Clinical Value of Acute Rest Technetium-99m Tetrofosmin Tomographic Myocardial Perfusion Imaging in Patients With Acute Chest Pain and Nondiagnostic Electrocardiograms

GARY V. HELLER, MD, PHD, FACC, STEPHEN A. STOWERS, MD, FACC,*
ROBERT C. HENDEL, MD, FACC,† STEVEN D. HERMAN, MD, FACC,‡
EDOUARD DAHER, MD, FACC, ALAN W. AHLBERG, MA, JACK M. BARON, MS,§
CARLOS F. MENDES DE LEON, PHD, MPH,† JOHN A. RIZZO, PHD,‖
FRANS J. TH. WACKERS, MD, PHD, FACC‖

Farmington and New Haven, Connecticut; Jacksonville, Florida; Chicago, Illinois; Pawtucket and Providence, Rhode Island; and Tel Aviv, Israel

Objectives. **We sought to evaluate the clinical use and cost-analysis of acute rest technetium-99m (Tc-99m) tetrofosmin single-photon emission computed tomographic (SPECT) myocardial perfusion imaging in patients with chest pain and a normal electrocardiogram (ECG).**

Background. **Current approaches used in emergency departments (EDs) for treating patients presenting with chest pain and a nondiagnostic ECG result in poor resource utilization.**

Methods. **Three hundred fifty-seven patients presenting to six centers with symptoms suggestive of myocardial ischemia and a nondiagnostic ECG underwent Tc-99m tetrofosmin SPECT during or within 6 h of symptoms. Follow-up evaluation was performed during the hospital period and 30 days after discharge. All entry ECGs, SPECT images and cardiac events were reviewed in blinded manner and were not available to the admitting physicians.**

Results. **By consensus interpretation, 204 images (57%) were normal, and 153 were abnormal (43%). Of 20 patients (6%) with an acute myocardial infarction (MI) during the hospital period, 18 had abnormal images (sensitivity 90%), whereas only 2 had normal images (negative predictive value 99%). Multiple logistic regression analysis demonstrated abnormal SPECT imaging to be the best predictor of MI and significantly better than clinical data. Using a normal SPECT image as a criterion not to admit patients would result in a 57% reduction in hospital admissions, with a mean cost savings per patient of $4,258.**

Conclusions. **Abnormal rest Tc-99m tetrofosmin SPECT imaging accurately predicts acute MI in patients with symptoms and a nondiagnostic ECG, whereas a normal study is associated with a very low cardiac event rate. The use of acute rest SPECT imaging in the ED can substantially and safely reduce the number of unnecessary hospital admissions.**

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Over 5 million U.S. patients annually present to the emergency department (ED) with complaints of chest pain, possibly of cardiac origin (1–4). Although ~50% of these patients are admitted to the hospital at an annual cost of $10 to $12 billion (4,5), acute myocardial infarction (MI) or unstable angina is confirmed in only a small proportion (10% to 15%), and many do not have coronary artery disease (3,4,6,7). Conversely, of patients not admitted to the hospital, 5% to 10% have unrecognized MI, with an annual mortality rate of 6% to 8%, and others have unstable coronary artery disease, resulting in a subsequent hospital admission, representing a group with high litigation risk (2,6–10).

To improve the efficacy and efficiency of treating patients in the ED, specialized chest pain centers, computerized algorithms, new cardiac enzyme markers and noninvasive diagnostic approaches have been introduced (11–27). Recent studies demonstrating the use of radionuclide myocardial perfusion imaging have been encouraging but are limited by the small number of patients involved and the lack of blinded imaging results (23–27). Technetium-based imaging agents, including technetium-99m (Tc-99m) sestamibi and tetrofosmin (recently

