The prognostic significance of stress-only myocardial perfusion scan: A 5 year observational study

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Abstract

Objective: Stress-only myocardial perfusion imaging protocol has a prognostic value similar to that of a stress-rest protocol. The aim of the study was to assess stress myocardial perfusion by gated single photon emission computed tomography (SPECT) myocardial perfusion imaging (GSMPI) in patients who had a normal stress-only study 4.9 years (mean time) before and assess the possible influence of various factors on the results. **Subjects and Methods:** Three hundred and forty patients who had a normal stress-only study in the past, were reexamined with GSMPI after a mean period of 4.9 years. **Results:** Thirty out of 340 patients (8.8%) had an ischemic result on stress and were therefore submitted to a rest study. Differences between normal and pathological results across levels of potential prognostic factors (age, gender, diabetes mellitus, dyslipidemia, arterial hypertension, smoking and family history), symptoms, left ventricular ejection fraction (LVEF) on ultrasound (U/S), coronary angiography and pre-test probability did not prove statistically significant. On multivariable analysis patients with the combination of family history, diabetes mellitus and hypertension had a 10.7 times higher risk of a pathological scan than the patients without. **Discussion:** The information delivered by stress-only GSMPI proved to be a prognostically reliable method for follow-up of low and intermediate pre-test probability coronary artery disease (CAD) patients. **Conclusion:** The 91.2% of the patients with an initial normal stress-only GSMPI had a repeat normal stress only GSMPI after a mean period of 4.9 years. The combination of family history, diabetes mellitus and hypertension increases the risk of a pathological scan significantly.

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Introduction

Gated single photon emission computed tomography (SPECT) myocardial perfusion imaging (GSMPI) is an established way of evaluating myocardial ischemia [1-3]. Despite the fact that GSMPI evaluates relative perfusion of the myocardium, indirect indices acquired like deterioration of left ventricular ejection fraction (LVEF) and/or wall motion, transient ischemic dilatation of the left ventricle and increased lung uptake are significant in assessing presence or absence of coronary artery disease (CAD) [4, 5].

As technology advances new protocols of GSMPI have been applied. Stress-only protocol is now a widely used method of evaluating myocardial perfusion, providing that the stress study fulfills the criteria of normalcy [6]. The growing evidence that stress-only protocols have similar prognostic value to the stress-rest protocols has modified recent guidelines of the American Society of Nuclear Cardiology, so that if the stress imaging is normal, the rest imaging of GSMPI can be omitted [6].

A cohort of 340 patients, who had undergone a stress-only GSMPI 4.9 years (mean time) before, were reexamined with GSMPI. The aim of the study was to assess the influence of various factors in the evolution of myocardial perfusion as assessed by GSMPI in these patients.

Subjects and Methods

Three hundred and forty patients who were studied with stress-only GSMPI 4.9 years (mean time) before, were reexamined with GSMPI as outpatients in the Nuclear Medicine Department of Onassis Cardiac Surgery Center, the referrals made by cardiologists on clinical judgement. If stress scan proved normal, the rest scan was omitted after pati-

ents' informed consent. In this cohort, 175 patients were men and 165 were women, with a mean age 66.8 years (SD 9.7), 131 (38.5%) being over 70 years of age. Eighty-seven patients (25.6%) were diabetics, 116 patients (34.1%) had known CAD, 234 (68.8%) had hypertension, 243 (71.5%) dyslipidemia and 124 (36.5%) a positive family history for CAD. Out of the 116 patients with known CAD, 29 patients (8.5%) had received a coronary artery bypass graft surgery (CABG) before the initial stress-only study and 98 patients (28.8%) a percutaneous transluminal coronary angioplasty (PTCA), respectively. Eight patients (2.4%) had a pacemaker implantation. Eighty-nine patients (26.2%) were smokers and 56 (16.5%) ex-smokers. The majority of the reexamined patients were asymptomatic and GSMPI was performed for follow-up purposes, while in the remaining the most referred symptoms were atypical chest pain (25.6%) and dyspnea (9.1%).

