Optimal management of patients with known or suspected coronary artery disease (CAD) includes assessing risk of future cardiac events, particularly myocardial infarction (MI) and death. This evaluation should discriminate between patients at high risk who may benefit from coronary angiography and revascularization, and those at lower risk who can be managed conservatively.

Like $^{201}$Tl imaging, technetium Tc 99m sestamibi (MIBI) myocardial imaging can be used with exercise and pharmacologic testing to assess the presence of coronary artery disease. An increasing body of literature indicates that MIBI can also be used to assess risk of future cardiac events such as myocardial infarction or death. This article summarizes the current status of MIBI imaging for evaluating prognosis in patients with known or suspected coronary artery disease. 

**Key words:** coronary disease; dipyridamole; exercise test; prognosis; single-photon emission CT; technetium-99m sestamibi

**Abbreviations:** CAD = coronary artery disease; CI = confidence interval; EBCT = electron-beam CT; MI = myocardial infarction; MIBI = technetium Tc 99m sestamibi; NS = not significant; SPECT = single-photon emission CT

Technetium Tc 99m sestamibi (MIBI) is a newer myocardial perfusion agent that has a higher photo-peak than $^{201}$Tl (140 vs 68 to 80 keV) and much shorter half-life (6 h vs 73 h). These characteristics allow use of larger doses of MIBI than $^{201}$Tl (up to 25 mCi vs 3 mCi for a single study), less soft-tissue attenuation, better counting statistics, and improved image quality with single-photon emission CT (SPECT).

Because MIBI undergoes minimal myocardial redistribution, rest and stress studies can be performed on the same or separate days, and images obtained hours after an injection will still reflect myocardial perfusion prior to a subsequent intervention such as thrombolytic therapy. This same characteristic, however, contributes to the modestly lower ability of MIBI myocardial perfusion imaging to identify viable myocardium relative to SPECT using $^{201}$Tl, or positron emission tomography with $^{18}$F-fluorodeoxyglucose. A protocol using rest myocardial imaging with $^{201}$Tl followed by a stress MIBI study can maximize the benefits of both agents.

Studies directly comparing exercise and pharmacologic testing with MIBI and $^{201}$Tl have shown them to have similar diagnostic value for CAD. An increasing literature also indicates that MIBI...
imaging provides prognostic information comparable to \(^{201}\)Tl. This report reviews the current status of MIBI myocardial perfusion imaging for assessing risk of future cardiac events.

**Prognostic Value of Exercise Testing With MIBI in Stable Patients**

CAD is present in > 11 million Americans.\(^{13}\) The prevalence of CAD and incidence of its most serious clinical manifestations (MI and sudden death) increase with advancing age.\(^{14}\) In the Framingham Study population, the age-adjusted rates for MI and sudden death between ages 35 and 64 years were, respectively, 7% and 1% per year for men, and 2% and < 1% for women. Between ages 65 and 94 years, the respective annual rates of MI and sudden death were 16% and 1% in men, and 7% and 2% in women.

Clinical information such as age, history of chest pain, sex, and risk factors such as hypertension and smoking can stratify patients into “low” (< 10%), “intermediate” (10 to 90%), or “high” (> 90%) likelihood of having CAD.\(^{15}\) Exercise stress testing provides further diagnostic and prognostic information, particularly in patients clinically considered at intermediate likelihood of having CAD. Duration of exercise and occurrence of ischemic ST depression are the most useful findings for risk stratification with symptom-limited exercise testing alone.\(^{16}\)

Use of planar or tomographic \(^{201}\)Tl myocardial perfusion imaging with exercise testing provides additional prognostic information comparable to that obtained by coronary angiography.\(^{17,18}\) The annual rate of death or MI in patients in stable condition with a normal \(^{201}\)Tl study is reported to be < 1%.\(^2\) Conversely, abnormal studies, particularly those showing a reversible defect, increased lung uptake, or transient left ventricular dilatation, predict a significantly higher likelihood of subsequent cardiac death or MI.\(^{1,2}\) Increasing extent and severity of perfusion defects are also associated with additional risk.

Though less extensively studied than \(^{201}\)Tl, MIBI imaging provides similar prognostic information in patients in stable condition with known or suspected CAD (Table 1). Stratmann et al\(^{19}\) found that the annualized incidence of nonfatal MI or cardiac death in 521 patients having symptom-limited exercise testing with MIBI tomography was 0.5% with a normal MIBI study, 7% with an abnormal study (\(p = 0.0002\)), and 8% with a reversible defect.

