Dipyridamole Thallium-201 Scintigraphy as a Preoperative Screening Test
A Reexamination of Its Predictive Potential

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Background. We examined the value of dipyridamole thallium-201 (201TI) scintigraphy as a preoperative screening test for perioperative myocardial ischemia and infarction.

Methods and Results. We prospectively studied 60 patients undergoing elective vascular surgery. We performed 201TI scintigraphy preoperatively and blinded all treating physicians to the results. Historical, clinical, laboratory, and physiological data were gathered throughout hospitalization. Myocardial ischemia was assessed during the intraoperative period using continuous 12-lead electrocardiography (ECG) and transesophageal echocardiography (TEE) and during the postoperative period using continuous two-lead ambulatory ECG. Adverse cardiac outcomes (cardiac death, myocardial infarction, unstable angina, severe ischemia, or congestive heart failure) were assessed daily throughout hospitalization. Twenty-two patients (37%) had defects that improved or reversed on delayed scintigrams (redistribution defects), 18 (30%) had persistent defects, and 20 (33%) had no defects on 201TI scintigraphy. There was no association between redistribution defects and adverse cardiac outcomes: 54% (seven of 13) of adverse outcomes occurred in patients without redistribution defects, and the risk of an adverse outcome was not significantly increased in patients with redistribution defects (relative risk 1.5, 95% confidence interval 0.6-3.9, p=0.43). Consistent with these findings, there was also no association between redistribution defects and perioperative ischemia: 54% (19 of all 35) of perioperative ECG and TEE ischemic episodes and 58% (14 of 24) of severe ischemic episodes occurred in patients without redistribution defects. The sensitivity of 201TI scintigraphy for perioperative ischemia and adverse outcomes ranged from 40% to 54%, specificity from 65% to 71%, positive predictive value from 27% to 47%, and negative predictive value from 61% to 82%.

Conclusions. These results differ from those of previous studies and suggest that the routine use of 201TI scintigraphy for preoperative screening of patients undergoing vascular surgery may not be warranted. (Circulation 1991;84:493-502)

Yearly in the United States approximately 50,000 patients sustain a myocardial infarction following noncardiac surgery, causing approximately 20,000 deaths.1,2 Previous studies consistently have identified two predictors of perioperative cardiac morbidity: recent myocardial infarction and current congestive heart failure.3-8 The importance of other potential preoperative predictors remains controversial.3

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Recently, two groups of investigators have found that reversible defects seen on preoperative thallium-201 (201TI) scintigraphy can identify those patients undergoing vascular surgery who are at high risk of adverse cardiac outcomes.9-14 These studies stimulated considerable interest in 201TI scintigraphy as a preoperative screening test. In all of these studies, however, treating physicians were not blinded to preoperative scintigraphic findings. As a result, refer-
r al bias may have occurred with perioperative care being altered in patients with redistribution defects: surgery was cancelled or modified, the use of invasive hemodynamic monitoring and therapy (such as nitroglycerin) was increased, and patients were monitored longer in the intensive care unit postoperatively. These changes in clinical management may have affected the true association between redistribution defects and perioperative morbidity and mortality. Furthermore, there is now evidence that the most important determinants of adverse cardiac outcome in high-risk patients undergoing noncardiac surgery are intraoperative and postoperative physiological changes—specifically myocardial ischemia. Since the previous 201TI studies did not measure such perioperative changes, they did not distinguish the relative contribution to adverse outcome of the preoperative disease state from that of dynamic intraoperative and postoperative physiological factors. Consequently, the previous studies did not fully determine the independent predictive value of 201TI scintigraphy.

Since 201TI scintigraphy is relatively expensive ($700–$1,300 per test), its use in even only a subset of the 350,000 patients undergoing vascular surgical procedures annually would substantially increase national health care costs. Given these considerations, we reexamined the usefulness of 201TI scintigraphy in patients undergoing vascular surgical procedures. Our study is unique in that there was no preselection of patients and we blinded all treating physicians to the results of the scintigraphic studies, measured ischemia continuously throughout the perioperative period, and assessed outcomes throughout hospitalization.

