

Coronary arteriography in the diagnosis results and prognosis analysis of suspected coronary artery disease in patients with normal SPET myocardial perfusion imaging

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Abstract

Objective: Anatomic coronary artery disease (CAD) can be determined by coronary angiography (CAG) in patients with normal stress single photon emission tomography (SPET) myocardial perfusion imaging (MPI). Coronary angiography results of patients with negative exercise MPI and the prognosis of these patients (CAG-diagnosed CAD vs. non-CAD) were investigated in the current study. **Subjects and Methods:** Suspected CAD patients who had SPET-MPI and subsequent CAG studies were retrospectively reviewed from May 2002 to November 2006. Siemens Diacam SPET and Siemens Ecam SPET γ -cameras were used for the examination of rest/exercise technetium-99m methoxy isobutyl isonitrile (^{99m}Tc -MIBI) myocardial imaging. Coronary angiography was performed with Philips arura angiography machine by the standard Judkins method. **Results:** In all, 6598 patients underwent clinically indicated rest/exercise ^{99m}Tc -MIBI SPET-MPI, and 133 patients underwent CAG despite negative MPI. Thirty one patients were diagnosed with CAD by CAG. Most of these lesions (66%) were located in distal vessels and most of these patients (68%) had 1 vessel disease. Age ($P<0.01$), hypertension ($P<0.01$), typical angina pectoris ($P<0.01$), high pretest likelihood of CAD ($P<0.001$), exercise induced angina ($P<0.05$), positive exercise ECG ($P<0.01$), and transient enlargement of scintigraphic left ventricular size ($P<0.05$) were significantly different between non-CAD and CAD groups. After median follow-up time of 53 ± 18 months, annualized cardiac event rate was 0.9% and 0.2% in CAD and non-CAD group, respectively ($\chi^2=1.22$, $P=0.27$). **Conclusions:** In all, 23% of 133 patients in our study we confirmed anatomic CAD by CAG, despite negative findings in SPET-MPI. Several clinical, stress, and MPI findings could be potential predictors. However, similar to non-CAD group, the CAG diagnosed CAD patients who had negative ^{99m}Tc -MIBI SPET-MPI exercise test had a good prognosis with annualized cardiac event rate less than 1.0%.

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Introduction

In the last few decades, single-photon emission tomography myocardial perfusion imaging (SPET-MPI) with exercise or pharmacological stress, either with thallium-201 (^{201}Tl) or technetium-99m methoxy isobutyl isonitrile (^{99m}Tc -MIBI), has been widely used to determine important prognostic information for risk stratification and guide management of patients with suspected or known coronary artery disease (CAD) [1-3]. It has been well established that a normal SPET-MPI examination is associated with a very low risk of cardiac events [4]. A meta-analysis of 17 studies identified that the annualized cardiac event rate associated with a normal exercise SPET study was $< 1\%$ [5]. The sensitivity and specificity of SPET-MPI is 87% (95% CI, 86%-88%) and 64% (95% CI, 60%-68%), respectively [6]. Although its sensitivity is particularly high compared to specificity, in clinical practice, cases with significantly stenotic lesions in coronary angiography (CAG) are sometimes encountered in patients with negative stress SPET-MPI [7].

Previous studies have assessed the value of a normal ^{99m}Tc -MIBI scan [8-12]. However, the acquired data had some limitations, such as the use of planar studies, no results of CAG and the fact that a few studies reported the prognosis differences between CAG diagnosed CAD and non-CAD patients with normal stress MPI.

The results of CAG in suspected CAD patients with negative exercise stress ^{99m}Tc -MIBI SPET-MPI, the prognosis of these patients (CAG diagnosed CAD vs. non-CAD), and the lesion morphology characteristics of CAG diagnosed CAD patients with negative exercise ^{99m}Tc -MIBI SPET-MPI were investigated in the current study. Our study which mainly focuses on the prognosis of these patients, in an Orient population is original and related to previous published data.