Written informed consent was obtained from each patient to be submitted to the stress-only protocol and for the use of the data for scientific purposes. Concerning the type of test 195 patients (57.4%) were submitted to a stress test by the Bruce protocol, 141 patients (41.5%) were tested by adenosine, 3 (0.9%) by a modified Bruce protocol and only one (0.3%) by dobutamine. Stress study was performed first with technetium-99m (^{99m}Tc) compounds (sestamibi or tetrofosmin) on a GE Millenium VG5/Discovery camera.

Attenuation correction was not used. In dubious cases a prone study was acquired. The scan results were evaluated visually and semi-quantitatively by two independent nuclear medicine physicians blindly. The normal pattern was homogeneous uptake of the radiopharmaceutical throughout the left ventricular myocardium, with an LVEF>50% and without LV dilatation. A stress total perfusion deficit over 4% was considered pathological. If the stress images were interpreted as completely normal in terms of perfusion and left ventricular function, the patients did not undergo a rest imaging. Patients' follow-up was accomplished on clinical criteria.

Statistical analysis

Categorical variables were summarized through their absolute (N) and relative (%) frequencies. Continuous variables were summarized through their mean and standard deviation (SD).

Differences in the proportions between pathological and normal results were summarized across levels of potential prognostic factors (age, gender, diabetes mellitus, arterial hypertension, dyslipidemia, smoking, family history of heart disease), as well as across symptoms, LVEF on ultrasound (U/S), coronary angiography and pre-test probability. We used two-way tables showing absolute frequencies and % proportions of normal and pathological results. The statistical significance of the observed differences was assessed through Fisher's exact tests.

Potential factors of a pathological result were also investigated through univariable and multivariable logistic regression models. Analyses were performed using Stata version 14.2 (Stata Corp.,TX USA), P-values less than 0.05 were considered as indicating statistical significance.

Results

The study population comprised 340 patients with a mean age of 66.8 years (SD 9.7), who had a normal stress-only GSMPI study 4.9 years (mean time) before. These patients were submitted to a new stress GSMPI. Concerning Diamond-Forrester pre-test probability 296 patients (87.1%) had the value of 1 (low pre-test probability), 35 patients (10.3%) of 2 (intermediate) and 9 patients (2.6%) of 3 (high), respectively [7].

During stress test patients developed the following: ST changes (29.4% of the studied population), leg fatigue (25.3%), arrhythmias (15.3%), chest pain (7.6%) and dyspnea (2.9%), respectively. One patient developed headache and another flashing. Three hundred and ten patients (91.2%) had a normal stress-only scan, while only 30 (8.8%) had a pathological stress scan and were submitted to a rest GSMPI study.

Differences in the proportion between normal and pathological results across levels of potential prognostic factors (age, gender, diabetes mellitus, dyslipidemia, arterial hypertension, smoking and family history) as well as across symptoms, LVEF on U/S, coronary angiography, where available, and pre-test probability, were not statistically significant (P> 0.05) (Table 1). However, on patients with diabetes mellitus a P value of 0.078 was found, which is possibly a trend, but did not prove to be statistically significant.

Potential prognostic factors for a pathological result in the second GSMPI study, after a former normal stress-only scan 4.9 years (mean time) before, were also investigated through univariable and multivariable logistic regression models. Concerning univariable logistic regression analysis, the odds ratios of a pathological result across age, gender, smoking, diabetes mellitus, dyslipidemia, arterial hypertension, family history, symptoms, LVEF on U/S, coronary angiography results and pre-test probability were small and without statistical significance (Table 2).