### Table 1—Prognostic Value of Exercise and Pharmacologic MIBI Tomographic Imaging in Stable Patients With Known or Suspected CAD\(^*\)

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of Patients</th>
<th>Type of Test</th>
<th>Cardiac Events</th>
<th>Mean Follow-up, mo</th>
<th>Univariate Predictors of Increased Risk</th>
<th>Multivariate Predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hachamovitch et al(^{10})</td>
<td>2,200</td>
<td>Exercise†</td>
<td>CD, nMI</td>
<td>19 ± 5</td>
<td>Rev, fixed, MVD, extent and severity of defects</td>
<td>NR</td>
</tr>
<tr>
<td>Berman et al(^{11})</td>
<td>1,702</td>
<td>Exercise†</td>
<td>CD, nMI</td>
<td>20 ± 5</td>
<td>Abn</td>
<td>NR</td>
</tr>
<tr>
<td>Stratmann et al(^{19})</td>
<td>521</td>
<td>Exercise</td>
<td>CD, nMI</td>
<td>13 ± 5</td>
<td>Abn, Rev</td>
<td>Abn, Rev</td>
</tr>
<tr>
<td>Boyne et al(^{12})</td>
<td>229</td>
<td>Exercise</td>
<td>CD, nMI</td>
<td>19 ± 5</td>
<td>Abn</td>
<td>NR</td>
</tr>
<tr>
<td>Zanco et al(^{13})</td>
<td>147</td>
<td>Exercise or dipyridamole</td>
<td>CD, nMI, UA</td>
<td>43</td>
<td>Abn, Rev, extent of stress defect</td>
<td>Abn, Rev, extent of stress defect</td>
</tr>
<tr>
<td>Nallamouthu et al(^{15})</td>
<td>412</td>
<td>Exercise</td>
<td>CD, nMI</td>
<td>17 ± 13</td>
<td>Abn</td>
<td>NR</td>
</tr>
<tr>
<td>Hachamovitch et al(^{26})</td>
<td>4,136</td>
<td>Exercise†</td>
<td>CD, nMI</td>
<td>20 ± 5</td>
<td>Abn, Rev, MVD, extent and severity of defects</td>
<td>NR</td>
</tr>
<tr>
<td>Travin et al(^{27})</td>
<td>2,377</td>
<td>Exercise or dipyridamole</td>
<td>CD, nMI</td>
<td>15 ± 8</td>
<td>Abn, Rev, extent of defect</td>
<td>Abn, Rev</td>
</tr>
<tr>
<td>Alkeylani et al(^{28})</td>
<td>1,086</td>
<td>Exercise or dipyridamole</td>
<td>CD, nMI</td>
<td>28 ± 12</td>
<td>Abn</td>
<td>Abn, MVD</td>
</tr>
<tr>
<td>Stratmann et al(^{44})</td>
<td>534</td>
<td>Dipyridamole</td>
<td>CD, nMI</td>
<td>13 ± 5</td>
<td>Abn, Rev, fixed</td>
<td>Abn, Rev, fixed</td>
</tr>
<tr>
<td>Heller et al(^{42})</td>
<td>512</td>
<td>Dipyridamole</td>
<td>CD, nMI</td>
<td>13 ± 7</td>
<td>Abn, Rev</td>
<td>Abn, Rev</td>
</tr>
<tr>
<td>Hachamovitch et al(^{44})</td>
<td>1,159</td>
<td>Adenosine†</td>
<td>CD, nMI</td>
<td>28 ± 9</td>
<td>Extent of stress defect</td>
<td>Extent of stress defect</td>
</tr>
<tr>
<td>Senior et al(^{35})</td>
<td>61</td>
<td>Dobutamine</td>
<td>CD, nMI, UA</td>
<td>19 ± 11</td>
<td>Rev, fixed, MVD, No. of Rev defects</td>
<td>MVD</td>
</tr>
<tr>
<td>Geleijnse et al(^{46})</td>
<td>392</td>
<td>Dobutamine</td>
<td>CD, nMI</td>
<td>22 ± 13</td>
<td>Abn, Rev, fixed</td>
<td>Abn, Rev, fixed</td>
</tr>
</tbody>
</table>

\(^*\)Abn = abnormal sestamibi study; CD = cardiac death; CHF = congestive heart failure; nMI = nonfatal myocardial infarction; MVD = multivessel disease pattern of perfusion defects; Rev = reversible sestamibi defect; UA = unstable angina; NR = not reported. Values given as mean ± SD.

†Dual-isotope studies (rest \(^{201}\)Tl and stress MIBI).
coronary artery bypass surgery.\textsuperscript{24} Fifteen patients (cardiac revascularization) in 75 patients with prior cardiac events (cardiac death, nonfatal MI, or repeat events) was done. Therefore, these results cannot be compared with studies that used only those two end points.

Exercise MIBI SPECT predicted the risk of late cardiac events (cardiac death, nonfatal MI, or repeat coronary revascularization) in 75 patients with prior coronary artery bypass surgery.\textsuperscript{24} Fifteen patients (20\%) had an event during a follow-up period of 38 ± 24 months. The summed reversibility score, reflecting both extent and severity of reversible MIBI defects, was an independent predictor of increased risk.

