Clinical Progress Series

Prognostic Value of Thallium-201 Myocardial Perfusion Imaging
A Diagnostic Tool Comes of Age

Kenneth A. Brown, MD

During the past 10 years, the use of thallium-201 myocardial perfusion imaging has undergone considerable expansion and evaluation. Originally conceived as a noninvasive diagnostic tool useful in determining the presence or absence of anatomical coronary artery disease,1-4 thallium-201 (201Tl) imaging has now been shown to have important prognostic value in a wide spectrum of patients with coronary artery disease.5-49 This prognostic value derives from the ability of 201Tl imaging to identify the presence and extent of jeopardized viable myocardium. After a brief background discussion, data are reviewed that concern the prognostic value of 201Tl imaging in three primary populations—1) patients presenting with known or suspected coronary artery disease, 2) post-myocardial infarction patients, and 3) patients undergoing noncardiac surgery. Data comparing the prognostic value of 201Tl predictors to other patient variables, including clinical, electrocardiographic, and angiographic variables, are discussed. Finally, the physiological basis of these observations are examined.

Background

201Tl is a monovalent metallic element that emits mercury radiographs of 69-80 keV that can be imaged by a conventional anger gamma camera. The uptake of 201Tl by myocardium occurs by both passive diffusion and active mechanisms involving Na-K, ATPase,50,51 resulting in a first-pass extraction of 88% by myocardium.52 Importantly, 201Tl extraction is not diminished when myocytes are subjected to ischemia or hypoxia that does not result in cell death53-57; only when myocytes are irreversibly damaged is 201Tl uptake depressed. Absolute myocardial 201Tl uptake expressed as a percent of the total intravenous injected dose represents the percent of total cardiac output that constitutes coronary blood flow—approximately 4% at rest or with dynamic exercise and 8-10% with a coronary vasodilator such as dipyridamole.58,59 Most importantly, uptake of 201Tl within the heart is linearly related to regional myocardial blood flow within physiological ranges of coronary blood flow, with a modest degree of underestimation of blood flow at very high flow rates and overestimation at very low rates.60-63 Therefore, regional inhomogeneity of myocardial blood flow caused by coronary artery disease will be manifest by regional differences in 201Tl uptake resulting in "defects" seen in myocardial images.

Thallium-201 Kinetics

Under conditions of coronary hyperemia induced by exercise or vasodilator drug (e.g., dipyridamole), normal myocardial 201Tl uptake is very brisk, reaching peak levels within several minutes after an intravenous injection.54,64 Thallium then washes out from the myocardium with a half-life of 4-8 hours.55,66 The washout rate of 201Tl in large part reflects the concentration gradient of thallium between myocardium and blood. In the presence of hemodynamically significant coronary artery disease, peak 201Tl uptake is relatively decreased and peaks somewhat later. Furthermore, because myocardial uptake is less than normal, the initial concentration gradient between myocardium and blood is less than in normally perfused areas. As a consequence, thallium will wash out more slowly in hypoperfused than in normally perfused myocardium. In addition, after initial uptake of 201Tl, a process of continuous 201Tl exchange between blood and myocyte compartments occurs with continuous extraction and release of ionic thallium by viable myocytes. As a result of such different washout rates between normal and hypoperfused myocardium, regions with decreased initial relative uptake of 201Tl will demonstrate a relative improvement in thallium activity when imaged 2-4 hours later. This phenomenon of a transient or reversible 201Tl defect or "fill-in" of a defect over time is generally referred to as "redistribution." Importantly, redistribution appears to be intrinsic to hypoperfused or jeopardized viable myocardium.56,67 Infarcted myocardium does not show this phenomenon. In areas of infarction, 201Tl uptake is markedly diminished and does not change substantially over time.56,70 As a result, initial defects remain fixed over time.56,67 Although there is evidence to suggest that not all fixed defects represent infarction,71-73 it is the presence and extent of 201Tl...
**Thallium-201 Lung Uptake**

Increased lung uptake of 201Tl activity has been shown to be a marker of severe coronary artery disease. Many techniques of evaluating lung uptake have been described, including qualitative, quantitative, and washout methods. Although the exact nature of the increased 201Tl content is incompletely understood, increased lung uptake of 201Tl has been positively correlated to stress-induced increases in pulmonary capillary wedge pressure and pulmonary transit time and negatively related to changes in cardiac output. These observations suggest that lung uptake of 201Tl depends on hydrostatic pressure in the pulmonary capillary bed and factors that influence pulmonary tissue contact time and extraction efficiency. Increased lung uptake of 201Tl during exercise in patients with coronary artery disease presumably reflects ischemia-induced left ventricular dysfunction related to severe, extensive coronary disease. However, left ventricular dysfunction from any cause, including cardiomyopathy and valvular or congenital heart disease, would be expected to increase lung uptake of 201Tl. As discussed below, the basis of the important prognostic value of increased lung uptake presumably reflects this relation to left ventricular dysfunction.

**Prognostic Value of Thallium-201 Imaging**

**Patients Presenting With Known or Suspected Coronary Artery Disease**

A direct relation between the presence or extent of jeopardized viable myocardium, as assessed by 201Tl imaging, and the risk of future cardiac events was first reported by Brown and colleagues in 1983. In a series of 100 patients without known prior myocardial infarction who presented for evaluation of chest pain, the predictive value of 201Tl imaging results was compared with clinical, exercise electrocardiographic, and angiographic data using multivariate logistic regression analysis (Table 1). The best predictor of future cardiac events (cardiac death or myocardial infarction) was the number of myocardial segments with transient 201Tl defects (Figure 1). Although the number of coronary vessels with angiographic disease was a univariate predictor of cardiac events, it added no significant prognostic value to the noninvasive index of extent of myocardium at risk. Subsequent studies have confirmed and extended this initial observation. Ladenheim et al found that among clinical and scintigraphic variables, the number of reversible 201Tl defects was the best predictor of future cardiac events in a large series of patients without known prior infarction presenting with suspected but not documented coronary artery disease (Figure 2). Similarly, the presence of any or multiple transient defects has been shown to have a sixfold to 12-fold increased risk of cardiac death or myocardial infarction compared with normal 201Tl studies. Several studies by Iskandrian and colleagues have found that the presence and number of perfusion defects (transient or fixed) were the only significant predictors of cardiac events but did not report the prognostic value of transient defects alone. More recently, these investigators found that the presence of reversible thallium defects, extensive perfusion abnormalities, and multivessel territory abnormalities each had significant univariate predictive value for cardiac death or nonfatal myocardial infarction, although an abnormal 201Tl image and multivessel perfusion abnormalities were the significant predictors by multivariate analysis.

In addition, other studies have found that increased lung uptake of 201Tl is a significant predictor of future cardiac events. Gill and colleagues found that increased thallium lung uptake was the best predictor of cardiac events among a series of patients with suspected coronary artery disease undergoing exercise 201Tl imaging. Although the presence and number of transient defects were highly significant univariate predictors of cardiac events (p<0.0001), these variables did not add any prognostic value to increased lung uptake of 201Tl in this study. More recently, two large follow-up studies compared 201Tl imaging with exercise, cardiac catheterization, and clinical data. Kaul and colleagues found that among all variables, increased 201Tl lung uptake was the best predictor of cardiac events, although both the number of angiographically diseased vessels and the presence of defects with redistribution (transient defects) had significant multivariate predictive value when lung activity was not considered. Furthermore, the overall prognostic information from 201Tl data was significantly superior to angiographic and exercise electrocardiographic data. In a separate study at a different institution, Kaul et al found that the number of diseased vessels was the best predictor of cardiac events and that the number of transient defects added significant prognostic value. They concluded that both overall exercise 201Tl data (including number of transient defects, change in heart rate during exercise, ST segment depression, and ventricular ectopy during exercise) and catheterization data were highly significant predictors of cardiac events (p<0.0001) and were equal in predictive power. Each was significantly superior to exercise data alone.