Subjects and Methods

Subjects

Suspected CAD patients who had SPET-MPI and subsequent CAG studies were retrospectively reviewed from May 2002 to November 2006. Inclusion criteria were: suspected CAD patients who had SPET-MPI examinations showing normal findings and subsequently had invasive CAG. Patients received CAG based on their own will within the next three months. Exclusion criteria included patients with: a) valvular heart disease, b) previous myocardial infarction (MI), c) idiopathic cardiomyopathy, d) patients with a history of coronary arterial revascularization, and e) only resting MPI. This study was approved by the Ethical Committees of our hospitals.

^{99m}Tc-MIBI SPET-MPI

Single photon emission tomography (Siemens AG, Munich, Germany) was used for the examination of rest/exercise ^{99m}Tc-MIBI MPI. For preparation, beta-blockers and calcium channel antagonists were terminated 48 hours before testing and nitrates at least 6 hours before testing. Patients were asked to exercise on a treadmill under a standard Bruce protocol [13].

Treadmill exercise was terminated prior to exhaustion, at peak heart rate of more than 85% of the age-predicted maximum heart rate, or at the appearance of typical angina and/or a positive exercise electrocardiography (ECG) findings (sustained ventricular tachycardia), or at the appearance of hemodynamically significant supraventricular dysrhythmias, or if exertional hypotension developed. A dose of 740 MBq of ^{99m}Tc-MIBI was injected as a compact bolus at near maximal exercise with additional exercise continued for an additional 1 minute afterwards.

The exercise test was considered to be positive if there was a horizontal or down sloping ST segment depression of more than 1mm for 80µsec after the J point. Imaging was performed 60-90min after the exercise. On the next day, 60min after the intravenous injection of 740MBq ^{99m}Tc-MIBI, the patients were asked to eat a fatty meal to accelerate the hepatobiliary clearance of ^{99m}Tc-MIBI. The resting SPET was performed 90min after the ^{99m}Tc-MIBI injection.

A double-head SPET scintillation camera, (Siemens AG, Munich, Germany) with low-energy, high-resolution collimators was used (64×64 matrix, auto contour, 180° orbit with 32 steps of 25-30s each). For each patient, all stress images were interpreted separately in comparison with the same rest image, by two nuclear medicine specialists (J-W Y and Y-T W). Negative myocardial imaging was defined as no reversible or reduced solid radioactive anomalies or defects identified in each segment of both rest and stress myocardial imaging. At exercise stress myocardial imaging, the uptake ratio of lung and heart was calculated. Increased lung uptake was defined as the ratio more than 0.41. Scintigraphic left ventricular size was categorized subjectively as no enlargement, equivocal, or definite enlargement.

Coronary angiography

The pretest likelihood of CAD was calculated based on symptoms, age, and gender, and classified into low (<15%), moderate (15%-65%) and high (>66%) [14]. Cardiovascular angiography was performed with allura angiography machine (Philips, Best, the Netherlands) by the standard Judkins method [15]. The degree of coronary stenosis was estimated visually by two experienced cardiologists who were not aware of the results of SPET-MPI. When main coronary artery or its main branches had more than 50% stenosis, the patient was defined as having CAD.

The patients were then divided into three groups on the basis of the results of coronary angiography: group 1 (severe CAD) in the presence of more than 50% stenosis of the left coronary artery and/or three-vessels CAD or at least 90% stenosis of the proximal left anterior descending (LAD) artery; group 2 (moderate CAD) in the presence of more than 50% stenosis in one to two epicardial coronary arteries other than the proximal LAD; group 3 (no CAD) in the absence of stenoses of more than 50% [16].

According to the involvement of the left main coronary artery (LM), the LAD, the left circumflex coronary artery (LCX) and the right coronary artery (RCA), coronary artery lesions were divided into LM disease, single vessel disease (1VD), double vessel disease (2VD) and triple vessel disease (3VD). Lesions in LM, before the first diagonal branch or in the septal branch of LAD, before the obtuse marginal branch of LCX and before the first turning of RCA were defined as proximal lesion, otherwise, as distal lesions. The extent of coronary stenosis was divided into mild stenosis (50%~70%), moderate stenosis (70%~90%), and severe stenosis (>90%).

