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Cardiac Image

Chest Pain with Normal Thallium-201 Myocardial Perfusion Image – Is It Really Normal?

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Background: Thallium-201 myocardial perfusion image (MPI) is commonly used to detect coronary artery disease in patients with chest pain. Although a normal thallium-201 MPI result is generally considered to be a good prognosis and further coronary angiogram is not recommended, there are still a few patients who suffer from unexpected acute coronary events. The aim of this study was to investigate the clinical prognosis in patients with normal thallium-201 MPI.

Methods: From January 2006 to August 2012, a total 22,003 patients undergoing thallium-201 MPI in one tertiary center were screened. Of these, 8092 patients had normal results and were investigated retrospectively. During follow-up, 54 patients underwent coronary angiogram because of refractory typical angina pectoris or unexpected acute coronary events. These 54 patients were divided into 2 groups: group I consisted of 26 (48.1%) patients with angiography-proven significant coronary artery stenosis, and group II consisted of 28 (51.9%) patients without significant stenosis.

Results: Patients in group I had a higher prevalence of prior coronary stenting and electrocardiographic features of ST depression compared with patients in group II. The multivariate analysis demonstrated that both prior coronary stenting and ST depression were risk predictors of unexpected acute coronary events in the patients with normal thallium-201 MPI [odds ratio (OR), 5.93; 95% confidence interval (CI): 1.03-34.06, p = 0.05 and OR, 7.10; 95% CI: 1.28-39.51, p = 0.03,respectively].

Conclusions: Although there is a low incidence of unexpected acute coronary events in patients with chest pain and normal thallium-201 MPI, physicians should be aware of the potentials risk in certain patients in this specific population.

Key Words: Acute coronary syndrome • False negative • Thallium-201

INTRODUCTION

Due to its high sensitivity and specificity in detecting coronary artery disease (CAD), thallium-201 myocardial perfusion imaging (MPI) is commonly used to evaluate patients with chest pain. Moreover, thallium-201 MPI has been demonstrated as a useful method to predict cardiovascular events.[1] The benign prognosis of patients with chest pain and normal stress thallium-201 MPI has been well-established.[2,3] It has been suggested that the incidence of major cardiovascular events in patients with chest pain and normal thallium-201 MPI is less than 1% per year.[4-7] However, although unexpected cardiovascular events still occur and result in catastrophic outcomes, unfortunately there have been few studies on the issue of normal thallium-201 MPI in angiographically significant CAD patients. Possible

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causes for false-negative myocardial perfusion scintigraphy have been reported and include a smaller number of involved vessels,[8] balanced triple-vessel disease,[9] circumflex coronary stenoses,[10] and use of caffeinated products prior to testing.[11] Nevertheless, very few studies have considered the issue of normal thallium-201 MPI in angiographically significant CAD patients, and none of them has systematically evaluated the clinical predictors in this population.[2] The present study thus aimed to determine the clinical prognosis in patients with normal thallium-201 MPI and to investigate the associated risk factors of unexpected acute coronary events.

MATERIALS AND METHODS

Study population and follow-up

From January 2006 to August 2012, a total of 22,003 consecutive patients who underwent thallium-201 MPI in one tertiary center were screened. Of these, 8092 (36.8%) patients had absolutely normal results from both visual and quantitative analyses and were followed retrospectively. We found that 79.08% of the patients were from the department of internal medicine, 12.65% from surgery, 0.41% from the health management center, and 7.86% from others. During follow-up, 66 patients underwent coronary angiography (CAG) after having normal thallium-201 MPI. Twelve patients were excluded because there was a second thallium-201 MPI study that showed dynamic ischemic change. Finally, a total of 54 patients underwent CAG because of unexpected acute coronary events, including unstable angina pectoris (UA), non-ST segment elevation myocardial infarction (NSTEMI) and ST segment elevation myocardial infarction (STEMI). Other reasons for CAG in these patients population include refractory typical angina despite optimal anti-angina therapy and persistent angina pectoris with discordant results compared to other non-invasive coronary evaluation, such as the treadmill exercise test. These 54 patients were divided into 2 groups, with 26 (48.1%) patients with angiography-proven significantly obstructive coronary artery disease being categorized as group I, and 28 (51.9%) patients with no significant coronary artery stenosis being categorized as group II (Figure 1).

