Pathologic Basis of Thallium-201 Scintigraphic Defects in Patients with Fatal Myocardial Injury

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SUMMARY Using a quantitative, computer-aided circumferential profile technique, we have shown that thallium-201 scintigrams with large defects can identify a group of patients with a high mortality after acute myocardial infarction. To determine whether high-risk thallium scintigrams predict poor survival because of a critical loss of myocardium, we correlated infarct size in 24 autopsied patients with the extent of thallium defect in three views. Of 13 patients with large defects (computer score ≥ 7.0) eight (62%) had >25% loss of left ventricular (LV) myocardium, but five (38%) had smaller infarcts (4-24% of LV myocardium), suggesting that part of the scintigraphic defect was related to ischemia without necrosis. Eight of nine patients with loss ≥25% LV myocardium had large defects. In 10 of 11 patients with small defects (computer score <7.0), infarcts involved <20% of LV myocardium. Although scintigrams with large defects predicted a critical loss of myocardium in over 60% of our patients, they included an important second group, in which the scintigraphic defect appeared to reflect a small infarct and a large surrounding area of reversibly ischemic myocardium.

CLINICAL STUDIES have shown the usefulness of thallium-201 scintigraphy for predicting mortality after acute myocardial infarction, and it is generally assumed that this reflects large perfusion defects corresponding to large areas of infarction and therefore a poorer prognosis.1,2 Although clinicopathologic studies are infrequent, the evidence suggests a high positive correlation between scan defect size and anatomic extent of infarction when the scan is performed within hours of the infarct. As a refinement of the thallium scintigraphic technique, we have applied a quantitative, computer-aided "circumferential profile" method to determine objectively a defect score.3 Using these quantitative scores, we found that initially hemodynamically stable (Killip class I-II) patients can be assigned to groups that are highly predictive of in-hospital and late mortality.2 Defect scores generally range from 0-20, with a score of zero representing no defect and scores above zero reflecting the amount of deviation from normal. Using this method, we have determined that patients can be divided into high-risk (score ≥7.0) and low-risk (score <7.0) groups on the basis of thallium scintigrams obtained within 12 hours of admission, the former carrying a 46% in-hospital mortality and the latter a 3% mortality. The early scintigraphic score is more predictive of outcome than initial functional class, age, sex, history of infarction, location of the acute infarct or peak CK, taken either singly or in combination.4 The prognostic significance of this scoring system for patients with old myocardial infarcts has not yet been examined.

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quantitative, objectively determined defect scores for both acute and chronic infarcts and to assess whether these scores correlate with size of infarction, we studied the hearts of 24 patients with coronary disease and recent or remote infarction who underwent thallium imaging and were autopsied. Thallium scintigrams generally correlate with infarct size, but in many patients, large defect scores appear to identify anatomically small infarcts and sizeable areas of surrounding ischemia. Moreover, large scores overestimated anatomic infarct size in some patients with both recent and remote infarcts.

Methods

Thallium Scintigraphy

Thallium scintigraphy was performed in the anterior and 40° and 60° left anterior oblique views 10 minutes after intravenous injection of 1.5–2.0 mCi of thallium-201 chloride. Images (400,000 counts full field) were acquired in a 128 × 128 matrix on magnetic disk (Medical Data Systems) using an Ohio Nuclear Series 420 mobile scintillation camera or an Ohio Nuclear Series 100 stationary camera with a parallel-hole collimator. The collected images were analyzed after a single nine-point weighted smoothing, without background subtraction or other image enhancement, using the computer-assisted "circumferential profiles" technique. In each view, an ellipse was placed around the left ventricle and the outer edge approximated by an isocount contour. Radii were then constructed from the image center to each point on the circumference (usually 75–125 points) (fig. 1). The average thallium activity per matrix point was determined along each radius and normalized to the highest radial value. These relative activities were displayed as a curve against angular position, which was then superimposed on a standard activity band, determined from 13 normal volunteers and representing the mean ± 2 SD for each radius. For any patient, an activity less than 2 SD below normal was defined as a defect. A defect score was obtained for each view by integrating the area of discordance between the two curves: The percentage of radii with reduced activity was multiplied by the average reduction in activity for these radii. For each patient, a total defect score was formed by summing the scores for the three views. Scintigraphic studies with a total score ≥ 7.0 were considered "high-risk," and those with a score < 7.0, "low-risk." The circumferential profile technique is applied by a nuclear medicine technician without knowledge of the patient's identification or clinical status.