We performed a multivariable logistic regression analysis, comparing the subgroup of patients who had diabetes mellitus combined with arterial hypertension and a family history of CAD with the subgroup of patients who had none of these risk factors. The group who had these three risk factors consisted of 19 patients, of whom 4 had a pathological scan (21.05%). The group without these risk factors consisted of 41 patients, of whom only one had a pathological scan (2.44%). On Fisher's exact test the difference in proportions of pathological results between the two groups was statistically significant (P-value 0.031) (Table 3). The odds ratio derived from logistic regression comparing the two groups over the probability of a pathological scan was 10.7 (95% CI 1.10-103.27) with a P value of 0.041 (Table 3). Despite statistical significance, these results should be interpreted with caution, since they are based on small numbers of cases (4/19 vs 1/41).

Discussion

Stress-only protocol of GSMPI has many advantages in terms of time and cost savings in a Nuclear Medicine Department, increasing thus patient throughput and reducing radiation

Table 1. *Proportions of pathological scan results by age, gender, diabetes mellitus, arterial hypertension, dyslipidemia, family history of heart disease, smoking, LVEF (echocardiogram), symptoms, coronary angiography and pre-test probability.*

	Normal scan N (%)	Pathological scan N (%)	Overall N (%)	P-value
Age				**0.563**
<70	192 (91.9)	17 (8.1)	209 (100.0)	
70+	118 (90.1)	13 (9.9)	131 (100.0)	
Gender				**0.572**
Female	152 (92.1)	13 (7.9)	165 (100.0)	
Male	158 (90.3)	17 (9.7)	175 (100.0)	
Diabetes mellitus				**0.078**
No	235 (92.9)	18 (7.1)	253 (100.0)	
Yes	75 (86.2)	12 (13.8)	87 (100.0)	
Arterial hypertension				**0.412**
No	99 (93.4)	7 (6.6)	106 (100.0)	
Yes	211 (90.2)	23 (9.8)	234 (100.0)	
Dyslipidemia				**0.531**
No	87 (89.7)	10 (10.3)	97 (100.0)	
Yes	223 (91.8)	20 (8.2)	243 (100.0)	
Family history of heart disease				**0.432**
No	199 (92.1)	17 (7.9)	216 (100.0)	
Yes	111 (89.5)	13 (10.5)	124 (100.0)	
Smoking				**0.537**
Non smoker	179 (91.8)	16 (8.2)	195 (100.0)	
Smoker	82 (92.1)	7 (7.9)	89 (100.0)	
Exsmoker	49 (87.5)	7 (12.5)	56 (100.0)	
LVEF (echocardiogram)				**0.217**
No test	116 (90.6)	12 (9.4)	128 (100.0)	
>=55%	175 (92.6)	14 (7.4)	189 (100.0)	
<55%	19 (82.6)	4 (17.4)	189 (100.0)	

Symptoms				**0.398**
No symptoms	178 (89.4)	21 (10.6)	199 (100.0)	
Atypical chest pain	81 (93.1)	6 (6.9)	87 (100.0)	
Dyspnea	30 (96.8)	1 (3.2)	31 (100.0)	
Fatigue	11 (100.0)	0 (0.0)	11 (100.0)	
Palpitation	10 (83.3)	2 (16.7)	12 (100.0)	
Coronary angiography I				**0.150**
No angiography	176 (93.6)	12 (6.4)	188 (100.0)	
No CAD or LM<50% other coronaries<70%	36 (85.7)	6 (14.3)	42 (100.0)	
Occlusion LM>50% Other coronaries> 70%	98 (89.1)	12 (10.9)	110 (100.0)	
Coronary angiography II				**0.580**
No CAD or LM<50% Other coronaries<70%	36 (26.9)	6 (33.3)	42 (27.6)	
Occlusion LM>50% Other coronaries> 70%	98 (73.1)	12 (66.7)	110 (72.4)	
Pre-test probability				**0.799**
1	268 (90.5)	28 (9.5)	296 (100.0)	
2	33 (94.3)	2 (5.7)	35 (100.0)	
3	9 (100.0)	0 (0.0)	9 (100.0)	

Table 2. *Results from univariable logistic regression models for the risk of a pathological result.*