Follow-up

Follow-up data were obtained from telephone interviews, and hospital records. Cardiac events were: cardiac death or non-fatal MI. Follow-up ended when a cardiac event appeared. In patients with no cardiac events. The last follow-up time was considered as the endpoint of the study.

Statistical analysis

Continuous variables were expressed as the mean± standard deviation (M±SD). The unpaired Student's t-test (for normally distributed variables) or the Wilcoxon rank-sum test (for nonparametrically distributed variables) was used to conduct group comparison. Categorical variables were compared using Pearson chi-squared tests or Fisher's exact test for cell counts <6. Kaplan-Meier survival analysis was applied to evaluate the effects of different variables on survival rates, and differences between groups were compared using log-rank tests. All statistical calculations were performed using STATA (version 7.0, Stata Corp LP, College Station, Texas, USA). P values < 0.05 were considered statistically significant and only two-sided tests were conducted.

Results

Patients

In all, 6598 patients underwent clinically indicated rest/exercise test with ^{99m}Tc -MIBI SPET-MPI from May 2002 to November 2006, resulting positive findings in 3731 (57%) and negative/normal in 2867 (43%) patients. One hundred and thirty three (4.6%) patients had CAG, within the next three months in the negative ^{99m}Tc -MIBI SPET-MPI findings group while 567 (23%) patients in the positive group. In addition, of the 133 clinically suspected CAD patients with normal MPI scan, 19 (14%) patients had a very high pretest likelihood of CAD; 97 (73%) patients had a moderate pretest likelihood of CAD and 17 (13%) patients had a low pretest likelihood of CAD. Risk factors for CAD were: hypertension in 50 (38%) patients, hyperlipidemia in 16 (12%) patients, and diabetes mellitus in 13 patients (10%).

Exercise stress test characteristics

The exercise stress/test characteristics in the 133 clinically suspected CAD patients with normal scan results were as follows: resting heart rate (HR), 71 ± 11 /min; peak HR, 129 ± 22 /min; exercise duration, 8 ± 3 min; 17 patients had abnormal ECG; and 11 patients had angina.

Coronary angiography results

One hundred and thirty three clinically suspected CAD patients with normal ^{99m}Tc -MIBI SPET-MPI results subsequently had CAG within three months in our study. Of the 133 patients, 102 (77%) patients were negative in CAG while 31 (23%) patients were diagnosed as CAD with main coronary artery or main branches more than 50% stenosis (Figure 1a). Of the 31 CAD patients (the results of CAG and ^{99m}Tc -MIBI SPET-MPI in a typical 66 years old female patient were demonstrated in Figure 2), 7 patients had severe CAD (one with LM disease, one with LM and 3VD, two with proximal disease of LAD, and three with 3VD only) and 24 had moderate CAD (Figure 1b). In all, 44 vessels were involved including 2 (5%) LM, 25 (57%) LAD, 9 (20%) LCX, 8 (18%) RCA (Figure 1c). Fifteen (34%) had proximal disease and 29 (66%) had distal disease (Figure 1d). Twenty one (68%), 6 (19%) and 4 (13%) had 1VD, 2VD and 3VD, respectively (Figure 1e). Seventeen (55%), 12 (39%) and 2 (6%) had mild, moderate and severe stenosis, respectively (Figure 1f).

In all, 31 patients were diagnosed as CAD by CAG and 41 vessels were involved. a, One hundred and two (77%) patients were negative in CAG while 31 (23%) patients were diagnosed as CAD by CAG. b, Seven patients had severe CAD and 24 had moderate CAD. c, Forty four vessels were involved including 2 (5%) LM, 25 (57%) LAD, 9 (20%) LCX, 8 (18%) RCA. d, Fifteen (34%) had proximal disease and 29 (66%) had distal disease. e, Twenty one (68%), 6 (19%) and 4 (13%) patients had 1VD, 2VD and 3VD, respectively. f, Seventeen (55%), 12 (39%) and 2 (6%) patients had mild, moderate and severe stenosis, respectively.