Autopsy Studies

Twenty-four consecutive, autopsied patients were identified who had thallium scintigraphy during life and who at autopsy had coronary disease and recent or remote myocardial infarction. For each patient, we reviewed the clinical records, gross heart specimens, histologic sections and postmortem coronary arteriograms prepared by using a radiopaque barium sulfate gel. The age of the infarcts was determined by histologic evaluation. Since all infarcts were at least 72 hours old, the age of infarction was readily determined by histologic examination of myocardial sections stained with hematoxylin and eosin. The infarctions were quantitated by examination of 1-cm thick transverse slices of ventricle, tracing each of the left

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Figure 1. Circumferential profile method of quantitating thallium-201 scan defects. On the lower right is an example of a thallium image with superimposed computer-constructed outlines and radii. Above is a thallium activity curve as a function of radii. Theordinate is activity normalized to the highest radial value. The two lines joined by the white bar represent the standard activity band; the lower curve shows the activity from the cardiac thallium scan in this view (60° left anterior oblique). The defect score is obtained by integrating the area of discordance between the thallium scan curve and the standard activity band (percent abnormal radii × average amount below normal for these radii).
ventricular (LV) slices minus the right ventricular (RV) free wall on transparent plastic sheets, outlining the areas of infarction on the tracings and weighing each LV slice minus the RV free wall. The tracings were planimetered electronically (Hewlett Packard Digitizer) by a technician. The percent of left ventricle involved by infarct and the weight of the infarct in grams was thereby determined. All tracings, planimetry and calculations were made without knowledge of the patient's identification or the results of thallium-201 scintigraphy. The percent LV necrosis determined for each heart represented the total of old and recent myocardial infarct observed at autopsy.

Comparison of Scintigrams and Autopsy Data

Thallium scintigraphic defect scores were compared with percent total LV necrosis by linear regression using the least-squares method. Large and small infarcts were examined in relation to high- and low-risk scintigrams and vice versa using the Fisher exact test.4

Results

Clinical Findings

The 24 patients ranged in age from 22–81 years (mean 56 ± 15 years), and 18 were men. In 23 patients, coronary obstructive disease was present, and in 22 there was > 75% atherosclerotic narrowing of at least one major coronary artery. In one patient, a 22-year-old woman, an anterior wall myocardial infarction was related to an anomalous left coronary artery arising from the pulmonary trunk; she died in ventricular fibrillation, with postresuscitation evidence of new anterior wall ischemia. In another patient, myocardial infarction occurred in the setting of a floppy mitral valve and recurrent ventricular tachycardia. Of the entire group, 13 had thallium imaging during their acute infarcts; seven patients were imaged within 24 hours of the acute event, four patients within 1 week and two within 3 weeks; of these, six had remote infarcts as well. All 13 of these patients died in the peri-infarction period; the interval between the onset of infarction and death was 1–27 days (mean 15 days). Eleven other patients with remote myocardial infarcts were imaged from 3 months to several years after the acute myocardial injury. Thirteen patients died during their acute myocardial infarction; 11 deaths were a direct result of the infarct and two of complications after coronary surgery. Of the 11 patients with remote infarcts, two died of ventricular arrhythmias, two of heart failure, and seven in the setting of coronary bypass surgery (one of respiratory complications, one in the setting of a ventricular septal defect repair and five of unknown causes). The intervals between thallium scintigraphy and death ranged from 36 hours to 65 days (mean 19 days) in 23 of the 24 patients; One patient with a remote infarct died 6 months after imaging. There was no clinical or pathologic evidence of an infarct more recent than the date of the thallium scan.

