Chapter 3

METHODOLOGY

Research Design : Prospective descriptive study for evaluating a new diagnostic test

Research Methodology : This study was performed in one group of patients who underwent successful PTCA by using exercise stress test Tc-99m sestamibi SPECT imaging for detection of restenosis after successful PTCA. This test was compared with coronary angiographic study which is a gold standard. The interpretation of both results was blind and dependent method for elimination a bias.

Sample Size Justification

To determine the acceptable sensitivity value of Tc-99m sestamibi SPECT imaging for detection of restenosis after PTCA is 95 %

$$p = 0.95$$

$$q = 1 - p = 0.05$$

To determine confidence interval value 95 %, $\alpha = 0.05$

$Z = 1.96$ (by Table)

d = error value of sensitivity of Tc-99m sestamibi SPECT imaging is 10%

Maximum permissible error = 0.1x p

$$n = \frac{Z^2 p q}{d^2}$$

$$n = \frac{(1.96)^2 \times 0.95 \times 0.05}{(0.1 \times 0.95)^2} = 20 \text{ lesion sites}$$

Due to the chance of restenosis after PTCA was 40 % or 0.4

Then, A sample size should be at least $\frac{20}{0.4}$ = 50 lesion sites

Patient Group

Between November 1995 and January 1997, 46 patients who underwent successful PTCA at Chulalongkorn University Hospital were enrolled in the study.

Inclusion criteria

All ages and sexes of patients with the history of coronary artery disease such as chronic stable angina, unstable angina will be interviewed and examined by the investigator. Patients will be enrolled into the study if:

1. Coronary angiographic findings show more than 75 % stenosis of diameter of vessel which is suitable for PTCA. The lesion may be single or multivessel disease.
2. The patients have abnormal exercise stress test or Tc-99m sestamibi SPECT imaging and have undergone coronary angiography which shows the same findings as shown in 1.
3. Patients have restenosis after previous PTCA and repeated coronary angiography findings show a lesion which is suitable for PTCA again, and the patients have recurrent chest pain.
4. Patients have undergone PTCA with stent placement.

Exclusion criteria

1. The patients could not perform exercise stress test.
2. The patients have the coexist diseases (such as malignancy, end stage renal failure, AIDS) that decrease longivity of life.
3. The patients have complications after PTCA and require emergency coronary bypass surgery such as acute abrupt closure, acute myocardial infarction etc.
4. The patients develope severe congestive heart failure (CHF, NYHA class 3,4) during the follow-up.
5. Serum creatinine levels over 2.0 mg/dl.

Data collection

We identified 46 patients with coronary artery disease and planned to performed percutaneous transluminal coronary angioplasy (PTCA). This included two groups of patients- one was with abnormal exercise stress test Tc-99m sestamibi SPECT imaging and with more than 75% (significant) stenosis of diameter at least one vessel, the other included restenosis patients with repeated PTCA. Then history taking and physical examination were filled in the protocol:

Demographic data : age, sex, address, telephone number

Risk factor of coronary artery disease : old age, cigarette smoking, hypercholesterolemia, hypertension, diabetic mellitus, history of sudden cardiac death

Indication of PTCA : stable angina, unstable angina, acute myocardial infarction (rescue PTCA), post myocardial infarction angina, restenosis after PTCA, congestive heart faiulre

History of previous myocardial infarction, PTCA, CABG

Result of exercise stress test, Tc-99m sestamibi SPECT imaging, Coronary angiography, Types of lesions for PTCA(table 5)

The follow-up with successful PTCA patients involved evaluation of clinical chest pain, exercise stress test and Tc-99m sestamibi SPECT imaging:

Week 3 and 4 : for determining whether the patient had complete or incomplete revascularization

Month 3 : for detection of early restenosis after PTCA

Month 6 : for detection of restenosis after PTCA at the end of the study

In case the patients developed recurrent chest pain at any time during the follow up, they had to take exercise stress test and Tc-99m sestamibi SPECT imaging as soon as possible.

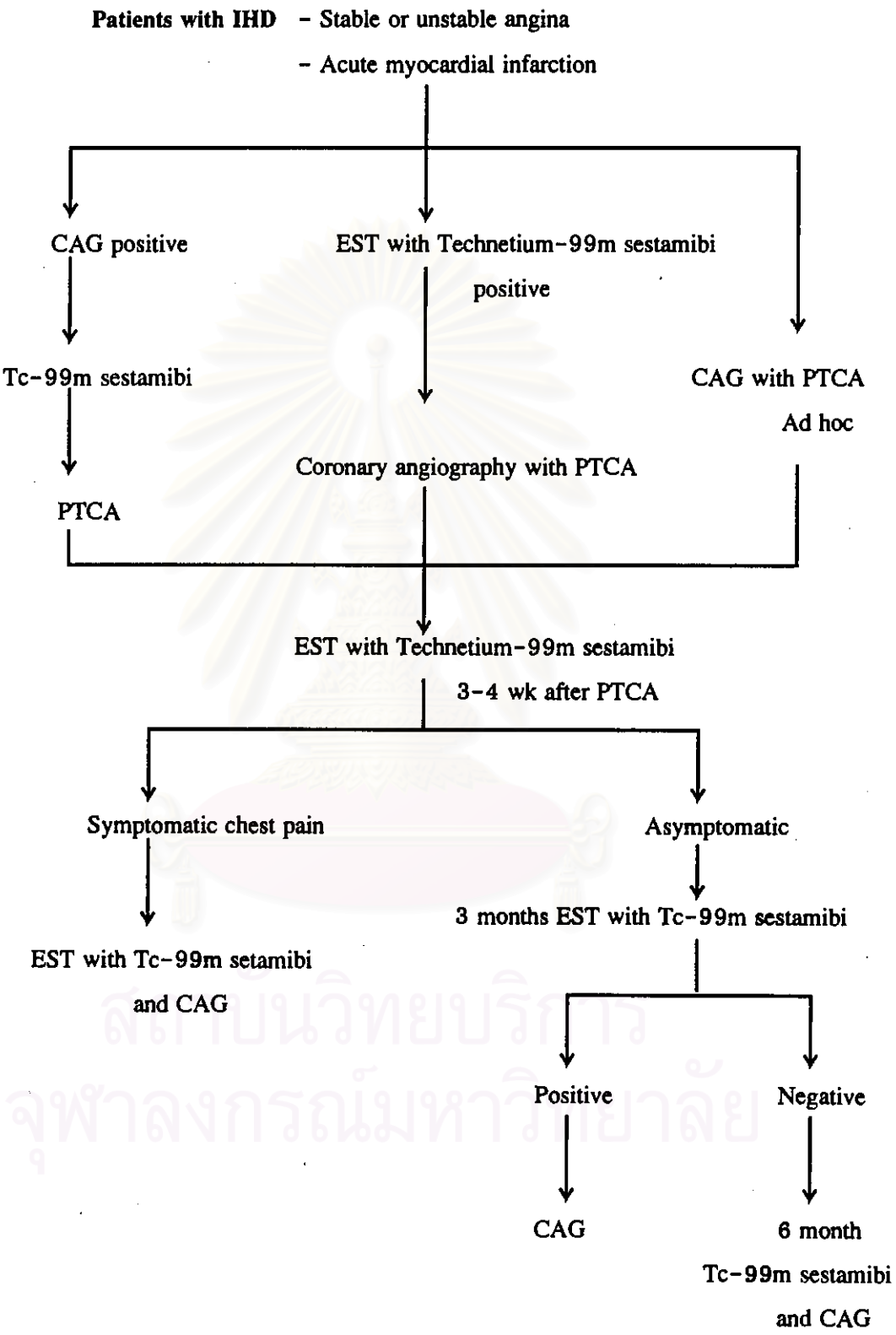
At month 6 of the study in asymptomatic patients or at anytime that the patients developed typical chest pain or had abnormal Tc-99m sestamibi SPECT imaging in which restenosis was suspected. The patients would have to repeat coronary angiography to confirm the diagnosis.