Methods

Setting and Subjects

We studied 60 patients (59 men, one woman) scheduled for elective vascular surgery at the Department of Veterans Affairs Medical Center in San Francisco. This was a consecutive series of eligible patients in whom scintigraphy could be obtained between admission and surgery. Patients with unstable heart disease (myocardial infarction within the previous 6 months, unstable angina, or decompensated heart failure) were excluded. Patients with cardiac pacemakers or left bundle branch block precluding interpretation of the electrocardiographic (ECG) data were ineligible for study, as were those with esophageal disease precluding placement of the transesophageal echocardiographic (TEE) probe. Our study protocol was approved by our Committee on Human Research, and all patients studied gave informed consent. Since preoperative scintigraphy data were blinded, vascular surgery was neither delayed nor modified, nor was care otherwise modified in any patient because of scintigraphic results.

Measurements and Perioperative Management

Research data were collected in parallel with clinical data, and all physicians caring for the patients were blinded to the research data. Preoperatively, a study physician performed routine clinical evaluation and chart review, using the guidelines of the Coronary Artery Surgery Study. Preoperative testing included 12-lead ECG and 201TI scintigraphy (as described later). Surgery was classified as major vascular (intrathoracic or intra-abdominal, 32 patients), carotid (four patients), or peripheral vascular (24 patients). Routine clinical monitoring included continuous arterial blood pressure monitoring, three-lead ECG, pulse oximetry, and mass spectroscopy. The primary anesthetic was isoflurane (nine patients), isoflurane/narcotic (46 patients), or narcotic (five patients). Intraoperative and postoperative medications, blood loss, total fluids infused, and duration of anesthesia and surgery were recorded. Patients were interviewed and examined by a study physician on each postoperative day until discharge. All cardiovascular medications were recorded. Creatine kinase levels with isoenzymes were obtained on postoperative days 1 and 5, and when clinically indicated, including whenever ECG changes consistent with ischemia or infarction occurred.

Thallium-201 Scintigraphy and Analysis

Intravenous 201TI scintigraphy was performed in all patients according to previously described protocols. Patients refrained from food and drink for a minimum of 8 hours and from caffeinated beverages for at least 12 hours before testing. No patient was taking oral or intravenous theophylline compounds within 48 hours of the study. Antianginal medications were continued as prescribed. Blood pressure (automated cuff cycled at 1-minute intervals) and continuous 12-lead ECG monitoring were performed 2 minutes before the start of the test (baseline) and continued until 20 minutes after its completion. Specialized electrodes and lead wires (Quinton Instruments, Seattle, Wash.) were used to allow continuous monitoring of the 12-lead ECG during scintigraphy. A study physician was in attendance throughout the study period. Dipyridamole (Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Conn.) was infused into the supine patient at the rate of 0.14 mg/kg body wt/min for 4 minutes. No additional stress or change in position was applied. Three minutes following infusion, 2.5 mCi of 201TI was administered intravenously. Beginning 3 minutes after the administration of the radiotracer, 8-minute stress scintigrams were obtained on a Siemens LEM gamma camera (Des Plaines, Ill.) interfaced with an MSA2D (Ann Arbor, Mich.) dedicated computer in the 45º left anterior oblique, anterior, and 70º left anterior oblique projections. Delayed scintigrams were obtained in the same projections after 3 hours. All scintigrams were interpreted from the computer display using a semiquantitative scoring system.
employing a 0-to-3 scale (0, no abnormality; 1, mildly decreased uptake; 2, moderately decreased uptake; and 3, uptake reduced to the level of background activity). In addition, circumferential profiles of relative activity were generated for the stress and delayed scintigrams, and these were used as adjuncts to the visual analysis. Abnormalities were not read on the basis of the profiles alone. Each set of images was divided into a total of nine segments that were scored individually. The scintigrams were classified as normal if no defects were observed, as having a persistent defect if the initial abnormality was unchanged on the delayed image, or as having a redistribution defect if the initial abnormality resolved completely or in part (by a grade of 1 or more) on the delayed scan. Interobserver differences in interpretation were resolved by consensus. The 201Tl studies were not analyzed until the patient was discharged from the hospital. The two independent investigators interpreting the scintigrams were blinded to the patient’s identity and all other measurements and outcomes. Their scintigraphic findings were, and have been, kept confidential from all referring and treating physicians.