Rest/stress ^{99m}Tc -MIBI SPET-MPI results

In 133 clinically suspected CAD patients the ^{99m}Tc -MIBI SPET-MPI resulted in no reversible or fixed reduction or defected tracer uptake. However, transient enlargement of scintigraphic left ventricular size was observed in 5 patients

and increase of lung uptake in 6 patients. When regarding CAG as a gold standard, ^{99m}Tc -MIBI SPET-MPI achieved a negative predictive value of 77% and a false negative of 23%

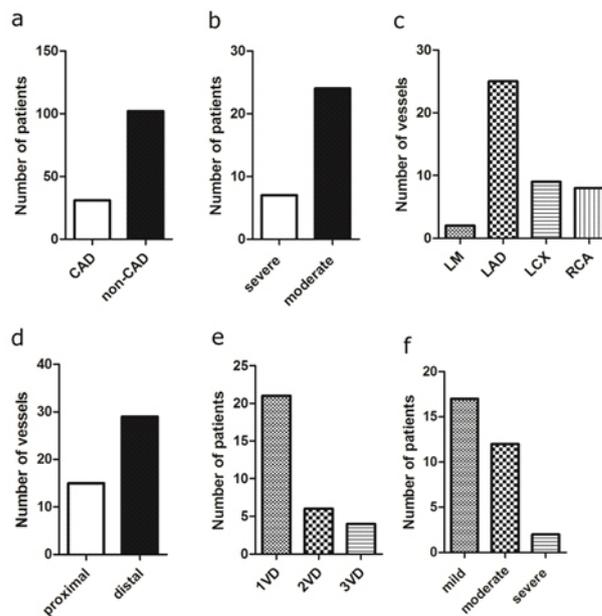


Figure 1. Results of CAG in clinically suspected CAD patients with normal ^{99m}Tc -MIBI SPET-MPI.

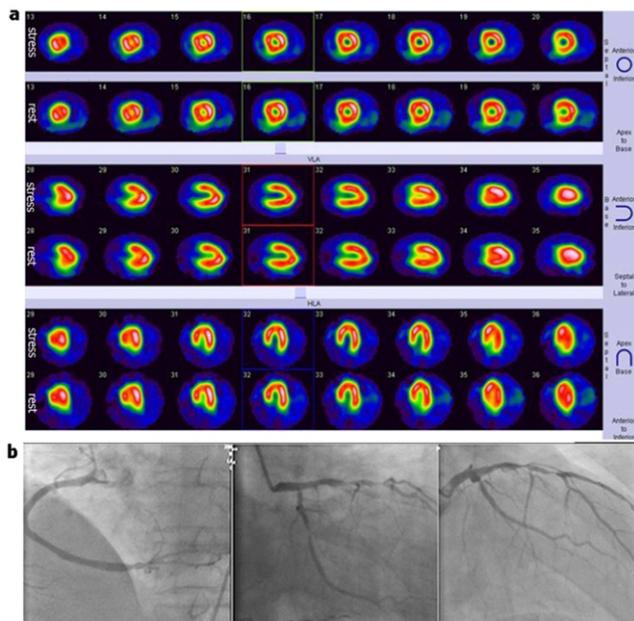


Figure 2. A 66 years old female with chest pain aggravated in the recent two months. The patient had paroxysmal chest pain and abnormal ECG for more than one year. **a**, Exercise/rest ^{99m}Tc -MIBI SPET-MPI demonstrated normal scintigraphic left ventricular size and homogeneous radioactivity distribution in each myocardial segment without perfusion defects. **b**, Coronary angiography showed in the LAD artery, 90% stenosis, in the LCX artery, 90% stenosis, the right coronary artery, widespread irregular lesions and in the PDA, total occlusion.