Table 5 Anticipated success in various lesions, according to morphological types(32)

Type A lesion (high [>85%] success with low risk)	
Discrete (<10 mm long)	Little or no calcification
Concentric	Less than total occlusion
Readily accessible	Not ostial
Nonangulated segment	No major branch involvement
Smooth contour	Absence of thrombus
Type B lesion (moderate [60-85%] success with moderate risk)	
Tubular (10-20 mm long)	Moderate calcification
Eccentric	Total occlusion < 3 months
Moderate tortuosity	Ostial location
Moderate (45-90 degree) angle	Treatable bifurcation lesion
Irregular contour	Some thrombus present
Type C lesion (low [<60%] success with high risk)	
Diffuse (<20 mm long)	Total occlusion > 3 months
Excessive tortousity of proximal segment	Bifurcation with nonprotectable side branch
Extremely angulated segments > 90 degree	Degenerated vein graft

(From Rya,T. J., Faxon, D. P., Gunnar, R. M.,et al. Guidelines of percutaneous transluminal coronary angioplasty. A report of the American College of Cardiology/American Heart Association Task Force on Assessment of diagnostic and therpeutic cardiovasculae procedures. J. Am. Coll. Cardiol. 1988;12:529)

Diagram showing the sequence and methods of this study



Methods and interpretation of the results

Exercise stress test : The study used standard treadmill exercise test and performed by Bruce or Naughton protocol. This exercise stress test was symptom limited. The patients could stop the exercise when they had exhaustion or dyspnea or developed anginal chest pain. The end point of exercise test was more than 85% of target heart rate.

Target heart rate = 220 - age of patient beats/min

Data recording : exercise time, % maximum heat rate, symptom of patients, ECG findings

If he patients could not perform exercise test to achieve 85 % of target heart rate or less than 65% in case of receiving beta blocker, the test was considered inadequate.

Interpretation:

1) Negative or nondiagnostic exercise stress test was defined by the following criteria:
   - 1.1) Normal electrocardiographic (ECG) study and no chest pain during the exercise test
   - 1.2) There was ST-T wave changes from ischemia or secondary ST-T changes from LV hypertrophy and bundle branch block at baseline before exercise in leads 4-6 or 2,3,AVF which could interfere with the interpretation of the result.
   - 1.3) Equivocal ST-T wave changes such as upslope ST changes, or ST depression less than 0.1 mV.

2) Positive exercise stress test
   - 2.1) Patients developed typical anginal chest pain during the exercise.
   - 2.2) Abnormal ECG findings
     - Ischemic pattern (Horizontal or downslope ST

depression >0.1 mV in leads V4-V6 or >0.2 mV in leads 2,3,AVF or ST elevation >0.1 mV in leads without Q wave) occurring during or after the exercise (recovery phase)

- Serious symptomatic ventricular Tachyarrhythmias

Technetium 99-sestamibi SPECT imaging(10,11,12) : We used a same-day imaging protocol involving a low-dose resting study followed by a high-dose stress study. These approach allowed the entire study to be completed within 5 hours, yielded high image quality for the more important stress study and circumvented the reported problem of difficulty in assessing defect reversibility when the stress study was first performed. The higher Tc-99m sestamibi dose for the stress day resulted in high-quality stress imaging and allowed for multiple gated tomography for assessment of wall thickening and wall motion.

Patient preparation(33): The standard doses given to a 70-kg patient were 8 to 10 mCi for the rest and 22 to 30 mCi for the exercise study, which is under the evaluation of the Food and Drug Administration. To ensure ideal image quality, we used the higher doses of 10 mCi and 30 mCi for an average-size man for rest and stress, respectively, and scaling up for heavier patients. The patient was instructed to drink 8 oz of whole milk or ingest a light, fatty meal 15 minutes before imaging to promote tracer clearance from the gallbladder. Alternatively, cholecystokinin could be administered intravenously for the same purpose. Resting images were acquired 1 hour after the injection.

An interval of 3 to 4 hours was recommended between rest and stress to allow the radioactivity from the resting dose to decay by 29% to 37% by the time of stress imaging. Symptom-limited treadmill exercise was performed, and Tc99m-seatamibi was injected at peak stress. Exercise was continued for at least 1 minute after the injection, and imaging was begun 30 minutes after the exercise. Due to slightly slower blood clearance than observed with thallium-201, the authors suggest continuing exercise at one stage lower than the maximal level than the maximal level for an additional 1 minute, stopping exercise 2 minutes 2 minutes postinjection.

Imaging can be performed with the patient in either the supine or prone position. Cardiac tomography with the patient in the prone position results in reduced inferior attenuation compared with supine imaging, but frequently produces an artifactual anteroseptal defect. Since supine imaging allows a shorter radius of rotation and thus superior image

quality, this position is preferred except when specific attention is being focused on the inferior wall.

Gated SPECT imaging

Due to Tc-99m sestamibi's redistribution and its long myocardial residence time, gated SPECT imaging is feasible with this agent. Gated SPECT may allow simultaneous assessment of ventricular function and myocardial perfusion. Our study also evaluated the multigated cardiac -blood pooled study in the second day by using Tc-99m label red blood cell. We could evaluate the left ventricular function by measuring end-diastolic and end- systolic volumes, ejection fraction and providing information regarding wall thickening and regional wall motion abnormality.

Interpretation of Tc-99m sestamibi SPECT imaging

Even when optimized qualititative analysis software is available, visual interpretation will remain an integral part of the final analysis of Tc-99m sestamibi SPECT studies. The following sections describe a systemaic approach to this visual assessment.

Quality control

At the time of imaging interpretation, several aspects of quality control should be checked. Since the patient's motion is the most common source of artifact on SPECT studies, every study should be evaluated for the presence or absence of motion. Other aspects of quality control that should be evaluated at the time of interpretation include slice alignment, axis selection, and intensity.

Display

Recently, committees of the American College of Cardiology, the American Heart Association, and the Cardiovascular Council of the Society of Nuclear Medicine have considered recommendations to standardize the image display for myocardial perfusion SPECT studies. In this study we displayed Tc-99m sestamibi in the following standard fashion.

The tomographic slices should be displayed in three different views: short axis, vertical long axis, and horizontal long axis(Fig 1). The short-axis view is displayed as though one is looking at the left ventricle end on, beginning at the apex and working through to the base of the heart. Preferably, appropriately aligned stress and rest images are

shown simultaneously. Images displayed should begin with the first image demonstrating the left ventricular cavity and base of the heart.

The vertical long-axis view is displayed with the apex either pointing to the left, as in an RAO contrast ventriculogram. The anterior wall is displayed on top and the inferior wall on the bottom. All slices containing left ventricular cavity should be displayed, beginning at the septal wall.

The horizontal long-axis view is displayed with the apex pointing to the top, the posterolateral wall on the right side, and the septal wall on the left side. Cavity-containing slices are displayed.

We routinely employed a semiquantitative visual analysis system that they previously developed for thallium-201 SPECT interpretation. For semiquantitative visual analysis, three sets of slices from the short axis views corresponding to the apical, midventricular, and basal regions of the left ventricle were scored. Each of these regions was divided into six segments. The vertical long axis was also divided into six segments, and the mid-left ventricular vertical long-axis slice was scored. The horizontal long-axis view is divided into five segments and the mid-horizontal long-axis view was selected for scoring.

