

# Detection of Restenosis After Percutaneous Transluminal Coronary Angioplasty Using the Exercise Treadmill Test and Technetium 99m-Sestamibi Scintigraphy

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## Abstract

**Background :** The detection of myocardial ischemia after percutaneous transluminal coronary angioplasty (PTCA) is important because 30-50 per cent of the patients will develop restenosis within 6 months. Symptoms of chest pain and exercise stress test (EST) have shown to be less sensitive for detection of ischemia than exercise Technetium-99m Sestamibi (Tc-99m MIBI). The purpose of this study was to compare the sensitivity and specificity of chest pain, EST and Tc-99m MIBI with coronary angiography (CAG).

**Method :** Tc-99m MIBI with SPECT imaging was performed at months 1, 3 and 6 and CAG was repeated 6 months after successful PTCA. Earlier Tc-99m MIBI and CAG were performed in patients with recurrent angina pectoris or suspected restenosis.

**Results :** Forty six patients (M 29, F 17) who had undergone successful angioplasty were prospectively enrolled. Their mean age was  $61 \pm 19$  yrs. Eighty eight lesions (LAD63%, LCX34%, RCA19%) were performed. Lesion characteristics were type A in 9 per cent, type in B 30 per cent and type C in 61 per cent. Fifty four per cent of PTCA were performed for single vessel disease and 46 per cent for multivessel disease. The mean duration of time between PTCA and follow-up CAG was  $6.1 \pm 2.7$  months. We detected restenosis from CAG in 58 per cent of the cases. The Tc-99m MIBI had higher sensitivity to detect restenosis than anginal pain (85.0% vs 39.4%  $p < 0.005$ ) or EST (85.0% vs 63.6%  $p < 0.05$ ) when compared with CAG. The overall accuracy of Tc-99m MIBI for the detection of restenosis was 80 per cent.

**Conclusion :** Tc-99m MIBI with SPECT imaging constitutes a better means than symptoms or exercise test to detect restenosis after successful coronary angioplasty.

**Key word :** Technetium-99m Sestamibi, Coronary Angioplasty, Restenosis

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Coronary restenosis after percutaneous coronary angioplasty (PTCA), occurs in 30 - 50 per cent of patients within 6 months<sup>(1-4)</sup> after successful procedures. Early detection is necessary to plan management for early revascularization. Coronary angiography (CAG) is the gold standard for detection of restenosis. However, it is time-consuming, costly and associated with risks. Many studies have shown the value of noninvasive testing, including exercise stress test alone<sup>(5,6)</sup> or in combination with thallium-201 scintigraphy<sup>(7-10)</sup> with radionuclide ventriculography, in restenosis after PTCA.

Technetium-99m Sestamibi SPECT imaging (Tc-99m MIBI) is a new myocardial perfusion imaging agent with physical characteristics superior to those of thallium-201<sup>(11-13)</sup>. The advantages of Tc-99m MIBI tracers over thallium-201 are ready availability, higher resolution, shorter half-life and minimal redistribution. The usefulness of Tc-99m MIBI for assessing myocardial perfusion has been shown in many circumstances<sup>(9-26)</sup>, but reports<sup>(27-30)</sup> regarding the usefulness of Tc-99m MIBI for the detection of restenosis after PTCA have been limited. In this study, we have evaluated the value of Tc-99m MIBI in detecting restenosis after successful PTCA by using coronary angiography as a gold standard.

## METHOD

Between November 1995 and February 1997, patients with successful PTCA in King Chulalongkorn Memorial Hospital were enrolled. Exclusion criteria were patients who could not perform the exercise test, or had an additional disease with a negative impact on their life expectancy or had severe congestive heart failure or serum creatinine levels above 2.0 mg/dl. Demographic data of the patients were recorded such as risk factors of coronary artery disease, indication for PTCA, previous history of myocardial infarction, previous PTCA or coronary artery by-pass graft (CABG), results of exercise stress test (EST-EKG) and Tc-99m MIBI, CAG before PTCA and the details of PTCA procedure. Clinical chest pain, EST-EKG and Tc-99m MIBI were evaluated at the 4<sup>th</sup> week, 3<sup>rd</sup> month and 6<sup>th</sup> month, respectively. The patients who developed recurrent chest pain at any time during follow-up, would have the exercise stress test and Tc-99m

MIBI as soon as possible. If Tc-99m MIBI showed restenosis, CAG was performed promptly. All asymptomatic patients would have CAG to confirm the diagnosis at the 6<sup>th</sup> month of the study.