Berman et al\textsuperscript{11} used a dual-isotope protocol incorporating a resting \textsuperscript{201}Tl study followed by exercise MIBI SPECT in 1,702 patients with known or suspected CAD. Only 2 of 1,131 patients with normal or equivocal studies (0.1\%) had a nonfatal MI or cardiac death during a follow-up of 20 ± 5 months, compared with 43 of 571 patients with an abnormal study (8\%). Normal or equivocal images were associated with a benign prognosis regardless of the preexercise or postexercise test likelihood of CAD.

These investigators also did a cost analysis of various strategies using exercise testing alone, exercise dual-isotope SPECT, and cardiac catheterization for risk stratification of patients with a pretest likelihood of CAD > 15\% based on clinical criteria. In patients with interpretable ECG responses (eg, those not taking digoxin or having baseline ST abnormalities), a strategy of sequential exercise testing, exercise testing with nuclear imaging, and cardiac catheterization was most cost-effective for identifying those at increased risk of future cardiac events. Other strategies—direct referral to cardiac catheterization, exercise testing alone followed by cardiac catheterization in patients with a postexercise test likelihood of CAD > 15\%, and exercise nuclear study followed by cardiac catheterization in those with an abnormal scan—were more costly without adding any significant prognostic value. In patients with uninterpretable 12-lead ECGs, exercise nuclear testing followed by cardiac catheterization in those with an abnormal scan was the most cost-effective strategy. These results confirmed the incremental value of dual-isotope testing for risk-stratifying patients and assessing the need for cardiac catheterization.

Similar results were found in 2,200 patients without documented CAD followed up after exercise testing with dual-isotope SPECT.\textsuperscript{10} The event rate (cardiac death or nonfatal MI) in 1,623 patients with normal SPECT studies was 0.5\%. Patients with these events had a significantly greater incidence of reversible defects, and an increasing extent and severity of these defects was also associated with higher risk. As in patients with known or suspected CAD, dual-isotope imaging with \textsuperscript{201}Tl and MIBI in this population provided incremental prognostic information compared with clinical and exercise testing variables alone.

Nallamouthu et al\textsuperscript{25} evaluated the prognostic value of both myocardial perfusion imaging with exercise stress-rest MIBI SPECT and left ventricular systolic function determined by first-pass angiography done with the rest MIBI perfusion study. In 412 patients with intermediate pretest probability of CAD followed up for 17 ± 13 months, an abnormal MIBI perfusion study was associated with a significantly increased incidence of cardiac death or nonfatal MI (13 of 117 patients [11\%]), vs only one event in 295 patients with normal studies (0.3\%; p < 0.0001).

In multivariable models incorporating clinical, exercise, and MIBI variables, only an abnormal MIBI study (relative risk, 11.9; 95\% confidence interval [CI], 1.6 to 89.4) or a reversible perfusion defect (relative risk, 2.9; 95\% CI, 1.2 to 7.0) were independent predictors for increased risk of late cardiac events.

The low risk of cardiac death or nonfatal MI associated with a normal MIBI study has been confirmed by other investigators.\textsuperscript{20–22} Brown et al\textsuperscript{20} found a 0.5\% annual event rate in 234 patients undergoing exercise or dipyridamole planar MIBI imaging followed up for (mean ± SD) 10 ± 2 months. Only two cardiac events occurred in a cohort of 155 patients with normal exercise MIBI tomographic images (0.8%/yr), compared with six events in 74 patients with abnormal MIBI studies (5.4%/yr; p < 0.02).\textsuperscript{21} In another study of 207 patients with normal planar or SPECT MIBI studies with exercise testing, none died during a follow-up period of 13.5 ± 2 months, while 1 patient (0.5\%) had a nonfatal MI and 4 (2\%) developed unstable angina requiring coronary revascularization.\textsuperscript{22} A higher rate of cardiac events was seen in the 33 patients who had exercise-induced ischemic ST depression than in those who did not (9\% vs 1\%; p = 0.025).

In a study of 147 patients followed up prospectively (mean, 43 months; range, 36 to 60 months) after exercise MIBI SPECT, a cardiac event (cardiac death, MI, or unstable angina) occurred in 29 patients.\textsuperscript{23} These events occurred in 2 of 54 patients with normal scans (4\%), compared with 27 of 91 patients with abnormal MIBI studies (30\%) and 25 of 73 with reversible defects (34\%); both differences were significant (p < 0.001). Multivariable models identified an abnormal MIBI study and a reversible defect as independent predictors of increased risk. However, no separate analysis of the nine patients with only “hard” events (cardiac death or nonfatal MI) was done. Therefore, these results cannot be compared with studies that used only those two end points.