CAD vs. non-CAD patients with negative ^{99m}Tc -MIBI SPET-MPI

Of the 133 patients, 102 (77%) patients with both negative CAG and ^{99m}Tc -MIBI SPET-MPI were defined as the non-CAD group,

while 31 (23%) patients with positive CAG and negative ^{99m}Tc -MIBI SPET-MPI were defined as the CAD group. The CAD group when compared to the non-CAD group, had elder ages ($P<0.01$), higher rate of hypertension ($P<0.01$), higher rate of typical angina pectoris ($P<0.01$), higher rate of high pretest likelihood of CAD ($P<0.001$), higher rate of exercise induced angina ($P<0.05$), higher rate of positive exercise ECG finding ($P<0.01$), and higher rate of transient scintigraphic enlargement of the size of the left ventricle size ($P<0.05$). Other parameters achieved no significant statistical differences between the CAD group and the non-CAD group (Table 1).

Follow-up and prognosis

During follow-up, 5 patients died (1 in the CAD group and 4 in the non-CAD group) with a loss rate of 3%. Excluding 7 CAD patients who received percutaneous coronary intervention therapy in the follow up, finally 121 patients were included for the prognosis analysis comprising 23 patients in the CAD group and 98 patients in the non-CAD group. Median follow-up time was 53 ± 18 months (CAD group, 58 ± 19 months and non-CAD group, 52 ± 17 months). Cardiac events happened in 2 patients with non-fatal MI (1 in the CAD group and 1 in the non-CAD group). Annualized cardiac event rate was 0.9 % and 0.2 % in the CAD and the non-CAD group, respectively and no significant statistical differences were found ($\chi^2=1.22$, $P=0.27$). Kaplan-Meier survival curves of the two groups were illustrated in Figure 3.

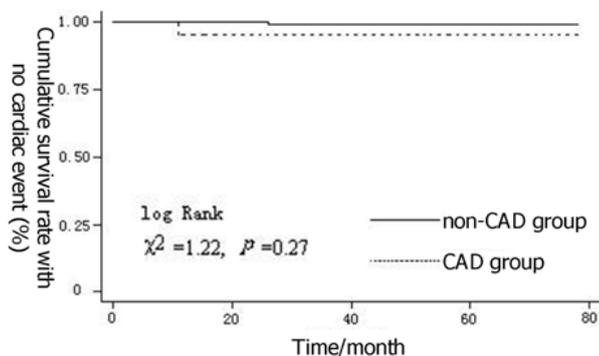


Figure 3. Kaplan-Meier survival curves in the two groups. Solid line: the non-CAD group; Dotted line: the CAD group.

Discussion

In the current study, the results of CAG in suspected CAD patients with negative exercise ^{99m}Tc -MIBI SPET-MPI were investigated and showed that 23% of the negative exercise ^{99m}Tc -MIBI SPET-MPI patients were diagnosed with CAD by CAG. Fujimoto et al. (2006) [17] investigated 58 consecutive patients who underwent CAG. These patients had normal stress SPET-MPI and significant stenotic lesions in CAG. The authors concluded that sufficient caution was needed in the interpretation of normal findings of stress myocardial perfusion SPET, when patients were elderly, had typical

anginal pain, or hypertension. According to these findings, we also found that age, typical anginal pain, and hypertension were significant predictors of false negative results in exercise ^{99m}Tc -MIBI SPET-MPI test. Recently, Nakanishi et al. (2015) [18] also reported that high-risk CAD was found in 42/580 patients (7.2%) undergoing CAG within 60 days after normal SPET-MPI scans. They also found high pretest probability of CAD, with mild/equivocal perfusion defects but on the contrary high transient ischemic dilatation ratio and abnormal stress and rest left ventricular ejection fraction response, which were significant predictors of CAD. In the current study, we found that high and moderate pretest likelihood of CAD, exercise induced angina, positive exercise ECG findings and transient enlargement of scintigraphic left ventricular size were significant predictors of CAD. Diabetes mellitus status was also an independent predictor of cardiac events in patients with normal perfusion imaging [19]. However, we did not find significant statistical differences between CAD and non-CAD group which could be mainly due to the limited number of our patients.