**EST-EKG :** All patients underwent the standard Bruce or Naughton protocol exercise testing to a symptom-limited maximum. If the patients could not achieve 85 per cent of the maximum predicted target heart rate, the test was considered inadequate. Each test was classified according to standardized criteria applying the following interpretation : (1) positive, if the ST segment depression  $\geq 0.10$  mV from the electrocardiograph baseline at 0.08 seconds after the J point, or the ST segment elevation  $\geq 0.10$  mV from the baseline in the non-Q wave leads; (2) negative, if the patients developed neither chest pain during exercise nor elicited any significant ST segment changes; (3) not interpretable, in the presence of left bundle branch block, secondary ST segment changes due to left ventricular hypertrophy or digoxin intake.

**Tc-99m MIBI :** On the same day, an imaging protocol involving a low-dose resting study was followed by a high-dose stress study. The standard doses were 8 to 10 mCi for rest and 25 to 30 mCi for the exercise study. An interval of 2-hour imaging was recommended between rest and stress study. After the resting imaging, a symptom-limited treadmill exercise was performed and Tc-99m MIBI was injected at peak stress. The exercise was continued for at least 1 minute after the injection and imaging was begun 1 hour after the exercise.

### Interpretation of Tc-99m MIBI

1. Stress induced reversible filling defect defined as myocardial ischemia if there was improvement by at least 1 point on the visual scale between exercise and redistribution imaging.
2. Irreversible (fixed) filling defect defined as myocardial infarction if there was no change of the filling defect between exercise and redistribution imaging.

Evaluation of revascularization after PTCA by using Tc-99m MIBI taken in the first month after the procedure and categorized as:

1. Complete revascularization, defined by absolute disappearance of myocardial ischemia after PTCA.

2. Partial revascularization, defined by partial improvement of myocardial ischemia after PTCA.

3. Unsuccessful PTCA, defined by deterioration or progression of myocardial ischemia after PTCA.

At the 3<sup>rd</sup> and 6<sup>th</sup> month of follow-up, Tc-99m MIBI was performed to detect restenosis or disease progression by using the following criteria

1. Restenosis, if

1.1 there was deterioration or progression of myocardial ischemia in the territory of the dilated vessels after having complete revascularization

1.2 there was persistent myocardial ischemia and no further improvement after the 3<sup>rd</sup> to 6<sup>th</sup> month

1.3 there was progression of myocardial ischemia (reversible filling defect) to myocardial infarction (fixed filling defect)

2. No restenosis, if

2.1 there was disappearance or no evidence of myocardial ischemia after PTCA.

2.2 there was improvement or slight myocardial ischemia after the follow-up period.

Coronary angiography : Coronary angiography was repeated 6 months after PTCA or any time if there was evidence of restenosis such as recurrence of chest pain or abnormal Tc-99m MIBI which suggested restenosis in asymptomatic patients. Coronary angiography was performed in multiple projections and interpreted visually without knowledge of the initial non-invasive test results. Restenosis was defined as relapse of a previously dilated vessel to a  $\geq 50$  per cent diameter stenosis.

### Statistical analysis

Variables are expressed as mean  $\pm$  standard deviation and per cent. The sensitivity, specificity and predictive values of a test were calculated according to standard definitions. The proportional *t*-test for comparing sensitivity, specificity and predictive values was used and a *p* value  $< 0.05$  was considered statistically significant.