Each segment was scored with a five-point scoring system:

0 = normal Tc-99m sestamibi uptake

1 = slight reduction of uptake that is not clearly abnormal

2 = moderate reduction of uptake, usually implying significant abnormality

3 = severe reduction of uptake

4 = absence of Tc-99m sestamibi uptake

In the CSMC approach, if two or more segments have a score greater than 2, the study is probably considered definitely abnormal, depending on the number of segments affected and the degree to which they correspond to a standard vascular territory. A single segment with a score of 3 or 4 is usually sufficient to consider a study definitely abnormal. When the resting stage and the exercise stage were compared, 2 following groups of myocardial defects were indicated.

1) Stress induced-reversible filling defect defined as myocardial ischemia if there was improvement of at least 1 point on the visual scale from exercise to redistribution imaging

2) Irreversible (fix) filling defect defined as myocardial infarction if there was no changed of filling defect from exercise to redistribution imaging

From the findings of short-axis, vertical long-axis, and horizontal long-axis views, we could interpret individual coronary artery territories.

Areas of myocardial perfusion filling defect	**correspond coronary artery territory**
Anterior wall, Anteroseptal, apical wall	Left anterior descending artery
Anterolateral wall	Left anterior descending artery or Left circumflex coronary artery
Inferolateral wall	Left circumflex coronary artery
Inferoseptal wall	Right coronary artery (RCA)

With this visual interpretative scheme, the score are individually assigned and then evaluated for their overall pattern. How abnormalities are ascribed to individual coronary artery territories is illustrated in Fig 1 and 2, which shows a polar map approach (bull eye view) that we have used for thallium-201 imaging.

Region of myocardial ischemic areas	**correspond to coronary artery territory**
Anterior wall, apex, and upper septum	Left anterior descending coronary
Posterolateral wall	Left circumflex coronary
Inferior wall	Posterior descending coronary, usually supplied by RCA

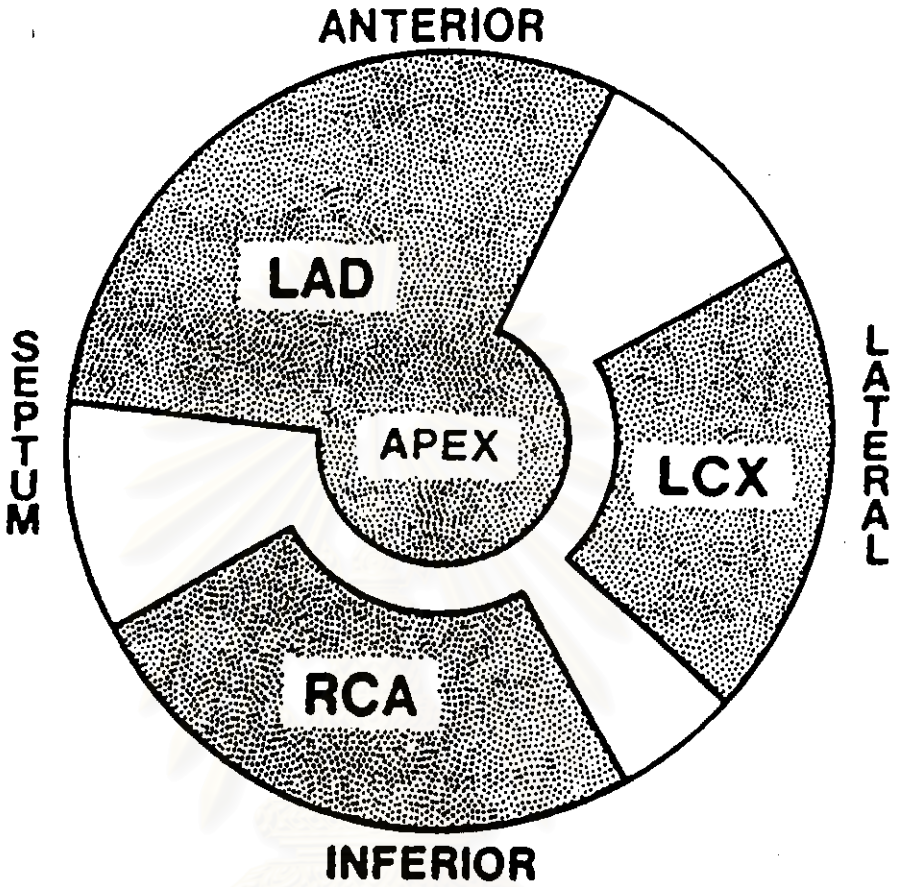


Fig 1. Diagram showing the relationship between defects on Tc 99m sestamibi SPECT inages and abnormalities of underlying coronary. This figure illustrates the conventional two-dimensional polar map used for Tc-99m Sestamibi SPECT imaging