Recently, several articles have reported that 201Tl imaging performed in conjunction with dipyridamole-induced coronary hyperemia also has important prognostic value. Compared with angiographic and clinical variables, reversible 201Tl defects on dipyridamole studies have been found to be the only significant predictors of cardiac events in asymptomatic patients with coronary artery disease. Patients with normal images or only fixed defects had low event rates. A larger study found that an abnormal dipyridamole-201Tl study was an independent significant predictor of
TABLE 1. Prognostic Value of Thallium-201 Imaging in Patients With Known or Suspected Coronary Artery Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Types of stress</th>
<th>Patients (n)</th>
<th>Mean follow-up (mo)</th>
<th>Clinical</th>
<th>ECG</th>
<th>Catheterization</th>
<th>201Tl</th>
<th>Cardiac events</th>
<th>Significant multivariate predictors of cardiac events*</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown et al(^6)</td>
<td>Ex</td>
<td>100</td>
<td>46</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>201Tl</td>
<td>CD, MI</td>
<td>Number of TD</td>
<td>None</td>
</tr>
<tr>
<td>Ladenheim et al(^6)</td>
<td>Ex</td>
<td>1,689</td>
<td>12</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>201Tl</td>
<td>CD, MI, CABG</td>
<td>Number of TD [1]</td>
<td>%MPHR [3]</td>
</tr>
<tr>
<td>Staniloff et al(^7)</td>
<td>Ex</td>
<td>819</td>
<td>12</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>201Tl</td>
<td>CD, MI, CABG</td>
<td>Severity of PD [2]</td>
<td></td>
</tr>
<tr>
<td>Iskandrian et al(^8)</td>
<td>Ex</td>
<td>743</td>
<td>13</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>201Tl</td>
<td>CD, MI</td>
<td>Severity of PD [1]</td>
<td></td>
</tr>
<tr>
<td>Felsher et al(^10)</td>
<td>Ex</td>
<td>123</td>
<td>21</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>201Tl</td>
<td>CD, MI</td>
<td>Number of PD</td>
<td>None</td>
</tr>
<tr>
<td>Kaul et al(^11)</td>
<td>Ex</td>
<td>449</td>
<td>25</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>201Tl</td>
<td>CD, MI</td>
<td>Number of PD</td>
<td>None</td>
</tr>
<tr>
<td>Gill et al(^12)</td>
<td>Ex</td>
<td>467</td>
<td>91</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>201Tl</td>
<td>CD, MI, CABG</td>
<td>Abnormal scan</td>
<td>None</td>
</tr>
<tr>
<td>Kaul et al(^13)</td>
<td>Ex</td>
<td>293</td>
<td>64</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>201Tl</td>
<td>CD, MI, CABG</td>
<td>Typical AP [2]</td>
<td></td>
</tr>
<tr>
<td>Kaul et al(^14)</td>
<td>Ex</td>
<td>383</td>
<td>55</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>201Tl</td>
<td>CD, MI, CABG</td>
<td>Prior MI [3]</td>
<td></td>
</tr>
<tr>
<td>Younis et al(^15)</td>
<td>DP</td>
<td>107</td>
<td>14</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>201Tl</td>
<td>Combined TD + FD</td>
<td>Lung: heart ratio [1]</td>
<td></td>
</tr>
<tr>
<td>Hendel et al(^16)</td>
<td>DP</td>
<td>516</td>
<td>21</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>201Tl</td>
<td>PD</td>
<td>Desease vessels [2]</td>
<td></td>
</tr>
<tr>
<td>Stratman et al(^17)</td>
<td>AtP</td>
<td>195</td>
<td>19</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>201Tl</td>
<td>CD, MI</td>
<td>Combined TD + FD</td>
<td></td>
</tr>
</tbody>
</table>

*Numbers in brackets indicate rank order of significant multivariate predictors when more than one. One study did not rank all significant, multivariate variables.\(^{16}\)

†This study did not perform multivariate analysis\(^{17}\); variables listed are significant univariate predictors.

ECG, electrocardiographic; Ex, exercise; DP, dipyridamole-induced coronary vasodilation; AtP, atrial pacing; CD, cardiac death; MI, myocardial infarction; CABG, coronary artery bypass graft surgery; UA, unstable angina; TD, transient defects; PD, perfusion defect; MTD, multiple coronary vascular territory defects; MPHR, maximal predicted heart rate; ST ↓, ST-segment depression; AP, angina pectoris; ΔHR, change in heart rate during exercise; VEA, ventricular ectopic activity; CHF, congestive heart failure; DM, diabetes mellitus; FD, fixed defect.

myocardial infarction or cardiac death and that the presence of 201Tl redistribution significantly increased the likelihood of a cardiac event.\(^{16}\) However, no angiographic data were available for comparison in this study. Significant predictive value of reversible defects has also been reported in a series of patients undergoing atrial pacing 201Tl studies.\(^{17}\)

Normal thallium-201 studies. A very important corollary to the above data is the clinical observation that a normal 201Tl study, even in the presence of angiographic coronary disease, predicts a very benign outcome.\(^{5,7,9,12,13,15–21,30,47–49}\) Many clinical series of patients with known or suspected coronary artery disease have consistently shown a very low cardiac event rate among patients with normal 201Tl studies—averaging less than 1.0% per year for death or myocardial infarction (Table 2), an event rate approaching that of the general population.\(^{22}\) This observation has important clinical impact because it means that regardless of either the presence of underlying coronary disease or the true ability of 201Tl imaging to detect coronary artery disease as defined angiographically, a normal 201Tl study identifies a very-low-risk group of patients whom any intervention, particularly invasive, is unlikely to benefit.

Regional thallium-201 perfusion defects. Although some angiographic data suggest that proximal left anterior descending coronary artery disease may have a worse prognosis than other coronary disease, there is little data regarding regional perfusion defects. In one study comparing regional transient 201Tl defects, transient septal defect was the only significant predictor of cardiac death or myocardial infarction.\(^{23}\) In another study, perfusion defects in the left
anterior descending coronary artery territory were found to have significant univariate predictive value for death or myocardial infarction.11

Summary. These tabulated studies (Table 1) clearly document that 201TI myocardial imaging has significant prognostic value for evaluating patients with known or suspected coronary artery disease. 201TI imaging therefore offers a means of identifying patients most likely to benefit from further diagnostic or therapeutic procedures, such as cardiac catheterization and revascularization. Among 201TI imaging variables, the presence and extent of transient defects, reflecting myocardium at risk, are the most consistent predictors of cardiac events. Increased lung uptake, indicating exercise-induced left ventricular dysfunction, and the presence of any perfusion defects have also been found to be important predic-