In our study, CAD and the non-CAD group patients achieved no significant statistical differences of prognosis after median follow-up time of 53 ± 18 months. Whereas excellent short-term risk for cardiac events was predicted by a normal exercise SPET-MPI study, various studies reported that the long-term risk can vary significantly according to various risk factors. Supariwala et al. (2011) reported that during follow-up for about 7 years 2,597 patients without a history of heart disease and with normal exercise SPET stress test showed an annualized mortality rate that varied markedly according to the number of CAD risk factors. Despite the overall excellent long-term prognosis of a normal exercise SPET test, the burden of traditional CAD risk factors, such as hypertension, diabetes, and smoking, exerted a strong synergistic influence on long-term survival and warranted aggressive treatment [20]. Recently, other researchers evaluated that CAD risk factors influenced long-term risk in more than 12000 patients with normal SPET-MPI exercise test. During a follow-up time of 11.2 ± 4.5 years, 8.6% of the patients died (annualized mortality rate of 0.8%/year) and the combination of lower exercise tolerance (<6 minutes of exercise), with the three CAD risk factors, smoking, hypertension, or diabetes increased the risk for all-cause mortality by over seven fold compared to patients exercising for >9 coronary angiography (CAG)min and having none of these risk factors [21].

Several limitations must be mentioned in the current study.

Firstly, semi-quantitative visual interpretation [22-24] was not performed. Negative myocardial imaging was defined as in each segment of the rest/stress myocardial imaging while no reversible or reduced solid radioactive anomalies or defects were identified. This subjective standard of ours may cause bias. In addition, the J-ACCESS (Japanese investigation of prognosis based on gated SPET) study, which involved 117 institutions and 4,629 patients, found that semi-quantitative gated myocardial SPET (QGS) was valua-

Table 1. Baseline clinical, exercise stress and myocardial perfusion imaging characteristics in CAD vs. non-CAD patients with negative ^{99m}Tc-MIBI SPET-MPI.

Characteristics	CAD group n=31(%)	non-CAD group n=102(%)	χ^2 -value	P-value
Gender (M/F)	17/14	55/47	0.008	0.928
Age (y)	63±11	57±11	2.694	0.004
Hypertension (%)	25(81)	25(24)	31.49	0.001
Diabetes (%)	5(16)	8(8)	1.85	0.170
Hypercholesterolemia (%)	7(23)	9(9)	0.008	0.928
Presence of typical angina (%)	8(26)	8(8)	7.25	0.007
Pretest likelihood of CAD				
High	14(45)	5(5)	31.47	0.001
Moderate	16(52)	81(79)	9.31	0.002
Low	1(3)	16(6)	3.31	0.069
Exercise stress				
Resting HR (beats/minute)	72±13	70±9	0.97	0.334
Exercise duration (minute)	7.9±2.5	8.2±2.5	0.56	0.579
Peak HR (beats/minute)	122±25	131±20	1.96	0.053
Abnormal ECG	9(29)	8(8)	9.57	0.002
Exercise induced angina	6(19)	5(5)	6.55	0.011
%MPHR	84±15	86±11	0.71	0.479
Myocardial perfusion imaging				
Lung uptake	0.33±0.07	0.31±0.05	1.26	0.211
Lung uptake increasing	3(10)	3(3)	2.50	0.114
Scintigraphic left ventricular size enlargement	3(10)	2(2)	3.91	0.048

SPET-MPI: single-photon emission computed tomography /myocardial perfusion imaging. CAD: coronary artery disease. ECG: electrocardiogram. HR: heart rate. M: male. F: female. MPHR: maximum predicted heart rate.

ble for predicting the prognosis of Japanese patients with known or suspected ischaemic heart disease [25] Momose et al. (2009) reported that MPI with QGS had incremental prognostic value in addition to CAG findings [26].

Secondly, the definition of CAD was based on anatomic coronary stenosis, rather than on functionally significant coronary stenosis studying fractional flow reserve. It is possible that many of the detected coronary lesions may not have been hemodynamically significant [27, 28].