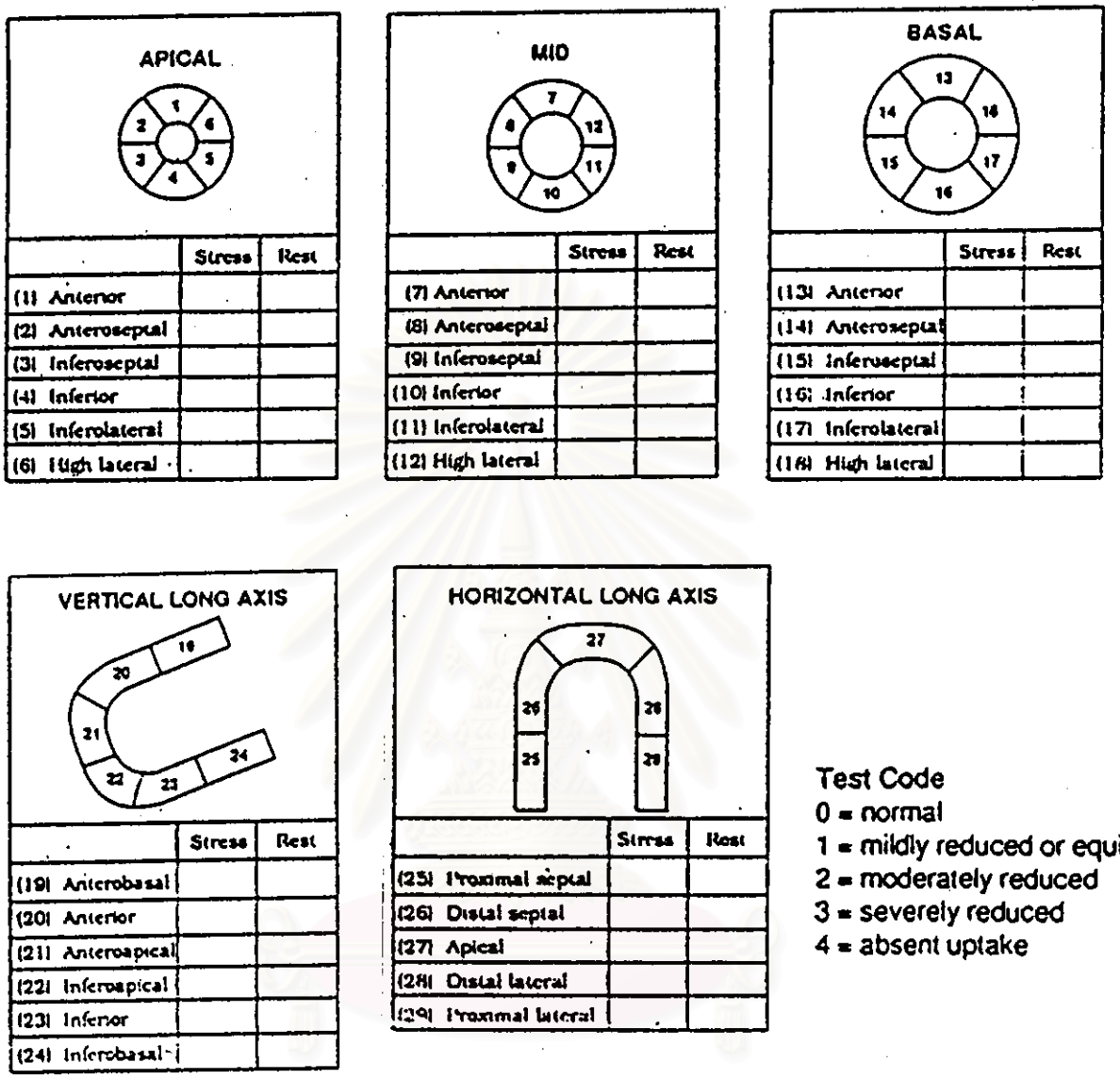


Fig 2. Diagram of segments observed in the short-axis, vertical long-axis, and horizontal long-axis views as shown on CSMC scoring sheet. The scoring sheet also gives the anatomic terms for the individual segments. (Reprinted with permission from Cedars Sinai Medical Center, Los Angels, CA.)

Evaluation of revascularization after PTCA by using Tc-99m sestamibi SPECT imaging was taken in the first month after procedure and category

1) Complete revascuralization is absolutely disappearance of myocardial ischemia after PTCA.
2) Partial revascularization is partial improvement of myocardial ischemia after PTCA
3) Unsuccessful PTCA is deterioration or progression of myocardial ischemia after PTCA

After month 1, we followed up Tc-99m sestamibi for detection restenosis or disease progression by using the following criteria:

1) Restenosis: I

1.1) There was deterioration or progression of myocardial ischemia in the territory of the dilated vessel after having complete revascularization.

1.2) There was persistent myocardial ischemia and no further improvement after 3 to 6 months.

1.3) There was changing of myocardial ischemia (reversible filling defect) to myocardial infarction(fixed filling defect).

However, at 1 month, if there was still persistent or worsening of myocardial ischemia from Tc-99m MIBI scan whereas the patients were asymptomatic, we did not perform CAG promptly, but we will follow-up Tc-99m MIBI scan again at 3 month. Because this abnormal findings may be due to delay of myocardial perfusion after revascularization or interventional induced myocardial ischemia which is transient and eventually improves in 2 or 4 months later.

2) No restenosis

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 .

3) Disease progression

3.1) There was a new ischemic area in the territory area of previous normal nondilated arteries.

Figure 3-10 show the examples of Tc-99m MIBI scan imaging for detection of restenosis after PTCA.

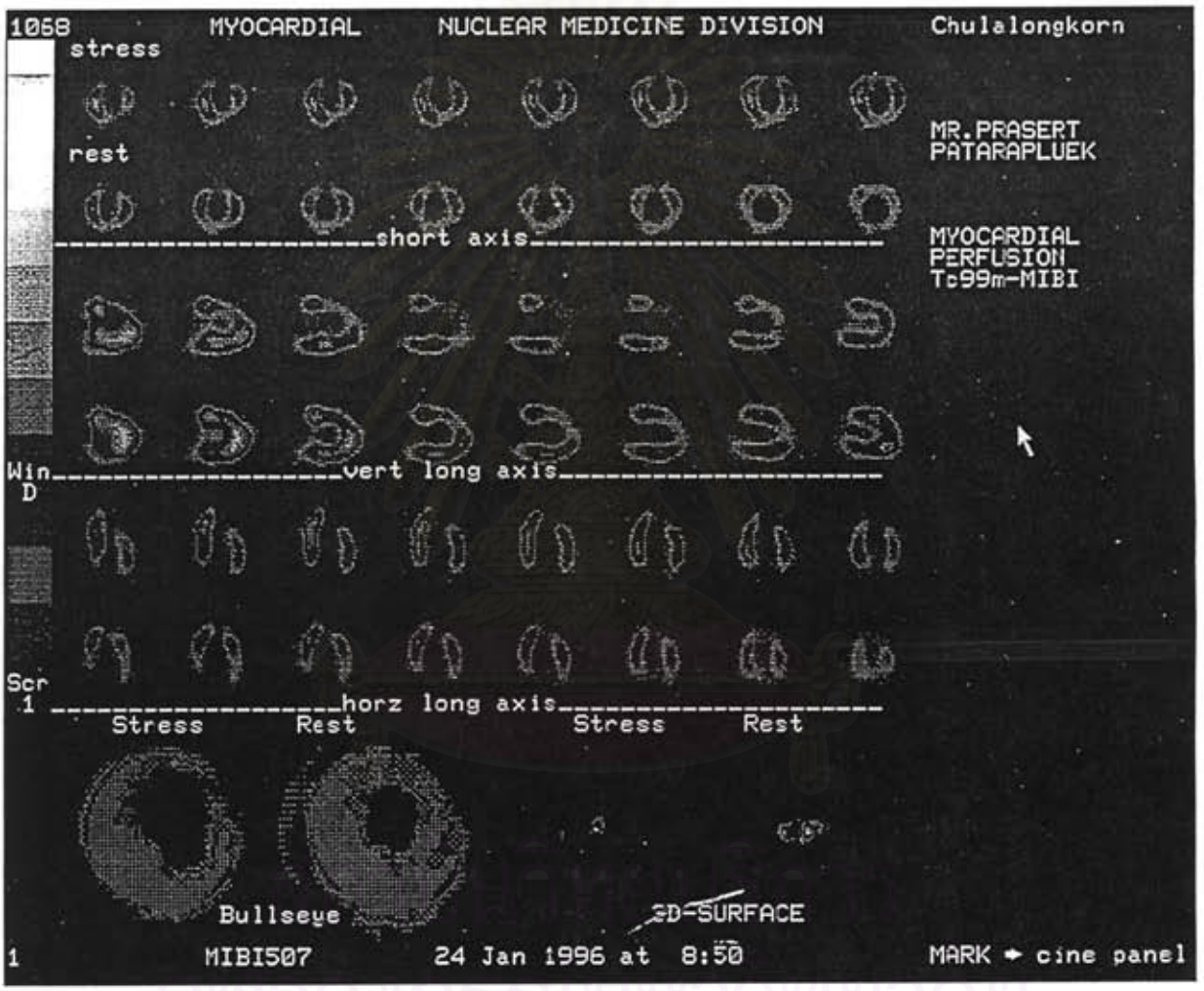


Figure 3 Tc-99m Sestamibi SPECT images before PTCA from a 73 year male patient with a reversible filling defect (myocardial ischemia) at anterior and apical wall corresponding to a significant left anterior descending artery (LAD)

