

Prognosis of normal stress-only gated-SPECT myocardial perfusion imaging: a single center study

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Abstract It has been advocated that using the stress followed by rest protocol, if the stress images were normal there is no need of rest images, reducing radiation exposure and costs. Our purpose was to assess the prognosis of a group of patients with normal stress-only gated-SPECT myocardial perfusion imaging. This was retrospective study that includes 790 patients with normal myocardial stressonly perfusion gated SPECT images. Images were considered as normal if a homogeneous myocardial distribution of the tracer was associated with a normal ejection fraction. The mean follow-up was of 42.8 ± 13.3 months. The considered events were death of all causes, myocardial infarction and myocardial revascularization. During this period there were 85 events (10.8 %), including 57 deaths of all causes (67.1 %), 9 myocardial infarctions (10.6 %), 19 revascularizations (2.4 %). In the first year of follow-up there were 32 events (4.0 %) and excluding non cardiac deaths there were 8 events (1.0 %). Using Cox survival analysis, diabetes (HR = 2.2; CI = 1.4–3.4; $p \leq 0.0005$), the history of

coronary artery disease (CAD) (HR = 2.1; CI = 1.3–3.2; $p \leq 0.001$), age (HR = 1.0; CI = 1.0–1.0; $p \leq 0.05$) and type of stress protocol were related with events (exercise test vs. adenosine) (Exercise test: HR = 0.5; CI = 0.3–0.8; $p \leq 0.01$). In a multivariate analysis the independent predictors were diabetes, CAD and the type of stress protocol. Based on these results, normal stress-only images are associated with an excellent prognosis even in patients at higher risk, diabetics and patients with known CAD.

Keywords Gated-SPECT · Myocardial perfusion imaging · Normal stress-only images · Prognosis · Outcomes

Background

Coronary artery disease is a major cause of death all over the world. Risk assessment of this condition includes functional and anatomic evaluation. The functional status is defined by the extent and localization of ischemia and by ventricular function. The anatomic substrate is related with the presence, localization and extent of atherosclerotic plaques in the coronary tree. Myocardial perfusion is commonly assessed by ECG gated myocardial perfusion SPECT and with the ageing of the population and the increase number of individuals with risk of coronary artery disease (CAD) it is expected that the performance of these exams will increase.

The rate of events associated with normal images on gated-myocardial perfusion SPECT (G-SPECT MPI) was reported, in previous published studies, of less than 1 % per year [1, 2].

G-SPECT MPI with Tc-99m tracers is usually performed using one of the recommended protocols: one-day

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stress followed by rest images or rest followed by stress images or a two-day protocol. All of them require two separate injections of the tracer and a 4–5 h stay in the laboratory (one-day protocol) or two sets of images in consecutive days (two-day protocol) [3].

Having this in mind it has been advocated that using the stress followed by rest protocol, if the stress images were normal there is no need of rest images, reducing radiation exposure, costs and improving laboratory efficiency. There is, however, still some concerns related with the reliance of using only stress images to report a perfusion study as normal [4, 5].

Objective

The purpose of this study was to assess the prognosis of a group of patients with normal stress only G-SPECT MPI.

Methods

Population

This was retrospective cohort study that includes patients with normal myocardial stress-only perfusion gated SPECT images performed in Coimbra University Hospital, between January 1st 2007 and December 31st 2008. From 1725 perfusion studies performed in the mentioned period, 857 had normal stress results.

The studied patients were characterized in what refers age, gender, type of stress test, presence of diabetes, history of CAD: percutaneous coronary intervention (PCI), coronary artery by-pass graft surgery (CABG) or non revascularized disease.

This study was performed according to the national and local ethical standards.

Follow-up

The follow-up was performed by consulting the hospital registries of those with normal studies. The subsequent end-points were considered: death of all causes, cardiovascular death, myocardial infarction and myocardial revascularization. The follow-up was completed in 31st January of 2012 or until the occurrence of an end-point (mean follow-up = 42.8 ± 13.3). There were 67 patients lost for follow-up. The final analysed cohort was of 790 patients.

Performance of gated myocardial perfusion study

All patients were injected with 370–555 MBq (according to their weight) of Tc-99m tetrofosmin during peak

exercise or maximal pharmacologic vasodilation with adenosine. The images were performed using a dual-head camera (*Ventri*TM gamma camera), step and shoot acquisition, with 64 stops and a 180° arc from right anterior oblique to left anterior oblique. Non-attenuation corrected and ECG-gated transverse images were reconstructed with filtered back-projection. Images were considered normal if a summed stress score ≤ 1 , in the semi-quantitative analysis of the 17 segments proposed in the current guidelines, was associated with a normal ejection fraction ($\geq 50\%$) and with no segmental abnormalities.

