The prognostic value of stress/rest gated myocardial perfusion SPECT in patients with known or suspected coronary artery disease

Original Article

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ABSTRACT

Introduction: Gated myocardial perfusion SPECT has diagnostic and prognostic values in coronary artery disease (CAD). We tried to determine prognostic values of the left ventricular perfusion & functional indices as well as transient left ventricular dilation (TID) derived from gated myocardial perfusion SPECT.

Methods: 1820 patients who underwent gated myocardial perfusion SPECT (Gated SPECT) were studied. The summed stress score (SSS), summed rest score (SRS) and summed difference score (SDS) were calculated. Cardiac events considered as nonfatal myocardial infarction, cardiac death, Coronary Care Unit admission and revascularization. Mean follow-up period after Gated SPECT was 23±10 months.

Results: 1599 patients didn't have any events, while from remaining 221, six patients had an acute MI, 90 patients had CCU admission, 42 patients underwent revascularization and 84 patients died. There was statistically significant difference in the cardiac events based on age, sex, SSS, SRS, SDS, TPD, TID, left ventricular volumes and LVEF. Multivariable Cox regression analysis showed the most and independent predictors of cardiac events are age (P=0.001), SSS (P=0.01) and history of coronary angiography (CA) (P=0.01). History of CA had a greater than 4.4 fold increased incidence of a cardiac event. With increase in SSS for 1 score, 1.4 times and with increase one year in age 1.4 fold increase in future cardiac event were seen.

Conclusion: There was a strong association between future cardiac events and clinical history, SSS, SRS, SDS, TPD, TID, left ventricular volumes and LVEF. The most and independent predictors were age, SSS and history of CA.

Key words: Myocardial perfusion SPECT; Gated SPECT; Cardiac events; Prognosis; Ejection fraction; Transient ischemic dilation

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INTRODUCTION

In the literature, there is some information about the important diagnostic and prognostic values for gated myocardial perfusion single photon emission computed tomography (SPECT) [1-6]. A normal myocardial perfusion SPECT has been shown to be predictive of a very low risk patients with an annual cardiac event rates of less than 1% [7]. Different radiotracers such as Tl-201, Technetium 99m-sestamibi and Tc99m-tetrofosmine were used for myocardial perfusion imaging. So there are different protocols for stress and rest phases imaging. However different studies showed prognostic impact of perfusion findings in this imaging [1-7]. The extent and severity of perfusion abnormalities is superior to clinical and electrocardiographic (ECG) data in risk-stratifying of patients [8, 9]. Using gating techniques, gated myocardial perfusion SPECT (Gated SPECT) could assess simultaneous assessment of myocardial perfusion and left ventricular (LV) function [8]. LV systolic function is a strong predictor of cardiac events in patients with coronary artery disease (CAD) [8, 10]. However few studies reported prognostic value for left ventricular ejection fraction and end-systolic volume derived from Gated SPECT. Data are limited and many reports are only about the perfusion indices [7]. On the other hand a little information was in the literature about the prognostic value of the transient left ventricular dilation (TID) on post-stress images as compared to the rest phase images [7, 11].

The objective of this study was to evaluate cardiac events in a large group of patients who underwent Tc9mm-sestamibi Dipyridamole stress/rest gated myocardial perfusion SPECT. We tried to determine prognostic values (in addition to clinical history) of the perfusion indices, left ventricular functional indices as well as TID derived from gated myocardial perfusion SPECT.

METHODS

Patients

2000 consecutive patients who underwent two-day dipyridamole stress/rest Tc-99m sestamibi gated myocardial perfusion SPECT (Gated SPECT) were studied. Patients who had a revascularization procedure within 60 days after Gated SPECT as well as patients with no cooperation for follow-up were excluded. 180 patients were excluded from the study. Complete follow-up was performed for 1820 patients. Thus 1820 (751 male; 41.3% & 1069 female: 58.7%, mean age 59.7±12.1) were studied. The study was approved with local ethical committee.