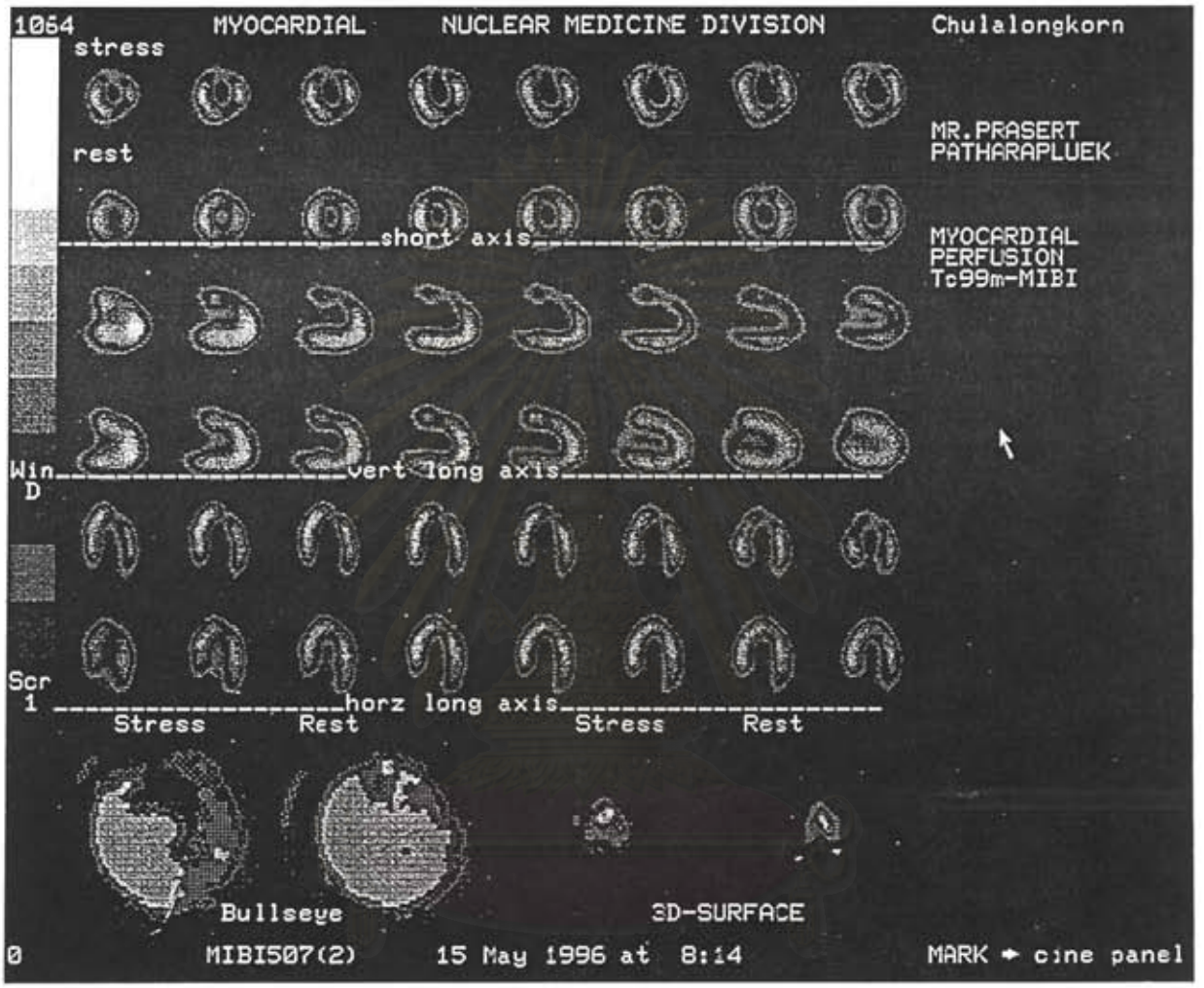


Figure 4 Stress and rest Tc-99m Sestamibi SPECT imaging after PTCA month 3 showing much improvement of myocardial ischemia at the anterior and apical wall

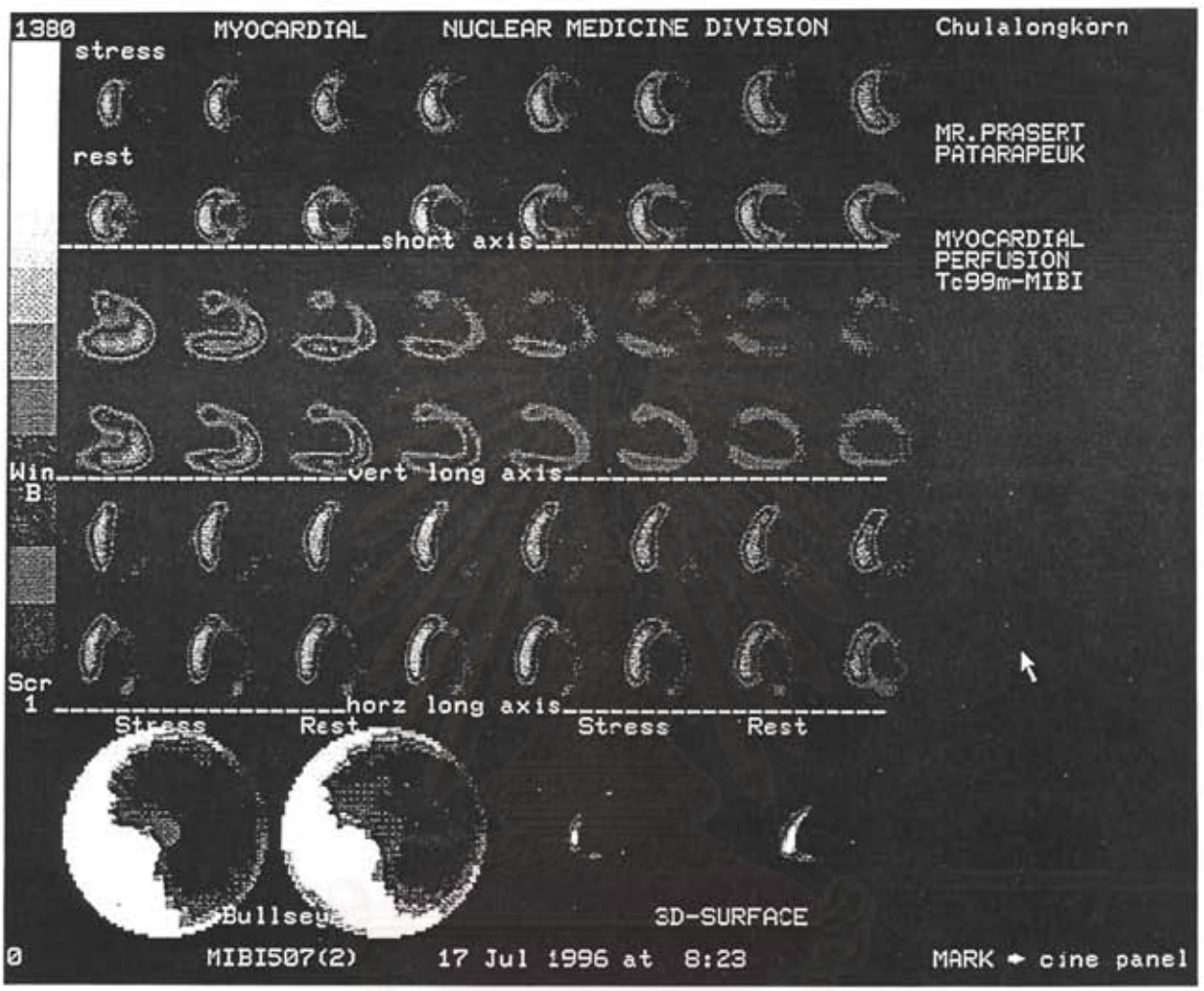


Figure 5 At the 6 months follow-up, Tc-99m Sestamibi SPECT imaging showed worsening of reversible filling defect of the anterior, lateral and apical wall corresponding to angiographic restenosis of LAD