Scintigram-Autopsy Correlation

Thallium defect scores in the 24 patients ranged from 0.1–41. There were 13 patients with high-risk (> 7.0) and 11 with low-risk scintigrams (< 7.0) (fig. 2). At autopsy, 10 patients had infarcts involving > 25% of the left ventricle, and 15 had infarcts involving ≤ 25% of the left ventricle. The correlation between absolute thallium defect score and the percent necrosis is poor (r = 0.27) (fig. 3). However, when we divided the patients into groups by high- and low-risk

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**Figure 2.** Each bar represents percent necrosis for a given patient. The dotted horizontal line is drawn at 25% necrosis. Patients above the line are considered to have "large" infarcts; those below, "small" infarcts.
TABLE 1. Thallium Scores as Predictors of the Extent of Infarction

<table>
<thead>
<tr>
<th></th>
<th>High-risk scan (&gt; 7)</th>
<th>Low-risk scan (&lt; 7)</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Large infarcts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&gt; 25%)</td>
<td>8 (62%)</td>
<td>1 (9%)</td>
</tr>
<tr>
<td>Small infarcts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&lt; 25%)</td>
<td>5 (38%)</td>
<td>10 (91%)</td>
</tr>
<tr>
<td>Mean percent necrosis</td>
<td>36%</td>
<td>13%</td>
</tr>
</tbody>
</table>

P values determined by Fisher's exact test.

scintigrams and by “large” (> 25% of the left ventricle) or “small” (< 25% of the left ventricle) infarcts, a significant relationship between infarct size and thallium defect risk group was present (table 1). Among the 13 patients with high-risk scintigrams, eight (62%) had large infarcts and five (38%) small infarcts. Of the 11 patients with low-risk scores, 10 patients (91%) had small infarcts and one (9%) had a large infarct. Eight of nine patients with large infarcts had high-risk scintigrams, while 10 of 15 patients with small infarcts had low-risk scintigrams. The mean percent necrosis was 36% for high-risk scores and 13% for low-risk scores (p < 0.01). Also, the association between scintigraphic score and infarct size was statistically significant by the Fisher exact test (p < 0.01). Examples of “accurate” correlations, i.e., high-risk scintigrams predicting large infarcts and low-risk scintigrams predicting small infarcts, are shown in figures 4 and 5.

Discrepancies Between Thallium Perfusion Defect and Infarct Size

There were six patients in whom defect score did not reflect infarct size. These discrepancies, however, clustered in one direction. Only one of the six (17%) errors occurred when a large infarct was assigned a low-risk defect score. The patient in whom this occurred was imaged 6 days after his acute infarct, while he was in severe heart failure and required vasopressors to maintain his systemic blood pressure. He died 2 weeks after infarction and 7 days after his thallium-201 scintigram. At autopsy there was no evidence of necrosis more recent than that seen on his thallium-201 scan to account for the discrepancy. Therefore, the inability to detect a significant focal thallium defect appears, in retrospect, to have been related to a diffuse decrease in thallium uptake by all myocardial segments, and an increased uptake of tracer by the lungs, causing a very low heart-to-background ratio. This is a technical limitation of

Figure 4. An example of a “high-risk” thallium scan in a patient with a large infarct at autopsy. The patient died in heart failure after an initial hemodynamically stable presentation. The scintigrams show defects in both anterior and posterior wall, which correspond to the healed anteroseptal wall infarct and the large acute transmural posterior wall infarct. LAO = left anterior oblique.
thallium perfusion imaging as currently performed. Perfusion scintigrams reflect only the relative distribution of blood flow: If all myocardial segments are equally ischemic, the image may appear normally homogeneous — another limitation of a computer method based on relative rather than absolute counts.