From the Nuclear Cardiology Laboratory, Division of Cardiology, Hartford Hospital, University of Connecticut School of Medicine, Farmington, Connecticut; *St. Luke's Medical Center, Jacksonville, Florida; †Northwestern University Medical Center, Northwestern University, Chicago, Illinois; ‡Division of Cardiology, Memorial Hospital, Pawtucket and Brown University School of Medicine, Providence, Rhode Island; §Tel Aviv Medical Center, Tel-Aviv, Israel; and ‖Cardiovascular Nuclear Imaging Laboratory, Departments of Radiology and Medicine, Yale University School of Medicine, New Haven, Connecticut.
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Address for correspondence: Dr. Gary V. Heller, Director, Nuclear Cardiology, Division of Cardiology, Hartford Hospital, 80 Seymour Street, P.O. Box 5037, Hartford, Connecticut 06102-5037. E-mail: gheller@harthosp.org

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Abbreviations and Acronyms

CI	=	confidence interval
CK	=	creatine kinase
ECG	=	electrocardiogram, electrocardiographic
ED	=	emergency department
MI	=	myocardial infarction
ROC	=	receiver operating curve
SPECT	=	single-photon emission computed tomography (tomographic)
Tc-99m	=	technetium-99m

approved by the Food and Drug Administration) may have advantages over thallium-201 in emergency situations because of better image quality and nonredistribution (28–30).

The present multicenter study sought to evaluate the use of Tc-99m tetrofosmin single-photon emission computed tomographic (SPECT) myocardial perfusion imaging in patients with acute chest pain and a nondiagnostic electrocardiogram (ECG) to confirm the presence of acute cardiac ischemia and to develop a net cost analysis of this approach.

Methods

Study design. The study was performed at six medical centers: Hartford Hospital, Hartford, Connecticut; Yale–New Haven Medical Center, New Haven, Connecticut; St. Luke's Medical Center, Jacksonville, Florida; Northwestern University Medical Center, Chicago, Illinois; Memorial Hospital, Pawtucket, Rhode Island; and Tel Aviv Medical Center, Tel Aviv, Israel. Patients presenting with symptoms suggestive of myocardial ischemia but with a normal or nondiagnostic ECG underwent Tc-99m tetrofosmin SPECT during or within 6 h of symptoms. Follow-up evaluation was performed during the hospital period and 30 days after discharge.

Patient selection. Entry criteria included 1) acute chest pain suggestive of myocardial ischemia, either ongoing or within 6 h before radiopharmaceutical injection; chest pain symptoms were scored on the basis of a previously published scale of 1 to 29 (31); 2) a normal or nondiagnostic ECG; 3) hospital admission (without imaging information); and 4) written, informed consent. Appropriateness of the patient for study inclusion was determined by the study site investigator. The decision for hospital admission was made by the attending physician. Exclusion criteria were acute MI at the time of evaluation, a history of previous MI or diagnostic Q waves, ECG changes (T wave inversions ≥0.2 mV) in two or more leads or ST segment depression ≥0.1 mV, a history consistent with unstable angina (32) or pregnancy.

Radionuclide imaging. Patients received an injection of 20 to 30 mCi of Tc-99m tetrofosmin at rest, and SPECT imaging data were acquired 15 min to 3 h after injection. SPECT imaging studies were performed according to standardized protocols, and the results were submitted to the Radionuclide Core Laboratory at Yale University for uniform processing (33).

Image and ECG interpretation. Interpretation of SPECT images was performed by consensus of four investigators (F.W., R.H., S.H., G.H.) who had no knowledge of patient identity or clinical information. The images were interpreted according to a five-point scoring system: 1 = definitely normal; 2 = probably normal; 3 = equivocal; 4 = probably abnormal; and 5 = definitely abnormal. The presence of a suspected artifact was also recorded. All entry ECGs were reinterpreted by the consensus of three investigators who had no knowledge of patient identification or imaging results. Patients whose ECGs did not meet the study criteria were retrospectively excluded.

Follow-up evaluation. All patients were monitored for the occurrence of cardiac events during the hospital period and 30 days after discharge by means of telephone contact with the patient or the patient's family or attending physician. *Primary cardiac events* included ischemic cardiac death (immediate consequence of ischemia) and nonfatal MI (rise in creatine kinase [CK] and its MB fraction [CK-MB] levels above the normal range in participating laboratories). *Secondary cardiac end points* included cardiac catheterization, coronary revascularization and readmission for unstable angina.