Gated myocardial perfusion SPECT

All patients underwent a 2-day protocol Dipyridamole Stress/Rest Tc99m-Sestamibi gated myocardial perfusion SPECT. For stress phase study, 740-925 MBq Tc99m-sestamibi was injected intravenously 4 min after infusion the dipyridamole. 90 minutes later, stress Gated SPECT images were acquired. Another day, rest Gated SPECT was performed 90 min after intravenous injection of 740-925 MBq Tc99m-sestamibi [9]. Gated SPECT was performed using a dual-head gamma-camera in the 90°-setting (Dual-Head Variable-Angle E.CAM; Siemens) equipped with high-resolution, low-energy collimators. Imaging was performed in the supine position. From RAO 45˚ to LPO 45˚, thirty two views over an 180˚ orbit were obtained in a step-and shoot format (25 seconds per view and 8 frames per cardiac cycle with a 20% acceptance window). Energy window centered at 140 ±20 keV. The zoom factor was1.46 and the images were stored in a 64×64 matrix in the computer. Reconstruction was performed by filtered back projection using a Butterworth filter (cut-off value was 0.35 cycle/cm for gated data but 0.55 cycle/cm for ungated data, order =5) [9, 10].

Myocardial perfusion was assessed visually and semi-quantitatively. Two nuclear medicine specialist blinded to clinical data performed interpretation and scoring.

The 17-segment five point scoring system was used for semi-quantitative assessment of myocardial perfusion. The 17 segments were six basal, six mid-ventricular and four apical segments in short axis slices and one additional mid-ventricular apical slice in the vertical long axis [9-11]. Each segment was scored by consensus of 2 expert nuclear medicine specialist as 0, normal uptake; 1, mildly reduced uptake; 2, moderately reduced uptake; 3, severely reduced uptake; and 4, absent uptake. By adding the scores in the 17 segments in stress phase or rest phase, the summed stress score (SSS), and summed rest score (SRS) were calculated and then summed difference score defined as SDS=SSS-SRS [12-15]. Using QPS software (Quantitative Perfusion SPECT) total perfusion deficit in both stress and rest phase images as well as transient left ventricular dilation ratio (TID ratio) were calculated. Transient ventricular dilation is larger left ventricle in the stress images (post-stress images) as compared to the rest phase images. TID ratio is ratio of LV cavity size in the post-stress images by LV cavity size in the rest phase images. Cedars Sinai Quantitative Gated SPECT (QGS) software [15] was used for automatic calculation of left ventricular ejection fraction (LVEF), end-diastolic volume (EDV) and end-systolic volume (ESV) in both stress (SEF, SEDV and SESV) and rest phases (REF, REDV, EESV). Difference in LVEF, EDV, and ESV between the gated stress and rest phase images was calculated as ΔEF=SEF-REF, ΔEDV=Stress EDV-Rest EDV and ΔESV=Stress ESV-Rest ESV. Heart rate was recorded during stress imaging acquisition as well as during rest

imaging acquisition while patient was under gamma camera.

Follow-up

Follow-up was performed by telephone or direct interviews. A review of hospital records, and death certificates was performed. Cardiac events considered as nonfatal myocardial infarction (MI), cardiac death (CD), Coronary Care Unit (CCU) admission and revascularization (Coronary artery bypass graft: CABG and Percutaneous Coronary Intervention: PCI). Mean follow-up period after Gated SPECT was 23±10 months (between 6 months and 43 months).

Statistical analysis

All analyses were done using SPSS 20 software. Continuous variables were described as mean ± SD. Descriptive statistics, Chi-square analysis testing, and Students t test were used to assess associations between the various clinical history, perfusion indices, LV functional indices and TID ratio variables. In the end of analysis. Cox Regression Analysis was performed. A P value of less than 0.05 was considered statistically significant.

RESULTS

Patients' characteristics

From 1820 patients, 898, 261, 538, and 720 patients had history of hypertension, smoking, Diabetes mellitus (DM) and hyperlipidemia respectively. 1311 patients had history of chest pain, while 180 patients as well as 135 patients had history of CCU admission and MI respectively. 513 patients had history of coronary angiography (CA) while 250 and 104 patients had history of CABG and PCI respectively. Nine patients had history of pulmonary edema.