Table 2. Prognostic Value of Normal Thallium-201 Images

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of stress</th>
<th>Patients (n)</th>
<th>Mean follow-up (mo)</th>
<th>Cardiac death/MI rate (%/yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown et al5</td>
<td>Ex</td>
<td>100</td>
<td>46</td>
<td>0.8</td>
</tr>
<tr>
<td>Staniloff et al7</td>
<td>Ex</td>
<td>374</td>
<td>12</td>
<td>0.5</td>
</tr>
<tr>
<td>Iskandrian et al9</td>
<td>Ex</td>
<td>402</td>
<td>13</td>
<td>1.1</td>
</tr>
<tr>
<td>Gill et al12</td>
<td>Ex</td>
<td>192</td>
<td>91</td>
<td>0.8</td>
</tr>
<tr>
<td>Kaul et al13</td>
<td>Ex</td>
<td>39</td>
<td>64</td>
<td>0.5</td>
</tr>
<tr>
<td>Fleg et al48</td>
<td>Ex</td>
<td>352</td>
<td>55</td>
<td>0.9</td>
</tr>
<tr>
<td>Wahl et al18</td>
<td>Ex</td>
<td>455</td>
<td>14</td>
<td>0.8</td>
</tr>
<tr>
<td>Pamelaia et al19</td>
<td>Ex</td>
<td>345</td>
<td>34</td>
<td>1.1</td>
</tr>
<tr>
<td>Wackers et al20</td>
<td>Ex</td>
<td>344</td>
<td>22</td>
<td>1.0</td>
</tr>
<tr>
<td>Heo et al21</td>
<td>Ex</td>
<td>519</td>
<td>27</td>
<td>0.5</td>
</tr>
<tr>
<td>Bairey et al47</td>
<td>Ex</td>
<td>144</td>
<td>12</td>
<td>2.1</td>
</tr>
<tr>
<td>Koss et al49</td>
<td>Ex</td>
<td>309</td>
<td>36</td>
<td>0.5</td>
</tr>
<tr>
<td>Younis et al15</td>
<td>DP</td>
<td>36</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>Hendel et al16</td>
<td>DP</td>
<td>172</td>
<td>21</td>
<td>1.7</td>
</tr>
<tr>
<td>Younis et al30</td>
<td>DP</td>
<td>14</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Stratman et al17</td>
<td>Atp</td>
<td>85</td>
<td>19</td>
<td>2.2</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>3,573</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weighted mean</td>
<td></td>
<td>28</td>
<td>0.9</td>
<td></td>
</tr>
</tbody>
</table>

MI, myocardial infarction; Ex, exercise; DP, dipyridamole; Atp, atrial pacing.

When compared with clinical and exercise electrocardiographic data, 201TI imaging appears to be consistently superior.5-13,15,16 Fewer studies have directly compared 201TI imaging with coronary angiography.5,13-15 Some investigators have found that among all patient variables, 201TI imaging data is the best predictor of cardiac events and that angiographic data do not add any significant prognostic value.5,15 Others have found that some angiographic variables have important primary or adjunctive predictive value,13,14 although 201TI data still had similar predictive value compared with angiography when it was combined with clinical and exercise variables.14

Post–Myocardial Infarction Risk Stratification

Although predischarge exercise electrocardiography has been shown to have important prognostic

Figure 1. Probability of a future cardiac event (cardiovascular death or myocardial infarction) and observed incidence of event as a function of number of transient thallium-201 (TI-201) defects in 100 patients without prior myocardial infarction. Reprinted with permission.5

Figure 2. Plot of risk of future cardiac events as a function of number of reversible thallium-201 defects. Relation is exponential (r=0.97, p<0.001). Reprinted with permission.6
value after an acute myocardial infarction,
exercise 
TIMI imaging offers several potential advantages: 1) increased sensitivity for detecting multivessel coronary disease, 2) the ability to localize ischemia to individual coronary territories, 3) the ability to distinguish infarct- from non-infarct-zone myocardium, and 4) the ability to identify exercise-induced left ventricular dysfunction, manifest by increased lung uptake. In addition, interpretation of the significance of ST segment changes is often limited because ST elevation may occur in electrocardiogram leads with Q waves that reflect regional asynergy rather than ischemia and may be associated with reciprocal ST segment depression that may also not reflect ischemia. Accordingly, an increasing number of studies have examined the prognostic value of TIMI myocardial imaging after an acute myocardial infarction.24–34

Gibson and colleagues in 198324 first compared the predictive value of predischarge submaximal exercise TIMI studies with clinical, exercise electrocardiographic, and coronary angiographic data. Among TIMI variables, the presence of redistribution, defects involving multiple vascular territories, and increased lung uptake had the most important prognostic value. Compared with exercise testing and coronary angiography, the combination of these TIMI criteria had significantly greater sensitivity for predicting future cardiac events. Furthermore, the ability to distinguish high- from low-risk groups was greatest for TIMI criteria (Figure 3). Several subsequent postinfarction risk stratification studies reported that submaximal exercise TIMI imaging had significant prognostic value but that TIMI predictors were not additive to exercise radionuclide ventriculographic data25 or were significant only when used in combination with stress electrocardiographic results (Table 3).26 However, a more recent study of patients who had acute myocardial infarction and one-vessel coronary artery disease found that late cardiac events were significantly related to the presence and number of transient defects on a submaximal predischarge TIMI study and that no clinical or exercise electrocardiographic variable showed significant relation to cardiac event.27

Although TIMI imaging appears to add significant sensitivity to exercise testing for the detection of underlying coronary artery disease83–86 and future cardiac events,5,7,8,13,14 dipiridamole-TIMI imaging may have particular advantage after myocardial infarction because it has been shown that TIMI imaging during maximal coronary hyperemia induced by dipiridamole has improved sensitivity for coronary disease compared with submaximal stress TIMI imaging.87 Leppo and colleagues28 compared the prognostic value of dipiridamole TIMI imaging at 10–16 days after infarction with clinical and radionuclide ventriculographic data and found that the presence of TIMI redistribution was the only significant predictor of late cardiac death or recurrent infarction. Similarly, patients with transient defects on dipiridamole TIMI imaging 5–13 days after infarction had a far higher incidence of late cardiac events (64%) compared with those without transient defects (8%; p<0.005).29

In a series of patients who had acute myocardial infarction or unstable angina, the presence of transient TIMI defects was again the best predictor of total cardiac events, although catheterization data were better predictors of death or myocardial infarction.30 More recently, the presence of TIMI redistribution outside the infarct zone was found to be the only significant predictor of cardiac events in patients with uncomplicated myocardial infarction.31

Early post–myocardial infarction risk stratification. In addition to its greater sensitivity for coronary disease than submaximal exercise studies, dipyr-
Table 3. Prognostic Value of Thallium-201 Imaging After Myocardial Infarction

<table>
<thead>
<tr>
<th>Study</th>
<th>Types of stress</th>
<th>Patients (n)</th>
<th>Mean time after MI</th>
<th>Mean follow-up (mo)</th>
<th>Data available</th>
<th>Cardiac events</th>
<th>Significant multivariate predictors of cardiac events*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gibson et al24</td>
<td>Submax ex</td>
<td>140</td>
<td>11 days</td>
<td>15</td>
<td>Clinical +</td>
<td>CD, MI, UA</td>
<td>TD, MTD 2 or 3 VD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ECG +</td>
<td>CD, MI, VF</td>
<td>Lung uptake ST ↓, AP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cathet.ization +</td>
<td>Extent of TD†</td>
<td>Extent of PD† ΔLVEF [1]</td>
</tr>
<tr>
<td>Hung et al25</td>
<td>Max ex</td>
<td>117</td>
<td>21 days</td>
<td>12</td>
<td>201Tl +</td>
<td>CD, MI, VF, UA</td>
<td>NIZ PD↑ ST ↓†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RVG +</td>
<td>CD, MI, UA</td>
<td>Number of TD† None</td>
</tr>
<tr>
<td>Abraham et al26</td>
<td>Max ex</td>
<td>103</td>
<td>24 days</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilson et al27</td>
<td>Submax ex</td>
<td>97</td>
<td>11 days</td>
<td>39</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Leppo et al28</td>
<td>DP</td>
<td>51</td>
<td>10–16 days</td>
<td>19</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pirelli et al</td>
<td>DP</td>
<td>35</td>
<td>9 days</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Younis et al30</td>
<td>DP</td>
<td>77</td>
<td>9 days</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gimple et al31</td>
<td>DP, submax</td>
<td>40</td>
<td>NA</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brown et al32</td>
<td>DP</td>
<td>50</td>
<td>2.6 days</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bosch et al33</td>
<td>DP</td>
<td>76</td>
<td>3 days</td>
<td>NA</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Gibson et al34</td>
<td>Submax ex</td>
<td>241</td>
<td>10 days</td>
<td>30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brown et al35</td>
<td>Max ex</td>
<td>61</td>
<td>10 mo</td>
<td>37</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Numbers in brackets indicate rank order of significant multivariate predictors of cardiac events when more than one.
†In some studies, multivariate analysis was not performed; variables listed are significant univariate predictors.