Concurrent ED registry. To evaluate whether the patients enrolled in the study were representative of eligible patients seen in the EDs, a registry of all patients presenting with chest pain was collected during a 5- to 6-month period in four of the participating U.S. centers. The same study criteria were applied, and in-hospital cardiac events were tabulated. Of 4,704 consecutive patients, 615 met the entry criteria. Of the eligible patients not enrolled, 35 (6.2%) had an acute MI.

Receiver operating curve analysis. To evaluate potential differences in the diagnostic approach to acute images, the interpretation of SPECT images was submitted to receiver operating curve (ROC) analysis (34–36) using the scoring system described. Eight interpretative scenarios were considered for classifying readings as abnormal, ranging from placing the cutoff between a score of 1 (definitely normal) and 2 (probably normal), to between 4 (probably abnormal) and 5 (definitely abnormal), with or without the presence of artifact (see Appendix).

Statistical analysis. Continuous variables are presented as the mean value ± SD. Significant differences were predetermined at $p \leq 0.05$. Univariate analysis of the relation between selected clinical variables, SPECT images and outcomes during the hospital period was performed using the chi-square test. To test the association between SPECT images and outcomes during the hospital period, independent of the other clinical variables, a multivariable logistic regression model was computed, retaining those clinical variables that showed significant associations ($p < 0.05$) on univariate analysis. Logistic regression coefficients (and their standard errors) were converted into odds ratios (ORs) and 95% confidence intervals (CIs). A hierarchic series of logistic regression models was computed to test the incremental predictive contribution of several sets of variables. A base model was computed using age and gender as predictor variables, followed by the number of risk factors and

Table 1. Characteristics and Univariate Analysis of 357 Patients With Acute Chest Pain and Rest Technetium-99m Tetrofosmin Single-Photon Emission Computed Tomographic Imaging for Prediction of Acute Myocardial Infarction

	No (%) of Patients	No. (%) of Events	RR (95% CI)	p Value
Age >55 yr	156 (44%)	12 (7.7%)	1.9 (0.8–4.5)	0.13
Male gender	201 (56%)	18 (9.0%)	7.0 (2.1–23.7)	0.002
≥3 risk factors	54 (15%)	6 (11.1%)	2.4 (1.0–5.9)	0.06
Hypertension	175 (49%)	9 (5.1%)	0.9 (0.4–2.0)	0.71
Hypercholesterolemia	136 (38%)	6 (4.4%)	0.7 (0.3–1.8)	0.44
Smoking	207 (58%)	15 (7.3%)	2.2 (0.8–5.7)	0.11
Diabetes	59 (17%)	9 (15.3%)	4.1 (1.9–9.1)	0.001
CP score ≥10	150 (42%)	9 (6.0%)	1.1 (0.5–2.7)	0.78
Nondiagnostic ECG	208 (58%)	17 (8.2%)	4.1 (7.4–12.3)	0.012
CP during injection	120 (34%)	8 (6.7%)	1.3 (0.6–3.1)	0.53
Abnormal SPECT	153 (43%)	18 (11.8%)	12.0 (4.0–36.6)	0.0001

CI = 95% confidence interval; CP = chest pain; ECG = electrocardiogram; RR = relative risk; SPECT = single-photon emission computed tomography.

then ECG changes and chest pain score. In the final model, abnormal SPECT image data were entered.

Economic evaluation of acute myocardial perfusion imaging. To consider the economic impact of an additional test in the triage process of patients with chest pain, net cost analysis was performed. Net cost analysis compared the potential cost savings from reduced hospital admissions with the increased diagnostic cost of SPECT imaging. Actual hospital charges for all patients and the charge of performing SPECT imaging (mean $487, including technical and professional charges) were obtained from the five U.S. medical centers participating in the study. To estimate the extent to which tetrofosmin SPECT imaging would reduce hospital admissions, two admission strategies were considered. *Strategy 1* assumed that all patients with abnormal SPECT images would be admitted to the hospital and that no patient with normal images would be admitted. *Strategy 2* arbitrarily assumed that, in addition to admitting all patients with abnormal images, 20% of patients with normal images would be admitted on the basis of clinical information. The net cost savings per patient for each strategy was estimated. As part of the analysis, two cost scenarios were considered: 1) mean cost for hospital stay and mean cost for SPECT imaging; and 2) mean lower 10th percentile hospital costs and mean cost for SPECT imaging. The second scenario assumed that the costs of SPECT imaging were relatively high, whereas the cost savings from reduced hospital admissions were relatively low, thus providing a conservative estimate of any net cost saving that may accrue from the use of SPECT imaging.