Follow-up

1599 patients didn't have any events, while from rest 221 patients, 6 patients had an acute MI, 90 patients had CCU admission with diagnosis of unstable angina, 42 patients underwent revascularization and 84 patients died. From 84 deaths, 16 patients had non-cardiac death, 19 cardiac deaths and in 49 patients the etiology of death was unknown. Etiology of cardiac death in 18 patients was fatal MI and in one patient was fatal arrhythmia.

Gated myocardial perfusion SPECT results

From 1820 patients, 1203, 310, 72 and 197 patients had normal myocardial perfusion SPECT, reversible defects, fixed defects and Fixed defects+reversible defects respectively in their myocardial perfusion SPECT. SSS, SRS and SDS were 3.43±6.09, 2.27±5.05 and 1.36 ±2.67 respectively. Table 1 showed other perfusion and left ventricular functional indices in the stress and rest phases.

Table 1: Perfusion and functional indices in the stress and rest gated myocardial perfusion SPECT (TPD: total perfusion deficit, EDV: end-diastolic volume, ESV: end-systolic volume, LVEF: left ventricular ejection fraction, TID: Transient left ventricular dilation, HR: hear rate).

Variable	Min	Max	Mean	SD
Stress TPD (%)	0.00	56.00	6.60	9.38
Rest TPD (%)	0.00	55.00	5.55	8.78
Stress EDV	13.00	319	62.37	33.57
Rest EDV	9.00	294	64.09	32.64
Stress ESV	0.00	218	22.78	27.28
Rest ESV	0.00	219	23.81	29.52
Stress LVEF	18.00	100	70.94	17.94
Rest LVEF	18.00	100	69.95	17.35
TID ratio	0.36	1.82	1.01	0.16
Stress HR	40.00	132	73.23	13.45
Rest HR	40.00	141	69.33	13.17

Relationship between patients' characteristics and cardiac events

Table 2 showed patients' characteristics with and without cardiac events.

Relationship of gated SPECT findings and cardiac events

Table 3 showed perfusion and functional indices derived from patients' gated SPECT with and without cardiac events.

Cox regression analysis

For this analysis, all variables that had statistically significant difference between patients with event and no event were considered (Table 4). From all variables, age, SSS and history of CA were independent predicting variables of cardiac events.

DISCUSSION

We tried to further explore the potential of perfusion and functional data derived from Dipyridamole stress/rest gated myocardial perfusion imaging in predicting subsequent cardiac events. We found that abnormal perfusion scan as well as LV functional indices could predict an increased incidence of cardiac events. Patients with abnormal Dipyridamole stress/rest gated myocardial perfusion SPECT have more risk of cardiac events in the future. Gated functional indices including the EDV, ESV and LVEF had a significant role in predicting the future cardiac events. There was statistically significant difference in the cardiac events based on age, sex, SSS, SRS, SDS, TPD, TID, left ventricular volumes and LVEF.

Table 2: Patients' characteristics (patient's history before the myocardial perfusion SPECT) with and without cardiac events (MI: myocardial infarction; CA: Coronary angiography, PCI: Percutaneous Coronary Intervention, CABG: Coronary artery bypasses graft).

Variable		Frequency of cardiac event in follow-up (%)	P value
Sex	Male	15.3%	0.001
	Female	9.6%	
History of MI	Yes	29.9%	0.001
	No	10.6%	
Hypertension	Yes	13.5%	0.060
	No	10.6%	
Smoking	Yes	18.4%	0.001
	No	10.9%	
Diabetes Mellitus	Yes	13.6%	0.180
	No	11.3%	
Hyperlipidemia	Yes	12.6%	0.500
	No	11.6%	
History of CA	Yes	16.4%	0.001
	No	10.3%	
History of PCI	Yes	17.5%	0.080
	No	11.7%	
History of CABG	Yes	18.8%	0.001
	No	10.9%	
History of pulmonary edema	Yes	55.6%	0.002
	No	11.8%	

Table 3: Perfusion and functional indices derived from patients' gated SPECT with and without cardiac events. (SSS: Summed stress score; SRS: summed rest score, SDS: Summed difference score, TPD: Total perfusion deficit, EDV: end-diastolic volume, ESV: end-systolic volume, LVEF: left ventricular ejection fraction, TID: Transient left ventricular dilation, HR: hear rate, FU: Follow-up).