Factor	Odds Ratio	95% C.I.	P-value
Age			
<70*	1		
70+	1.24	(0.58, 2.65)	**0.572**
Gender			
Female*	1		
Male	1.26	(0.59, 2.68)	**0.552**
Diabetes mellitus			
No*	1		
Yes	2.09	(0.96, 4.54)	**0.063**
Arterial hypertension			
No*	1		
Yes	1.54	(0.64, 3.71)	**0.335**
Dyslipidemia			
No*	1		
Yes	0.78	(0.35, 1.73)	**0.543**
Family history of heart disease			
No*	1		
Yes	1.37	(0.64, 2.93)	**0.415**
Smoker			
Non smoker*	1		
Smoker	0.96	(0.38, 2.41)	**0.922**
Ex smoker	1.60	(0.62, 4.10)	**0.330**
LVEF (echocardiogram)			
No test*	1		
>=55%	0.77	(0.35, 1.73)	**0.532**
<55%	2.04	(0.59, 6.97)	**0.258**
Symptoms			
No symptoms*	1		
Atypical chest pain	0.63	(0.24, 1.61)	**0.334**
Dyspnea	0.28	(0.04, 2.18)	**0.225**
Palpitation	1.70	(0.35, 8.26)	**0.514**

(continued)

Coronary angiography			
No angiography*	1		
No CAD or lum. occl. LM<50% othercoron. <70%	2.44	(0.86, 6.94)	**0.093**
Occlusion LM >50%, other coronaries>70%	1.80	(0.78, 4.15)	**0.171**
Pre-test probability			
1	1		
2	0.58	(0.13, 2.55)	**0.471**
3**	0	0	**0**

**Reference group **Category "3" in Pre-test probability not shown because there were no pathological results*

Table 3. *Multivariable logistic regression analysis for the risk of a pathological result in patients with combined diabetes mellitus, hypertension and family history.*

	dm+htn+fh**		
Scan results	No N (%)	Yes N (%)	Total N (%)
Normal scan	40 (97.56)	15 (78.95)	55 (91.67)
Pathological scan	1 (2.44)	4 (21.05)	5 (8.33)
Total	41 (100.00)	19 (100.00)	60 (100.00)

Fisher's exact **P-value= 0.031**
**diabetes mellitus+hypertension+family history

Outcome variable: pathol (Scan results), n=60

Covariate	Odds Ratio	95% C.I.	**P-value**
dm+htn+fh			
No*	1		
Yes	10.667	(1.102, 103.271)	**0.041**

**Reference group*

burden of patients and personnel drastically [8]. In the framework of the International Atomic Energy Agency Nuclear Cardiology Protocols Study (INCAPS) a large registry of 7911 patients undergoing myocardial perfusion imaging in 308 laboratories in 65 countries showed that when stress-only protocol was used, a dose reduction by 80% was achieved (INCAPS) [9].

Since stress-only GSMPI is nowadays routinely applied, researchers have investigated its prognostic value by assessing the annual frequency of major adverse cardiac events (death, nonfatal myocardial infarct) and revascularization versus that of a stress-rest study. Many publications have compared prognostic value of stress-only protocol versus stress-rest protocol interms of hard cardiac events between the two groups. The results have shown that annual prognosis of normal stress-only GSMPI does not differ significantly from that of normal stress-rest GSMPI. As shown in various studies hard cardiac event rate (cardiac deaths, nonfatal infarcts) has been proven <1% on more than 20,000 patients, who received a stress-only myocardial perfusion imaging, a rate comparable to that of a normal combined stress-rest scan [10-17]. On a meta-analysis including 26,757 patients undergoing myocardial perfusion imaging and followed up for five years or more, a pooled negative predictive value was 91%, which allows identification of low-risk patients for CAD [18]. However, a better risk stratification for low risk CAD patients is obtained by CZT cameras rather than by NaI cameras [19].