In one study,25 univariate 201Tl predictors are included, although they were not multivariate predictors when other data were available. ECG, electrocardiographic; RVG, radionuclide ventriculogram; submax, submaximal; ex, exercise; max, maximal; DP, dipyridamole-induced coronary vasodilation; NA, not available; CD, cardiac death; MI, myocardial infarction; UA, unstable angina; VF, ventricular fibrillation; CABG, coronary artery bypass graft surgery; TD, transient defects; MTD, multiple coronary vascular territory defects; PD, perfusion defect; NIZ, noninfarct zone; IZ, infarct zone; ST †, ST segment depression; AP, angina pectoris; LVEF, left ventricular ejection fraction; VD, vessel disease.

dipyridamole-201Tl imaging has some advantages that may allow this technique to play an important role in the early, in-hospital management of acute myocardial infarction. Unlike exercise, dipyridamole-201Tl studies are associated with only modest changes in determinants of myocardial oxygen demand88–90 but provide superior-quality images compared with resting studies, with a sensitivity for coronary disease equal to that of maximal exercise 201Tl imaging.88,89,91–95 In addition, hemodynamic effects of dipyridamole are brief when used intravenously, and its actions are rapidly reversed with theophylline.90 Thus, dipyridamole-201Tl imaging may be particularly well suited for studying patients within the first few days after acute myocardial infarction. Recently, Brown and colleagues32 reported a series of 50 patients undergoing dipyridamole-201Tl imaging 1–4 days (mean, 62±21 hours) postinfarction. Half the patients had received thrombolytic therapy. No serious adverse effects occurred during the protocol. The predictive value of 201Tl data was compared with clinical, electrocardiographic, and cardiac catheterization data. By multivariate analysis, the only significant predictor of in-hospital cardiac events was the presence of infarct-zone 201Tl redistribution (p=0.0001); nine of 20 patients (45%) with infarct-zone redistribution had in-hospital cardiac events compared with none of 30 patients without infarct-zone redistribution (Figure 4). During a 12±7 month follow-up, three additional patients with infarct-zone redistribution had cardiac events compared with none without infarct-zone redistribution (Figure 4). Angiographic variables were not significant predictors of cardiac events. Thus, it appears that the presence of jeopar-
dized viable myocardium, regardless of underlying coronary anatomy, may be the best predictor of early and late cardiac events after an acute myocardial infarction. Dipyridamole-$^{201}$TI imaging performed very early after acute myocardial infarction may allow a rational approach to deciding at an earlier time in their hospitalization who may benefit most from further invasive diagnostic or therapeutic procedures. The presence of infarct-zone $^{201}$TI redistribution identifies a subgroup of patients at high risk for early and late cardiac events who may benefit most from an aggressive management strategy. In contrast, patients without infarct zone $^{201}$TI redistribution appear to be at very low risk for early and late cardiac events and may be candidates for early discharge. Recent research by Bosch et al$^{33}$ confirms these observations. They found that dipyridamole-$^{201}$TI imaging performed in 76 patients $3 \pm 1$ days after infarction was safe and that the presence of transient $^{201}$TI defects was significantly related to development of an in-hospital cardiac event.

Another innovative approach combines $^{201}$TI imaging (as a marker of perfusion) and indium-111-labeled antimyosin antibodies (a specific marker of acute infarction).$^{34}$ Myocardial segments that show a $^{201}$TI perfusion defect at rest with localized antimyosin antibody uptake (mismatched defects) may represent ischemic but viable myocardium or old scar. Areas with both $^{201}$TI and antimyosin antibody uptake (overlap) may represent nontransmural infarction or reperfused infarct zones with residual nonjeopardized myocardium. Johnson and colleagues$^{35}$ found that patients with matched defects had neither recurrent ischemic events nor a positive 6-week postinfarction stress test. However, 16 of 23 patients with mismatched defects had recurrent in-hospital postinfarction chest pain or a positive 6-week postinfarction stress test. Interestingly, patients with overlap also had a high frequency (four of five) of recurrent ischemia. Only a small minority of patients had delayed $^{201}$TI imaging, so dual-isotope imaging could not be compared with serial rest $^{201}$TI imaging for prognostic value. However, four of five patients with thallium redistribution had recurrent ischemia. Future studies will be required to confirm and compare the prognostic value of the dual-isotope approach with that of $^{201}$TI imaging and assess whether imaging after dipyridamole vasodilation will augment the results.

Non-$Q$ wave myocardial infarction. Risk stratification may be particularly important in this subgroup of patients because such infarctions are often considered to be “incomplete” and at relatively high risk for recurrent cardiac events. A study by Gibson and colleagues supports this concept.$^{34}$ They found that the prevalence and extent of residual jeopardized

![Flow-chart of in-hospital and postdischarge outcome of patients based on presence or absence of infarct-zone thallium-201 (TL-201) redistribution seen on early post-myocardial infarction dipyridamole-TL-201 imaging study. CABG, coronary artery bypass graft surgery; MI, myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; ST ↓, ST segment depression; UA, unstable angina. Reprinted with permission.$^{32}$](http://circ.ahajournals.org/doi/10.1161/CIRCULATIONAHA.117.028142)
viable myocardium in the infarct zone, manifest by 
\( ^{201} \text{Tl} \) redistribution on submaximal exercise studies, was greater in patients with non-Q wave infarction than in those with Q wave infarction. Furthermore, recurrent infarctions were more common in the non-Q wave group (18% versus 6%), and the large majority (14 of 16) occurred in the same vascular territory as the original infarction (compared with only two of 10 recurrent infarctions among Q wave patients). Importantly, infarct-zone \( ^{201} \text{Tl} \) redistribution was present in 15 of 16 patients who later developed recurrent infarction as well as in 18 of 21 patients who suffered a late cardiac death. Thus, although patients with non-Q wave infarctions may be at relatively increased risk for recurrent events, \( ^{201} \text{Tl} \) imaging may be useful in identifying those in whom aggressive approaches would be most likely to benefit. Further research is needed in this area.

**Postthrombolysis patients.** An area of increasing interest involves the use of myocardial perfusion imaging to detect reperfusion and to risk-stratify patients receiving thrombolytic therapy for acute myocardial infarction. \( ^{201} \text{Tl} \) imaging may be particularly well suited for risk stratification because of its ability to identify the presence of residual jeopardized viable myocardium. Initial reports of resting \( ^{201} \text{Tl} \) studies performed at the time of thrombolytic therapy suggest that the presence of “reverse redistribution,” which is usually defined as the appearance of a regional uptake defect on the delayed view when the initial images are normal or as a worsening of an initial defect,\(^{95} \) may indicate the presence of a patent infarct vessel and preserved regional wall motion.\(^{96,97} \) The nature of this relation is unclear. Rapid washout of infarct-zone \( ^{201} \text{Tl} \) activity has been observed experimentally with reperfusion of an infarct.\(^{98} \) However, in this circumstance, rapid washout reflected not salvaged myocardium but rather rapid clearance from reperfused but irreversibly damaged myocardium. Others have postulated that the rapid washout reflects regional hyperemia in the infarct zone after reperfusion that results in higher regional uptake and hence higher regional clearance.\(^{96,97} \) Rapid clearance of \( ^{201} \text{Tl} \) from the infarct zone has also been explained as an artifact of background subtraction used in the quantitative methods to analyze myocardial washout.\(^{99} \)