Variable	Patients with cardiac event in FU	Patients without cardiac event in FU	P value
age	68.2±12.6	58.5±11.6	0.001
SSS	8.2±5.5	3.2±5.7	0.001
SRS	3.5±6.7	2.1±4.7	0.003
SDS	2±3.7	1.3±2.5	0.005
Stress TPD	6.2±8.7	1.4±13.7	0.001
Rest TPD	9.5±13.3	5.2±8.1	0.002
Stress EDV	69.3±45	61.4±31.6	0.010
Rest EDV	68.5±41	63.5±31.3	0.100
Stress ESV	29.8±37	21.8±25.5	0.003
Rest ESV	28.2±34	23.2±25.3	0.500
Stress LVEF	66.6±19.9	71.5±17.6	0.001
Rest LVEF	68±19.6	70.2±17	0.100
Stress HR	72.1±14.5	73.4±13.3	0.260
Rest HR	68.3±15.6	69.5±12.8	0.380
ΔEDV	0.84±12.30	-0.64±9.6	0.060
ΔESV	1.7±9.9	-0.35±7.2	0.001
ΔLVEF	-1.3±17.4	0.68±8	0.001
ΔTPD	2.4±4.5	1.3±4.2	0.020
ΔHR	3.6±9.9	3.7±8.9	0.900
TID ratio	1.01±0.16	1±0.16	0.200

Table 4: Cox Regression Analysis of different clinical, perfusion and left ventricular functional indices. (SSS: Summed stress score; SRS: summed rest score, SDS: Summed difference score, TPD: Total perfusion deficit, EDV: end-diastolic volume, ESV: end-systolic volume, LVEF: left ventricular ejection fraction, TID: Transient left ventricular dilation, MI: myocardial infarction; CA: Coronary angiography, PCI: Percutaneous Coronary Intervention, CABG: Coronary artery bypasses graft).

Variable	OR	95% CI	P value
Age	1.04	1.02-1.07	<0.001
SSS	1.06	0.99-1.14	0.09
SDS	1.01	0.92-1.11	0.84
Stress TPD	0.99	0.94-1.02	0.40
Stress EDV	0.99	0.95-1.01	0.37
Stress ESV	1.02	0.98-1.07	0.22
Stress LVEF	1.02	0.99-1.04	0.13
ΔEDV	0.99	0.96-1.04	0.96
ΔESV	0.98	0.93-1.04	0.63
ΔLVEF	0.98	0.93-1.02	0.28
ΔTPD	0.98	0.91-1.04	0.48
TID ratio	1.07	0.23-4.85	0.94
Hx of MI	0.58	0.29-1.13	0.11
Hx of CA	0.44	0.24-0.84	0.01
Hx of CABG	1.17	0.61-2.23	0.63
Hx of PCI	1.41	0.65-3.08	0.38
Hx of pulmonary edema	2.96	0.34-26.24	0.33
Hx of Hypertension	1.22	0.76-1.95	0.40
Smoking	0.79	0.43-1.47	0.46
Diabetes Mellitus	0.71	0.45-1.13	0.15
Angina	0.89	0.53-1.51	0.69

Considering the clinical background, history of previous MI, hypertension, pulmonary edema, smoking, DM, hyperlipidemia, CA, PCI, and CABG are predictors of future cardiac events. However, based on multivariable Cox regression analysis the most and independent predictors of cardiac events are age (P=0.001), SSS (P=0.01) and history of CA (P=0.01). Based on this analysis, a patient with history of CA had a greater than 4.4 fold increased incidence of a cardiac event. With 1 score increased in SSS, 1.4 times as well as with one year increase in patient's age 1.4 fold increased in future cardiac event were seen.