Statistical analysis

Continuous variables were presented as mean \pm standard deviation and categorical variables were presented as a proportion.

Cox proportion hazards regression models were used to model the effects of covariates on the survival and to identify the independent predictors of outcome. Variables were selected in a stepwise forward manner with entry and retention in the multivariate model at a level of significance of 0.05. Kaplan–Meier statistics were used to calculate unadjusted survival. The Log-rank (Mantel-Cox) test was used to compare survival curves. All statistical analysis were performed using StatView 5.0.1, version for Macintosh and Windows, SAS Institute.

Results

The studied patients had a mean age of 63.1 ± 12.0 years, 240 patients (30.4 %) were aged between 61 and 74 years and 131 (16.6 %) were over 75 years. 52.2 % of the studied patients were females. 68.2 % of the exams were performed through adenosine stress test. The demographic characteristics of the group are shown in Table 1.

From those with CAD, 96 (12.2 %) were evaluated for a previous PCI, 61 had a history of CABG (7.7 %) and 33 had non revascularized disease (4.2 %).

The mean follow-up was of 42.8 ± 13.3 months with a minimum of 2 months and a maximum of 60 months. During this period there were 85 events (10.8 %), including 57 deaths of all causes (67.1 %), including 10

Table 1 Patient demographics

Age	63.1 \pm 12.0
Gender (male)	378 (47.8 %)
Diabetes	175 (22.1 %)
CAD	190 (24.1 %)
Exercise test	250 (31.6 %)

CAD coronary artery disease

Table 2 Differences between patients with and without events

	With events (85)	Without events (705)	<i>p</i>
Age	65.7 ± 10.6	62.8 ± 12.1	≤0.05
Gender (M)	55.3 % (47)	46.9 % (331)	ns
Diabetes	37.6 % (32)	20.3 % (143)	≤0.0005
ET	21.2 % (18)	32.6 % (232)	≤0.05
CAD	38.8 % (33)	22.3 % (157)	≤0.001
PCI	21.2 % (18)	11.1 (78)	≤0.05
CABG	7.1 % (6)	7.8 % (55)	ns
Non revasc. disease	10.6 % (9)	3.4 % (24)	≤0.01

ET exercise test, CAD coronary artery disease

Table 3 Cox univariate analysis concerning all events and cardiovascular events

	All events			Cardiovascular events		
	HR	CI	<i>p</i>	HR	CI	<i>p</i>
Age	1.0	1.0–1.0	≤0.05	1.1	0.9–1.0	ns
Gender (M)	1.4	0.9–2.2	ns	1.6	0.8–3.0	ns
Diabetes	2.2	1.4–3.4	≤0.0005	2.4	1.3–4.6	≤0.005
CAD	2.1	1.3–3.2	≤0.001	4.1	2.2–7.8	≤0.0001
PCI	2.0	1.2–3.4	≤0.01	3.9	2.0–7.8	≤0.0001
CABG	0.9	0.4–2.0	ns	1.4	0.5–3.4	ns
Non revasc. disease	3.0	1.5–6.0	≤0.005	3.3	1.1–8.5	≤0.05
ET	0.5	0.3–0.8	<0.01	0.7	0.4–1.5	ns

HR hazard ratio, CI confidence interval

cardiac deaths (11.8 %), 9 myocardial infarctions (10.6 %), 16 PCI (18.8 %) and 3 CABG (3.5 %). There were during the follow-up period 38 cardiovascular events (44.7 %). In the first year of follow-up there were 32 events (4.0 %) and excluding non cardiac deaths there were 8 events (1.0 %).

Table 2 shows the differences between the group of patients with and without events during the follow-up.

Patients with events and normal stress myocardial perfusion SPECT seemed to be older with a higher prevalence of diabetes and history of CAD.

Cox analysis was performed for each variable regarding all the events and cardiovascular events (Table 3). For the values related with the occurrence of events, Kaplan–Meier statistics were used to show the cumulative survival curves (Figs. 1, 2, 3).

According to Table 4, the presence of diabetes, the history of CAD and the capacity of performing an exercise test were all independent variables related with the occurrence of all events. Diabetes and history of CAD were independent variables related with cardiovascular events.