Myocardial perfusion single-photon emission computed tomography imaging

Patients fasted for at least 4 hours and were asked to abstain from caffeine-containing foods, beverages and medications containing methylxanthine for 24 h. Dipyridamole (0.56 mg/kg) was infused over 4 minutes with the patient in a supine position. Twelve-lead electrocardiography and a pulse oximeter were applied to monitor each of the patients; heart rate and blood pressure were recorded at rest and every 2 minutes after the initiation of dipyridamole infusion for a total of 8 minutes. After measurement was completed, Tl-201 was injected into each patient. If there was any adverse effect caused by dipyridamole, 25 mg of aminophylline was intravenously administered 2 minutes after Tl-201 injection to reverse the adverse effects. Stress and rest scans were acquired with the patient in a supine position starting 5-10 min and 4 h after Tl-201 injection. A dual-head gamma camera equipped with a low-energy high-resolution collimator was used. The acquisition comprised 32 projections, with 40 s of data collection per projection, obtained over a 180° arc extending from the 45° right anterior oblique to the 45° left posterior oblique position. A 15% window was centered over the 72 and 167 keV Tl-201 photopeaks. The projection images were acquired into 64 × 64 matrices with a 1.3 acquisition zoom and were reconstructed by filtered back-projection with a Butterworth filter (order 10, cut-off frequency 0.33 cycles per pixel).

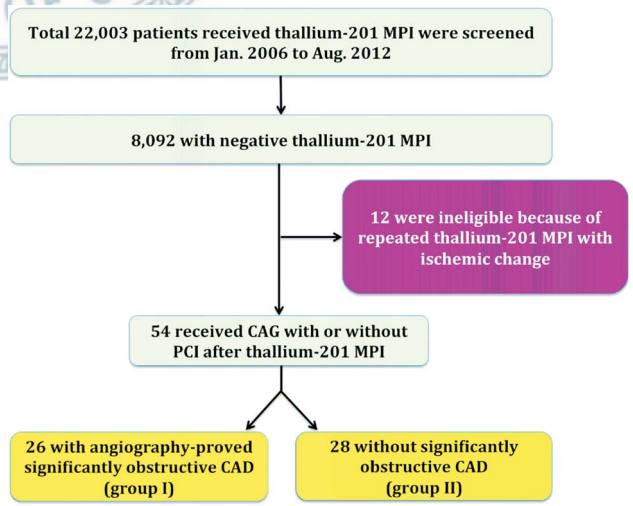

Figure 1. *Algorithm of the examination procedures and results. CAD, coronary artery disease, MPI, myocardial perfusion imaging.*

Cardiac catheterization

Cardiac catheterization was performed using a standard protocol. Digital coronary angiograms were analyzed with an automated flat detector system (Allura Xper FD 10/10; Philips Medical Systems, Netherlands) by using a dye-filled guiding catheter as a reference. The measurement of the lesion diameter was taken during the diastolic phase. The stenotic lesion of the coronary artery was defined as a > 50% stenosis in a native vessel. Coronary artery lesions were classified according to the modified American Heart Association/American College of Cardiology grading system.[12] A false negative Tl-201 perfusion single-photon emission computed tomography (SPECT) study was defined as normal myocardial perfusion image in the patient who had a single vessel disease with > 50% stenosis in a coronary angiogram. There was no fractional flow reserve (FFR) or intravascular ultrasound (IVUS) study to define whether the stenotic lesion was hemodynamically obstructive.

Clinical characteristics of patients received CAG after normal thallium-201 MPI

All 54 patients received CAG after the normal thallium-201 MPI were studied. Body mass index (BMI) was calculated by dividing body weight in kilograms by the square of body height in meters (kg/m^2). Hypertension was defined as systolic blood pressure of ≥ 140 mmHg, and/or diastolic blood pressure of ≥ 90 mmHg or with current antihypertensive agents. Diabetes mellitus was defined as a fasting blood glucose level of ≥ 126 mg/dl, glycosylated hemoglobin (HbA1c) level of > 6.5%, or current insulin or oral antidiabetic agents therapy. Dyslipidemia was defined as patients with hypercholesterolemia (total cholesterol level of ≥ 220 mg/dl) and/or hypertriglyceridemia (serum triglyceride level of ≥ 150 mg/dl) and/or current lipid lowering therapy. Peripheral arterial disease (PAD) was defined from previous medical history and/or an ankle brachial index of 0.9. Left ventricular end diastolic diameter (LVDd), left ventricular systolic diameter (LVDs), and left ventricular ejection fraction (LVEF) were measured by M-mode echocardiography within 1 month after CAG.