The dipyridamole infusion resulted in a decrease in the mean ± SD systolic blood pressure from 137±21 to 127±21 mm Hg and an increase in the heart rate from 71±14 to 78±14 beats/min (both p=0.001). In two of the 60 patients (one with a redistribution defect, one with a persistent defect), chest pain occurred and resolved spontaneously without treatment within 1 minute. One additional patient (with a redistribution defect) had four episodes of ECG ST segment depression, three of which were silent. No other complications, such as dysrhythmia, congestive heart failure, or myocardial infarction, occurred during dipyridamole testing.

**Monitoring**

**Echocardiography.** TEE was performed continuously from anesthetic induction until skin closure using a 3.5- or 5-MHz echocardiographic probe (Diasonic 6400, Milpitas, Calif.; General Electric RT5000, Milwaukee, Wisc.; or Corometrics 860, Wallingford, Conn.) positioned and maintained at the level of the midpapillary muscles to obtain a short-axis view of the left ventricle. Interpretable images were available for 50 patients (mean monitoring time 6.3 hr/patient). Blinded investigators used standard analytical techniques to analyze left ventricular wall motion in each of four segments. The variability of echocardiographic interpretation in our laboratory has been reported previously; interobserver, intraobserver, and interexamination concordances exceed 90%. Each segment was assigned one of five grades: normal, mild hypokinesis, severe hypokinesis, akinesis, or dyskinesis. Baseline wall motion for each segment was defined by the most normal motion in that segment throughout the study. An ischemic episode was defined as a reversible change of two or more grades lasting 1 minute or more in the wall motion of any segment or deterioration from akinesis to dyskinesis in a segment with normal wall thickness.

**Electrocardiography.** A 12-lead ECG was obtained preoperatively, daily for the first 7 postoperative days, on the tenth and fourteenth postoperative days, weekly thereafter, on the day of discharge, and whenever clinically indicated by shortness of breath, chest pain, or syncope. Preoperative abnormalities, including evidence of prior infarction, left ventricular hypertrophy, conduction abnormalities, dysrhythmias, and nonspecific ST-T wave abnormalities, were recorded. Intraoperatively (and for up to 1 hour preoperatively and postoperatively), continuous 12-lead ECG recordings were obtained using a microcomputer augmented exercise stress system (MAC II, Marquette Electronics, Milwaukee, Wis.) with a frequency response of 0.01–100 Hz at −3 dB (mean monitoring time 7.3 hr/patient). Signal detection was based on a noise-filtered, time-averaged complex for each lead. All possible ischemic episodes were reviewed independently by two investigators blinded to the patient’s outcome, using ST segment criteria previously described. Patients were monitored using a two-channel AM Holter ECG recorder (Series 8500, Marquette Electronics) for 2 days postoperatively (mean monitoring time 37.8 hr/patient). Fifty-five of 60 patients had interpretable data. The frequency response of the recorders is 0.5–80 Hz at −3 dB. Two bipolar leads, CC5 and CM5, were used. Silver/silver chloride electrodes were used, and skin impedance was less than 5 kΩ in all patients. The effect of positional variation on ECG morphology was measured before study in the supine, upright, left lateral decubitus, and right lateral decubitus positions. Patients were instructed to keep a diary of activity and symptoms during the postoperative period and were questioned daily by a study physician. Holter tapes were analyzed for ST segment deviation after all abnormal QRS complexes such as ventricular ectopic beats and beats with conduction abnormalities were excluded. The ST segment was then trended continuously in the two leads for the duration of the tape. The baseline ST segment level was defined as the average ST segment over a stable period (usually 15–60 minutes) preceding each episode. All possible ischemic episodes (using individual ECG complexes) were reviewed independently by two investigators blinded to the patient’s identity and clinical course. (The variability of ECG interpretation in our laboratory has been previously reported; interobserver, intraobserver, and interexamination concordances exceed 94%.) ECG ischemic episodes were defined as reversible ST segment changes lasting at least 1 minute and involving either a shift from baseline (adjusted for positional changes) of 1.0 mm (0.1 mV) or more of ST depression with a slope of 0 or less or a 2.0-mm or more ST elevation at the J point. ST segment depression was measured 60 msec after the J point unless that point fell within the T wave, in which case it was shortened to a minimum of J+40 msec. To be considered reversible, an ST
segment change had to return to baseline for at least 1 minute. The maximum ST segment change from baseline was measured for each episode.