These investigators also did a cost analysis of various strategies using exercise testing alone, exercise dual-isotope SPECT, and cardiac catheterization for risk stratification of patients with a pretest likelihood of CAD > 15\% based on clinical criteria. In patients with interpretable ECG responses (eg, those not taking digoxin or having baseline ST abnormalities), a strategy of sequential exercise testing, exercise testing with nuclear imaging, and cardiac catheterization was most cost-effective for identifying those at increased risk of future cardiac events. Other strategies—direct referral to cardiac catheterization, exercise testing alone followed by cardiac catheterization in patients with a postexercise test likelihood of CAD > 15\%, and exercise nuclear study followed by cardiac catheterization in those with an abnormal scan—were more costly without adding any significant prognostic value. In patients with uninterpretable 12-lead ECGs, exercise nuclear testing followed by cardiac catheterization in those with an abnormal scan was the most cost-effective strategy. These results confirmed the incremental value of dual-isotope testing for risk-stratifying patients and assessing the need for cardiac catheterization.

Similar results were found in 2,200 patients without documented CAD followed up after exercise testing with dual-isotope SPECT.\textsuperscript{10} The event rate (cardiac death or nonfatal MI) in 1,623 patients with normal SPECT studies was 0.5\%. Patients with these events had a significantly greater incidence of reversible defects, and an increasing extent and severity of these defects was also associated with higher risk. As in patients with known or suspected CAD, dual-isotope imaging with \textsuperscript{201}Tl and MIBI in this population provided incremental prognostic information compared with clinical and exercise testing variables alone.

Nallamouthu et al\textsuperscript{25} evaluated the prognostic value of both myocardial perfusion imaging with exercise stress-rest MIBI SPECT and left ventricular systolic function determined by first-pass angiography done with the rest MIBI perfusion study. In 412 patients with intermediate pretest probability of CAD followed up for 17 ± 13 months, an abnormal MIBI perfusion study was associated with a significantly increased incidence of cardiac death or nonfatal MI (13 of 117 patients [11\%]), vs only one event in 295 patients with normal studies (0.3\%; p < 0.0001).
Event-free survival was not significantly different in patients with left ventricular ejection fraction ≥ 50% or < 50%.

The prognostic value of exercise MIBI SPECT has also been assessed based on sex and race. In a series of 4,136 consecutive patients (2,742 men and 1,394 women) who underwent exercise testing with dual-isotope SPECT, perfusion imaging added significant prognostic information over clinical and exercise variables in both men and women.26 Event rates for both men and women with normal results of studies and increased clinical risk (prescan likelihood of CAD > 15%) were similar (1.9% vs 0.8%). An abnormal study result, presence of a reversible perfusion defect, and summed scores reflecting the extent and severity of perfusion defects were associated with increased risk of cardiac death and nonfatal MI in both sexes. However, the overall cardiac event rate was greater in women with an abnormal study result than in men (11.5% vs 5.8%; p < 0.0001).

Based on this latter finding, the investigators concluded that dual-isotope SPECT is able to risk stratify women more effectively than men.

Travin et al27 reported on 1,226 men and 1,151 women who underwent MIBI SPECT with either exercise or dipyridamole testing. As in other studies, a normal rest-stress MIBI study was associated with a low annual rate of cardiac death or nonfatal MI—1.7% in men and 0.8% in women. Conversely, unlike the earlier study using dual-isotope SPECT,26 this investigation showed that an abnormal MIBI study was associated with a higher rate for these cardiac events in men than in women (7.6% vs 4.1%; p < 0.05).

Possible explanations for the conflicting conclusions of these two large studies26,27 regarding the relative ability of an abnormal myocardial perfusion study using MIBI to risk-stratify men and women include differences in their study populations and the types of tests used (exercise dual-isotope SPECT vs exercise or dipyridamole with MIBI SPECT). However, the exact reasons for their different results remain uncertain, and further studies are needed to resolve this issue.

The prognostic value of exercise or pharmacologic MIBI SPECT was compared in 864 white and 222 African-American patients with stable angina pectoris.28 The latter had a greater incidence of cardiac events (2.3% vs 1.0%; not significant [NS]) and all-cause mortality (11.6% vs 4.2%; p < 0.05) than whites. Normal MIBI studies were seen in 36% of whites and 39% of African-Americans (NS), and similar rates of cardiac death or nonfatal MI were also found in both groups. In patients with abnormal MIBI studies, these cardiac events occurred in 11.8% of whites and 11.0% of African-Americans (NS). Both groups also had similar rates of all-cause mortality (10.0% in whites and 11.8% in African-Americans). Overall, MIBI SPECT provided similar prognostic information in both groups, with patients with abnormal study findings demonstrating a significantly greater risk of cardiac death or nonfatal MI than those with normal scans did.

Limited data are currently available comparing the prognostic value of exercise MIBI studies to other noninvasive tests for evaluating CAD, such as exercise echocardiography and electron-beam CT (EBCT). These alternative tests have the potential advantages of being less costly to perform than exercise MIBI SPECT, and providing additional diagnostic information (eg, assessing possible valvular disease with echocardiography).