### RESULTS

Between November 1995 and February 1997, 46 cases who had undergone 54 successful PTCA were enrolled. The baseline characteristics

of the patients are shown in Table 1. Their mean age was  $61.3 \pm 19.0$  years. Eighty five per cent of the patients had angina chest pain prior to PTCA. Most of the patients received anti-angina medications. Angiographic characteristics and results are depicted in Table 2. Fifty four per cent of the cases were single vessel disease and the left anterior descending artery (LAD) was the vessel most commonly dilated. More than 90 per cent of the lesions were type B and C. Intracoronary stents were implanted in 42 per cent. At 4-6 weeks after successful PTCA, Tc-99m MIBI was performed for evaluating the efficacy of PTCA and showed complete revascularization in 32 per cent and partial revascularization in 68 per cent. None of the patients had any recurrent angina chest pain. At the 3<sup>rd</sup> and 6<sup>th</sup> month of follow-up, a non-invasive test was performed for detection of restenosis. The results are shown in Table 2. Symptomatic angina pain was found in only 37 per cent, whereas, positive EST-EKG was detected in 45 per cent but 17 per cent of the tests couldn't be interpreted. Tc-99m MIBI was the

**Table 1. Baseline characteristic of the patients.**

Characteristics	No. of patients or %
Total number of cases	46
Total number of procedures	54
Total number of dilatable lesions	88
Mean age (yr)	$61.3 \pm 19.0$
Sex; M : F	1.7:1
Chest pain prior to PTCA (%)	85
Anti-anginal medication	
Nitrates (%)	83
Beta-blocker (%)	57
Calcium-blocker (%)	24
Previous myocardial infarction (%)	30
Previous PTCA (%)	20
Previous coronary artery bypass graft (%)	2
Single vessel disease (%)	54
Double vessel disease (%)	33
Triple vessel disease (%)	13
Type of lesion	
Type A (%)	9
Type B (%)	30
Type C (%)	61
Vessel dilated	
Left anterior descending artery (%)	55
Left circumflex artery (%)	29
Right coronary artery (%)	16
Intracoronary stent implantation (%)	42

PTCA : percutaneous transluminal coronary angioplasty

**Table 2. Clinical symptoms and results of restenosis test.**

	Per cent
Recurrent anginal chest pain	37
EST-EKG	
Positive EST	45
Negative EST	39
Uninterpretation	17
Restenosis evidence from Tc-99m MIBI	63
Angiographic-case restenosis	58
Angiographic-lesion restenosis	51

EST-EKG : exercise stress test using electrocardiograph

Tc-99m MIBI : exercise stress test using Technetium-99m Sestamibi SPECT imaging

most sensitive non-invasive test for detection of restenosis. Sixty three per cent of the patients showed evidence of myocardial ischemia upon Tc-99m MIBI. The angiographic case restenosis rate was 58 per cent and the lesion restenosis rate was 51 per cent.

The sensitivity, specificity and accuracy of Tc-99m MIBI for detection of restenosis were 84.8 per cent, 71.4 per cent and 79.7 per cent, respectively, and had the highest predictive value but only sensitivity and accuracy showed statistically significant differences when compared with clinical chest pain and abnormal EST-EKG. Positive and negative predictive values of Tc-99m MIBI were also higher than chest pain and EST-EKG with a *p* value below 0.05. Sensitivity, specificity, accuracy, positive predictive value and negative predictive value are shown in Table 3. Table 4 demonstrates the individual vessel sub-

classified for sensitivity, specificity and accuracy. LAD was most sensitive for detection of restenosis but less specific and accurate when compared with left circumflex (LCX) and right coronary artery (RCA).

## DISCUSSION

Restenosis is still the major problem after successful PTCA and hence early detection is important. Clinical chest pain and abnormal EST-EKG test are not sensitive enough for this purpose. In this study, only 37 per cent of the patients with angiographic restenosis experienced chest pain. This is similar to previous reports (5,6,10) and confirmed it to be an insensitive marker for detection. The reasons for low incidence of recurrent angina chest pain may be symptom unawareness, self-limited activity and concomitant anti-angina medications.