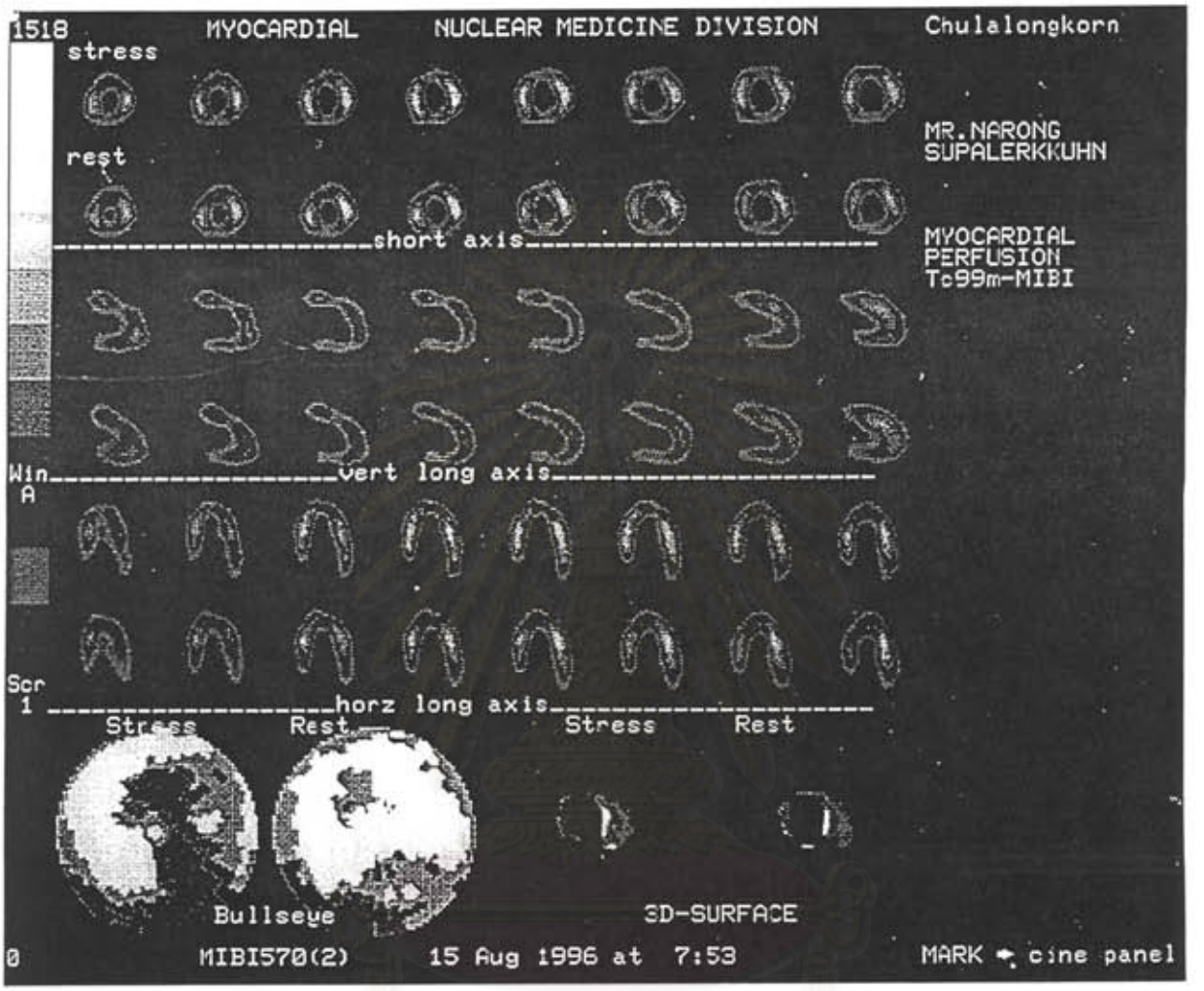


Figure 6 Stress and rest Tc-99m Sestamibi SPECT imaging after PTCA month 1 from a 59 year male patient showing much improvement of reversible filling defect (myocardial ischemia) at anterolateral and apical wall

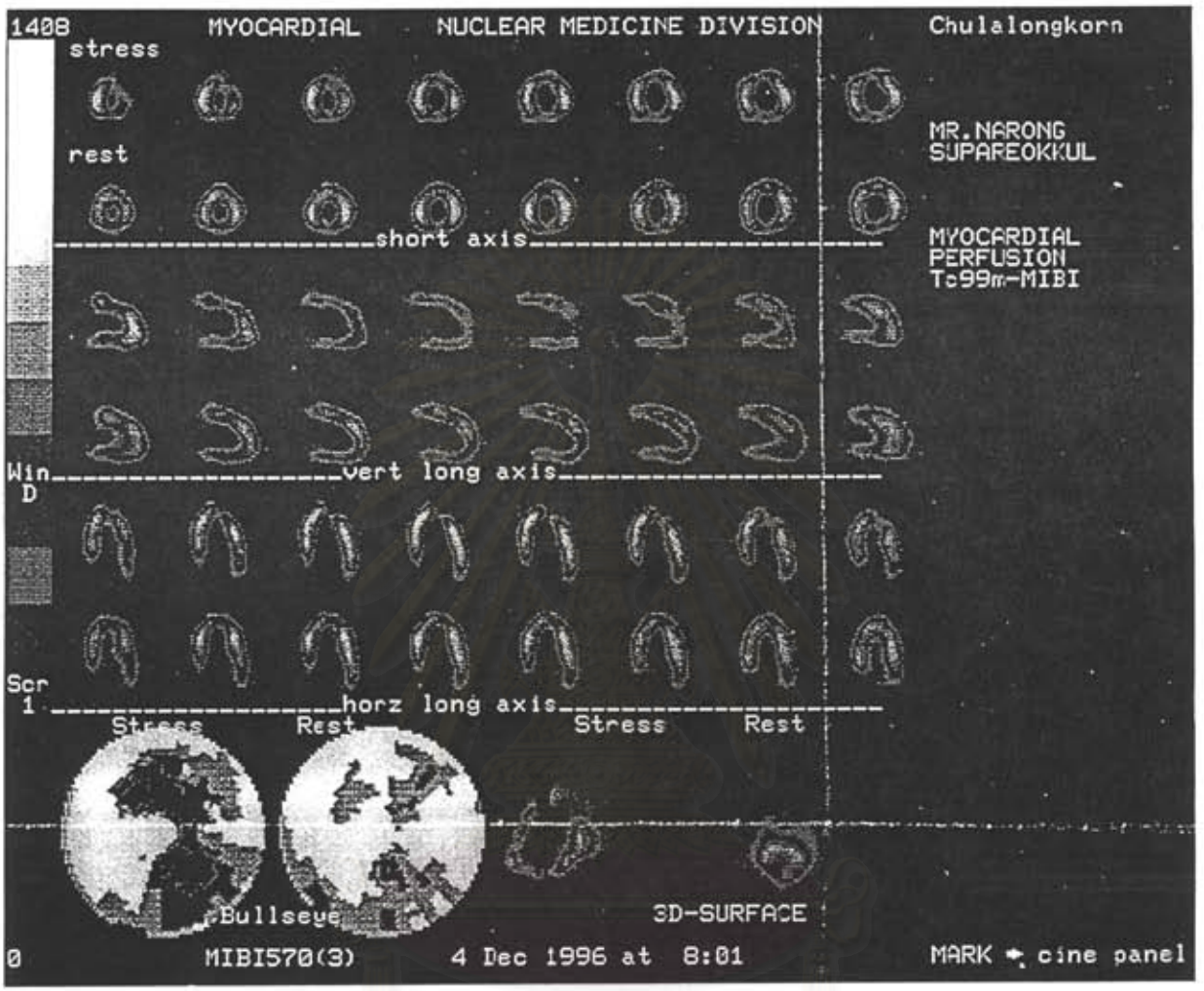


Figure 7 At month 3 of the follow-up, the stress study reveals deterioration of ischemia at anterior wall with suggested restenosis of LAD and corresponding to coronary angioghraphy