Patients with CAD undergoing stress echocardiography may have wall motion abnormalities at rest. They may develop new or worsened wall motion abnormalities with exercise, indicating myocardial ischemia. Studies of patients undergoing both exercise echocardiography and either 201-Tl or MIBI SPECT imaging indicate a tendency for myocardial perfusion imaging to have a slightly greater sensitivity but lower specificity than echocardiography for detecting CAD.29–31

Reports involving patients who performed exercise testing with either myocardial perfusion scintigraphy or echocardiography have shown comparable rates of late cardiac events when either type of imaging study was abnormal. As with 201-Tl and MIBI imaging, a normal stress echocardiogram has also generally been associated with a benign prognosis regarding subsequent cardiac death or MI, with an annual event rate of about 1%.32–34 However, at present (to our knowledge), no large studies have directly compared the prognostic value of exercise echocardiography and myocardial perfusion imaging using 201-Tl or MIBI in the same patients, particularly in specific populations (eg, those at low, intermediate, or high clinical risk of having CAD).35 Thus, the relative ability of each kind of test to predict risk of late cardiac events remains uncertain.

EBCT can be used to diagnose significant CAD by assessing the presence of and quantitating calcification in coronary arteries.36 Exercise EBCT can also be performed, with injection of nonionic contrast material at peak exercise.37 Changes in global ejection fraction and development of new left ventricular wall motion abnormalities indicating development of myocardial ischemia can be assessed by comparing rest and exercise studies. Preliminary reports indicate that EBCT might be as sensitive as exercise MIBI for detecting CAD, and may help predict risk of subsequent cardiac death or MI.36–40 However, further studies are needed to better define the
Prognostic Value of Pharmacologic Testing With MIBI in Patients in Stable Condition

Pharmacologic testing with MIBI SPECT has been used to assess risk of future cardiac events in patients in stable condition unable to perform an exercise test. Stratmann et al followed up 534 patients with stable chest pain for 13 ± 5 months after dipyridamole MIBI SPECT. In multivariable models, several clinical and ECG variables—history of congestive heart failure or diabetes mellitus, and Q waves on the pretest ECG—were independent predictors for occurrence of cardiac death or nonfatal MI. However, the strongest predictors were an abnormal MIBI study (relative risk, 5.8; 95% CI, 1.8 to 19.0) and a reversible defect (relative risk, 2.1; 95% CI, 1.2 to 3.5). Only 2% of patients with a normal MIBI study had a cardiac event during follow-up, compared with 15% of those with an abnormal study and 17% with a reversible perfusion defect (both p < 0.01). A fixed perfusion defect was also associated with increased risk, with 16% of patients with this finding having a cardiac event (p < 0.01).

Heller et al reported similar results in a comparable group of 512 patients. A normal MIBI study was associated with cardiac death or nonfatal MI in 1.4% of their patients, compared with 7.4% of the patients who had an abnormal study and 8.6% of those who had a reversible defect (both p < 0.01). Patients with a fixed perfusion defect had an increased risk of a cardiac event (4%) compared with those who had normal studies, but this did not reach statistical significance. Multivariable analysis demonstrated a relative risk of 3.73 (95% CI, 1.08 to 12.93) for an abnormal MIBI study and 4.41 (95% CI, 1.25 to 15.61) for a reversible defect. The highest risk, however, was associated with a “large” perfusion defect (relative risk, 6.77; 95% CI, 1.83 to 25.08), defined in this study as one involving three vascular territories.

These investigators also found that left ventricular cavity dilation with dipyridamole MIBI testing was associated with increased risk. Transient left ventricular dilation was seen in 70 (14%) and fixed cavity dilation in 74 (14%) of their 512 patients. Cardiac death or nonfatal MI occurred in 1.9% of patients with normal left ventricular size, compared with 11.4% of those with transient and 13.5% of those with fixed left ventricular dilation (both p < 0.01). Patients with transient dilation were more likely to have a nonfatal MI than were those with normal cavity size (8.6% vs 1.4%; p < 0.01), while those with fixed dilation were more likely to have cardiac death (10.8% vs 0.5%; p < 0.05) or require hospitalization for congestive heart failure (14.9% vs 2.2%; p < 0.05).

Hachamovitch et al used adenosine dual-isotope imaging in 1,159 patients followed up for 28 ± 9 months. “Hard” events (cardiac death or nonfatal MI) occurred in 120 patients (11%). Normal and mildly abnormal studies were associated with an annual rate of 1.6% and 3.5%, respectively, for these events, compared with a 10.6% annual rate for patients with the most severely reversible and extensive perfusion defects.

Comparable prognostic information has been obtained using dobutamine MIBI SPECT. In one series of 61 patients, the number of reversible MIBI segments and the presence of defects in multiple vascular territories were independent predictors of increased risk of nonfatal MI, death, unstable angina, or congestive heart failure.