Most of the discrepancies occurred when the defect scores overestimated the infarct size. This was observed in five of six patients, and the most marked example is shown in figure 6. In this patient, a defect score of 10 was obtained shortly after his admission with an acute anteroseptal subendocardial myocardial infarct. Although recurrent chest pain and recurrent ST-segment depression in V2-V4 occurred over the next several days, the serum CK rose to a peak of only 230 IU/l. He developed progressive LV dysfunction, ventricular dysrhythmias and elevation of his pulmonary wedge pressure to 30 mm Hg, and finally died in ventricular fibrillation. At autopsy, a remote high-posterior infarct that involved about 3% of the left ventricle was identified, and there were also small foci of subendocardial necrosis in the anterior and anteroseptal myocardium that involved a little over 1% of the left ventricle and were in the distribution of a critically narrowed proximal left anterior descending (LAD) coronary artery. Thus, although the infarct was small, the clinical evidence suggested a large ischemic zone in the LAD distribution which accounted for persistent electrocardiographic abnormalities, a large anteroseptal thallium defect and severe LV dysfunction and arrhythmias. The other four instances of discrepancy between scintigraphic defect and infarct size included one patient who was imaged while in cardiogenic shock 5 days after an acute infarct and died 2 days later, and three patients who died with remote infarcts. One of the latter three patients was imaged after a cardiac arrest and was hemodynamically unstable, one had a ventricular septal defect and a low-output state requiring an intraaortic balloon, and one had class IV angina pectoris, pending a coronary bypass procedure. In all five patients, therefore, there was at least some clinical history to suggest coronary plus infarction as explanation for large thallium defects and small infarct size.

The discrepancies between scintigraphic defect size and anatomic infarct size were present with the same frequency, regardless of the interval between the beginning of the infarct and the thallium scintigram. Seven patients were scanned within 24 hours of infarction, and the infarct size was overestimated in one (14%); six patients were scanned 1–21 days after infarction, and the infarct size was overestimated in one (17%) and underestimated in one (17%); 11 patients were scanned more than 30 days after infarction, and the infarct size was overestimated in two (18%).

Nine patients with acute infarcts had high-risk thallium-201 scores, but two (22%) had small infarcts at autopsy; the other seven had large infarcts. Four patients with remote infarcts had high-risk scans, and three had small infarcts at autopsy.

**Figure 5.** An example of a “low-risk” scan in a patient with a small infarct. A small posterior wall defect denoted by the thallium scintigrams corresponds to the acute subendocardial posterior wall defect present at autopsy. LAO = left anterior oblique.
Discussion

Thallium-201 perfusion imaging is a useful noninvasive means of assessing myocardial infarct size and location. Autopsy studies have shown a generally good correlation between postmortem myocardial infarction size and the estimated size of the thallium defect. Methods for objectively quantitating thallium defects, however, are just being developed. We used a computer-aided circumferential profile technique to determine thallium defect scores objectively. Clinical evidence suggests that the scoring system provides a reasonable index of infarct size and shows that a strong correlation exists between high-risk scintigraphic scores (≥7) and high in-hospital and first-year mortality, and between low-risk scores and low mortality in a population of hemodynamically stable (Killip classes I-II) patients in the setting of acute myocardial infarction. In an attempt to define more precisely the meaning of high- and low-risk defect scores in patients with both acute and remote infarcts, we examined the relation between infarct size and defect score in 24 autopsied patients. High-risk scans generally correlated with large infarcts. The mean infarct size represented by the high-risk scan was 36% of the left ventricle, compared with 16% necrosis for the low-risk scans. Thus, the better prognosis associated with the low-risk scores might, in large part, be due to the smaller sized myocardial infarcts. The high-risk scintigraphic scores may identify patients who have lost a nearly critical amount of myocardium and will predictably do poorly, despite initially stable hemodynamic presentation.