The presence of transient \( ^{201} \text{Tl} \) redistribution would be expected to identify patients with residual jeopardized viable myocardium after thrombolysis. Defects that show redistribution have been associated not only with patent infarct vessels but also with improvement of or with near-normal predischarge infarct-zone regional wall motion.\(^{97} \) Whether infarct-zone \( ^{201} \text{Tl} \) redistribution after thrombolysis also identifies patients at high risk for cardiac events, as it does in other postinfarction subgroups, awaits further investigation. In the series of patients undergoing early postinfarction dipyridamole-\( ^{201} \text{Tl} \) imaging reported by Brown and colleagues,\(^{32} \) half of the study cohort received thrombolytic therapy. Interestingly, the incidence of infarct-zone \( ^{201} \text{Tl} \) redistribution in this subgroup was identical to that of the subgroup who did not receive thrombolytic therapy. Three of 10 patients (30%) with infarct-zone redistribution who had received thrombolytic therapy had recurrent in-hospital ischemic cardiac events compared with none of 15 patients who did not. In a more heterogeneous group of patients who had received thrombolytic therapy, many of whom had undergone coronary angioplasty, the absence of transient \( ^{201} \text{Tl} \) defects predicted a very benign postdischarge course, at least during a 6-month follow-up.\(^{100} \)

**Late post–myocardial infarction.** The presence of \( ^{201} \text{Tl} \) redistribution in exercise studies in patients who present with recurrent angina late (postdischarge) after prior myocardial infarction also predicts future cardiac events.\(^{35} \) \( ^{201} \text{Tl} \) redistribution limited to the infarct zone was the only significant predictor of overall cardiac events (cardiac death, reinfarction, or unstable angina) or “hard” end points of death or reinfarction during a 37-month mean follow-up. Most patients (10 of 15) with evidence of ischemia outside the infarct zone by \( ^{201} \text{Tl} \) imaging were sent to coronary revascularization without antecedent ischemic events compared with only six of 29 patients with infarct-zone–only ischemia. However, patients with jeopardized viable myocardium limited to the infarct zone cannot be considered to be at low-risk; 28% (eight of 29) developed recurrent cardiac events compared with none of 15 patients without redistribution (\( p < 0.05 \)).

**Summary.** Multiple studies indicate that the presence and extent of transient defects, reflecting residual viable myocardium at risk, have important prognostic value in predischarge risk stratification after acute myocardial infarction (Table 3). In studies that distinguished infarct-zone from non–infarct-zone ischemia, the results were mixed with some studies indicating that both early\(^{32,34} \) and late\(^{35} \) infarct-zone transient defects were more important prognostically, whereas others found the converse,\(^{26,31} \) although these latter studies did not use multivariate analysis. Relatively few studies have compared \( ^{201} \text{Tl} \) imaging with cardiac catheterization results, with studies fairly consistently favoring transient \( ^{201} \text{Tl} \) defects as the best predictor.\(^{24,27,30,32,35} \) Surprisingly, even fewer studies have directly compared predischarge submaximal exercise testing with \( ^{201} \text{Tl} \) imaging. Although each of these have shown \( ^{201} \text{Tl} \) results to be superior predictors of cardiac events,\(^{24,27,31} \) consistent with its greater sensitivity for coronary artery disease, more data would clearly be welcome. The prognostic value of postdischarge maximal exercise \( ^{201} \text{Tl} \) imaging has been less impressive,\(^{25,26,31} \) perhaps because a very-low-risk group has been selected. In contrast, among patients presenting late after myocardial infarction with recurrent angina, defining a higher-risk group, maximal exercise \( ^{201} \text{Tl} \) imaging has superior prognostic value compared with other patient variables, including clinical, electrocardiographic, and catheterization data.\(^{35} \) In general, the earlier risk stratification is applied, the greater the value because
## Table 4. Prognostic Value of Dipyridamole–Thallium-201 Imaging for Postoperative Risk Stratification

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (n)</th>
<th>Types of surgery</th>
<th>Data available</th>
<th>Cardiac events</th>
<th>Significant multivariate predictors of cardiac events*</th>
<th>Frequency of perioperative cardiac events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Clinical ECG</td>
<td>Catheterization</td>
<td>201TI RVG</td>
<td>201TI</td>
</tr>
<tr>
<td>Boucher et al(^{36})</td>
<td>48</td>
<td>AA, LEV</td>
<td>+ +</td>
<td>+ +</td>
<td>0 + + 0</td>
<td>CD, MI, UA</td>
</tr>
<tr>
<td>Leppo et al(^{37})</td>
<td>89</td>
<td>AA, LEV</td>
<td>+ +</td>
<td>+ +</td>
<td>0 + + 0</td>
<td>CD, MI</td>
</tr>
<tr>
<td>Eagle et al(^{38})</td>
<td>111</td>
<td>AA</td>
<td>+ +</td>
<td>+ +</td>
<td>0 + + 0</td>
<td>CD, MI, UA, IPE</td>
</tr>
<tr>
<td>Lette et al(^{41,43})</td>
<td>66</td>
<td>AA, LEV, major general surgery</td>
<td>+ +</td>
<td>+ +</td>
<td>0 + + 0</td>
<td>CD, MI</td>
</tr>
<tr>
<td>Lane et al(^{42})</td>
<td>101</td>
<td>AA, LEV, C</td>
<td>+ +</td>
<td>+ +</td>
<td>0 + + 0</td>
<td>CD, MI, UA, CHF</td>
</tr>
<tr>
<td>Brown et al(^{44})</td>
<td>65</td>
<td>Renal Tx candidates</td>
<td>+ +</td>
<td>+ +</td>
<td>0 + + 0</td>
<td>CD, MI</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>82/280</strong></td>
<td></td>
<td><strong>9/370</strong></td>
<td></td>
<td></td>
<td><strong>82/280</strong> (29)</td>
</tr>
</tbody>
</table>

*Numbers in brackets indicate rank order of significant multivariate predictors of cardiac events when more than one.
†In some studies, multivariate analysis was not performed; variables listed are significant univariate predictors.
‡Multivariate predictors of long-term nonperioperative cardiac events.


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more cardiac events can be prevented. The ability of dipyridamole-201TI imaging to identify apparently stable patients at high risk for cardiac events as early as 24 hours after infarction offers potential advantages over routine predischarge risk stratification because management strategies and the need for cardiac catheterization can be accelerated by as much as 1 week. If standard predischarge testing is elected, the decision to use 201TI imaging instead of stress electrocardiography may be influenced by several factors. The increased cost of 201TI imaging must be weighed against 1) the probable improved sensitivity for predicting future cardiac events evident in prior studies, 2) the ability to distinguish infarct-zone from non–infarct-zone ischemia and to quantitate extent of myocardium at risk, and 3) the difficulty in interpreting exercise-induced ST segment changes in the setting of Q wave infarctions and baseline ST abnormalities. Finally, local expertise must be strongly considered. Among medical communities in which 201TI imaging is available, the quality of studies is likely to vary greatly and be dependent on available hardware and software and on the training and experience of the physicians interpreting the studies.