**Hemodynamics.** Blood pressure was recorded intraproactively from an arterial line that was linked to a microcomputer. Transducers were calibrated and referenced to the right atrium. For each patient, an analog representation of the digitized data was created, and spurious abnormalities (e.g., catheter movement, transducer flushing) were eliminated manually before analysis. Heart rate was recorded from the Holter monitor. Hypertension (hypotension) was defined as a systolic blood pressure of more than 160 (less than 90) mm Hg for at least 5 minutes and tachycardia (bradycardia), as a heart rate of more than 100 (less than 50) beats/min.

**Outcome Measurements**

Adverse outcomes were noted by study physicians and validated separately by two investigators blinded to the patient’s scintigraphic and monitoring data; disagreements were resolved by consensus, involving a third investigator if necessary. Outcomes were defined in the following order of severity: cardiac death, nonfatal myocardial infarction, unstable angina or ischemia, and congestive heart failure. When a patient had several outcomes, only the most severe was assigned. Cardiac death was diagnosed if the patient died of either a dysrhythmia or congestive heart failure caused primarily by a cardiac condition. Myocardial infarction required 1) an elevation of the creatine kinase MB isoenzyme concentration (≥0.83 μmol/sec/l, equivalent to 50 units/l and 2) the development of either new Q waves (as defined by the Minnesota Code: I, 2\text{a}) or persistent ST-T wave changes (Minnesota Code: IV, V\text{2a}) or 3) necropsy evidence of acute infarction. Unstable angina required severe precordial chest pain that was 1) nonsurgical, lasting 30 minutes or more, 2) unresponsive to standard therapeutic maneuvers (nitroglycerin, rest), and 3) associated with transient ST segment or T wave changes without the development of Q waves or diagnostic enzyme abnormalities. Severe postoperative ECG ischemia required 2 mm or more of ST deviation from baseline and a duration of 30 minutes or more. Congestive heart failure required 1) symptoms or signs of pulmonary edema (shortness of breath, rales) documented by chest radiography (vascular redistribution, interstitial edema, alveolar edema), 2) signs of new left or right ventricular failure (cardiomegaly, S\text{3}, jugular venous distension, peripheral edema), and 3) a change in medication involving at least treatment with diuretics.

**Data Analysis**

Potential univariate predictors of adverse cardiac outcomes were identified using \( \chi^2 \) analysis or Fisher’s exact test (for dichotomous predictors)\textsuperscript{24} and logistic regression (for categorical and continuous predictors).\textsuperscript{25} Continuous variables were compared using analysis of variance for repeated measures; these values are reported as mean±SD. The \( \chi^2 \) analysis was used to compare the characteristics of patients with redistribution, persistent, or no defects.\textsuperscript{24} Two-sided probability values and 95% confidence intervals are reported. All analyses were performed using SAS software (SAS Institute Inc., Cary, N.C.).

**Results**

The patients were typically middle-aged or elderly men who smoked and had a history of hypertension and chronic medical problems (Table 1). There were similar numbers of patients in each of the three scintigraphic groups (redistribution defects, persistent defects, and no defects), and there were no substantial differences in their demographic characteristics, with the exception of diabetes mellitus, which was more common in the group with no defects.