A discrepancy between the thallium defect score and the anatomic infarct size occurred mostly in patients who had small infarcts at autopsy despite high-risk scores. The most extreme example of this, a patient with a 4% infarct and a high-risk score of 10, had recurrent and persistent ischemic changes on the ECG and progressive LV dysfunction and dysrhythmias leading to death, which suggested the presence of a large infarct despite the small CK elevation. The small subendocardial infarct found at autopsy in what appeared to be a transmural perfusion defect can best be explained in retrospect by a large area of anteroseptal ischemia that was persistent enough to lead to severe LV dysfunction and death. Although the other four patients with high-risk scores and disproportionately small infarcts at autopsy did not have such a convincing clinical story of ischemia coincident with the scintigraphic study, two of them were imaged after cardiac arrest and two others were imaged the day before coronary bypass surgery for class III-IV angina.

Infarct size was overestimated without regard to the temporal relationship of the thallium-201 scintigram and the onset of infarction; 14% of seven patients scanned within 24 hours, 17% of six patients scanned between 24 hours and 21 days, and 18% of 11 patients scanned 30 days or more after infarction had a high-risk score and a small infarct at autopsy. These findings suggest that a peri-infarction ischemic zone may
be present during acute infarction, which is not surprising in the light of animal studies by Pohost et al., who examined redistribution of thallium-201 to ischemic myocardium in a temporary coronary occlusion infarct model. Similarly, the observation that sequential thallium-201 scintigrams performed over the first few days after infarction\(^8\) may show a decreasing defect size in a given patient suggests, at least in some situations, that a peri-infarction ischemic zone large enough to be detected by thallium scintigraphy is present and may recover enough metabolically to concentrate thallium-201. However, the overestimation of infarct size in some patients with remote as well as acute infarcts also suggests that some patients with severe coronary disease and no evidence of ischemia by acute symptoms or electrocardiographic changes may have clinically silent areas of myocardial ischemia at rest that may also be in jeopardy for irreversible loss. Of the four remote infarction patients with high-risk scans, three (75%) had small infarcts at autopsy. Although the numbers are small, this suggests that the scoring index has a different meaning in patients with old infarcts. We do not know whether the high score in such patients with chronic coronary disease has the same prognostic significance as it does in the acute infarct group. If it does, the thallium-201 scan might be identifying a group of patients with a high incidence of jeopardized but salvageable myocardium in whom surgical intervention might be especially valuable.

If these data for the patients with high-risk scintigrams and acute infarcts reflect the distribution of infarct size in the living population, the findings also suggest that 20% or more of patients falling into the group with poor prognosis designated by high-risk scores after acute infarction may have a sizeable zone of salvageable myocardium that is severely ischemic but has not yet infarcted. Accordingly, one could broadly categorize patients presenting with infarcts into three groups (table 2).

Group 1 consists of patients with large, critical-sized infarcts, either remote or recent, with or without an ischemic border zone, in whom the amount of myocardium already lost is the limiting factor. Group 2 would be patients with moderate-to-small-sized infarcts but large ischemic border zones who will do poorly because a critical mass of myocardium is dysfunctioning although not yet infarcted, or because they will go on to infarct that additional myocardial mass. Group 3 includes patients with small infarcts and little or no ischemic border zone who should do well whatever is done — intervention, early hospital discharge or conventional medical treatment. The patients in group 1 will probably do poorly regardless of management. The group 2 patients, however, who represent as many as one-third of patients with high-risk scores, hold the greatest promise for intervention studies. For patients presenting with acute infarction, the differentiation of those with high-risk thallium-201 scans may be possible using a variety of clinical techniques. Repeat thallium-201 scans several days or weeks later showing a marked diminution in thallium defect score would suggest the presence of a small infarct and a resolving ischemic border zone. A combination of other noninvasive measurements of infarct size might also be of value. Technetium-99m pyrophosphate scintigraphy\(^10\) may be used to size infarcts, as well as electrocardiographic\(^11\) and serum enzyme\(^12\) techniques; these methods might suggest that the amount of irreversible injury is not as great as suggested by the thallium score. In retrospect, the small peak rise of CK to 230 IU/l in one patient with a high-risk score but a small infarct at autopsy might have suggested that his cardiac dysfunction and high-risk thallium defect score reflected ischemia more than infarction.

