoQuant® follows the same concept (6). Hence, this value termed as EI, evaluates the deviation of the LV from its normal elliptical shape.

The LV dynamics is affected by the chamber shape since it is a determinant of mechanical wall stress (9,10). A spherical LV causes an increase in LV end-diastolic wall stress, reducing its contractile efficiency (9). A spherical LV can be considered to be operating in a mechanical disadvantage (10). Therefore, reduced LV function may be seen in LV with low EI, as shown in this study. The difference in the strength of correlation of EI with LVEDV, LVESV, and LVEF between the findings of Gimelli et al. (13) and this research may be attributed to the 16-frame per cardiac cycle of gated SPECT acquisition in the former in contrast to the 8-frame per cardiac cycle used in the latter. Sixteen frame per cardiac cycle gated SPECT obtains significantly different LVEDV, LVESV and LVEF values when compared to 8-frame per cardiac cycle acquisition (14).

Several literatures documented the association between LV shape and the presence of LV myocardial ischemia. More abnormal EI values were correlated with more impaired measures of myocardial perfusion heterogeneity, independent on resting LV systolic function (7). Presence of myocardial ischemia on MPS and of abnormal values of post-stress LV EI among patients who underwent stress test were found to be independent predictors of the presence of multivessel CAD (13). However, change in LV shape is not specific for CAD as it can be found in cardiomyopathy and valvular heart diseases (9).

Interestingly, our study demonstrated that EI at rest was only correlated with the other scintigraphic parameters among male patients. This may be explained by the findings of Medrano-Gracia et al. (14) that a significant difference in LV shape at end-diastole between males and females exists. Using cardiac magnetic resonance imaging (CMR), they found that males have less spherical LV (14). This would mean that a greater increase in the short-axis diameter relative to the long-axis diameter may be a more sensitive indicator of LV remodelling in the male population.

Although our study established a significant correlation of EI with some of the MPS parameters, the level of association was not as strong when compared to the findings of Gimelli et al. (7). This may be explained by the differences in the gamma camera and image reconstruction algorithm that were used. Our images were acquired using a sodium iodide (NaI)-based detector, while those of Gimelli et al. (7) utilized a CZT detector. The latter was known to provide higher image resolution and better counting statistics (15,16). This was further supported in literature comparing the use of SPECT

NaI to CZT camera in equilibrium radionuclide angiography to determine LV function (16). It was observed that there was significant difference in the estimation of LVEDV, and consequently LVEF, between the two (17). However, the accuracy of the obtained values for both detectors was not ascertained by comparing it to a gold standard. Another difference is their use of an iterative reconstruction algorithm in contrast to our study, which employed filtered back projection in processing the images. In literature comparing the two methods, LVEDV, LVESV, and LVEF were found to be significantly different (18).

Majority of the available literatures on LV geometry used various indices derived from 2D echocardiography measurements. However, in clinical practice, quantification of LV shape is not routinely reported. CMR is currently considered the modality of choice in evaluating the LV geometry for certain conditions, but is not widely utilized and indicated particularly in most of the patients sent for MPS (19). A prospective study comparing the LV shape measurement determined using SPECT to a gold standard is recommended to determine their agreement and the former's diagnostic accuracy.

All patient data, including the MPS parameters, were collected from the Division's database. Re-processing of the images was not done, which should ideally be performed by a single technologist. This will eliminate the possibility of inter-operator variability that may affect the values of the measured MPS parameters, albeit a study by Akesson et al. (20) evaluating the variability in the quantitative analysis of MPS showed a high reproducibility between different operators.

CONCLUSION

The correlation of LV shape as characterized by EI, with LV myocardial perfusion, LV cavity volumes, and LV systolic function is shown in this study. These parameters are available with commonly used softwares for cardiac SPECT. Since the strength of the correlation among the study variables is not similar to the published literatures, further research to determine its possible prognostic value, independent of other MPS parameters, is recommended.

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