**Adverse Cardiac Outcomes**

Thirteen patients (22%) had in-hospital adverse cardiac outcomes, hierarchically classified as fatal myocardial infarction in one, nonfatal myocardial infarction in two, unstable angina or severe postoperative ischemia in five, and congestive heart failure in five. Six of these had redistribution defects, four had persistent defects, and three had no defects on
201TI scintigraphy (Table 2). Figures 1–3 illustrate scintigrams from three patients; the first had a normal scintigram and developed a postoperative fatal myocardial infarction, the second had a persistent defect and also developed a myocardial infarction, and the third had a redistribution defect and developed congestive heart failure postoperatively. The sensitivity of redistribution defects for in-hospital outcomes was 46%, the specificity was 66%, the positive predictive value was 27%, and the negative predictive value was 82% (Table 3). The association of redistribution defects with adverse cardiac outcomes was not significant (p=0.43). Similarly, the association of persistent defects with adverse outcomes was not significant (p=0.97); the sensitivity was 46%, the specificity was 53%, the positive predictive value was 21%, and the negative predictive value was 78%. For any abnormality (reversible or persistent) the sensitivity was 77%, the specificity was 36%, the positive predictive value was 25%, and the negative predictive value was 85%. No significant association was found between reversible or persistent defects and adverse cardiac outcome (p=0.38).

**Perioperative Myocardial Ischemia**

Thirty-five patients (58%) had perioperative myocardial ischemia. Intraoperative ECG ischemia occurred in 18 of 60 (30%), intraoperative TEE changes indicative of ischemia in 13 of 50 (26%), and postoperative ECG ischemia in 20 of 55 patients (36%). Patients with redistribution defects had a higher incidence of intraoperative and postoperative ECG and TEE ischemia than patients with persistent or no defects, but the differences were not significant (Table 4). Similarly, 27% of patients with redistribution defects did not develop perioperative ischemia versus 50% with persistent or no defects. The incidence of severe ECG ischemic episodes was similar in patients with redistribution defects and those with persistent or no defects (36% versus 32%, p=0.89), as was the incidence of severe TEE episodes (dura-

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**TABLE 2. Characteristics and Results of 13 Patients With In-Hospital Adverse Cardiac Outcomes**

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Intraoperative ischemia</th>
<th>Postoperative ischemia (two-lead ECG)</th>
<th>In-hospital outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12-Lead ECG</td>
<td>TEE</td>
<td></td>
</tr>
<tr>
<td>No defect</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>43</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>57</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Persistent defect</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
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<td>Yes</td>
<td>No</td>
</tr>
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<td>37</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>40</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>53</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Redistribution defect</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>28</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>50</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>52</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>55</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

ECG, electrocardiography; TEE, transesophageal echocardiography.

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**FIGURE 1.** Above: Scintigrams from patient 16 (Table 2) with normal dipyridamole thallium-201 study who subsequently sustained perioperative myocardial infarction and died. Stress (DYP) and delayed (3Hr) scintigrams are shown. No abnormalities are seen at either time. Below: Circumferential profiles from left anterior oblique (LAO) 45° images. These indicate no areas of hypoperfusion or changes in relative distribution between DYP (dashed line) and 3Hr (solid line) studies.
tion 30 minutes or more and magnitude 3 grade changes or more; 20% versus 17%, p=0.77). There was no difference in the dipyridamole findings or the ischemic or outcome results with respect to anesthetic type.

Scintigraphic defects characterized by redistribution were reasonably specific (65–71%) but insensitive (40–54%) predictors of intraoperative (ECG, TEE) or postoperative (ECG) ischemia (Table 3). Fifty-four percent of all ischemic episodes and 58% of severe ischemic episodes occurred in patients without redistribution defects. Neither the positive nor the negative predictive values were high.

**Discussion**

Our results suggest that preoperative 201Tl scintigraphy has limited sensitivity for the detection of perioperative ischemia and adverse cardiac outcomes in patients undergoing vascular surgery. Patients with redistribution defects had incidences of intraoperative and postoperative ischemia and adverse outcome similar to those in patients with persistent or no defects. Therefore, we conclude that the routine use of 201Tl scintigraphy for preoperative screening of patients undergoing vascular surgery may not be warranted.

Early studies of 201Tl scintigraphy demonstrated its usefulness in the diagnosis of coronary artery disease and in determining prognosis following myocardial infarction. More recent work suggested that preoperative 201Tl scintigraphy was a sensitive and specific predictor of adverse cardiac

**FIGURE 2.** Above: Scintigrams from patient 37 (Table 2) with prior myocardial infarction who sustained subsequent perioperative myocardial infarction. Stress (DYP) and delayed (3Hr) scintigrams are shown. Anterior, septal, and apical defects are seen. Below: Circumferential profiles from left anterior oblique (LAO) 45° images. No evidence of redistribution between DYP (dashed line) and 3Hr (solid line) studies on either scintigrams or profiles.