Regarding the EST-EKG test, the sensitivity for detection of restenosis is higher than that of clinical chest pain alone (63.6% vs 39.4%) but it seems to be lower than that of Tc-99m MIBI. Accuracy, positive and negative predictive values are also significantly lower than those of Tc-99m MIBI. The limitation of EST-EKG interpretation of restenosis may lie in the inability to achieve the target heart rate due to anti-angina medications, abnormal baseline EKG, multivessel disease or small side-branches which could not receive complete revascularization, moderate degree or insufficient stenosis (50-75%) which did not produce exercise related EKG changes but led to an insufficiency of coronary perfusion. Therefore, when comparing EST-EKG alone with Tc-99m MIBI, especially for the detection of moderate

**Table 3. Comparison of sensitivity, specificity, accuracy, positive and negative predictive value between angina chest pain, EST-EKG and Tc-99m MIBI for detection of restenosis after PTCA by using CAG as a gold standard.**

	Sensitivity	Specificity	Accuracy	PPV	NPV
Angina chest pain	39.4	66.7	50.0	65.0	41.2
EST-EKG	63.6	66.7	64.8	75.0	53.8
Tc-99m MIBI	84.8*	71.4	79.7*	82.4*	75.0*

*p* value < 0.05

PPV - positive predictive value; NPV - negative predictive value

EST-EKG - exercise stress test using electrocardiograph

Tc-99m MIBI - exercise stress test using Technetium-99m Sestamibi SPECT imaging

**Table 4. Comparison of sensitivity, specificity and accuracy of Tc-99m MIBI for detection of restenosis in individual vessels (n=84).**

	Sensitivity	Specificity	Accuracy
LAD	95.2*	60.6	74.0
LCX	55.6	97.8*	90.8*
RCA	60.0	100*	95.3*

p value < 0.05

LAD - left anterior descending artery; LCX - left circumflex artery;  
RCA - right coronary artery

degree coronary narrowing, the EST-EKG was not sensitive enough to be an early indicator for detection of restenosis.

In this study, complete revascularization was achieved in only 32 per cent of the lesions performed and the rest only showed improvement or partial revascularization. In the previous study with EST-thallium 201, the average of complete revascularization was 79-86 per cent after PTCA (7-9). However, the optimal timing to perform perfusion study after angioplasty is controversial. In our study, the false positive transient myocardial perfusion abnormality early after revascularization (32% had complete revascularization and 68% had partial revascularization at 4-6 weeks post PTCA) was demonstrated because all exercise-related perfusion scans subsequently normalized at 2-4 months. This is presumably caused by a delayed return of coronary artery perfusion. If the Tc-99m MIBI had been performed too early after PTCA, it would have demonstrated a false positive result in predicting of restenosis (19). Therefore, Tc-99m MIBI probably should not be performed earlier than 6 weeks after PTCA.

For detection of restenosis, Tc-99m MIBI had the highest sensitivity, accuracy, positive and negative predictive value compared with clinical

chest pain or EST-EKG alone with a p value below 0.05. The specificity tended to be higher but didn't reach statistical significance.

When we sub-classified to detect restenosis of individual vessels, LAD had the highest sensitivity (95.2%) but lowest specificity (60.6%) compared with both LCX and RCA. The result may be due to many side-branches, the large area of myocardial supply and stent jail or obliterate side-branches of LAD.

### Clinical implications

The clinical implications of Tc-99m MIBI for the routine detection of restenosis of patients undergoing PTCA remain to be established. Certainly, an abnormal non-invasive test resulting early after PTCA is an indicator for close clinical monitoring in view of the high probability of recurrence of symptoms. Tc-99m MIBI imaging should be performed (after 6 weeks) in case of highly suspected restenosis such as chest discomfort, abnormal EST-EKG to confirm the true presence of restenosis and consider further management. However, the EST-EKG alone is still the first cost-effective step for screening asymptomatic cases.

### SUMMARY

Tc-99m MIBI imaging is a better non-invasive investigation for early detection of restenosis after PTCA within 6 months compared with anginal chest pain and EST-EKG. Tc-99m MIBI imaging has the highest sensitivity for detection of restenosis in the LAD distribution compared with LCX and RCA, and also it has a higher specificity and accuracy for detection of restenosis in LCX and RCA compared with LAD.