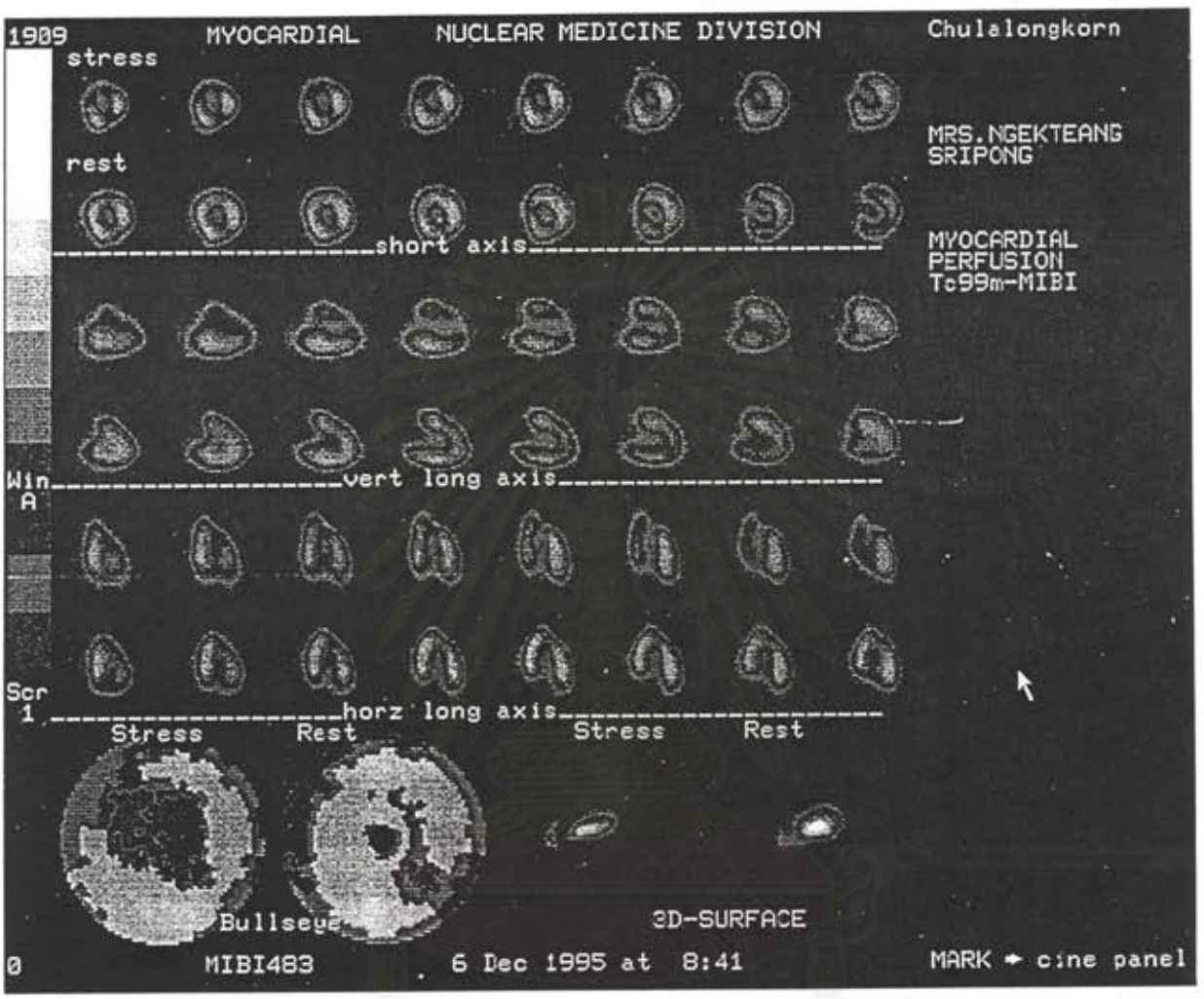


Figure 8 Tc-99m Sestamibi SPECT images before PTCA from a 65 year female patient with a reversible filling defect (myocardial ischemia) at anteroseptal and apical wall corresponding to a significant LAD coronary artery stenosis

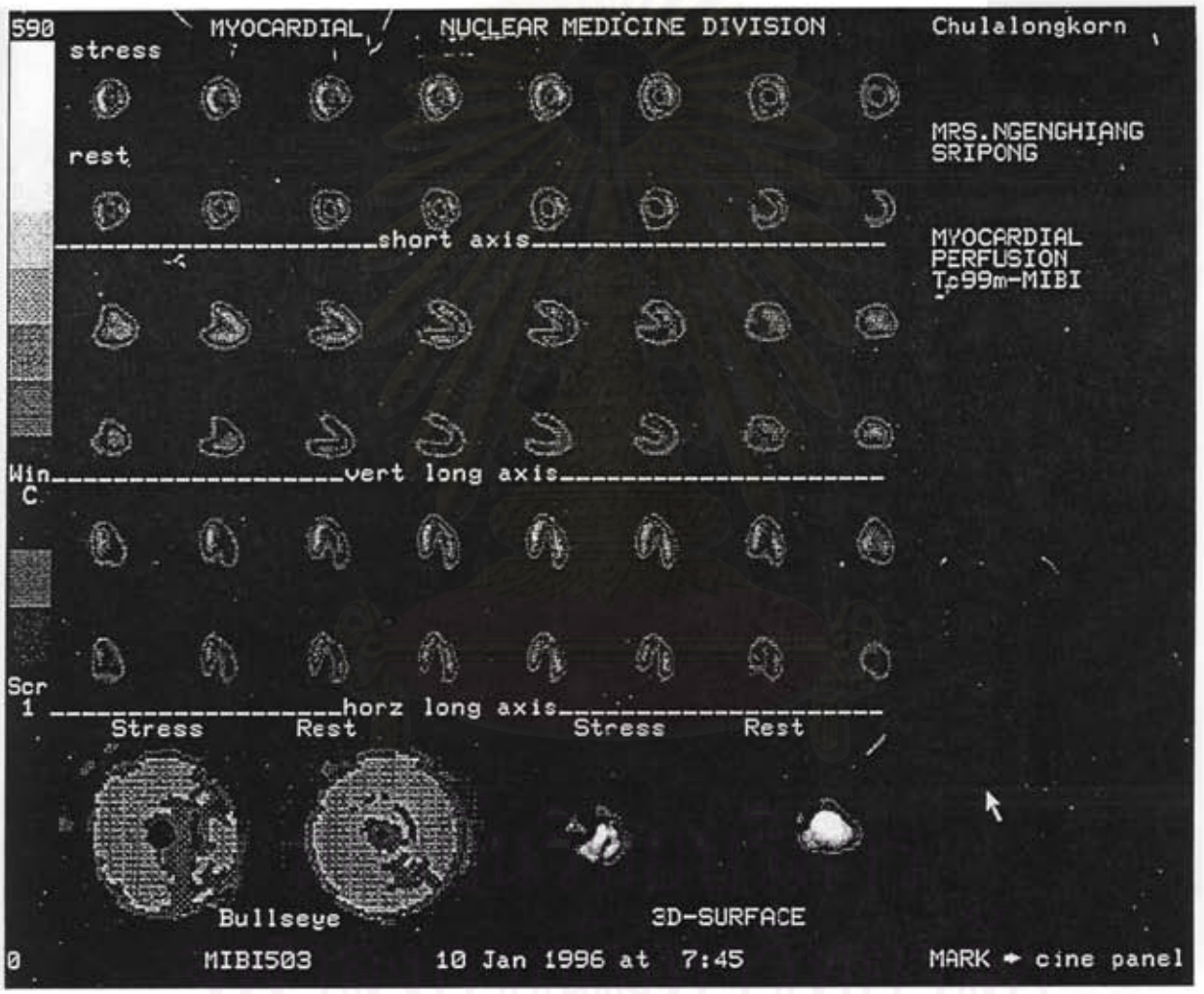


Figure 9 At month 1 of the follow-up, there is much improvement of myocardial ischemia at anterior, anterolateral and inferolateral wall.