Statistical analysis

The data are presented as mean values and standard deviations from continuous variables and proportions for categorical variables. The statistical differences between the continuous values were assessed using an unpaired two-tailed t-test or one-way ANOVA analysis of variance, Bonferroni post hoc test for normally distributed continuous variables, and the Mann-Whitney rank-sum test was used for skewed variables. The Chi-square test was applied to compare the difference of nominal variables, and Fisher's exact test was used if the categorical variable had a count of less than 5. For regression analysis, the variables of significant differences were brought into a regression test, and a univariate Cox regression analysis of the various clinical variables was used to determine the predictors of unexpected major acute coronary events in patients with normal thallium-201 MPI. The selected variables tested in the multivariate analysis were those with a p-value < 0.05 in the univariate model. All statistical significances were set at a p-value < 0.05 and all statistical analyses were performed by using SPSS 20.0 software (SPSS Inc., Chicago, IL, USA).

RESULTS

Follow-up of unexpected major acute coronary events

A total of 8092 patients with normal thallium-201 MPI from January 2006 to August 2012 were enrolled and followed up till August 2013. The mean duration of follow-up in these patients with normal thallium-201 MPI was 43.9 ± 19.1 months. During this period, 26 patients suffered from unexpected acute coronary events and were defined as group I. Of these, 17 (65.4%) patients presented with UA, 7 (26.9%) patients with NSTEMI, and 2 (7.7%) patients with STEMI. The incidence rate of unexpected acute coronary events in patients with normal thallium-201 MPI was 0.09% per year. None of these 26 patients suffered from cardiovascular death. The average time interval between normal thallium-201 MPI and acute coronary events was 8.09 months (range from 2 days to 37.6 months).

Phenotype of coronary artery in patients with normal thallium-201 MPI

As mentioned above, all of the group I patients underwent primary percutaneous trans-luminal coronary

intervention (PTCA). The phenotypes of coronary artery in these patients are shown in Table 1. Ten (38.5%) patients had triple vessel disease and the most common culprit lesion was left anterior descending artery (LAD). One (3.8%) patient had total occlusion and two (7.7%) patients had in-stent restenosis.

In contrast to the patients who suffered from unexpected acute coronary events, 28 patients had received elective CAG examination because of refractory angina pectoris despite receiving optimal medication. All of these patients had no significant angiography-proven coronary stenosis. In spite of not having coronary artery stenosis, 8 (28.6%) patients were found to have myocardial bridge in LAD.

Table 1. Phenotypes of coronary artery in patients with normal thallium-201 MPI suffering from unexpected acute coronary events

Patient	Gender/ age	Number of diseased vessel/clinical diagnosis	Coronary angiogram (stenotic vessels)			Culprit lesion	ISR	Prior stenting	Interval between Tl-201 MPI and CAG (months)
			LAD-DB	LCX-OM	RCA-PL, PDA				
1	F/83	3VD/NSTEMI	M	D	D	RCA			6.20
2	F/85	1VD/NSTEMI	M, D			LAD			3.10
3	F/54	1VD/NSTEMI		P		LCx			1.83
4	F/65	3VD/STEMI	M	D	D	RCA			8.53
5	M/63	2VD/UA	P: ISR	P		LAD	Y	Y	1.43
6	F/43	2VD/UA	P	P: s/p stenting		LAD		Y	11.00
7	F/72	3VD/UA	M	D	D	RCA			0.07
8	F/85	3VD/UA	M	OM1	PL, PDA	LAD			0.47
9	M/72	1VD/NSTEMI			D; PDA	RCA			5.77
10	M/62	1VD/UA	D			LAD			7.90
11	M/52	1VD/UA	OS; M: s/p stenting,			LAD		Y	6.10
12	M/91	3VD/NSTEMI	D	D	D	LCX, RCA			12.10
13	F/92	2VD/UA	P	D		LAD, LCX			0.57
14	M/80	3VD/UA	M: s/p stenting	D	M: s/p stenting	LCX		Y	7.97
15	M/75	3VD/STEMI	M; s/p stenting	OM2	M	LAD,OM2	Y	Y	12.13
16	F/67	1VD/UA	DB1			DB1			18.00
17	M/77	1VD/NSTEMI	P			LAD			0.40
18	M/60	2VD/UA	M		D: s/p stenting	LAD		Y	7.10
19	F/71	1VD/UA		D		LCX			0.17
20	M/76	3VD/UA	M: s/p stenting	D	D	RCA		Y	2.20
21	F/59	3VD/UA	P	D: s/p stenting	D	RCA		Y	8.77
22	M/54	1VD/UA		P		LCX			25.53
23	M/53	1VD/UA	P			LAD			0.73
24	M/60	1VD/UA	D			LAD			6.07
25	M/64	1VD/UA	D			LAD			18.67
26	F/63	3VD s/p CABG/NSTEMI	M	P	P	VG-RCA			37.63

