A Comparison of Myocardial Perfusion Gated SPECT Studies Obtained at Rest and after Stress

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Key Words

Myocardial perfusion imaging · Gated single-photon emission tomography · Post-stress stunning

Abstract

Objective: To perform a comparison between post-stress and rest gated single-photon emission computer tomography (SPECT) myocardial perfusion imaging (MPI) studies to assess post-stress stunning and the variables underlying this phenomenon. **Subjects and Methods:** This was a prospective study of 318 consecutive adult patients undergoing stress and rest gated SPECT using a 2-day ^{99m}Tc-tetrofosmin protocol. Bruce protocol treadmill stress (n = 93) or i.v. dipyridamole pharmacologic stress (n = 225) were used as stressors. Ejection fractions (EF) and left ventricular (LV) end-diastolic (EDV) and end-systolic volumes (ESV) were calculated using the Cedars Sinai Quantitative Gated SPECT software. Perfusion defects were visually scored using a 20-segment model to obtain summed stress scores. Statistical analysis was performed by applying paired t test and multi-regression. Statistically significant (p < 0.05) paired differences between post-stress and rest EF and ESV and type of stressing were noted. **Results:** Analysis of patient groups based on the type of stress showed significantly low EF on post-stress studies for both treadmill and dipyridamole stressing and also significantly high ESV on post-stress stud-

ies for dipyridamole. Multi-regression analysis using differences in post-stress and rest EF, EDV and ESV as dependent and summed stress scores, type of stress, delay time, previous myocardial infarction and size of LV as independent variables showed statistically significant associations between high summed stress scores (>13) and size of post-stress LV for EDV and ESV differences. High volumes were noted on post-stress studies. The magnitudes of the observed differences were well within the reproducibility of LV volume calculations. **Conclusions:** Patients showing stunning had significant ischemia or a dilated LV. The stunning manifested as high EDV and ESV differences. The magnitude of the differences observed in EF and LV volumes were not clinically significant.

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Introduction

Myocardial perfusion imaging (MPI) studies are among the most common investigations performed for the diagnosis, evaluation of treatment response and prognosis of ischemic heart disease. Gated single-photon emission computer tomography (GSPECT) using ^{99m}Tc-radiopharmaceuticals has become the procedure of choice for MPI since it provides functional and perfusion assessment simultaneously. The functional aspects of a

GSPECT study derive from analysis of the myocardial wall motion at the time of imaging. By contrast, the perfusion study reflects the distribution of blood to the myocardium at the time of injection. All other factors being constant, rest and post-stress studies should ideally provide the same cardiac functional parameters in contrast to the perfusion assessment.

Some gated MPI studies have pointed to a phenomenon termed 'transient post-stress stunning'. This may lead to an underestimation of quantitative functional parameters from post-stress studies [1–4]. However, no firm conclusion has been drawn on post-stress stunning and its significance and implications for patient management. Similarly, factors which may be causing or contributing to this phenomenon, such as type of stress, extent of ischemia and previous myocardial infarction (MI), have not been investigated thoroughly.

The aims of this study were to compare post-stress and rest quantitative GSPECT functional parameters [ejection fraction (EF), end-diastolic volume (EDV) and end-systolic volume (ESV)] in a patient population referred to evaluate ischemic heart disease by GSPECT. Statistically significant lower cardiac function parameters on post-stress study would support the transient stunning hypothesis and allow a further study into the impact of variables such as the severity of ischemic heart disease (as determined by perfusion defects), type of stress, previous episodes of MI, gender and age on the transient post-stress stunning.

Subjects and Methods

This was a prospective consecutive case study. Each patient underwent a 2-day MPI protocol with stress imaging, usually followed by rest imaging. Our standard procedure was to first perform a stress study and, if normal, terminate the investigation. The study involved 318 patients. Of these, 93 were stressed by treadmill exercise according to the modified Bruce protocol, reaching at least 85% of the target heart rate ($220 - \text{age in years}$) or developing positive signs of ischemia (e.g. ECG changes, chest pain, blood pressure and heart rate changes), while 225 patients were stressed by i.v. infusion of dipyridamole (0.142 mg/kg/min while not exceeding 60 mg in total). The mean age of the patients was 55 ± 11 years. A dose of 740 MBq of ^{99m}Tc -tetrofosmin was injected at peak treadmill exercise and the stressing was terminated after a further 60 s. For pharmacological stress the radiopharmaceutical was injected 2–3 min after completion of the infusion. For the rest study, each patient was also injected with a dose of 740 MBq of ^{99m}Tc -tetrofosmin. The rest study was performed on average 6 days after the stress study.