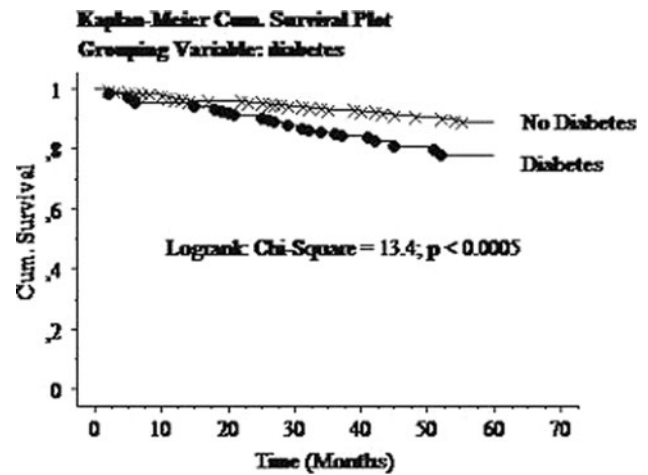


Fig. 1 Survival analysis comparing patients with and without diabetes

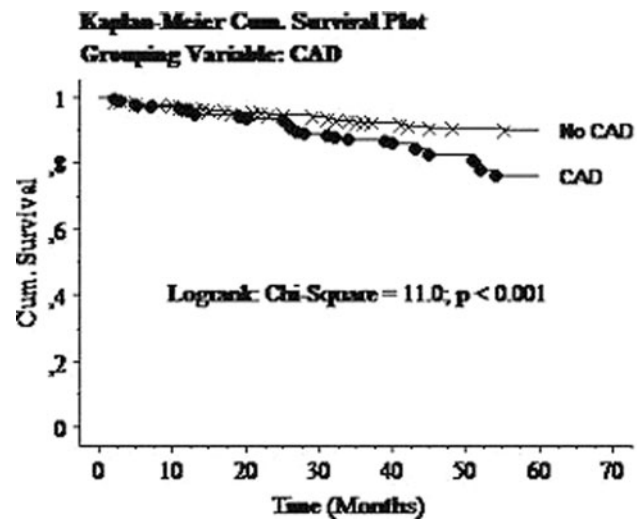


Fig. 2 Survival analysis comparing patients with a history of CAD with those with suspected disease

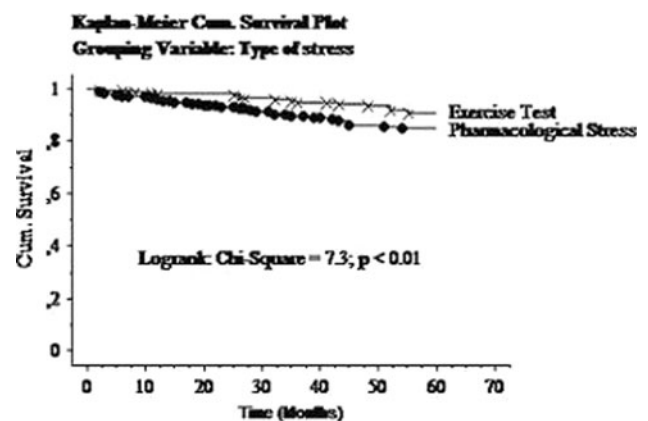


Fig. 3 Survival analysis comparing patients who were able to perform exercise with those where pharmacological stress was applied

Table 4 Cox multivariate analysis considering all events and cardiovascular events

	All events			Cardiovascular events		
	HR	CI	<i>p</i>	HR	CI	<i>p</i>
Age	1.0	1.0–1.0	ns	1.0	0.9–1.0	ns
Gender (M)	1.4	0.9–2.2	ns	1.4	0.8–2.8	ns
Diabetes	2.3	1.5–3.6	<0.0005	2.4	1.3–4.7	<0.01
CAD	1.9	1.2–3.0	<0.01	3.8	2.0–7.3	<0.0001
ET	0.5	0.3–0.9	<0.05			

HR hazard ratio, CI confidence interval

Discussion

Previous published studies had shown that a normal G-SPECT MPI is associated with an excellent short term prognosis. [1, 2, 6–8]. Recently a study published by Shinkel et al. was devoted to the very long outcome after a normal perfusion scan—15 years. Their conclusion was that patients with suspected or known CAD and normal exercise (99m)Tc-sestamibi myocardial perfusion SPECT have a favourable 15-year prognosis although the follow-up should be closer in patients with known CAD, and/or having clinical and exercise parameters indicating higher risk status [9].

Our results support the fact that even in high risk patients, a normal perfusion stress-only study is related with a low risk of cardiovascular events in the first year of follow-up. After that period, patients with diabetes, unable to exercise or with previous CAD were at a higher risk.

These results seemed to be similar to those obtained with stress followed by rest or rest followed by stress one-day or two-day protocols [1, 2, 6–9].