CAG, coronary angiography; D, distal; DB, diagonal branch; ISR, in-stent restenosis; LAD, left anterior descending artery; LCX, left circumflex artery; M, middle; NSTEMI, non ST segmental elevation myocardial infarction; OM, obtuse marginal; P, proximal; PDA, posterior descending artery; PL, postero-lateral branch; RCA, right coronary artery; s/p, status post; STEMI, ST segmental elevation myocardial infarction; Tl-201 MPI, thallium-201 myocardial perfusion imaging; UA, unstable angina; VD, vessel-disease; VG, vein graft; Y, yes.

Clinical characteristics of patients with normal thallium-201 MPI who received CAG

There was no difference in the time interval between normal thallium-201 MPI and CAG (8.09 ± 8.82 vs. 9.71 ± 10.15 months, p = 0.53). Patients in group I tended to be older than those in group II (68.39 ± 12.81 vs. 61.36 ± 15.47 years, p = 0.07). In contrast, similar characteristics in the 2 groups included sex, body mass index (BMI), smoking habits, hypertension, diabetes mellitus, previous myocardial infarction, previous cerebral stroke, dyslipidemia, valvular heart disease, congestive heart failure, peripheral artery disease, and uremia. However, there were more patients with previous coronary stenting in group I than in group II (30.8% vs. 7.1%, p = 0.04). The baseline clinical characteristics of the subjects in the two groups are listed in Table 2.

For the electrocardiographic findings, Table 3 shows that the baseline heart rate, PR interval, QTc, the presence of T wave inversion and Q wave were similar between these 2 groups. There was a higher prevalence of ST depression in patients of group I (33.3% vs. 7.1%, p = 0.03). Regarding the echocardiographic features, there were no significant differences in the LVDs, LVDd, right ventricular systolic pressure, and LVEF.

Predictors of unexpected major acute coronary events

In the univariate logistic regression analysis, prior coronary stenting and electrocardiographic features of ST depression predicted the risk of unexpected acute coronary events in patients with normal thallium-201 MPI [odds ratio (OR), 5.78; 95% confidence interval (CI): 1.10-30.45, p = 0.04 and OR, 6.50; 95% CI: 1.22-34.53, p = 0.03, respectively; Table 4]. In the multivariate logistic regression analysis, both of prior coronary stenting and electrocardiographic feature of ST depression independently predicted the unexpected acute coronary events in the patients with normal thallium-201 MPI (OR, 5.93; 95% CI: 1.03-34.06, p = 0.05 and OR, 7.10; 95% CI: 1.28-39.51, p = 0.03).

DISCUSSION

Main findings

In this study, we demonstrated that although not common, there is still a risk of unexpected major acute coronary events in patients with chest pain and normal thallium-201 MPI, and the incidence rate is approxi-

Table 2. Baseline clinical characteristics of patients with normal thalium-201 myocardial perfusion image

Variables	Normal thallium-201 MPI		p-value
	Group I (N = 26)	Group II (N = 28)	
Time interval (months)*	8.09 ± 8.82	9.71 ± 10.15	0.53
Age (years)	68.39 ± 12.81	61.36 ± 15.47	0.07
Male (N, %)	14 (53.8)	15 (53.6)	0.98
Body mass index (BMI)	24.74 ± 4.04	25.12 ± 4.07	0.73
Smoking (N, %)	10 (38.5)	8 (28.6)	0.57
Hypertension (N, %)	21 (80.8)	19 (67.9)	0.36
Diabetes mellitus (N, %)	9 (34.6)	4 (14.3)	0.11
Prior MI (N, %)	3 (11.5)	2 (7.1)	0.66
Prior coronary stenting (N, %)	8 (30.8)	2 (7.1)	0.04
Prior cerebral stroke (N, %)	1 (3.8)	0 (0)	0.48
Dyslipidemia (N, %)	13 (50)	14 (50)	1.00
Valvular heart disease (N, %)	2 (7.7)	6 (21.4)	0.25
Congestive heart failure (N, %)	7 (26.9)	3 (10.7)	0.13
Peripheral artery disease (N, %)	1 (3.8)	1 (3.6)	0.96
Status post CABG	1 (3.8)	0 (0)	0.48
Uremia (N, %)	3 (11.5)	1 (3.6)	0.34
eCCr	72.74 ± 35.96	92.94 ± 49.05	0.09

* Time interval: the mean time interval between thallium-201 MPI and coronary angiography.
CABG, coronary artery bypass grafting; eCCr, estimated creatinine clearance; MI, myocardial infarction.

