Chapter 1

LITERATURE REVIEW

Introduction

The introduction of percutaneous transluminal coronary balloon angioplasty (PTCA), in 1977 by Andreas Gruentzig has led to dramatic fundamental changes in the treatment of patients with stable and unstable angina pectoris who have single and multi-vessel obstructive coronary artery disease.(1) The procedure successfully dilates vessels more than 90% of the time by clinical criteria, and the occurrence of acute complications requiring surgery is less than 2%. Unfortunately, restenosis after an initially successful PTCA remains a significant problem, occurring in 30% to 40% of patients within the first 6 months after the procedure.(2,3) Additionally, since there has been no effective prevention for restenosis; therefore the long-term efficacy of PTCA is uncertained.

Although percutaneous transluminal coronary angioplasty is performed most frequently to relieve anginal symptom which is unresponsive to medical treatment, unfortunately, as has been well reviewed, symptom status is not a useful clinical indicator for detection of restenosis. The percentage of patients with symptoms who have restenosis by angiography averages 67% (range, 48% to 92%) is based on nine studies.(3) Thus the positive predictive value of symptoms for restenosis is 67%. Conversely, the negative predictive value of symptoms averages 85% (range, 70% to 98%). In other words, about 15% of patients with angiographic restenosis will be symptom-free whereas 33% of patients without restenosis will have symptom recurrence. Therefore, symptom is not a good predictor of restenosis.

Coronary angiography has been used to detect restenosis and to aid decision making about the need for further intervention. However, it is time-consuming, costly and risky. Many studies have examined the value of noninvasive testing, including an exercise treadmill test alone(4,5) or in combination with thallium-201 scintigraphy(6,7,8) and exercise radionuclide angiography for detecting restenosis after successful PTCA (Table 1).

Table 1 Result of detection restenosis by clinical symptom and noninvasive tests(9)

	Positive predictive value (%)	Negative predictive value (%)
Symptoms	44-92	70-95
Treadmill exercise test		
without Thallium	30-60	50-95
with Thallium	40-90	70-96
Radionucide angiography		
exercise test	40-80	80-95

(Derived from Freed M, Grines C. Manual of Interventional Cardiology 1992:241)

From table 1, many studies have shown that exercise testing alone or in combination with thallium-201 imaging yields predictive values similar to symptoms. Between noninvasive tests, the positive and negative predictive values of exercise testing combined with thallium imaging are better than exercise testing alone and can be used for screening restenosis after PTCA. Additionally, the negative predictive value of exercise testing conbined with thalliun-201 imaging is better than the positive predictive value. Thus a negative result makes restenosis unlikely. In short, if restenosis is suspected in a patient 6 months after PTCA based on symptoms, exercise testing with thallium imaging will be the test of choice. If the test is negative, the predictive value for the absence of restenosis is better than 90%. However, if the test is positive, the likelihood of restenosis ranges from 37% to 89% with an average of 67%.(3) Thus, a positive test will require cardiac catheterization in almost all situations to confirm the true presence of restenosis.

Technetium-99m (Tc-99m) sestamibi is a new myocardial perfusion imaging agent with physical characteristics superior to those of thallium-201.(10,11,12,13) In December 1990, treadmill exercise test combined with Tc-99m sestamibi was approved by the Food and Drugs Administration for the assessment of myocardial perfusion in chronic coronary artery disease(10,14) and efficacy in acute myocardial infarction.(15)

The advantages of Tc-99m Sestamibi tracers over thallium-201 are summarized in Table 2.

Table 2 Comparision of Tc-99m Sestamibi and Thallium-201(10,11,12)

Property	Tc-99m sestamibi	Thallium-201
Availability	Generator-produced and thus available 24 hr.	Cyclotron-produced and thus available on order from vendor
Energy (for gamma energy camera)	Optimum energy and thus high resolution	Lower-than-optimum energy and thus lower resolution
Radiation (dosimetry)	Shorter half-life and thus greater dose can be administered	Longer half-life and thus lower dose must be administered
	Cardiac gating First-pass study	No cardiac gating Only"equilibrium" study feasible
Redistribution	Minimal, allowing uncoupling of injection and imaging times	Present, necessitating imaging soon after injection, but also making Tl 201 useful for viability
	Cannot distinguish resting ischemia from infarction	assessment in resting ischemia

(From Daneil S. Berman, Hosen Kiat, Kenneth Van Train, et al. Technetium 99m Sestamibi in the Assessment of Chronic Coronary Artery Disease. Seminars in Nuclear Medicine 1991;21:191)