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## การตรวจหาการตีบซ้ำภายหลังการทำการบอลลูนขยายหลอดเลือดด้วยวิธีการเดินสายพานร่วมกับการใช้ Technetium 99m-Sestamibi Scintigraphy

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**ภูมิหลัง** ผู้ป่วยที่ได้รับการรักษาโรคหลอดเลือดหัวใจตีบด้วยการขยายหลอดเลือดโดยใช้บอลลูนมีโอกาสดังกล่าวจะกลับตีบซ้ำ 30-50 เปอร์เซ็นต์ภายใน 6 เดือน จากการศึกษาเดิมพบว่าการเจ็บหน้าอกและการตรวจคลื่นหัวใจในขณะที่ออกกำลังกายมีความไวต่ำในการตรวจเส้นเลือดตีบซ้ำหลังขยายด้วยบอลลูน ในขณะที่มีรายงานว่าการศึกษาการฉีดสารกัมมันตรังสี Technetium-99m Sestamibi (Tc-99m MIBI) ในขณะที่ออกกำลังกายน่าจะมีความไวสูงกว่า การศึกษานี้มีความประสงค์เพื่อเปรียบเทียบความไว และความจำเพาะของการเจ็บหน้าอก การตรวจคลื่นหัวใจและการฉีด Tc-99m MIBI ในขณะออกกำลังกาย โดยใช้ผลจากการฉีดสีเส้นเลือดหัวใจเป็นมาตรฐาน

**วิธีการ** การศึกษาแบบไปข้างหน้า โดยใช้ผู้ป่วยเส้นเลือดหัวใจตีบที่ได้รับการขยายด้วยบอลลูนเป็นผลสำเร็จ ผู้ป่วยจะได้รับการตรวจคลื่นหัวใจ และ Tc-99m MIBI โดย SPECT imaging ในขณะออกกำลังกาย ที่เดือนที่ 1, 3 และ 6 และฉีดสีเส้นเลือดหัวใจที่เดือนที่ 6 หรือเร็วกว่านั้นในกรณีที่มีอาการเจ็บหน้าอก หรือสงสัยว่ามีการตีบซ้ำของเส้นเลือด

**ผลการศึกษา** ผู้ป่วย 46 ราย (ชาย 49, หญิง 17) ที่ได้รับการขยายเส้นเลือดหัวใจตีบด้วยบอลลูนเป็นผลสำเร็จ มีอายุเฉลี่ย  $69 \pm 19$  ปี จำนวนตำแหน่งที่ตีบ 88 ตำแหน่ง (LAD 63%, LCX 34%, RCA 19%) ลักษณะของเส้นเลือดที่ตีบเป็นแบบ A 9% แบบ B 30% แบบ C 61% ร้อยละ 54 ของผู้ป่วยมีเส้นเลือดหัวใจตีบ 1 เส้น และร้อยละ 46 มีเส้นเลือดหัวใจตีบหลายเส้น ระยะเวลาเฉลี่ยระหว่างการทำการบอลลูนและการติดตามโดยการฉีดสีเส้นเลือดหัวใจเท่ากับ  $6.1 \pm 2.7$  เดือน จากการฉีดสีพบว่ามีการตีบซ้ำร้อยละ 58 ของผู้ป่วย Tc-99m MIBI มีความไวในการตรวจหาการตีบซ้ำมากกว่าอาการเจ็บหน้าอกอย่างเดียว (85.0% vs 39.4%,  $p < 0.005$ ) หรือการตรวจคลื่นหัวใจในขณะออกกำลังกาย (85.0% vs 63.6%,  $p < 0.05$ ) ความแม่นยำของการตรวจ Tc-99m MIBI ในการตรวจหาการตีบซ้ำเท่ากับ 80%

**บทสรุป** Tc-99m MIBI ร่วมกับ SPECT imaging มีความไวในการตรวจหาการตีบซ้ำภายหลังจากการทำการบอลลูนขยายหลอดเลือด ดีกว่าการใช้การเจ็บหน้าอกหรือการตรวจคลื่นหัวใจในขณะออกกำลังกาย

**คำสำคัญ** : Technetium 99m-Sestamibi, การทำการบอลลูนขยายหลอดเลือด, การตีบซ้ำ

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