Imaging was usually 60 min after injection of the radiopharmaceutical, using a dual-headed GE Millennium MG gamma

camera (GEMS, Milwaukee, Oreg., USA). Patients were imaged in the supine position. Image acquisition was performed over 101 degrees of rotation, which provides 202 degrees of projection data, in 72 projection data sets. The projections were acquired into a 64×64 matrix, with a zoom of 1.33 and a 20% symmetrical energy window around 140 keV. Gating was performed into 8 bins per (RR) ECG cycle. The acquisition time per projection was 25 s and 15 min in total.

Reconstruction was performed using filtered back projection techniques on a GE Genie P/R workstation (GEMS). A Butterworth filter with a cutoff frequency of 0.43 and power of 7 was used for all studies. The QGS program from Cedars Sinai was used to calculate EDV, ESV and evaluation of myocardial wall motion. The left ventricular ejection fraction (LVEF) is calculated as EDV minus ESV divided by EDV. The validation of LVEF calculations by QGS has been reported by numerous authors [5–7]. The QGS software package is known to produce physiologically high EFs for small hearts [8] and 8-frame RR gating produces EFs that are 4–5 percentage points lower than 16-frame gating.

The evaluation for possible ventricular perfusion defects was performed following the method of Berman and colleagues [9, 10]: the myocardium is divided into 20 segments, with each segment being visually assigned a score from 0 to 4, with 0 being normal. The summed stress score (SSS) is the sum of these 20 segment scores. Based upon previous prognostic work, the patients were divided into four SSS subgroups for evaluation of correlations between functional and perfusion deficits: $\text{SSS} < 4$ is considered normal while an SSS of 4–8 is considered mildly abnormal, an SSS of 9–13 moderately abnormal and an $\text{SSS} > 13$ severely abnormal [9, 10].

For evaluation of ventricular dysfunction the SPSS software package (version 11.0; SPSS Inc., Chicago, Ill., USA) was used to study correlations amongst the variables. The differences between stress and rest values of EF, EDV and ESV were investigated using a paired t test since the data consists of values from the same patient under two different situations (stress and rest). Multiple linear regression was used to study the effect of changes in the independent variables (age, SSS, history of previous MI, type of stress, LV dilatation, time between stress and rest studies and time from injection to imaging) on the dependent variables (EF, EDV and ESV).

Results

The mean delay time between the injection and start of imaging was 79 ± 27 min in stress and 83 ± 34 min in rest studies, the difference between these times was not statistically significant (paired t test: $t = -1.56$, $p = 0.12$).

Of the 318 cases studied, the pattern of myocardial perfusion was normal on both stress and rest images in 93, showed completely reversible perfusion defects in 115 patients, partially reversible perfusion defects in 61, mixed reversible and fixed perfusion defects in 17 and fixed perfusion defects or apparent scars in 32.

Table 1. Means, SD, paired t test p value, and number of patients for EF in type of stress against SSS

Groups	SSS				
	all	<4	4–8	9–13	>13
Total					
Stress	56 ± 14	62 ± 10	58 ± 12	46 ± 13	39 ± 14
Rest	57 ± 14	64 ± 11	59 ± 11	48 ± 13	41 ± 14
p value	0.000**	0.007**	0.124	0.053	0.059
n	318	157	68	59	34
Dipyridamole					
Stress	55 ± 15	63 ± 11	58 ± 12	45 ± 12	39 ± 15
Rest	57 ± 15	64 ± 11	60 ± 10	47 ± 13	41 ± 15
p value	0.001**	0.034*	0.119	0.168	0.185
n	225	103	49	44	29
Treadmill					
Stress	57 ± 12	61 ± 10	57 ± 12	47 ± 14	39 ± 5
Rest	59 ± 13	63 ± 11	57 ± 13	50 ± 15	43 ± 5
p value	0.018*	0.087	0.774	0.156	0.005**
n	93	54	19	15	5

* Differences were significant ($p < 0.05$) between post-stress and corresponding rest parameter in the same group.