The radionuclide used, Tc-99m, is available via generator 24 hours a day. In contrast, cyclotron-generated Thallium-201 requires off-site delivery. The higher 140-keV energy of the monoenergetic Tc-99m is ideal for standard gamma camera imaging. On a counter-count basis, the emissions of Tc-99m result in higher resolution because they undergo less scatter and attenuation and are associated with a brighter flash within the scintillation crystal of the gamma camera. It is important that because of the shorter 6 hour half life of Tc-99m sestamibi, a radiation dose which is approximately ten times stronger than thallium-201 should be injected. Although the myocardial extraction fraction of Tc-99m sestamibi is lower than that of thallium-201, the uptake of Tc-99m sestamibi is parallel to that observed with thallium-201 in the myocardial flow ranges associated with rest and exercise. The higher dose, coupled with the high net extraction of Tc-99m

sestamibi, results in a higher count rate. The high count rate, in turn, permits the use of gating to improved resolution, whether single photon emission computerized tomography (SPECT) or planar imaging is used, and the performance of first-pass acquisition to assess ventricular function ,regional myocardial wall motion and wall thickening. With Tc-99m sestamibi, there is little redistribution over time. Thus, imaging can be performed over a substantial time span after injection, making the use of this tracer more convenient. The minimal redistribution of Tc-99m sestamibi allows for an uncoupling of the time of injection from the time of imaging, so that injection and imaging need not be performed in nearby locations.

The sensitivity and specificity for detecting angiographically significant coronary artery disease (>50% diameter stenosis) of Tc-99m and thallium-201 have been assessed in several reports(10) on planar and SPECT imaging.(Table 3)

Table 3 Overall sensitivity and specificity of Tc-99m sestamibi and thallium-201 by planar imaging and SPECT imaging for detection of angiographic coronary artery disease.(10)

	Sensitivity (%)		Specificity (%)	
	Tc-99m	Thallium-201	Tc-99m	Thallium-201
Planar imaging	73-89	73-97	75-100	50-100
SPECT imaging	82-95	82-84	75-100	75-82

(Derived from Daneil S. Berman, Hosen J Kiat, Kenneth Van Train, et.al. Technetium 99m Sestamibi in the assessment of chronic coronary artery disease. Seminars in Nuclear Medicine 1991;21:207-8)

In conclusion, the results of sensitivity and specificity of Tc-99m sestamibi and thallium-201 by either planar imaging or single photon emission computed tomography (SPECT) imaging are equal. Tc-99m sestamibi SPECT appears to be superior to Tc-99m sestamibi planar imaging because the former provides a higher defect contrast, minimizes regional myocardial overlap and is more accurate for detection of disease in individual coronary arteries. The sensitivity and specificity of Tc-99m Sestamibi SPECT imaging for detection of CAD in individual coronary arteries is shown in table 4.

Table 4 Sensitivity and specificity of Tc-99m sestamibi SPECT imaging for detection of CAD in individual coronary arteries.(10)

Vessel	Sensitivity (%)	Specificity (%)
Left anterior descending (LAD)	72-74	83-87
Left circumflex (LCX)	57-91	76-85
Right coronary artery (RCA)	74-75	69-90

(From Jamshid Maddahi, Hosen Kiat, Kenneth Van Train, et.al. Myocardial perfusion imaging with Technetium-99m sestamibi SPECT in the evaluation of coronary artery disease. Am J Cardiol 1990;66:58E)

The usefulness of Tc-99m Sestamibi SPECT imaging for assessment myocardial perfusion has shown in many entities such as:

- Detection and localization of coronary artery disease(10,11,13, 14,15)
- Assessment of perfusion defect extension and the evaluation of prognosis(16,17)
- Assessment of treatment efficacy in acute myocardial infarction(18,19,20)
- Evaluation of the effectiveness of thrombolytic agent and PTCA(21)
- Assessment of myocardial viability, stunned myocardium(22,23)
- Evaluation of risk stratification and prognosis of patient with stable angina, unstable angina, acute myocardial infarction(24,25,26)

Tc-99m Sestamibi SPECT imaging is particularly useful after coronary angioplasty because often only one vessel is dilated and its vascular territory can be evaluated readily with SPECT imaging. For this reason, tomographic localization of perfusion abnormality allows us to determine whether clinical ischemia is likely to be caused by restenosis at the site of angioplasty, coronary graft closure or progression of disease in other coronary arteries.

Limited research(28,29,30,31) has shown the usefulness of Tc-99m sestamibi SPECT imaging in the evaluation of myocardial ischemia and the detection of restenosis after PTCA. In this study we evaluate the value of Tc-99m sestamibi SPECT imaging for detecting restenosis in patients with successful PTCA by comparison with a coronary angiography which is the gold standard.