Results

Study patients. Three hundred eight-five nonconsecutive patients were enrolled in the study. Twenty-eight patients (7%) were retrospectively excluded from the analysis: 8 whose entry ECG did not meet predefined criteria, 15 with injection of a radiopharmaceutical but who did not undergo imaging for clinical reasons and 5 whose SPECT images were considered uninterpretable. Thus, 357 patients constituted the study cohort (Table 1). There were slightly more men (57%) than women (43%). One-third of the patients (n = 120) underwent injection of a radiopharmaceutical during chest pain, whereas two-thirds (n = 237) underwent injection after resolution of symptoms (median interval 170 min, range 5 to 360). The distribution of patients undergoing injection after resolution of pain was 0 to 2 h in 87 patients, 2 to 4 h in 86 patients and 4 to 6 h in 55 patients. In 11 patients, the interval between chest pain and imaging was not documented.

Cardiac events during the hospital period. The median length of hospital stay was 2 days (range 0.5 to 24). No patient died of ischemic cardiac-related causes. Twenty patients (5.6%) had an acute MI (Table 2), with a mean peak CK of 565 ± 385 U/liter. This MI rate was not significantly different from that of the eligible but nonenrolled patients identified in the registry (see Methods). A total of 88 patients (25%) underwent cardiac catheterization, and 34 (10%) underwent coronary revascularization.

SPECT imaging and in-hospital cardiac events. A normal reading constituted those images interpreted as “definitely normal” in the presence or absence of a recognized artifact

Table 2. Primary and Secondary Cardiac Events in 357 Patients With Acute Chest Pain and Technetium-99m Tetrofosmin Single-Photon Emission Computed Tomographic Imaging

	In-Hospital	30-Day Follow-Up
Primary cardiac event		
Ischemic death	0	0
Nonfatal MI	20 (6%)	0
Secondary cardiac event		
Cardiac catheterization	88 (25%)	6 (2%)
Coronary revascularization	34 (10%)	4 (1%)
No event	256 (72%)	250 (70%)

Data presented are number (%) of patients. MI = myocardial infarction.

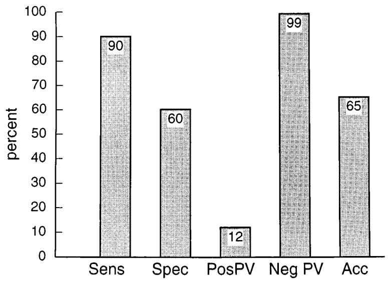


Figure 1. Sensitivity (Sens), specificity (Spec), positive predictive value (PosPV), negative predictive value (NegPV) and accuracy (Acc) of rest Tc-99m tetrofosmin SPECT imaging in the ED for detection of acute MI.

(scenario 7 in Appendix). All other interpretations were considered abnormal. SPECT images were normal in 204 patients (57%) and abnormal in 153 patients (43%). The distribution of abnormal images was not significantly different in patients with an injection during symptoms (39%) or any time after resolution of symptoms (hourly range 32% to 40% abnormal). Of 20 patients with an acute MI, images were abnormal in 18 (sensitivity 90%, 95% CI 87% to 93%) (Fig. 1). Of 337 patients without infarction, images were abnormal in 135 (specificity 59.5%, 95% CI 55% to 65%). The positive predictive value was 12%, and the negative predictive value was 99%.

Patients with abnormal images and an acute MI included all those with an anterior or Q wave MI, 13 of whom underwent cardiac catheterization, with seven requiring revascularization. Two patients with normal images had a non–Q wave MI (mean CK 310 U/liter), and one underwent catheterization but did not require revascularization.