** Differences were highly significant ($p < 0.01$) between post-stress and corresponding rest parameter in the same group.

The mean $\pm$ SD for both post-stress and rest studies in all patients, along with the subgroups based on the method of stressing, are shown for EF in table 1, EDV in table 2 and ESV in table 3. The paired differences between post-stress and rest EFs were statistically significant based on Student's paired t test for both stressing types. The paired ESV differences were statistically significant for the total and dipyridamole populations. The EF was high on rest studies and the ESV was large on post-stress studies.

In the SSS subgroups, the paired differences between rest and post-stress EFs and EDVs were significantly high in the rest studies for the SSS <4 group for both the total and dipyridamole stressing populations. In the group with SSS >13, the EDV and ESV values were high for post-stress studies, and the ESV and EDV paired differences were highly significant for both the total and dipyridamole stressing populations.

The multiple linear regression analysis results are summarized in table 4. The SSS >13 subgroup showed statistically significant differences for EDV and ESV. A significant association with LV size on post-stress studies (dilated or normal size) was observed. Other significant paired differences previously noted in SSS subgroups based on type of stressing were not seen in this multiple regression analysis.

Discussion

Transient post-stress stunning during MPI has been described in recent years [11–13]; however, factors playing a role in this phenomenon and the implications are not well understood. Transient stunning has been attributed to stress-induced ischemia [11], circulating levels of catecholeamine [1], previous MI [14] and to the pharmacologic effects of dipyridamole [1]. Transient ischemic dilatation of the LV, despite being well documented, has no definite explanation. Possible explanations for transient ischemic dilatation include subendocardial hypoperfusion, systolic LV dysfunction and even actual physical dilatation with ischemia [3, 15, 16]. Both stunning and transient ischemic dilatation are associated with cardiac stress and ischemia and may impact on wall motion and quantitative measures as reported [3, 15, 16]. These phenomena would result in post-stress parameters being less reliable than rest measures for LV function and wall motion.

A 2-day protocol is preferable in investigating post-stress stunning since the duration of stunning is unknown. Some studies have suggested that it lasts for less than 1 h while others say it continues for days [1].

The means of the functional LV parameters on post-stress GSPECT, i.e. EF, EDV and ESV in all patients, sub-

Table 2. Means, SD, paired t test p value, and number of patients for EDV (ml) in type of stress against SSS

Groups	SSS				
	all	<4	4–8	9–13	>13
All					
Stress	93 ± 45	77 ± 27	84 ± 26	113 ± 48	150 ± 70
Rest	93 ± 42	79 ± 27	85 ± 25	112 ± 47	143 ± 65
p value	0.428	0.001**	0.407	0.558	0.023*
n	318	157	68	59	34
Dipyridamole					
Stress	94 ± 48	75 ± 27	80 ± 22	115 ± 47	153 ± 75
Rest	94 ± 44	77 ± 26	81 ± 20	114 ± 45	143 ± 70
p value	0.830	0.011*	0.587	0.500	0.004**
n	225	103	49	44	29
Treadmill					
Stress	90 ± 36	81 ± 28	92 ± 33	106 ± 51	135 ± 31
Rest	92 ± 37	84 ± 28	94 ± 35	105 ± 63	144 ± 29
p value	0.052	0.056	0.458	0.922	0.182
n	93	54	19	15	5

* Differences were significant ($p < 0.05$) between post-stress and corresponding rest parameter in the same group.

** Differences were highly significant ($p < 0.01$) between post-stress and corresponding rest parameter in the same group.