Table 3. Electrocardiographic and echocardiographic features of patients with a normal thalium-201 myocardial perfusion image

Variables	Normal thallium-201 MPI		p-value
	Group I (N = 26)	Group II (N = 28)	
Electrocardiographic parameters			
Baseline heart rate (bpm)	71.30 ± 16.86	66.30 ± 11.10	0.23
PR interval (ms)	171.59 ± 25.21	163.89 ± 41.03	0.42
QTc (ms)	432.48 ± 40.10	418.07 ± 43.04	0.23
ST depression (N, %)	8 (33.3)	2 (7.1)	0.03
T wave inversion (N, %)	8 (33.3)	7 (25.0)	0.55
Q wave (N, %)	8 (33.3)	3 (10.7)	0.09
Echocardiographic parameters			
LVDs (mm)	28.80 ± 6.07	29.42 ± 6.61	0.82
LVDd (mm)	44.90 ± 6.05	46.83 ± 4.17	0.39
RVSP (mmHg)	31.22 ± 8.04	34.18 ± 16.79	0.63
LV EF (%)	58.60 ± 15.04	67.00 ± 14.53	0.20

bpm, beats per minute; LVDd, left ventricular dimension in diastole; LVDs, left ventricular dimension in systole; LV EF, left ventricular ejection fraction; N, number; RVSP, right ventricular systolic pressure.

Table 4. Univariate and multivariate logistic regression analysis for predictors of unexpected major acute coronary events in patients with normal thallium-201 myocardial perfusion image

Variable	Univariate analysis (Crude)			Multivariate analysis (Adjusted)		
	OR	95% CI	p value	OR	95% CI	p value
Age	1.04	0.995-1.08	0.08	-	-	-
Prior coronary stenting	5.78	1.10-30.45	0.04	5.93	1.03-34.06	0.05
ST depression	6.50	1.22-34.53	0.03	7.10	1.28-39.51	0.03
Presence of Q wave	4.17	0.96-18.08	0.06	-	-	-

CI, confidence interval; OR, odds ratio.

mately 0.09% per year. Both prior coronary stenting and electrocardiographic features of ST depression were associated with an increased risk of unexpected acute coronary events in patients with normal thallium-201 MPI. Moreover, in patients with normal thallium-201 MPI and no angiography-proven coronary stenosis, LAD myocardial bridge was found to be the most common abnormal coronary feature.

Unexpected acute coronary event rates and normal thallium-201 MPI

Our study confirmed the predictive importance of a normal thallium-201 MPI result. Previous investigations showed that a normal exercise thallium response or a normal thallium SPECT imaging significantly predicts a low cardiovascular mortality of 0.1% to 0.5% and an incidence of non-fatal myocardial infarction of 0.45% to 0.98%.[6,13-15] In our study, the unexpected major acute coronary event rate in patients with normal Tl-201 MPI was 0.32%, which is similar to previous investigations, but which is lower than the overall complication rate of 0.74% of adult diagnostic cardiac catheterization procedures.[16] Additionally, the majority of those truly false-negative cases for SPECT imaging were within a one-year period. Among the angiographically significant CAD group, there were only two cases with an interval of more than two years. Most unexpected events occurred within one year of normal Tl-201 MPI (Table 1). The average time interval between normal thallium-201 MPI and major acute coronary events was 8.09 months (range from 2 days to 37.6 months). This provides evidence to suggest that among these cases, the disease progression of pre-existing CAD contributed more to the unexpected event.