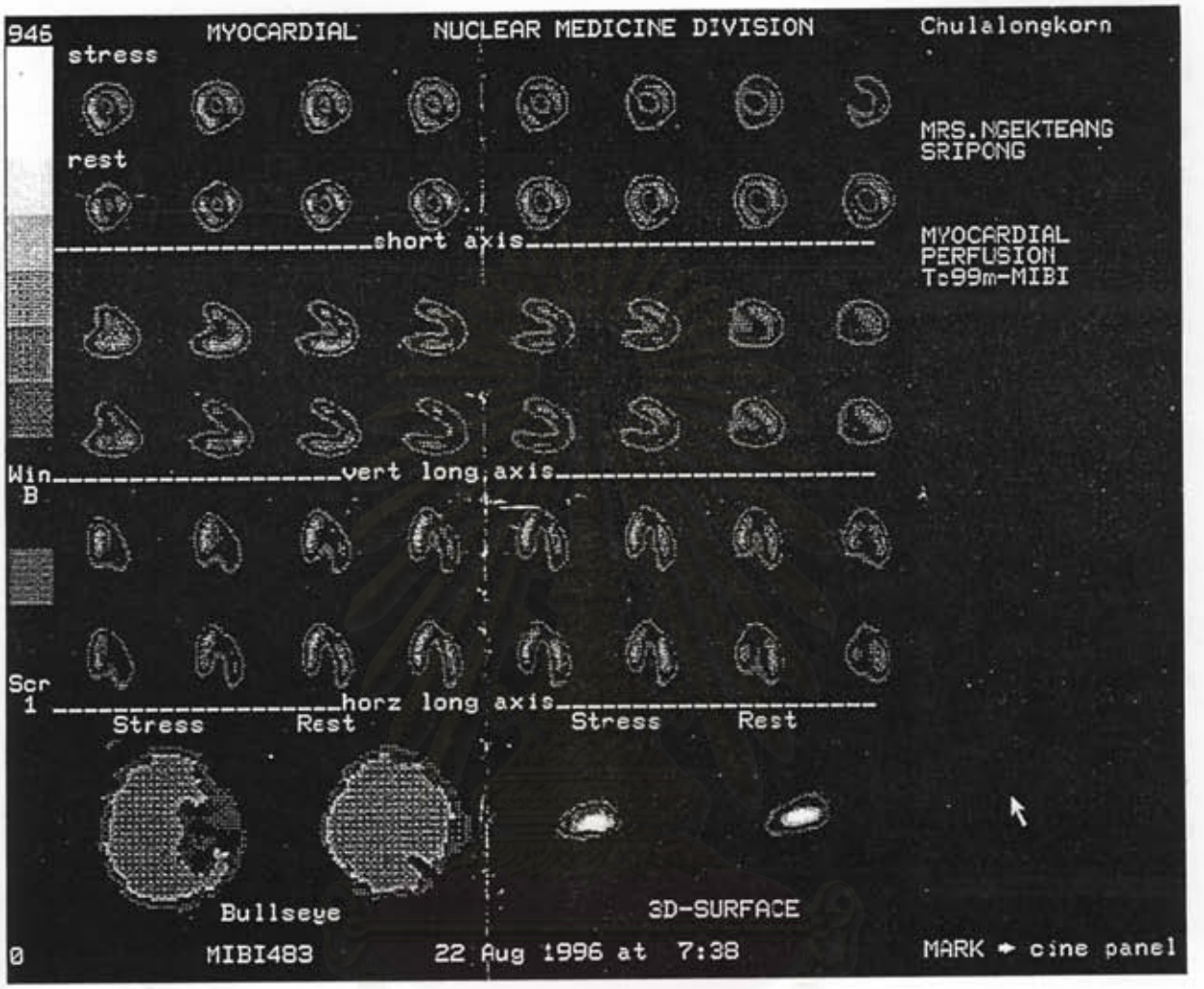


Figure 10 At month 6 of the follow-up, Tc-999m Sestamibi showed improvement of myocardial ischemia at anterior, anterolateral and inferolateral wall corresponding to a nonsignificant stenosis (<50 % stenosis) of previous dilated LAD lesion

Coronary angiography

Coronary angiography was be repeated at month 6 or the end of the study at anytime when the patients showed the evidence of restenosis such as recurrence chest pain, and abnormal Tc-99m sestamibi which suggested restenosis in asymptomatic patients. Coronary angiography was performed in multiple views and were interpreted visually without knowledge of the initial noninvasive test results. In addition, in the equivocal cases, quantitative analysis of the dilated stenosis was obtained in the same angiographic projection for each angiogram by means of our computer-based coronary angiographic analysis system.

1) Clinical angiographic restenosis was an increase of the diameter stenosis of the dilated lesion above the 50 % level

2) Disease progression was defined in the case that increased percentage of stenosis in the previous nondilated arteries or detection of new coronary stenosis in the previous normal nondilated arteries

Results were presented as percentage stenosis of coronary artery, such as left anterior descending artery, left circumflex artery, right coronary artery.

Follow up

After successful PTCA, the patients was followed up for three times:

First time at week 3 and 4 : For evaluation of complete or partial revascularization after PTCA

Second time at month 3 : For evaluating the changing of myocardial perfusion and detection early restenosis

Third time at month 6 : For detection restenosis at the end of the study

Statistical Analysis

1) Sensitivity, Specificity, Positive predictive value, Negative predictive value and Accuracy for evaluation of detection restenosis after PTCA by using clinical recurrent chest pain, exercise treadmill test, Tc-99m sestamibi SPECT imaging.

2) Sensitivity, Specificity and Accuracy in the detection of restenosis of individual vessels by using Tc-99m sestamibi SPECT imaging

3) Proportional t-test for comparision the accuracy between clinical recurrent chest pain, exercise treadmill test, and Tc-99m sestamibi SPECT imaging

4) Proportional t-test for comparision sensitivity, specificity, accuracy, postive and negative predictive value for detection of restenosis by Tc-99m Sestamibi SPECT imaging in individual vessel and any type of CAD

Ethical Consideration

There would be no ethical problem because the exercise treadmill test and Tc-99m sestamibi SPECT imaging were noninvasive standard test and no harmful with approval by the Food and Drug Administration for the assessment of myocardial perfusion. According to the expensive cost of test, we selected the patients who could reimburse from the government or had pension for alleviation the response of the patients. All patients in this study were conformed by verbal consent before enrollment in the study.

Limitations of the study

Population of the sample in this study could not represent the whole population; because of the expensive cost of the test, the patients who could reimburse from the government or had pension were selected. Therefore the percentage of restenosis from this study could not be calculated.