Compatible with our findings, Schinkel et al, reported incremental prognostic information for exercise Tc-99m tetrofosmin SPECT myocardial perfusion imaging [16]. Patients with normal MPS have a very low risk of cardiac event (usually less than 1%/year) [1, 7, 11, 17-19]. An abnormal scan was associated with significantly increased in cardiac death rate. Consistent with our findings they found that abnormal scan and a higher SSS score were related to increase future cardiac events [16].

In an abnormal scan, we can see reversible perfusion defects (ischemia) or fixed defects (MI). Fixed defects with several mechanisms may cause tachycardia resulting the sudden death. MI may be related to left ventricular dysfunction too. Reversible perfusion defects are susceptible for future ischemic cardiac events [16]. Several studies reported favorable outcome in patients with normal gated myocardial perfusion SPECT [1, 2, 4-6, 16, 17, 20-22].

Galassi et al, reported that patients with normal scans had an annual event rate of 1%, whereas those with abnormal had an annual event rate of 4.9% for hard cardiac events and 10.3% for soft cardiac events [1]. Many evidence demonstrated direct relationship between the extent and severity of perfusion abnormalities on MPS and increase in risk of cardiac events [22-24]. In our study, myocardial perfusion scores (SSS, SRS, SDS and TPD) were related to future cardiac events. Based on multivariable Cox regression analysis, SSS was an independent prognostic factor for cardiac events.

Different studies also demonstrated a significant impact of DM on cardiac risk and future cardiac events [25-27]. Hachamovitch et al. found that age, gender, DM, type of stress, and a history of known CAD are multivariable predictors of cardiac events in low-risk patients [17]. So previous clinical history of patients had a prognostic impact on subsequent cardiac events.

In addition, left ventricular functional indices derived from the gated myocardial perfusion imaging (EDV, ESV and LVEF) in addition to myocardial perfusion scores had prognostic information for future cardiac events. Sharir et al. showed that LVEF and ESV have incremental prognostic values over clinical and

myocardial perfusion indices in predicting cardiac death [28]. In J-ACCESS study by Nishimura et al, 12.42% 3-year death rate for males with ESV>60 ml and 16.06% 3-year death rate for females with ESV>40 ml was reported [25].

In our study in the stress phase, Gated SPECT images were obtained 90 minutes after Dipyridamole stress. We previously showed that LV function (such as LVEF) in the post-stress images may be different with resting ventricular function in some patients [14]. A diminished LVEF on the post-stress images is due to stress-induced ischemic myocardial stunning which is correlated with the presence of extensive perfusion abnormalities. So difference between EDV, ESV and LVEF between post-stress and rest images may have potential impact on prediction of cardiac events.

In our study, in addition to myocardial perfusion scores, LV function was also evaluated. In addition, we sought another variable derived from nongated myocardial perfusion tomograms as TID ratio. We noticed that TID ratio could have an impact on future cardiac events. Abidov et al. reported that automatically measured TID yielded incremental prognostic value over clinical variables in patients with otherwise normal MPS results. The patients with high TID ratio had a higher cardiac event rate compared with the other patients [11]. So transient LV dilation in stress images is associated with higher risk of cardiac event rates. Few studies evaluated the impact of TID on cardiac events. Two hypotheses were considered for underlying mechanisms of TID. Pseudodilation in the stress images by nonvisualization of the extensive amount of subendocardial myocardium secondary to diffuse and severe stress-induced sub-endocardial hypoperfusion (ischemia). Another mechanism is true LV dilation during stress secondary to stress-induced myocardial stunning resulting increase in ESV during LV contraction [11, 29].

CONCLUSION

Our findings are in agreement with prior information and show a strong association between future cardiac events and both different perfusion and functional indices derived from gated myocardial perfusion SPECT. Difference between EDV, ESV and LVEF in the post-stress and rest phase images may have prognostic potential. In addition, previous clinical history had a major impact. We also showed Transient LV dilation has an impact on prediction of future cardiac events. Based on multivariable Cox regression analysis the most and independent predictors of cardiac events were age, SSS and history of CA.

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