One limitation of thallium imaging was exemplified by the patient who had a low-risk score and a large infarct. The best explanation for this is a diffuse reduction in thallium uptake related to three-vessel disease. Such discrepancies should be suggested, however, by the overall clinical setting, as well as by evidence of LV dilatation on thallium images and poor LV function on other noninvasive studies, such as echocardiography or gated cardiac blood pool imaging.

In summary, large thallium defect scores most often predict poor prognosis after acute infarction by identifying patients with a critical loss of myocardium. The findings also suggest, however, that high-risk scores may identify another group of patients with small infarcts but large areas of reversible ischemia and an unfavorable prognosis. Interventions to limit infarct size and improve mortality after acute infarction should have the greatest impact in the latter group. The findings in this study also support the concept of an ischemic border zone in at least some patients with acute infarction, and even in some with chronic ischemic heart disease.

| Table 2. Possible Outcome Groups after Infarction as Extrapolated from the Current Study |
|-----------------------------------|--------------------------------|--------------------------------|
| Myocardium infarcted              | Large infarct                  | Small infarct                  |
| Ischemic                          | With or without ischemia       | Large ischemic zone            |
|                                   | ↓                               | ↓                              |
| Prognosis                         | Poor (> 50% Mortality)          | Poor (> 50% Mortality)          |
| Intervention to limit infarct size| Little value                   | Great potential                |
|                                   |                                 | Little value                   |
The Effects of Coronary Artery Disease on the Ventricular Fibrillation Threshold in Man

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SUMMARY The ventricular fibrillation threshold (VFT) was measured in 28 patients at the time of cardiac surgery. The VFT was measured with a 100 Hz train of 24 rectangular pulses positioned across the ST segment and T wave. Current was applied to the epicardial surface of either ventricle with a bipolar electrode probe. In six patients, the normal right VFT was 24.3 ± 5.2 mA, and in 10 patients the normal left VFT was 33.6 ± 9.5 mA (p < 0.05). In 12 patients with ≥ 75% obstruction of the left anterior descending coronary artery, the left VFT was 18.6 ± 6.9 mA. This value was significantly less than the left VFT in patients without coronary artery disease (p < 0.001). This study shows that the VFT can be measured in man and that coronary artery disease reduces this parameter.

IN 1940, Wiggers and Wegria reported that a single electrical stimulus of appropriate intensity delivered to the ventricles during late systole could induce ventricular fibrillation. These investigators suggested that this phenomenon could be standardized to assess vulnerability of the ventricle to fibrillation. Since then, many studies have used this technique to assess ventricular vulnerability during experimentally induced pathologic states and after the administration of antiarrhythmic drugs. However, the relationship of these studies to ventricular vulnerability to fibrillation in man is not clear.

In the present study we measured electrically induced fibrillation threshold in man to evaluate ventricular vulnerability and to evaluate the effects of coronary artery disease on ventricular vulnerability.

Methods and Materials

The ventricular fibrillation threshold (VFT), an index of ventricular vulnerability, was measured in 28 patients undergoing cardiac surgery for congenital, valvular, or coronary heart disease. All patients gave written informed consent. The VFT was defined as the minimal current (mA) required to initiate ventricular fibrillation when applied to the ventricles during the vulnerable period. The routine procedure during surgery requiring cardiopulmonary bypass at the...
Pathologic basis of thallium-201 scintigraphic defects in patients with fatal myocardial injury.
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