Overall, cardiac catheterization was performed significantly less frequently in patients with normal images than in those with abnormal images (Fig. 2). Similarly, patients with normal images who underwent cardiac catheterization had significantly less coronary artery disease and required less revascularization than those with abnormal SPECT images.

Figure 2. In-hospital outcomes of patients with normal (**open bars,** n = 204) and abnormal (**gray bars,** n = 153) rest Tc-99m tetrofosmin SPECT imaging in the ED. Patients with abnormal SPECT images had significantly more acute infarction (Acute MI), cardiac catheterization (Cath), angiographic coronary artery disease (CAD) and coronary artery revascularization (Revasc). **Numbers on the abscissa** indicate number of patients with an adverse outcome.

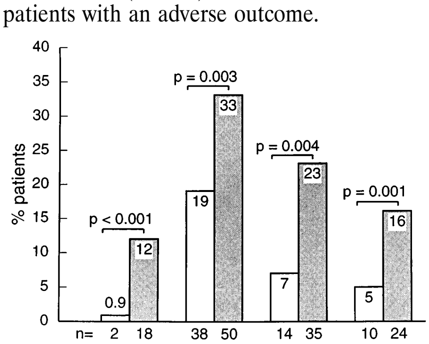


Table 3. Multiple Logistic Regression Analysis of Univariate Predictors of Acute Myocardial Infarction

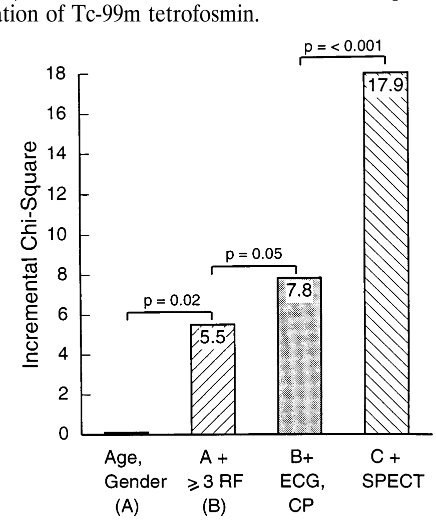
	OR (95% CI)	p Value
Male gender	7.24 (1.56–33.54)	0.01
Risk factor—diabetes	4.06 (1.45–11.35)	0.008
Nondiagnostic ECG	3.93 (1.07–14.47)	0.04
Abnormal SPECT	8.07 (1.78–36.54)	0.007

OR = odds ratio; other abbreviations as in Table 1.

Relation between clinical variables, SPECT imaging and acute MI. On univariate analysis, abnormal SPECT images were highly predictive of acute MI during the hospital period, even after controlling for male gender, diabetes and nondiagnostic ECG (Table 1). Multiple logistic regression analysis was performed on the positive univariate predictors described (Table 3). Male gender, diabetes and an abnormal SPECT image remained predictors of acute MI, although abnormal SPECT imaging had the highest odds ratio. The incremental chi-square results demonstrate that the addition of abnormal SPECT imaging added significantly to the prediction of acute MI compared with clinical data and ECG results (Fig. 3).

SPECT imaging and 30-day follow-up. Follow-up after hospital discharge was complete in 329 patients (91%). The 31 patients (9%) lost to follow-up were not statistically different from the follow-up group in terms of admission demographic data. No patient with follow-up died of ischemic cardiac-related causes or had an MI. Nine patients (2.3%) were readmitted with chest pain symptoms (study SPECT images were normal in four and abnormal in five). Six patients underwent subsequent cardiac catheterization, and four patients had coronary revascularization (SPECT images normal in two and abnormal in two).

Figure 3. Incremental prognostic value of rest Tc-99m tetrofosmin SPECT imaging in the ED over clinical variables such as age and gender (base model A), three or more risk factors for coronary artery disease (RF) and a normal admission ECG and chest pain (CP) during administration of Tc-99m tetrofosmin.