**FIGURE 3.** Above: Scintigrams from patient 50 (Table 2) who developed congestive heart failure postoperatively. Stress (DYP) and delayed (3Hr) scintigrams are shown. This patient exhibits large, partly reversible defect involving inferior wall and apex, as well as inferior portion of interventricular septum. Below: Circumferential profiles from left anterior oblique (LAO) 45° images. Redistribution defect between DYP (dashed line) and delayed (solid line) studies is confirmed on profiles. This patient also developed chest pain and ischemic ST segment changes during test.

### Table 3. Sensitivity, Specificity, and Predictive Value of Redistribution Defect on Dipyridamole Thallium-201 Scintigraphy

<table>
<thead>
<tr>
<th>Event</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Predictive value</th>
<th>Relative risk</th>
<th>95% Confidence interval</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraoperative ischemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12-Lead ECG</td>
<td>44%</td>
<td>68%</td>
<td>38%</td>
<td>74%</td>
<td>1.45</td>
<td>0.67–3.15</td>
</tr>
<tr>
<td>Transesophageal echocardiography</td>
<td>54%</td>
<td>65%</td>
<td>35%</td>
<td>80%</td>
<td>1.75</td>
<td>0.69–4.46</td>
</tr>
<tr>
<td>Postoperative ECG ischemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe ischemia</td>
<td>45%</td>
<td>71%</td>
<td>47%</td>
<td>69%</td>
<td>1.55</td>
<td>0.77–3.13</td>
</tr>
<tr>
<td>Adverse outcome</td>
<td>46%</td>
<td>66%</td>
<td>45%</td>
<td>61%</td>
<td>1.15</td>
<td>0.62–2.13</td>
</tr>
</tbody>
</table>

ECG, electrocardiography.
outcome following vascular surgery. Several groups of investigators found that all or nearly all adverse outcomes in this surgical population occurred in patients with redistribution defects, resulting in greater than 80% sensitivity and a nearly 100% negative predictive value for this test (Table 5). These results have generated strong arguments that \(^{201}\)TI scintigraphy be used to identify at-risk patients undergoing vascular surgery.

Because our findings differ from those of the previous studies and suggest a more limited role for the use of preoperative \(^{201}\)TI scintigraphy, it is important to examine the similarities and differences between these studies and ours. With respect to similarities, both our study and the previous six studies cited\(^{9–14}\) addressed the same general patient population (viz., patients undergoing vascular surgery), 2) used similar techniques for performing \(^{201}\)TI scintigraphy, and 3) measured similar outcome variables. However, a number of differences exist, including 1) the use of consecutive versus selected patients, 2) blinding of the clinicians to the scintigraphy results, 3) perioperative clinical management of patients, 4) intensity of outcome variable measurements, and 5) measurement of perioperative myocardial ischemia as an intermediate of outcome. Each difference will be discussed in turn.

First, with respect to the patient population, patients in our study were consecutively enrolled, whereas most previous studies did not enroll consecutive patients but included only those patients referred by a consulting physician\(^{13,14}\) or patients presumed to be at higher risk\(^{9,10}\). That methodology may have resulted in those studies’ having a selection bias toward patients with unstable or severe symptoms who likely benefited from this investigational diagnostic procedure. As a result, their referral bias might increase the sensitivity of the test. This argument is consistent with our findings of a relatively low incidence of signs and symptoms of ischemia during dipyridamole infusion. Another possible difference is patient selection. Although our patients did not have unstable symptoms and were admitted for elective vascular surgery, there was a high prevalence of risk factors for coronary artery disease (Table 1). Thus, there may have been a higher incidence of diffuse coronary disease in our population, and this type of anatomy may have a higher incidence of false-positive studies based on the more homogeneous decrease in coronary blood flow.\(^{30,31}\)

Second, there is always the potential that there were differences between our and others’ interpretation of the \(^{201}\)TI scintigrams that contributed to the differences in findings. It is possible that using a delay of