### Preoperative Risk Stratification

**Peripheral vascular disease surgery.** A logical extension of research demonstrating the important prognostic value of 201TI imaging in patients with chest pain or acute myocardial infarction has been application of this technique to preoperative risk stratification (Table 4). Patients undergoing peripheral vascular disease surgery are particularly suitable candidates for 201TI imaging because there is a high prevalence of underlying, often asymptomatic coronary artery disease\(^{101–103}\) and dipyridamole-201TI imaging allows application of the imaging technique to a group of patients who often have very limited exercise capacity due to claudication. Boucher and colleagues\(^{36}\) screened a series of stable patients with objective evidence of coronary artery disease (e.g., history of myocardial infarction, chest pain, or abnormal electrocardiogram) with dipyridamole-201TI imaging before nonemergency peripheral vascular surgery. Perioperative ischemic cardiac events, which occurred in eight patients, could not be predicted by clinical factors. However, eight of 16 patients (50%) with 201TI perfusion defects that showed redistribution had car-
diac events compared with none of 32 patients with fixed defects only \((n=12)\) or with normal studies \((n=20)\) \((p<0.0001)\). Thus, like prior studies involving other patient groups, the presence of jeopardized viable myocardium had important prognostic value. This provocative study has been confirmed by many subsequent studies.\(^{37-44}\) Leppo and colleagues\(^{37}\) took the next step by comparing the relative predictive value of dipyridamole-\(^{201}\)TI results with clinical variables using a multivariate analysis in patients undergoing peripheral vascular surgery. Patients were not selected on the basis of suspected coronary disease; only 51\% had a history of coronary artery disease. Among many patient variables examined, the presence of \(^{201}\)TI redistribution was the best predictor of perioperative cardiac events: 14 of 42 patients (33\%) with \(^{201}\)TI redistribution had perioperative death or nonfatal myocardial infarction compared with one of 47 patients (2\%) with fixed defects only or normal studies \((p<0.0001)\). In a subgroup of patients who also underwent exercise \(^{201}\)TI studies, the presence of \(^{201}\)TI redistribution remained the best predictor of cardiac events.

These studies raised additional questions regarding the relative merits of dipyridamole-\(^{201}\)TI imaging versus combinations of various clinical variables (e.g., Goldman criteria\(^{104,105}\) and modifications\(^{106,107}\)) that have been the gold standard for perioperative risk evaluation. One problem with such prior clinical studies is that the patients who were studied generally had a very low prevalence of coronary artery disease and a low incidence of ischemic perioperative cardiac events.\(^{104,105}\) The validity of applying such clinical criteria to populations of patients like those undergoing peripheral vascular surgery, who have a much higher incidence of underlying coronary disease and ischemic cardiac events, has never been confirmed. It is well known that many patients with underlying coronary disease may be asymptomatic.\(^{108}\) Therefore, clinical criteria concerning presence or absence of angina, myocardial infarction, or abnormal resting electrocardiograms may have insufficient sensitivity or specificity to be of value in populations in whom coronary disease has a high prevalence. Risk stratification using \(^{201}\)TI imaging may have significant advantages in this setting. On the other hand, certain clinical criteria may define a population of patients at such low risk of cardiac events that preoperative \(^{201}\)TI imaging may not be necessary, allowing a selective approach.

Eagle and colleagues\(^{38}\) studied a cohort of 61 patients scheduled for major abdominal aortic vascular surgery with preoperative dipyridamole-\(^{201}\)TI imaging. Among patients with clinical risk factors of angina, prior myocardial infarction, congestive heart failure, diabetes, or \(Q\) waves on their electrocardiogram, approximately half (15 of 32) had reversible defects. Of these patients, nearly half (seven of 15) had perioperative cardiac events compared with none of 17 without reversible defects \((p=0.002)\). In contrast, only 10\% of patients (three of 29) without these clinical risk factors had a reversible \(^{201}\)TI defect; one of the three had a perioperative cardiac event compared with none of 26 without reversible defects. Similar findings were observed when these criteria were applied prospectively to an additional 50 patients. This study suggested that clinical criteria might be useful in selecting patients who would best benefit from the time and expense of perioperative dipyridamole-\(^{201}\)TI imaging. More recently, Eagle et al\(^{40}\) reported their observations concerning a larger group of 200 patients undergoing dipyridamole-\(^{201}\)TI imaging before planned peripheral vascular surgery. In this cohort, patients undergoing carotid or femoropopliteal bypass surgery were also included and constituted 34\% of the total. Using multivariate logistic regression analysis, \(^{201}\)TI redistribution was the best predictor of perioperative cardiac events. In addition, dipyridamole-induced ST segment depression and five clinical variables (history of angina, ventricular ectopy requiring therapy, \(Q\) waves, diabetes, and age of more than 70 years) were also significant predictors. Using clinical factors as the first level of screening, \(^{201}\)TI results appeared to be of most benefit in patients with one or two clinical risk factors (Figure 5); patients with \(^{201}\)TI redistribution had a 10-fold increased risk of perioperative cardiac events compared with those without redistribution. Patients with three or more clinical risk factors had a very high perioperative risk regardless of \(^{201}\)TI results, but this group constituted only 10\% of the overall cohort. Patients with no clinical risk factors, representing nearly one third of the overall group, had a relatively low risk of perioperative cardiac events (3\%), and the authors argued that this group need not undergo \(^{201}\)TI imaging. This type of approach allows a rational application to perioperative risk evaluation of dipyridamole-\(^{201}\)TI imaging, which, although minimally invasive, has significant cost.

However, some caution should be taken in accepting the specific algorithms of these studies as the new gold standard. Additional corroboration with larger studies is needed. In addition, the subgroup of patients with no clinical risk factors may be problematic. Even in this relatively low-risk group, dipyridamole-\(^{201}\)TI imaging may still have important prognostic value; none of 47 patients without redistribution had a perioperative cardiac event compared
with two of 17 (12%) with redistribution. Therefore, the consulting clinician and surgeon need to decide what is an acceptably low level of perioperative risk and at what threshold of risk additional studies (e.g., coronary angiography) are warranted. In addition, in the study by Eagle et al,40 approximately one third of the patients underwent nonaortic surgery, which has a significantly lower overall perioperative cardiac risk than aortic surgery.45 However, the prevalence of such patients among each clinical risk factor subgroup is unclear. Therefore, it is not known whether the same overall low risk found in patients without clinical risk factors would apply to patients undergoing aortic reconstructive surgery. In a recent series of patients undergoing major vascular and general surgery,41 no clinical factor risk stratification scheme, including Eagle’s criteria,40 Goldman,104,105 Detsky modified,106,107 and Dripps ASA score,109 was useful in predicting perioperative cardiac death or myocardial infarction. However, nine of 21 patients (42%) with reversible 201Tl defects had perioperative cardiac death or infarction compared with none of 30 without reversible defects (p<0.0001).

Additional data are also needed regarding the preoperative prognostic value of other features of 201Tl imaging. As discussed above, the extent of myocardial at risk, manifest by the number of myocardial segments with transient 201Tl defects, may have important prognostic value beyond simply the presence or absence of reversible defects. Eagle and colleagues38 did not find that perioperative risk was related to the number of transient defects. However, more recently, perioperative risk was found to be directly related to the number of reversible 201Tl defects in diabetic patients undergoing vascular surgery.42 Patients with five or more (of a possible 10) reversible defects had a 44% probability of a perioperative cardiac event compared with a 14% probability in patients with one or more reversible defects and a 3% probability in patients without reversible defects (p<0.01). In addition, Lette and colleagues43 identified a subgroup based on the extent and severity of transient 201Tl defects that comprised 17% of all patients undergoing major vascular and general surgery and had an 80% probability of perioperative death or myocardial infarction. Furthermore, on reanalysis of one of their previous studies,40 Eagle and colleagues110 also found that perioperative risk was related to extent of myocardium with transient defects. More information is needed to draw further conclusions regarding the extent of jeopardized myocardium in preoperative evaluation.