Thirdly, as mentioned above, long-term mortality risk following normal exercise SPET-MPI imaging could vary markedly according to the magnitude of CAD risk factors and other clinical parameters. The median follow-up time in the current study was about 4 1/2 years which could be considered short in order to increase statistical significance of our findings.

Fourthly, the number of patients with 'negative' SPET-MPI and CAG diagnosing CAD was rather small. Further evaluation of the findings in a larger patient population is needed. Finally, the retrospective nature of the current study could be another limitation.

In conclusion, the results of CAG in 133 suspected CAD patients with negative exercise ^{99m}Tc -MIBI SPET-MPI were analyzed in the current study and showed that 31 patients (23%) were diagnosed with anatomic CAD by CAG, mostly with 1VD and with mild/moderate stenosis. Several clinical, stress, and MPI findings could be potential predictors for false negative ^{99m}Tc -MIBI SPET-MPI. However, after a median follow-up time of 53 ± 18 months, the annualized cardiac event rate was 0.9% and 0.2% in the CAD and the non-CAD group and no significant statistical differences were shown ($\chi^2=1.22$, $P=0.27$) in these two groups. Increased number of patients studied would have increased statistical results.

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The authors declare that they have no conflicts of interest

Bibliography

- Doukky R, Hayes K, Frogge N et al. Impact of appropriate use on the prognostic value of single-photon emission computed tomography myocardial perfusion imaging. *Circulation*. 2013; 128:1634-43.
- Chhabra L, Ahlberg AW, Henzlova MJ et al. Temporal trends of stress myocardial perfusion imaging: Influence of diabetes, gender and coronary artery disease status. *Int J Cardiol*. 2015 202: 922-929. doi: 10.1016/j.ijcard.2015.09.020. [Epub ahead of print]
- Mizutani A, Matsunari I, Kobayashi M et al. Impact of injection dose, post-reconstruction filtering, and collimator choice on image quality of myocardial perfusion SPECT using cadmium-zinc telluride detectors in the rat. *EJNMMI Phys*. 2015 Dec;2(1):7. doi: 10.1186/s40658-015-0111-6. Epub 2015 Mar 11.
- Yokota S, Mouden M, Ottervanger JP et al. Prognostic value of normal stress-only myocardial perfusion imaging: a comparison between conventional and CZT-based SPECT. *Eur J Nucl Med Mol Imaging*. 2015 Sep 21. [Epub ahead of print].
- Metz LD, Beattie M, Hom R et al. The prognostic value of normal exercise myocardial perfusion imaging and exercise echocardiography: a meta-analysis. *J Am Coll Cardiol* 2007; 49: 227-37.
- Fleischmann KE, Hunink MG, Kuntz KM, Douglas PS. Exercise echocardiography or exercise SPECT imaging? A meta-analysis of diagnostic test performance. *JAMA*. 1998;280:913-20
- Kamínek M, Metelková I, Budíková M et al. Diagnosis of high-risk patients with multivessel coronary artery disease by combined cardiac gated SPET imaging and coronary calcium score. *Hell J Nucl Med*. 2015 18(1):31-4.
- Raziei G, Tavakoli A, Seifollahi Asl S et al. One-year prognosis of patients with normal myocardial perfusion imaging using technetium-99m sestamibi in suspected coronary artery disease: a single-center experience of 1,047 patients. *Perfusion*. 2011;26:309-14.
- Brown KA, Altland E, Rowen M. Prognostic value of normal technetium-99m-sestamibi cardiac imaging. *J Nucl Med*. 1994; 35:554-7.
- Boyne TS, Koplan BA, Parsons WJ et al. Predicting adverse outcome with exercise SPECT technetium-99m sestamibi imaging in patients with suspected or known coronary artery disease. *Am J Cardiol*. 1997;79:270-4.