Geleijnse et al followed up 392 patients with chest pain and dobutamine MIBI studies for 23 ± 13 months. An abnormal MIBI study was the strongest independent predictor of increased risk of nonfatal MI or cardiac death (odds ratio, 10.0; 95% CI, 2.3 to 43.0). A reversible defect was also associated with significantly increased risk (odds ratio, 3.2; 95% CI, 1.6 to 6.4). Patients with the smallest, least severe reversible defects had an event rate of 2.1%, compared with 14.6% for those with the most extensive and severe defects. In an analysis by these same investigators of 80 women with normal dobutamine-MIBI studies, none of the patients died or had a nonfatal MI during a follow-up period of 23 ± 13 months.

In summary, the prognostic value of exercise and pharmacologic testing with MIBI or dual-isotope SPECT in patients in stable condition is similar to that reported for 201Tl imaging. As with 201Tl imaging, a normal MIBI study is generally associated with a low annual event rate (≤ 2%) for nonfatal MI or death. Conversely, abnormal MIBI studies, particularly those showing a reversible defect, are associated with significantly increased risk, with annual event rates as high as 15% for nonfatal MI and 17% for death. Extent and severity of reversible perfusion defects and the presence of left ventricular dilation may provide additional prognostic information in these patients.

Evaluation of Patients With Unstable Angina

Patients presenting with unstable angina can be stratified into low-, intermediate-, and high-risk
groups based on clinical and ECG criteria. Low-risk and many intermediate-risk patients whose conditions can be stabilized with medical therapy can be further evaluated using stress testing to determine whether coronary angiography is indicated.

At present, few investigators have evaluated the ability of stress testing with $^{201}$Tl or MIBI imaging to risk stratify these patients. Stratmann et al followed up 128 medically treated patients who were hospitalized with unstable angina and referred for dipyridamole MIBI SPECT before hospital discharge. All were intermediate risk by pretest clinical and ECG evaluation. During follow-up of 16 ± 11 months, 68 had cardiac events (53%)—recurrent unstable angina in 36 (28%), cardiac death in 26 (20%), and nonfatal MI in 6 (5%). A normal MIBI study was seen in 29 patients, with 2 (7%) having a nonfatal MI or dying during follow-up, compared with 30 of 99 patients with an abnormal MIBI study (30%) and 17 of 64 patients with a reversible defect (27%; for both comparisons, p < 0.05).

In these patients, the only clinical or scintigraphic variables found to be independent predictors of any type of cardiac event in multivariable models were an abnormal MIBI study (relative risk, 4.3; 95% CI, 1.5 to 12.0), a reversible perfusion defect (relative risk, 1.8; 95% CI, 1.1 to 2.9), and a fixed perfusion defect (relative risk, 2.9; 95% CI, 1.6 to 5.4). When only “hard” cardiac events (cardiac death or nonfatal MI) were analyzed, a history of congestive heart failure (relative risk, 4.0; 95% CI, 1.9 to 8.3), a reversible perfusion defect (relative risk, 2.4; 95% CI, 1.1 to 5.2), and a fixed perfusion defect (relative risk, 3.4; 95% CI, 1.3 to 8.8) were associated with increased risk. The investigators attributed the risk associated with a fixed MIBI defect to the potential presence of severely ischemic myocardium rather than scar, or as a possible marker for extensive myocardial damage.

This same group also reported their experience with a similar series of 126 men with unstable angina who underwent prehospital discharge exercise testing with MIBI SPECT. Over a mean follow-up period of 12 ± 7 months, 2% of patients with normal MIBI studies had nonfatal MI or cardiac death, compared with 14% of those with abnormal scans and 25% of those with reversible defects (both p < 0.05). Unlike these investigators’ previous study using dipyridamole MIBI imaging, a fixed perfusion defect was not associated with increased risk in this study. In multivariable analyses of clinical, stress testing, and scintigraphic variables, the only independent predictor of increased risk was a reversible perfusion defect, with a relative risk of 19.2 (95% CI, 2.2 to 167.0).

Thus, in limited reported experience using exercise or dipyridamole testing in patients with unstable angina, MIBI tomography provides important prognostic information. A normal MIBI study with exercise testing confers a low risk similar to that reported for patients in stable condition, while those with a reversible defect have up to a 27% rate of death or MI within 1 year.

**Risk Stratification After Acute MI**

As described in a recent review, exercise or pharmacologic testing with $^{201}$Tl imaging may provide limited prognostic information following an acute MI. At present, few studies have assessed the value of MIBI imaging for risk stratification after an MI. Travin et al followed up 87 medically treated patients who underwent exercise testing (predominantly low-level) with MIBI imaging within 2 weeks after an acute MI. During a follow-up period of 15 ± 10 months, 13 patients had a cardiac event—recurrent MI (n = 3), cardiac death (n = 3), or rehospitalization for unstable angina (n = 7). Cox regression analysis of clinical, stress, and imaging variables showed that the number of reversible MIBI segments (five-segment model) was the only significant predictor of increased risk. The cardiac event rate was 7% in patients without reversible defects, 12% in those with one or two defects, and 38% in those with three or more defects.