**Other noncardiac surgery.** The impressive ability of 201Tl imaging to risk-stratify patients undergoing peripheral vascular surgery begs the question of whether this technique is applicable to other noncardiac surgery. However, little data are available. One study included patients undergoing vascular or nonvascular major general surgery but did not separately evaluate this latter subgroup.41,43 The perioperative and long-term prognostic value of dipyridamole-201Tl imaging, radionuclide ventriculography, and clinical variables were recently evaluated in a series of patients with renal failure who were candidates for renal allograft surgery.44 Such a population of patients is known to be at increased risk for clinical or occult coronary artery disease and ischemic complications.111-113 By multivariate regression analysis, the presence of a transient 201Tl defect and left ventricular ejection fraction were the only significant predictors of future cardiac death or myocardial infarction. Only patients without transient defects underwent allograft surgery. There were no perioperative cardiac events among the 35 patients, although 13 (37%) had depressed ejection fractions. Other investigators have found dipyridamole-201Tl single-photon emission computed tomography imaging to be insensitive for anatomical coronary disease or long-term cardiac events in patients with end-stage renal failure.114 However, another study46 found that pretransplant and postoperative cardiac death and myocardial infarction occurred only in patients with transient defects and did not occur in patients with fixed defects or normal images.

Although there are very little specific data available to the clinician to base recommendations for using 201Tl imaging for preoperative risk stratification of patients undergoing nonvascular, noncardiac surgery, several principles may help guide patient selection until more information is available. First, 201Tl imaging, like any risk stratifier, is likely to be most useful in patients undergoing noncardiac surgery that carries the greatest perioperative risk. Therefore, 201Tl imaging will be more useful in risk-stratifying patients undergoing major orthopedic, bowel resection, or gastrectomy surgery compared with patients undergoing procedures such as transurethral resection of prostate or herniorrhaphy because of their substantially higher perioperative cardiac risk.104,105,112 Cholecystectomy carries an intermediate risk.115 Second, 201Tl imaging is most likely to be useful in patients with a high risk of underlying coronary artery disease. Patients with known prior myocardial infarction by history or electrocardiography or with a history suggestive of angina will more likely benefit from 201Tl risk stratification than will patients without clinical evidence of cardiac disease. As discussed above, asymptomatic coronary artery disease may be problematic. However, unlike peripheral vascular surgery in which the patient population itself defines a cohort of patients at high risk for coronary artery disease independent of symptomatology, it may be more appropriate to use clinical evidence of coronary disease in other types of general noncardiac surgery to determine whether to proceed further with a 201Tl study.

**Proposed algorithm for preoperative risk stratification.** It is reasonable to recommend the use of dipyridamole-201Tl imaging in all patients undergoing aortic reconstructive surgery who have any clinical risk factors (e.g., those defined by Eagle et al38,40) (Figure 6). Patients without clinical risk factors who are scheduled to have aortic reconstructive surgery would probably also benefit from such risk stratifica-
tion because of the major cardiovascular impact of the surgery, its overall relatively high ischemic perioperative event rate, and the known high prevalence of asymptomatic coronary artery disease. In patients undergoing nonaortic vascular surgery (including femoropopliteal bypass and carotid endarterectomy), the use of clinical criteria to select patients to undergo further risk stratification with $^{201}$Tl imaging may be reasonable because the overall risk of the procedure is substantially lower. However, more research is needed to clarify this issue.

Following the principles described above, for nonvascular, noncardiac surgery $^{201}$Tl imaging might be best reserved for patients who have a high probability of underlying coronary artery disease based on clinical grounds and who are undergoing major general surgery that has a known overall high risk of perioperative cardiac events (Figure 6).

Basis of Thallium-201 Prognostic Value

The results of the many studies cited above using $^{201}$Tl imaging in a wide range of clinical settings have been remarkably consistent: Transient $^{201}$Tl defects (i.e., defects that show redistribution) predict future cardiac events. $^{201}$Tl uptake, as discussed, reflects both relative myocardial perfusion and viability.\textsuperscript{56,60–63,67} Transient defects define the presence of jeopardized or hypoperfused viable myocardium. Although the mere presence of angiographic coronary disease establishes an increased risk of cardiac events,\textsuperscript{116,117} risk appears to be more specifically related to the presence of 1) a hemodynamically significant lesion that 2) supplies viable myocardium. Angiographically defined anatomical assessment of coronary artery disease, particularly qualitative visual analysis, often does not accurately reflect the hemodynamic impact on coronary blood flow.\textsuperscript{118–121} In contrast, $^{201}$Tl uptake reflects relative perfusion independent of anatomical considerations. This may be why normal $^{201}$Tl studies, indicating normal perfusion, so consistently predict a benign outcome, even in the presence of underlying angiographic coronary disease.\textsuperscript{5,7,9,12,13,15–21,30,47–49} In addition, coronary disease that supplies an area of old infarction would not be expected to have the same risk of future cardiac events as the same lesion that supplies viable myocardium. This may explain the very consistent lack of predictive value of fixed $^{201}$Tl defects.\textsuperscript{5,12,14–17,24,27–44} Such defects generally reflect prior infarction or scar.\textsuperscript{56,67,122} Some recent studies have shown that some apparently fixed defects will improve after revascularization\textsuperscript{72} or will demonstrate some degree of redistribution if reimaged 18–72 hours later\textsuperscript{73} (see below). However, regardless of these observations, there seems to be a fundamental difference in the prognostic significance of transient versus fixed defects that in some way probably reflects differences in the presence or degree of jeopardized viable myocardium.

Newer Perfusion Agents

On the horizon are new, exciting myocardial perfusion agents that use technetium-99m–based organic compounds and have distinct advantages because of improved imaging characteristics, particularly with tomographic imaging. A detailed comparison of these agents to $^{201}$Tl imaging is beyond the scope of this review. However, they differ from $^{201}$Tl in that they show little or no redistribution, requiring sequential injection and imaging at rest and during
stress,123–130 Early studies suggest comparable diagnostic accuracy for detecting angiographic coronary disease.131,132 However, in view of the now well-established prognostic value of $^{201}$TI imaging, the new perfusion agents will need to be held to an additional standard of clinical usefulness.

**Limitations of Prior Studies**

Taken as a whole, the many studies described unequivocally establish the importance of $^{201}$TI imaging as a prognostic tool; however, conclusions must be somewhat tempered by consideration of the following several factors.

**Definition of “Cardiac Event” Varies Among Studies**

Some studies have defined “cardiac events” as “hard” end points of cardiac death or nonfatal myocardial infarction,5,8–11,15,16,25,28,30,35,37,41,43 whereas others have lumped such events together with “soft” end points, including unstable angina or coronary revascularization.6,7,12–15,24,26,27,29–34,36,38,39,42 These latter events are generally included to increase the number of events and improve statistical analysis but are substantially less important clinically and tend to obscure the true clinical usefulness of the predictive variables. In addition, the results of $^{201}$TI imaging, coronary angiography, and the exercise stress test may have direct causative impacts on decisions regarding revascularization because such data are usually available to treating physicians. Some studies have attempted to minimize this impact by including as cardiac events only those revascularization procedures performed more than 2–3 months after testing, making the assumption that such procedures would be unlikely to have been influenced by test data.6,7,12–14,17

**Not All Variables That Fully Characterize Each Diagnostic Modality Are Analyzed**

For example, some studies analyzed the prognostic value of the presence of transient defects or the number of perfusion defects but not the number of transient defects.8–11,15,17,24,26,28–36,40 Others did not evaluate increased lung uptake.6,7,17,25–27 In addition, angiographic data are based on qualitative analysis and are generally simplistically presented as the number of coronary vessels with significant disease. It is possible that with a more-detailed, quantitative analysis using other variables such as maximal stenosis, minimal cross-sectional area, or length of a lesion, coronary angiography might have performed more favorably compared with $^{201}$TI imaging data. On the other hand, clinical decisions regarding patient management are generally based on qualitative assessment of the number of vessels diseased; therefore, such a variable offers a reasonable representation of the technique. Analyses of exercise electrocardiograms have generally been more sophisticated, using not only the presence of significant ST segment depression as a potential predictor but also the magnitude of depression, number of leads with ST depression, type of ST depression, development of angina, and numerous chronotropic, hemodynamic, and workload parameters.7–14,24,27

**Type of Analysis Differs Among Studies**

For multivariate analysis, logistic regression,5,6,15,16,28,30,32,35,37–40 Cox survival analysis,8–14,25 and discriminant analysis2 were variously used. Most studies evaluated all potential variables in multivariate analysis, but one included only those with univariate predictive value.6 Many studies did not use multivariate analysis at all,17,26,27,29,31,33,34,36,41–43 In some studies, $^{201}$TI variables (particularly transient defects) were the only significant univariate predictors, making multivariate analysis moot.27,29,31,36,41,42 However, in other studies, the lack of multivariate analysis precludes any comparison between $^{201}$TI data and any other potential predictor.