In a cohort of 5890 Korean patients with typical or atypical chest pain it was found that aging and insignificant coronary artery stenosis (<70%) correlated strongly with long term hard cardiac events [20]. In particular, patients with insignificant coronary stenosis had a probability of major adverse cardiac events (death, nonfatal myocardial infarction), coronary revascularization, stroke and hospitalization due to heart failure of 3.5% to 7.8% in a five-year follow-up.

Concerning diabetes mellitus Giri et al. (2002) [21] found that two years after a normal myocardial perfusion scan the event rates were higher in diabetics than non-diabetics, since diabetes affects progression of CAD [22]. Acampa et al. (2020) found that two factors influence the warranty period of a myocardial perfusion scan, diabetic status and post stress LVEF [23, 24]. Caobelli et al. (2021) emphasizes on the prognostic significance of myocardial perfusion imaging, which when normal gives a warranty period over 5 years, with mortality rates similar to normal population (0.6%/year) [30].

We performed an observational study. In our cohort consisting of 340 reexamined cases with a normal GSMPI 4.9 years (mean time) before, 30 patients (8.8%) had an ischemic result on stress and were therefore submitted to a rest study. No hard cardiac event i.e. nonfatal infarct or revascularization was reported or noticed in our studied population.

Assessment of the observed differences in the proportions of pathological over normal stress GSMPIs showed that none of the studied potential risk factors (age, gender, diabetes mellitus, dyslipidemia, arterial hypertension, smoking and family history), nor symptoms, or LVEF on U/S, coronary angiography results and pre-test probability influenced the development of CAD to a significant degree, so to produce a positive myocardial perfusion scan. As far as diabetes mellitus is concerned which is an independent predicting factor of hard cardiac events (cardiac deaths/nonfatal infarcts) in patients with a normal stress scan [25-28], in our study the percentage of pathological new GSMPI studies was higher among diabetics than non-diabetics, however the difference, although suggestive was statistically non-significant (P=0.078). If the numbers of diabetic patients reexamined were higher, statistical significance might have been achieved.

As far as coronary angiography is concerned, in our cohort the presence of serious obstructive coronary disease did not produce a statistically significant difference in pathological results over cases with an insignificant or no obstructive disease or over cases without coronary angiography. This happened because the size of our sample was very small and although the pathological results on high coronary obstruction were twice as many as those on low or absent coronary obstruction (12 vs 6), statisticall significance could not be derived.

As far as pre-test probability is concerned, 90.5% of patients with low pre-test probability and 94.3% of patients with intermediate pre-test probability had a second normal scan after the elapse of 4.9 years (mean time). In our cohort the high pre-test probability group consisting only of 9 patients did not have any pathological results.

Concerning univariable logistic regression analysis for the risk of a pathological result, no statistically significant hazard ratio was found across the variables studied. On the contrary, on multivariable logistic regression analysis patients with a combination of diabetes mellitus, hypertension and family history of CAD had a 10.7 times higher risk (P=0.041) of having a pathological result over patients without. However, despite statistical significance, this result should be interpreted with caution, since it is based on small numbers of cases (4/19 vs 1/41).

The strong point of this paper is that 91.2% of the patients with an initial normal stress-only GSMPI had once more a normal stress-only study after a mean period of 4.9 years. Thirty patients (8.8%) of our cohort were risk stratified to a higher post-test probability for CAD and were treated by referring cardiologists accordingly. Stress-only GSMPI proves to be once again a prognostically reliable technique as a means to follow-up patients of low and intermediate probability for CAD [29]. The limitation of the study is the relatively restricted number of patients which may hinder statistical significance.

In conclusion, in a population of 340 reexamined individuals with an initial normal stress-only GSMPI the percentage of pathological new stress GSMPI, after a mean period of 4.9 years, was low (8.8%). Patients with a combination of diabetes mellitus, hypertension and family history of CAD had a 10.7 times higher risk of a pathological newer scan compared with those without, however larger studies are needed to confirm it.

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