However, a later study did not confirm the prognostic value of an exercise-induced reversible MIBI defect following acute MI. Nonfatal MI (n = 15) or cardiac death (n = 15) occurred in 30 of 133 male patients (23%) with acute MI who underwent submaximal exercise MIBI tomography prior to hospital discharge and were followed up for 35 ± 19 months. Using multivariable analysis, only a history of congestive heart failure (relative risk, 4.2; 95% CI, 1.7 to 10.4; p < 0.002) and an isolated fixed MIBI defect (relative risk, 2.1; 95% CI, 1.1 to 4.3; p < 0.05) were independent predictors of increased risk. Neither the presence of a reversible perfusion defect nor semiquantitative analysis of images for the extent and severity of reversible defects correlated with significantly increased cardiac risk.

Dipyridamole MIBI testing can be performed safely as early as 2 to 4 days after the first MI. However, in a group of 89 patients followed up for 2 years post-MI, dipyridamole testing using a high-dose protocol (0.84 mg/kg over 6 min) with both MIBI tomography and echocardiography found that neither a reversible defect nor a new wall motion abnormality was predictive of increased risk for cardiac death or recurrent MI.

As with $^{201}$Tl, based on these preliminary studies,
the value of exercise or pharmacologic MIBI imaging for risk stratification post-MI remains uncertain.

**Preoperative Cardiac Risk Stratification**

The usefulness of dipyridamole testing with $^{201}$Tl imaging for preoperative assessment of patients being considered for vascular surgery has been evaluated extensively. Most early studies using planar imaging found that a reversible defect was associated with increased perioperative cardiac risk, especially when correlated with clinical risk factors and the extent and severity of defects. More recent reports using tomographic imaging, however, have not confirmed this association.

Several studies have assessed the perioperative and long-term prognostic value of dipyridamole MIBI imaging in vascular surgery patients. A retrospective analysis of 31 patients failed to show that a reversible MIBI defect was able to predict perioperative risk. In another study, Stratmann et al evaluated 197 patients undergoing a vascular procedure ≤ 3 months after dipyridamole MIBI tomography. Only 7 of 197 patients underwent coronary revascularization following dipyridamole testing and before vascular surgery. Nine patients had perioperative cardiac events: cardiac death in three; nonfatal MI in one; and ischemic pulmonary edema in five. No clinical or imaging variables were found to be significantly more frequent in patients having events than in those who did not. Cardiac events occurred in 3% of patients with normal MIBI studies, compared with 6% of those with reversible defects (NS). However, in 172 of these patients without perioperative cardiac events followed up for 21 ± 14 months after surgery, MIBI imaging was predictive of late cardiac death or nonfatal MI. Both an abnormal MIBI study (relative risk, 3.7; CI, 1.2 to 11.4; p < 0.05) and a reversible defect (relative risk, 2.7; CI, 1.2 to 6.1; p < 0.05) were independent predictors of late cardiac events. Thus, although dipyridamole MIBI testing had limited value for assessing perioperative risk, it successfully identified vascular surgery patients who were at increased risk for late cardiac events.

These same investigators also reported their experience with 229 patients who underwent dipyridamole MIBI tomography prior to nonvascular surgery. In 89 patients undergoing minor procedures (eg, inguinal hernia repair), only one perioperative cardiac event (unstable angina) occurred in 64 patients with abnormal MIBI studies, and none occurred in the 25 patients with normal images. Of the 140 patients who underwent major surgical procedures (eg, bowel resection or thoracotomy), 11 had perioperative events: cardiac death in 8; unstable angina in 2; and ischemic pulmonary edema in 1. Only one of the 80 Goldman class I patients had a cardiac event, and MIBI imaging was not predictive of increased risk in these patients. In the remaining 60 patients (Goldman class II or higher), event rates were 4% for a normal MIBI study, 27% for an abnormal study (p < 0.05), 24% for a reversible defect (p = 0.45), and 37% for a fixed defect (p < 0.01). Thus, while dipyridamole MIBI tomography was not useful for risk stratification in patients undergoing minor procedures or who were at low clinical risk (Goldman class I) for major nonvascular surgery, it did provide prognostic information for those at greater clinical risk (Goldman class II or higher).

Adenosine testing with dual-isotope tomography was used to assess risk of perioperative unstable angina, MI, and cardiac death in 43 patients undergoing major noncardiac surgery (vascular procedures in 26, nonvascular in 17). Perioperative cardiac events occurred in 4 of 15 patients with reversible defects and none of the 28 without a reversible defect (p = 0.02). However, given the small number of patients and events, as well as the inclusion of both vascular and nonvascular procedures, the significance of these results is uncertain.

In a prospective study of 142 patients undergoing vascular surgery following dobutamine echocardiography and MIBI imaging, a reversible MIBI defect and new or worsened wall motion abnormality were significant predictors of perioperative risk. However, these findings were predictive of increased risk only in the 76 patients with clinical or ECG (eg, Q waves consistent with prior MI) evidence of CAD.