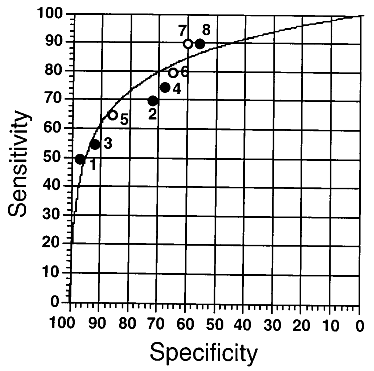


Figure 4. Receiver operating characteristic curve displaying the diagnostic yield of various interpretative scenarios 1 through 8 (see Appendix). The results of the present study are those of interpretative scenario 7 **(open circle).** Three scenarios are at approximately the same distance from the point of optimal performance (scenarios 5, 6 and 7), although scenario 7 yielded the highest sensitivity for detecting acute MI.

ROC analysis and economic impact of SPECT image interpretation. The diagnostic impact of identifying acute MI using varying interpretive cutoff values is demonstrated in Figure 4. Sensitivity ranged from 90% to 50%, depending on the strictness of criteria for consideration of a normal image (Appendix). The interpretive scenarios 5, 6 and 7 (present data) were almost equidistant from the point of optimal performance (upper left corner) and represent reasonable alternative image interpretations. Using scenario 5, seven small, uncomplicated acute MIs would go undetected.

The economic impact of SPECT imaging by net cost analysis is shown in Table 4, demonstrating the mean cost savings resulting from the use of SPECT imaging. By applying either of the considered strategies, SPECT imaging would reduce costs. The largest cost savings is achieved when only patients with abnormal SPECT images are admitted to the hospital and mean costs are considered. However, even the least favorable scenario (admission of all patients with abnormal images and 20% of those with normal images while considering the lowest 10th percentile of hospital costs) resulted in a cost savings of $543 per patient.

Discussion

This multicenter trial of patients with chest pain and nondiagnostic ECGs demonstrated that abnormal rest Tc-99m tetrofosmin myocardial perfusion imaging in the ED was strongly associated with acute MI and revascularization. Moreover, a normal rest SPECT image was associated with a very low likelihood of cardiac events. Using a triage strategy of admitting only patients with abnormal images would result in a >50% reduction in hospital admissions at a substantial cost savings, with a significantly lower risk of MI (1%) for discharged patients, compared with reports of conventional strategies (5% to 10%) (7–10).

Comparison with previous acute rest imaging studies. Several previous studies have suggested a role for acute rest myocardial perfusion imaging in patients presenting to the ED with chest pain (22–27). The results of our study are similar to those of previous studies for the detection of MI and the very high negative predictive value of normal images (Table 5) (22,24–27). In contrast to previous studies, the current trial included institutions of varying size and geographic location. Image interpretation was performed in blinded manner, and attending physicians did not use imaging results for clinical decisions. As a result, the potential value of SPECT imaging in our patients was evaluated in an unbiased and more generalizable manner than in previous studies.

Importance of a normal image. Patients with definitely normal SPECT images had a very low cardiac event rate both during the hospital period and the short-term follow-up period, with a high negative predictive value (99%). Thus, under most circumstances, patients with normal SPECT images may not warrant hospital admission. This approach is corroborated by a recent observational study demonstrating a low cardiac event rate (0% for MI, 2% for revascularization) in nonhospitalized patients with normal Tc-99m sestamibi SPECT images (27,37). However, physicians may choose to admit patients with a high likelihood of coronary artery disease and MI on the basis of clinical features such as male gender, diabetes and characterization of symptoms. Cost data for strategy 2 (Table 4) was developed to reflect such decisions.

It should be emphasized that although cardiac event rates were low in patients with normal rest SPECT images, coronary artery disease may be stable. In our study, and that of Tatum

Table 4. Net Cost and Cost-Effective Analysis of Early Rest Technetium-99m Tetrofosmin Single-Photon Emission Computed Tomographic Imaging in Relation to Varying Intepretation Criteria

Interpretative Scenarios	Acute MI Detected (sensitivity)	Acute MI Undetected [no. (%) of pts]	Patients Admitted	Potential Cost Savings*			
				Mean Cost/ MI Missed	Mean Individual Cost Savings	Mean Low Cost Savings†	Mean Low Cost/ MI Missed†
Less strict	65%	7 (35%)	17%	$73,850	$6,422	$1,371	$37,317
Intermediate	80%	4 (20%)	38%	$73,850	$4,674	$901	$37,317
Strict	90%	2 (10%)	43%	$81,372	$4,258	$789	$44,520

*Cost savings including cost of single-photon emission computed tomographic (SPECT) imaging, assuming that patients with normal SPECT images are not admitted to the hospital. †Mean lower 10th percentile hospital costs. MI = myocardial infarction; pts = patients.