**There Are No Data Available Regarding Whether Any Intervention Can Lower the Risk of Patients Identified by Thallium-201 Imaging to Have an Increased Probability for Cardiac Events**

High-risk $^{201}$TI studies often lead to cardiac catheterization and hence to revascularization independent of symptomatology. In patients with chronic stable coronary artery disease, data from both the Coronary Artery Surgery Study and the European Coronary Surgery Study indicate that bypass surgery improves prognosis compared with medical treatment in patients with provachable ischemia assessed by stress electrocardiography.133,134 Although it is reasonable to hypothesize that patients demonstrated by $^{201}$TI imaging to be at greatest risk for cardiac events are the most likely subgroup to benefit from revascularization, this is unproven. Particularly difficult management decisions may arise in potential vascular surgery patients identified by $^{201}$TI imaging to be at greatest risk for perioperative cardiac events. Such patients are often poor candidates for coronary bypass surgery because of their general condition, age, coexisting cerebrovascular disease, and the potential morbidity associated with delay of planned vascular surgery. Although coronary angioplasty may allow some of these patients to avoid surgery, the risk of acute occlusion during angioplasty requires assessment of the risk of bypass surgery in these patients as well. There is a very obvious need for a large randomized study to compare intervention with modern aggressive medical treatment strategies in post-infarction, preoperative, and chronic coronary artery disease patients identified by $^{201}$TI imaging to be at high risk for future cardiac events. Meanwhile, it is important to remember that whether an interventional approach improves prognosis compared with aggressive medical treatment is unproven and that the risk-to-benefit ratio of revascularization should be carefully assessed on an individual basis for each patient.
Benign Outcome of Patients With Normal Thallium-201 Studies May Not Apply to Those Able to Achieve Only a Very Low Level of Stress

In such patients, the sensitivity of 201Tl imaging for underlying coronary artery disease may be diminished, although some studies show no significant impact on sensitivity at low levels of exercise.

Effect of Medical Treatment on Prognostic Value of Thallium-201 Imaging Is Unknown

Although medical treatment may reduce or eliminate exercise-induced ischemia seen on 201Tl imaging, the impact on prognosis of such an improvement is unknown. This issue may be especially relevant in post-infarction risk stratification concerning whether to test patients on or off medical treatment such as β-blockers. Because many if not most patients will be treated on a long-term basis with β-blockers, it is reasonable to perform risk stratification with 201Tl imaging while patients are receiving such treatment. However, prior studies (Table 3) have not controlled for β-blockers or other treatment at the time of imaging. Whether treatment affects imaging results and prognosis concordantly or masks potentially high-risk coronary artery disease is unknown and requires further study.

Not All Fixed Defects Represent Infarction

Recently, several studies have challenged the concept that fixed defects represent scar or infarction. Earlier reports suggested that some fixed defects will show improved perfusion after revascularization but that the more severe the defect, the less likely to be improvement. However, regional or global improvement in left ventricular function was far more likely to occur after revascularization when transient defects were present compared with fixed defects. More recently, Liu and colleagues reported that 75% of fixed defects normalized after coronary angioplasty. However, this was a highly selected group of patients since only 8% had electrocardiographic evidence of myocardial infarction. In a larger, prospective study, 22% of all nonreversible defects at 4 hours showed redistribution at 18–72 hours. Interestingly, approximately 10% of defects showing reversibility at 4 hours appeared fixed on late imaging. This latter study did not differentiate partial redistribution from fixed defects, an important issue because most of the prognostic studies discussed in this treatise have found significant predictive value for the presence of any significant redistribution, lumping partial and total redistribution together. In addition, imaging quality and counting statistics may be a problem with late (especially 72 hours) imaging and may reduce the reliability of such results, although investigators have attempted to minimize this by additional imaging time. Nevertheless, such technical factors may explain why some defects appeared reversible at 4 hours but fixed at late imaging.

Results from metabolic imaging studies using positron-emission tomography have suggested that fixed defects have viable myocardium within the segment. Investigators found that fixed 201Tl defects frequently demonstrate evidence of metabolic activity manifest by increased F18-2-fluoro-deoxyglucose uptake. However, these studies allowed patients to drink fluid between initial and delayed 201Tl images, which may have caused a significant underestimation of 201Tl redistribution. Previous research has shown that carbohydrate intake substantially reduces the degree of 201Tl redistribution and may turn potentially transient defects into fixed defects. Nevertheless, it would not be surprising to find that fixed defects do have viable myocardium within them. Most infarct zones contain a mixture of dead and viable myocardium. Furthermore, the large majority of fixed defects show some 201Tl uptake in the defect—less than surrounding myocardium but not an absence of uptake. Therefore, demonstration of viable myocardium by metabolic imaging in the corresponding fixed 201Tl defect segment should not be surprising.

In summary, fixed defects probably do contain some viable myocardium, which is consistent with the uptake of some 201Tl activity. Some defects that do not show redistribution at 2–4 hours probably do not represent infarction, particularly in the absence of Q waves or with known normal regional wall motion, and may show redistribution if imaged at 18–72 hours. The frequency of this observation is not clear. However, regardless of these observations, prior studies have shown a remarkably consistent lack of prognostic value for defects that are fixed at 2–4 hours. The prognostic value of defects that show redistribution only at 18–72 hours or after reinjection of 201Tl before 4-hour imaging is unknown. It is possible that turning fixed defects into transient defects by either late imaging or reinjection will dilute the prognostic value of transient defects. Caution should be used in changing standard imaging protocols before the prognostic significance of this phenomenon is demonstrated.

Not All Nuclear Cardiology Laboratories Are Created Equal

A basic premise in transferring the results of the studies reviewed in this treatise to local practice is that high-quality studies are available locally. Such quality depends greatly on not only the available imaging equipment but also on local expertise for interpretation.

Conclusion

201Tl myocardial perfusion imaging has been shown to have the ability to predict important cardiac events in a wide variety of clinical settings and with different stress modalities. Beginning as a strictly diagnostic tool, it has evolved into a powerful risk stratifier that can have a major impact on patient management by allowing a rational application of additional, more invasive and costly diagnostic and therapeutic interventions.
References


32. Brown KA, O'Meara J, Chambers CE, Plante DA: Ability of dipyridamole-thallium-201 imaging 1 to 4 days after acute myocardial infarction to predict in-hospital and late recurrent myocardial ischemic events. Am J Cardiol 1990;65:160-167


34. Chamberlain RS, Beller GA, Cheghrih M, Nygaard TW, Watson DD, Huey EL, Sayre SL, Kaiser DL: The prevalence and clinical significance of residual myocardial ischemia 2 weeks after uncomplicated non-Q-wave myocardial infarction: A


52. Weich HF, Strauss HW, Pitt B: The extraction of thallium-201 by the myocardium. *Circulation* 1977;56:188–191


imaging and its fate after myocardial revascularization: Does it represent scar or ischemia? Am Heart J 1985;110:996–1001


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K A Brown

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