### Table 5. Comparison With Previous Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>No.</th>
<th>DPT result</th>
<th>Outcome</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Predictive value</th>
<th>Relative risk</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>R</td>
<td>F/N</td>
<td>R</td>
<td>F/N</td>
<td>Positive</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Boucher et al(^{19,10})</td>
<td>48</td>
<td>16</td>
<td>32</td>
<td>8</td>
<td>0</td>
<td>100%</td>
<td>80%</td>
<td>50%</td>
</tr>
<tr>
<td>Cutler and Leppo(^{11})</td>
<td>101</td>
<td>104</td>
<td>2</td>
<td>90</td>
<td>0</td>
<td>100%</td>
<td>89%</td>
<td>23%</td>
</tr>
<tr>
<td>Leppo et al(^{12})</td>
<td>89</td>
<td>82</td>
<td>17</td>
<td>14</td>
<td>1</td>
<td>93%</td>
<td>62%</td>
<td>33%</td>
</tr>
<tr>
<td>Eagle et al(^{13,14})</td>
<td>200</td>
<td>178</td>
<td>22</td>
<td>55</td>
<td>5</td>
<td>83%</td>
<td>66%</td>
<td>30%</td>
</tr>
<tr>
<td>Total</td>
<td>438</td>
<td>396</td>
<td>42</td>
<td>56</td>
<td>6</td>
<td>90%</td>
<td>67%</td>
<td>58%</td>
</tr>
<tr>
<td>Present study</td>
<td>60</td>
<td>50</td>
<td>10</td>
<td>6</td>
<td>7</td>
<td>46%</td>
<td>66%</td>
<td>27%</td>
</tr>
</tbody>
</table>

DPT, dipyridamole thallium-201; R, redistribution defect; F/N, fixed or no defect.

* Calculated relative risk was infinite (no false negatives). Value shown is calculated using one false negative.
longer than 3 hours between scintigrams or using a reinjection technique would have improved the sensitivity of the test since several of the persistent defects may have redistributed over longer periods. However, four of the early studies\(^9,10,13,14\) used a similar 3-hour delay, with the fifth study\(^11\) using a 2.5–3-hour delay and the sixth study\(^12\) using a 3–4-hour delay. The use of single-photon emission computed tomography (SPECT) might also have improved the sensitivity of our results; however, the comparative studies did not use SPECT and there is recent controversy regarding the impact of SPECT,\(^32–34\) with the most recent study reporting a specificity of only 62% compared with angiography.\(^35\) Our technique also appears to be similar to the techniques used in previous studies in that the incidence of redistribution defects in our patients (22 of 60, 37%) is similar to that reported in other studies, ranging from 33\(^%\)\(^9,10\) to 47\(^%\).\(^12\) In addition, it appears that the pharmacological stress imposed by dipyridamole, as assessed by hemodynamic changes, was similar to that reported in previous studies.\(^9,10\)

Third, an important difference between our study and previous studies is the blinding of the clinicians to the \(^{201}\)Tl scintigraphic results. No previous study blinded attending clinicians (cardiologists, surgeons, anesthesiologists) from the preoperative scintigraphic findings. Such “unblinding” in those studies at times resulted in altered surgical, anesthetic, and perioperative medical management.\(^9,14\) In approximately 10% of patients (presumably those with the most severe redistribution defects), vascular surgery was cancelled and cardiac catheterization and subsequent coronary bypass grafting were performed. In the patients with redistribution defects who underwent vascular surgery, perioperative management was modified by the performance of more conservative operations,\(^11,12\) the increased use of invasive hemodynamic monitoring,\(^9,14\) and therapy (such as nitroglycerin),\(^13,14\) and longer intensive care unit monitoring and care.\(^13,14\) Such unblinding in these previous studies could have had differing effects on the predictive accuracy of \(^{201}\)Tl scintigraphy. For example, if enhanced perioperative care (in patients with redistribution defects) decreased the outcome rate, then the true positives would have decreased at the expense of the false positives, thereby decreasing the sensitivity, specificity, and positive predictive value with no change in the negative predictive value. On the other hand, the increased intensity and duration of perioperative monitoring in patients with redistribution defects may have enhanced the recognition of postoperative complications, thereby increasing the sensitivity, specificity, and positive predictive value of the test. Thus, one may speculate that only by blinding the treating clinicians from the test results, as was done in our study, can the independent value of \(^{201}\)Tl scintigraphy be determined fully.