Table 5. Abnormal Rest Myocardial Perfusion Imaging in the Emergency Department for Prediction of Cardiac Death or Acute Myocardial Infarction

Study (ref no.)	Year	No. of Pts	Sens	Spec	PPV	NPV	Diag Acc
Wackers et al. (22)	1979	203	100%	72%	52%	100%	79%
Varetto et al. (24)	1993	64	100%	67%	43%	100%	73%
Hilton et al. (25)	1994	102	100%	76%	38%	99%	79%
Present study		357	90%	60%	12%	99%	65%

Diag Acc = diagnostic accuracy; NPV = negative predictive value; PPV = positive predictive value; Pts = patients; ref = reference; Sens = sensitivity; Spec = specificity.

et al. (27), 2% to 5% of patients with normal rest SPECT images underwent subsequent revascularization. This indicates that selected patients with normal SPECT images warrant further (outpatient) evaluation.

ROC analysis of image interpretation. Our study suggests that in patients with acute chest pain imaging, it may be prudent to use more strict interpretative criteria for rest myocardial perfusion images than the criteria usually employed for standard stress imaging. In rest SPECT imaging studies, only one image set and no stress data are available to the interpreting physician, making the distinction between artifact and a true positive finding more difficult. In contrast, for patients undergoing elective stress evaluation, imaging studies are part of a more extensive data set that assist in determining management decisions.

Study limitations. A limitation of this study is the lack of an objective standard for acute myocardial ischemia. Only acute MI was well defined by a serial rise and fall in cardiac enzymes. We hypothesized that patients with abnormal myocardial perfusion images but no acute MI may have myocardial ischemia. The significant association between abnormal SPECT images and the clinical need for cardiac catheterization and revascularization corroborates this notion but does not provide objective proof in all patients, as not all patients underwent catheterization. In contrast, some patients with normal images who were injected after resolution of symptoms may have had ischemia that was resolved at the time of injection.

Conclusions. Abnormal rest Tc-99m tetrofosmin SPECT myocardial perfusion imaging in patients with acute chest pain and nondiagnostic ECGs is highly associated with acute MI or the need for subsequent coronary revascularization. Patients with chest pain and definitely normal rest SPECT images are unlikely to have acute MI and may have an uncomplicated subsequent course and may not need to be hospitalized. Acute rest SPECT imaging can be safely used to achieve efficient treatment of patients with chest pain in the ED at substantial cost savings.

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Appendix

Tabulation of Shifts of Interpretative Scores in Various Interpretative Scenarios for Receiver Operating Curve Analysis

Scenario	Normal Interpretative Scores	Abnormal Interpretative Scores
1	1, 2, 3, 4, 6-1, 6-2, 6-3, 6-4	5, 6-5
2	1, 2, 3, 4	5, 6
3	1, 2, 3, 6-1, 6-2, 6-3	4, 5, 6-4, 6-5
4	1, 2, 3	4, 5, 6
5	1, 2, 6-1, 6-2	3, 4, 5, 6, 6-3, 6-4, 6-5
6	1, 2	3, 4, 5, 6
7	1, 6-1	2, 3, 4, 5, 6-2, 6-3, 6-4, 6-5
8	1	2, 3, 4, 5, 6

Scores: 1 = definitely normal; 2 = probably normal; 3 = equivocal; 4 = probably abnormal; 5 = definitely abnormal; 6-1 = artifact but definitely normal; 6-2 = artifact but probably normal; 6-3 = artifact but equivocal; 6-4 = artifact, probably abnormal; 6-5 = artifact, definitely abnormal.

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