- Raiker K, Sinusas AJ, Wackers FJ, Zaret BL. One-year prognosis of patients with normal planar or single-photon emission computed tomographic technetium 99m-labeled sestamibi exercise imaging. *J Nucl Cardiol*. 1994; 1:449-56.
- Hachamovitch R, Berman DS, Kiat H et al. Exercise myocardial perfusion SPECT in patients without known coronary artery disease: incremental prognostic value and use in risk stratification. *Circulation*. 1996;93:905-14.
- Rao NS, Kumar JV. Role of Perceptual Factors on Endurance Profiles on Treadmill Exercise. *J Clin Diagn Res*. 2015 Jun;9(6):CC13-5. doi: 10.7860/JCDR/2015/12359.6063. Epub 2015 Jun 1.
- Montalescot G, Sechtem U, Achenbach S et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J*. 2013; 34:2949-3003.
- Yang RF, Liu XY, Lin Z et al. Correlation study on waist circumference-triglyceride (WT) index and coronary artery scores in patients with coronary heart disease. *Eur Rev Med Pharmacol Sci*. 2015 19(1):113-8.
- Diamond JA, Makaryus AN, Sandler DA et al. Normal or near normal myocardial perfusion stress imaging in patients with severe coronary artery disease. *J Cardiovasc Med (Hagerstown)*. 2008;9: 820-5.
- Fujimoto S, Wagatsuma K, Uchida Y et al. Study of the predictors and lesion characteristics of ischemic heart disease patients with false negative results in stress myocardial perfusion single-photon emission tomography. *Circ J*. 2006; 70:297-303.
- Nakanishi R, Gransar H, Slomka P et al. Predictors of high-risk coronary artery disease in subjects with normal SPECT myocardial perfusion imaging. *J Nucl Cardiol*. 2015. [Epub ahead of print]
- Acampa W, Petretta M, Cuocolo R et al. Warranty period of normal stress myocardial perfusion imaging in diabetic patients: a propensity score analysis. *J Nucl Cardiol*. 2014; 21:50-6.
- Supariwala A, Uretsky S, Singh P et al. Synergistic effect of coronary artery disease risk factors on long-term survival in patients with normal exercise SPECT studies. *J Nucl Cardiol*. 2011; 18:207-14.
- Rozanski A, Gransar H, Min JK et al. Long-term mortality following normal exercise myocardial perfusion SPECT according to coronary disease risk factors. *J Nucl Cardiol*. 2014; 21:341-50.
- Cerqueira MD, Weissman NJ, Dilsizian V et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation*. 2002; 105:539-42.
- Leslie WD, Tully SA, Yogendran MS et al. Prognostic value of automated quantification of ^{99m}Tc -sestamibi myocardial perfusion imaging. *J Nucl Med*. 2005; 46:204-11.

24. Berman DS, Abidov A, Kang X et al. Prognostic validation of a 17-segment score derived from a 20-segment score for myocardial perfusion SPECT interpretation. *J Nucl Cardiol*. 2004; 11:414-23.
25. Nakajima K, Nishimura T. Cardiovascular events in Japan. Lessons from the J-ACCESS multicenter prognostic study using myocardial perfusion imaging. *Circ J*. 2012; 76: 1313-21
26. Momose M, Nakajima K, Nishimura T. Prognostic significance of stress myocardial gated SPECT among Japanese patients referred for coronary angiography: A study of data from the J-ACCESS database. *Eur J Nucl Med Mol Imaging*. 2009; 36: 1329-37.
27. Melikian N, De Bondt P, Tonino P et al. Fractional flow reserve and myocardial perfusion imaging in patients with angiographic multivessel coronary artery disease. *JACC Cardiovasc Interv*. 2010; 3: 307-14.
28. Tonino PA, Fearon WF, De Bruyne B et al. Angiographic versus functional severity of coronary artery stenoses in the FAME study fractional flow reserve versus angiography in multivessel evaluation. *J Am Coll Cardiol*. 2010; 55: 2816-21.



Albrecht Dürer, Four Horsemen of the Apocalypse. Woodcut, 39.2x27.9 cm.