Fourth, we assessed outcomes prospectively throughout hospitalization using investigators blinded to the preoperative scintigraphic results, whereas in several previous studies outcome assessment may have been affected by the use of unblinded clinicians\(^11,12\) or chart review.\(^12–14\)

Fifth, since previous studies did not report on perioperative hemodynamic or ischemic changes, it is difficult to contrast the perioperative clinical management of patients. In our patients, perioperative hemodynamics were tightly controlled, resulting in a less than 10% incidence of tachycardia, hypertension, or hypotension. Such hemodynamic control may have mitigated the effects of the preoperative disease state on outcome, thereby decreasing the sensitivity of the test in our patients.\(^3\) Thus, a higher proportion of our adverse outcomes may have reflected thrombotic events, which would be less likely to be predicted by a physiological test for ischemia.

Finally, the phenomenon of declining test accuracy as a new test enters more widespread use has been observed previously for other tests of coronary artery disease, including radionuclide ventriculography and exercise scintigraphy.\(^36\) The primary reason for this is thought to be altered referral patterns (pretest referral bias), a factor that may have been operational for \(^{201}\)Tl scintigraphy.

Our findings with respect to adverse cardiac outcomes were substantiated by the perioperative ischemia results. We found that \(^{201}\)Tl scintigraphy in our surgical population was not particularly sensitive or specific for the detection of intraoperative ECG or TEE indices of ischemia, postoperative ischemia, or adverse cardiac outcomes (cardiac death, myocardial infarction, unstable angina, severe ischemia, or congestive heart failure). In fact, the majority of all ischemic episodes (54\%), severe ischemic episodes (58\%), and adverse cardiac outcomes (54\%) occurred in patients without redistribution defects.

Our findings should not be completely surprising, however. Multiple physiological changes, including marked increases in myocardial oxygen demand,\(^37,38\) occur perioperatively. The preoperative disease state may be only one factor that affects outcome. Even in patients with stable preoperative disease (for example, no redistribution defect), multiple physiological changes that can adversely affect outcome (fluid shifts, aortic cross-clamping, respiratory effects, incisional pain, temperature changes) could occur intraoperatively and postoperatively. In addition, \(^{201}\)Tl scintigraphy assesses only those changes that may occur with alteration of relative perfusion to the heart. This technique, therefore, may be an insensitive test for the prediction of ischemic events that are triggered primarily by increases in myocardial oxygen demand. Furthermore, thrombotic complications, which often occur at the site of noncritical lesions, may not be predictable by stress scintigraphy.

Several other points merit comment. The use of improved scintigraphic techniques and stress procedures, such as hand-grip exercise, SPECT, reinjection techniques, or semiquantitative analysis,\(^39\) might have increased our sensitivity for reversible defects. However, none of these procedures, as stated earlier, were used in previous studies reporting a higher
sensitivity and nearly perfect negative predictive value. Furthermore, all of these approaches are likely to increase the number of patients with reversible defects who do not have adverse outcomes. Such a result would not help achieve the goal of detecting a small high-risk group. Second, although we studied 60 patients intensively, an argument can always be made for studying more patients, especially when a negative result is discovered. However, our principal findings would not have changed even if a substantially larger population were studied. For example, to achieve the same sensitivity for adverse outcomes as previous studies (90%), an additional 342 patients would have to be studied and all 57 outcomes (13%) would have to occur only in those patients with redistribution defects.

In conclusion, our results suggest that preoperative \(^{201}\)TI scintigraphy has limited sensitivity for the detection of perioperative ischemia or adverse cardiac outcome and a lower negative predictive value than previously appreciated. Our findings differ from those of previous studies and suggest that the routine use of \(^{201}\)TI scintigraphy for preoperative screening of patients undergoing vascular surgery may not be warranted.

Appendix

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### References


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