Table 3. Means, SD, paired t test p value, and number of patients for ESV (ml) in type of stress against SSS

Groups	SSS				
	all	<4	4–8	9–13	>13
All					
Stress	46 ± 38	31 ± 20	37 ± 19	66 ± 40	98 ± 62
Rest	45 ± 37	31 ± 20	37 ± 20	63 ± 41	91 ± 59
p value	0.019*	0.936	0.882	0.121	0.005**
n	318	157	68	59	34
Dipyridamole					
Stress	47 ± 41	30 ± 19	35 ± 16	67 ± 39	101 ± 66
Rest	46 ± 39	30 ± 19	34 ± 15	65 ± 39	93 ± 63
p value	0.009**	0.913	0.429	0.155	0.005**
n	225	103	49	44	29
Treadmill					
Stress	43 ± 30	34 ± 21	43 ± 26	61 ± 42	84 ± 25
Rest	42 ± 31	33 ± 21	44 ± 28	59 ± 47	83 ± 23
p value	0.789	0.752	0.483	0.502	0.888
n	93	54	19	15	5

* Differences were significant ($p < 0.05$) between post-stress and corresponding rest parameter in the same group.

** Differences were highly significant ($p < 0.01$) between post-stress and corresponding rest parameter in the same group.

Table 4. Results of the multiple linear regressions in p values

Parameter	Differences		
	EF	EDV	ESV
Type of stress (treadmill vs. dipyridamole)	0.746	0.108	0.433
History of previous MI	0.881	0.477	0.813
SSS			
<4 (n = 157)	–	–	–
4–8 (n = 68)	0.800	0.541	0.948
9–13 (n = 59)	0.634	0.703	0.736
>13 (n = 34)	0.481	0.015*	0.021*
LV dilatation	0.571	0.007**	0.043*
Age	0.537	0.984	0.464
Difference in days between stress and rest			
≤1 (n = 25)	–	–	–
1–2 (n = 29)	0.274	0.903	0.421
3–5 (n = 66)	0.111	0.095	0.095
6–7 (n = 150)	0.570	0.095	0.213
>7 (n = 48)	0.476	0.303	0.594
Time between stress injection and imaging, h			
<1 (n = 87)	–	–	–
1–1.5 (n = 141)	0.499	0.713	0.669
1.5–2 (n = 64)	0.146	0.917	0.342
>2 (n = 26)	0.154	0.364	0.387

* Differences were significant ($p < 0.05$) between post-stress and corresponding rest parameter in the same group.

** Differences were highly significant ($p < 0.01$) between post-stress and corresponding rest parameter in the same group.

groups based on SSS and on stress type are comparable to those previously reported [17, 18]. This suggests that any difference in our methodology and population had no significant effect. The expected trend of smaller EF and LV dilation with increasing SSS score was observed for all patient populations.

The paired t test results show significance for EF differences in both types of stressing while ESV changes are seen only in the dipyridamole group. The dipyridamole stress group shows significant differences in EDV and ESV only in the SSS <4 and SSS >13 subgroups. The treadmill stress group shows no significant differences in either EDV or ESV. Consequently, stunning phenomena may manifest differently in the same type of stress due to a different physiological response.

The findings of this study suggest that the subgroup of patients who have significant reversible ischemia will manifest LV dysfunction on post-stress MPI and GSPECT studies. These patients show marginal improvement on

rest studies. However, the reproducibility in calculating EF from ventricular volumes for patients is 5% and can thus account for these marginal improvements [19]. The EF paired differences have a 95% confidence interval of –28 to 24; thus we conclude that although pairing tests give statistically significant differences, these were clinically inconsequential in this study – in contrast to previously reported stunning phenomena results [11–13].

Transient LV dysfunction has diagnostic and prognostic utility [20]. It has been shown that this finding is associated with severe and extensive coronary artery disease. Some studies have even reported a higher specificity of this finding in the diagnosis of coronary artery disease than in multiple perfusion defects [21, 22]. The LV dilatation ratio has been found to be a reliable quantitative indicator of the severity of coronary artery disease [20]. Another study showed that the overall prognosis for patients with transitory LV changes on post-stress study is worse, as they show a high rate of cardiac events and mortality [23]. This study demonstrated a relationship between transient ischemic dilatation, severe perfusion defects and transient stunning. Our results indicate that transient stunning is clinically insignificant for this patient population and imaging protocol.

Conclusion

This study demonstrated post-stress stunning in an SSS subgroup of patients with severe ischemia and established an association between LV dysfunction and LV dilatation on post-stress studies. This finding was observed in all stress type subgroups. As many factors probably play a role in this phenomenon, a detailed analysis of variables by applying multiple linear regression is preferable in such studies. The observed stunning was not clinically significant in this study.

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