In summary, preliminary reports suggest that dipyridamole, adenosine, and dobutamine testing with MIBI imaging may be effective for perioperative and long-term risk stratification in some patients undergoing noncardiac surgery. However, more studies are needed to better define which patients may benefit from testing based on clinical risk factors, type of surgery, etc.

**Emergency Department Assessment of Chest Pain**

The short-term prognostic value of resting MIBI imaging in patients presenting to emergency departments with chest pain has been reported in recent studies. Hilton et al followed up 102 patients presenting with angina-like chest pain and normal or nondiagnostic 12-lead ECGs. None of the 70 patients with normal MIBI studies had an acute MI or died within 90 days of testing, and only 1 (1%) required early coronary revascularization. Con-
versely, 12 of 17 patients with abnormal MIBI studies (71%; \( p = 0.0004 \)) had a prehospital discharge cardiac event, defined in this study as cardiac death, nonfatal MI, use of thrombolytic therapy, or early coronary revascularization.

These same investigators followed up 112 hospitalized patients who underwent resting MIBI tomography after presenting with chest pain and had no in-hospital adverse cardiac event.72 No subsequent cardiac events occurred within 90 days of testing in 87 patients with normal MIBI studies. Conversely, 2 of 25 patients with an abnormal MIBI study (8%; \( p = 0.008 \)) had an event (cardiac death, nonfatal MI, or a second hospital admission for recurrent chest pain). A subsequent cost analysis based on a strategy of hospitalizing patients with chest pain who have abnormal MIBI studies and discharging those with normal scans from the emergency department showed this approach to be safe, accurate, and potentially cost-effective.73

Varetto et al74 studied 64 patients who underwent resting MIBI SPECT after they presented to emergency departments with chest pain within the preceding 12 hours and nondiagnostic ECGs. None of the 34 patients with normal MIBI studies were subsequently found to have had an acute MI, and CAD was not present in the 22 patients who later underwent coronary angiography. Among the 30 patients with abnormal MIBI studies, an MI was subsequently diagnosed based on cardiac enzyme levels in 13, and CAD was diagnosed in 14 other patients based on findings from coronary angiography. During follow-up of these 64 patients for 11 + 3 months (maximum 18 months), none of the patients who had had normal MIBI study findings had a cardiac event (MI, death, or coronary revascularization), compared with 6 of those who had had abnormal results of studies (30%).

Tatum et al75 performed rest MIBI studies on 438 emergency department patients with chest pain who had been assessed clinically as being at low-to-moderate risk of having an acute MI or unstable angina. MIBI study findings were normal in 338 patients (76%). None had an MI or died within 1 year of presentation. Conversely, 7 of 100 patients with abnormal MIBI studies were found to have had an acute MI (relative risk, 50; 95% CI, 2.8 to 890), and 11 either died or had another MI between 1 and 12 months after initial presentation with chest pain (11%).

The extent of rest MIBI perfusion defects in 274 patients with acute MI was assessed quantitatively both at hospital presentation and shortly before discharge.76 A total of 237 patients (86%) underwent “reperfusion” therapy (thrombolysis, coronary angioplasty, and/or coronary artery bypass grafting). Two-year mortality was 7% when the predischarge study MIBI perfusion defect was ≥ 12% of the total left ventricle, whereas no patient whose MIBI defect was < 12% died. There was no association between subsequent mortality and improvements in MIBI perfusion defect size between initial and predischarge post-MI studies, reflecting the amount of myocardium “salvaged.”

Resting MIBI perfusion and gated SPECT studies were performed in 532 consecutive patients hospitalized with chest pain.77 MIBI study findings were abnormal (perfusion defect associated with abnormal wall motion and thickening) in 171 of these patients (32%). An acute MI was later diagnosed based on cardiac enzyme levels in only 2 of 361 patients with normal results of studies (0.6%), compared with 26 of 171 with abnormal scans (15%). Overall, an abnormal MIBI study had a sensitivity of 85%, specificity of 76%, and negative predictive value of 95% for predicting acute MI or early coronary revascularization.

In summary, rest studies using MIBI SPECT can be used to help risk stratify patients presenting to emergency departments with chest pain. However, the safety of using MIBI imaging for deciding whether such patients should be hospitalized or not requires further confirmation before it can be recommended as a routine practice.

CONCLUSION

Like 201Tl imaging, MIBI myocardial perfusion imaging with exercise and pharmacologic testing provides important prognostic information in patients with known or suspected CAD. Its value has been most strongly established in patients in stable condition, with a normal MIBI study indicating ≤ 2% annual risk of cardiac death or nonfatal MI. Although less extensively evaluated, MIBI imaging may also assist in risk stratification of patients with unstable angina or recent MI, and of those who present to an emergency department with chest pain or are evaluated for noncardiac surgery. More studies are needed to better define the role of MIBI testing in these latter patient populations.

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