Recently it was advocated that a normal stress-only G-SPECT MPI had similar prognostic value compared with the classical protocols. Gibson et al. in 2003 published a study where patients with low to medium probability of disease referred to MPI due to chest pain were scheduled for a two-day protocol but if stress images were normal they won't come for the rest study. Their conclusion was that stress-only imaging in patients with low to medium probability for CAD was a safe, time- and cost-efficient imaging modality [4]. Two studies published in 2010, compare normal stress-only versus stress/rest or rest/stress MPI and both concluded that normal stress-only images had an excellent short-term prognosis similar to the classical protocols with Tc-99m tracers [10, 11].

The advantages of eliminating the rest images, in patients with a normal stress perfusion, allow the completion of the study in 90 min, which is more comfortable for the patient and more efficient for the laboratory turning the imaging modality more competitive but most important

it reduces radiation exposure. Radiation exposure is especially important in younger patients [5].

The present study was not performed with any attenuation correction technique. In 2013, there was a study published by Mathur et al. [12] that emphasizes the importance of attenuation correction in stress-only SPECT images. In this study, with attenuation correction, 83 % of the initial (without attenuation correction) abnormal images were re-classified as normal. Attenuation correction could further improve the identification of the low risk group of patients that won't require rest images.

There are some problems associated with stress-only images which are related with the possibility of under-diagnosis significant CAD. Balanced ischemia could be an issue in patients with left-main or three vessels disease [13]. ECG gating, attenuation correction and quantification of perfusion increase confidence in the interpretation of a normal study where a normal perfusion has to be associated with normal left ventricular ejection fraction and normal volumes. Even though, stress-only images, don't allow the observation or even the quantification of transient ischemic dilation (TID) which is an important prognostic marker usually associated with left ventricular stress dysfunction and severe ischemia [14–16].

Considering the limitations of stress-only images, there are studies that emphasize the importance of using stress-stress protocols based on the fact that Tc-99m redistribute. The dynamic “uptake-release” model seemed to be superior to the common “uptake-retention” model. Considering the dynamic model, a single injection of the tracer with images at 5 and 60 min will allow the identification of the true negative studies. Uptake is dependent on isotope availability and cellular health; retention is transient and redistribution occurs. An abnormal uptake of the tracer at 5 min reflects a delay in the delivery that is not seen if stress imaging is limited to 60 min images. This is a possibility to explore especially when dealing with high risk populations [17].

Reporting to the present study and its results, diabetes is an equivalent of CAD and even with a normal stress scan, patients with diabetes had more events than the rest of the population [2]. In the DIAD study a group of asymptomatic type 2 diabetics, with normal perfusion scans were followed for 3 years. 90 % remained normal and 10 % developed perfusion abnormalities [18, 19]. It is not clear if there is any advantage of screening asymptomatic patients with diabetes but in our population diabetes is associated with symptoms and/or known disease. A recent published study advocates the importance of the duration of the disease and also the type of therapy prescribed for risk stratification of these patients [20].

If we think about patients undergoing exercise test the association with younger age and a healthy status is

almost immediate and having this in mind it was not unexpected that these patients were at a lower risk of events. Rozanski published a study where the purpose was to compare the outcomes in patients with normal scans between those who performed images through exercise test and those who underwent adenosine stress. The conclusion points to a worse prognosis of the adenosine group comparable to the prognosis of patients that exercise very poorly [21].

The presence of CAD was also a strong predictor of events in our population. This is the highest risk group. In spite of normal scans it is common knowledge that these patients should be looked carefully for new symptoms or signs of instability [2, 22]. Almost all the events occurred in patients with non revascularized disease or patients referred for the perfusion study to evaluate PCI. These are, in fact, at higher risk of developing instability of their condition and where false negative results would probably be more frequent because of balanced ischemia. TID is also important in these patients for the possibility of representing severe ischemia. Even though, a normal perfusion reports a good short term prognosis according to our results.

As far as it concerns the age of the patients we found that it was a predictor of all events, but not an independent one. Co-morbidities, progression of disease by the influence of risk factors are all associated with age. Previous studies report a good prognosis for normal scans in the elderly (80 years or more) [23–25].

Limitations

Our study had a main limitation due to the fact that is a retrospective study and information about patient symptoms was not assessed. It was assumed that the guidelines and the appropriateness criteria were followed [3, 26]. It would be interesting to have information about risk factors to have a better categorization of our population. Also, in this type of study, hospital registries are not always clear about the cause of death causing sometimes constraints in dealing with data.

Conclusions

Having our results in mind we can conclude that normal stress-only images with Tc-99m Tetrafosmin are associated with excellent prognosis even patients at higher risk. Diabetic patients and patients with a history of CAD should be followed carefully looking for signs of progression of disease or instability.

Conflict of interest The authors declare they have no conflict of interest.

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