Mechanism of false-negative in thallium-201 MPI

As mentioned above, several factors can contribute

to the false negative results of thallium-201 MPI.[8-11] Balanced ischemia was proposed as one of the factors in patients with triple-vessel disease.[9,17] Interestingly, Sugi et al. studied the results of stress SPECT in asymptomatic patients after coronary stent implantation and suggested that the negative predictive value tended to be lower in patients with triple vessel disease.[18] Aarnoudse et al. and Madias reported that the mechanism of balanced three-vessel disease, evidenced by FFR (fractional flow reserve) could cause false negative thallium-201 scintigraphy results, even with an intermediate stenosis of 50 to 70%.[9,17] In our study, although 10 patients (38.5%) had triple-vessel disease among 26 patients with negative result of thallium-201 MPI, 11 patients (42%) had single vessel disease. This is consistent with the study from Osbakken et al. indicating that the sensitivity of thallium-201 scans decreases significantly with a smaller number of diseased vessels.[8]

In addition, Rigo et al. suggested it is less sensitive for detecting circumflex coronary artery stenosis because of the smaller perfused and more posteriorly located myocardial mass.[10,18] However, Niemeyer et al. reported that most CAD patients judged as being negative from visual or quantitative analysis are single-vessel disease in the left anterior descending artery.[19] The current study reveals that LAD was the most common culprit lesion (12/26, 46%) in this population.

Clinical predictors of unexpected acute coronary event in patients with normal thallium-201 MPI

With respect to the outcome of normal thallium-201 MPI, Brown et al. reported the annual major cardiovascular event rate of 0.7% to 1.0% per year with an event interval of up to 23 to 28 months.[2] Patients with normal exercise thallium-201 imaging have a benign prognosis over a mean 2-year follow-up. There was no difference found in cardiac event rates between angiographyically normal and significant CAD groups.[2]

There have been scant data with regard to clinical predictors of normal thallium-201 MPI with unexpected cardiovascular events. Our study demonstrated that in univariate logistic regression, prior stenting, ST depression, age, and presence of Q waves were correlated to clinical predictors. Among them, age and the presence of Q waves seemed to be neutralized and showed no significant independent correlation in the multivariate logistic regression analysis. As a result, both prior stenting and resting ST depression can be considered as independent clinical predictors for unexpected acute coronary events in this study. 6 out of 26 patients (group I) had treadmill exercise testing (TET) and 4 patients had positive results. Among these 4 TET-positive patients, 3 patients already had resting ST-depression. That is, patients with resting ST depression may have positive TET, despite of false-negative thallium-201 (the so-called true-positive exercise electrocardiogram and false-negative thallium-201 discrepancy). According to Vasim et al., The in-stent restenosis rates of bare metal stent and drug eluting stent are as high as 16-44% and 0-16%, respectively.[20] Those who had prior stenting may have higher incidence of recurrent acute coronary syndrome. In present study, we concluded a similar result. Patients with prior stenting were associated with more unexpected coronary events despite of normal Tl-201 MPI results. Although there remains a number of issues that still require resolving, including the mechanism of prior stenting and ST segment depression in predicting unexpected coronary events, we are confident that our study provides critical evidence supporting the important roles of these two factors in diagnosing chest pain patients with negative thallium-201 MPI results.

Study limitations

There are some limitations to the present study. First, we did not compare these two groups of patients to those who were uneventful or needing CAG (n = 8026), due to data integrity and lacking of angiographic evidence of coronary conditions. Second, we enrolled the only patients with coronary angiography, thus the number of enrolled patients is relative small. This may lead to selection bias and this study may be underpowered. Heterogeneity of patients undergoing Tl-201 MPI for diverse indications and followed at different doctors' service makes this study limited. Third, the longer the interval, the higher the possibility that de novo lesions developed. The appropriate interval for excluding de novo CAD in this series is problematic. Rather than "false-negative", some events might be derived from de novo lesions developed after normal Tl-201 MPI results. At last, the normal rate of MPI in this series (36.8%) seems to be higher. It may be resulted from not routinely applied gated-MPI in our center, which may

lower the sensitivity, resulting in higher normal rate. ECG-gated thallium-201 dipyridamole SPECT has been suggested as making a more accurate diagnosis of CAD in borderline cases of myocardial perfusion scan, which could be performed in high CAD probability patients with normal myocardial perfusion scan to enhance the sensitivity of the clinical predictors found in our study.[21] In addition, some authors suggest QTc heterogeneity parameters of rest magnetocardiography could reduce the possibility of underestimation of disease severity in Tl-201 MPI.[22]

CONCLUSIONS

In summary, although rare, there are potential risks of unexpected acute coronary events in patients with chest pain and a normal thallium-201 MPI. Clinicians should therefore be aware of false negative results of thallium-201 MPI in patients with a history of prior coronary stenting and EKG manifestation of ST segment depression. Further large scale, prospective studies are needed to clarify the effects of these two factors in chest pain patients with normal thallium-201 MPI.

CONFLICTS OF INTEREST

The authors have no funding, financial relationships, or conflicts of interest to disclose.

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