Comparison of Early Thallium-201 Scintigraphy and Gated Blood Pool Imaging for Predicting Mortality in Patients with Acute Myocardial Infarction

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SUMMARY The extent of abnormality in early thallium-201 and gated cardiac blood pool scintigrams has been reported to be useful for predicting mortality in patients with acute myocardial infarction (AMI). To compare the two techniques, 91 patients admitted consecutively with evident or strongly suspected AMI underwent both imaging studies within 15 hours of the onset of symptoms. Patients with pulmonary edema or shock were excluded. AMI developed in 84% of patients, and 6-month mortality for the entire group was 16%. A thallium defect score of 7.0 or greater (corresponding to at least a moderate reduction of activity involving 40% of the left ventricular circumference) identified a subgroup of 14 patients with 64% 6-month mortality rate. Similarly, a left ventricular ejection fraction of 35% or less identified a high-risk subgroup of 10 patients with a 6-month mortality of 60%. Mortality in the remaining patients was 8% for thallium score less than 7 and 11% for ejection fraction greater than 35%. The mortality rate was highest among patients who had discordant high-risk scintigrams (five of six, 83%), lowest in those with concordant low-risk studies (five of 64, 8%) and intermediate in those with discordant results (four of 11, 36%). Of a number of clinical variables, only the appearance of Q waves, peak creatine kinase > 1000 IU/l, and history of infarction were significantly associated with mortality. High-risk thallium or blood pool scintigraphic results were significantly more predictive and a thallium score of 7 or greater was more sensitive for detecting nonsurvivors than ejection fraction 35% or less at a similar level of specificity. Stepwise multiple logistic analysis showed that the thallium score was the best predictor of mortality, but that appearance of Q waves and ejection fraction were additive. Using these three variables, 11 patients were calculated to have a 50% or greater chance of dying and eight (73%) actually died, compared with six of 70 (9%) with a calculated chance of death of less than 50%. These results in a prospectively identified and consecutive group of patients support the value of early thallium and blood pool scintigraphy for separating high- and low-risk subgroups of hemodynamically stable infarct patients.

PATIENTS with acute myocardial infarction admitted in pulmonary edema or cardiogenic shock are at a high risk for early death. Those who demonstrate lesser degrees of hemodynamic compromise, in clinical class I or II, have a much better prognosis as a group, but among these patients is a subset with poor prognosis. Early identification of those at highest risk would allow optimal application of aggressive therapeutic interventions with the minimum exposure of low-risk patients to adverse effects. Initiation of treatment before hemodynamic deterioration should permit salvage of jeopardized, but not yet infarcted, myocardium with subsequent improvement in prognosis.

A number of approaches have been used for early identification of high-risk patients, including clinical classifications based on the degree of heart failure, invasive hemodynamic characterization, and multivariate equations using combinations of clinical variables. We previously reported the use of early thal-
lium-201 scintigraphy for this purpose. In 42 patients with acute myocardial infarction admitted in clinical class I or II, a large perfusion defect, measured by an objective computer-assisted method, identified a subgroup of 13 patients with a 46% in-hospital and 62% 6-month mortality. The remaining patients had a mortality rate of 3% in hospital and 7% at 6 months. A large thallium defect was significantly more predictive than a number of important clinical variables, taken singly or in combination.

Another approach of potential value is early measurement of global and regional left ventricular function by noninvasive radionuclide ventriculography. The degree of functional impairment early in the course of infarction would be expected to reflect the combination of old and new irreversible injury of the left ventricle plus the amount of concurrently ischemic myocardium that may be present. Left ventricular function, measured scintigraphically before hospital discharge, is an important determinant of subsequent outcome. Recent reports suggest that earlier measurements of left ventricular function may also be helpful in assessing short-term prognosis.

In the present study, we sought to validate the predictive value of early thallium-201 myocardial imaging in a large series of hemodynamically stable patients with suspected acute myocardial infarction gathered prospectively and consecutively. We also examined the predictive value of radionuclide ventriculography in this population and compared it with that of thallium-201 scintigraphy, and used the results from the ventriculographic study to further characterize patients with large and small thallium-201 defects.

Materials and Methods

Patients

The study population consisted of 91 consecutive patients with evident or strongly suspected acute myocardial infarction admitted to the hospital within 12 hours of the onset of symptoms in clinical class I or II. A subsequent diagnosis of acute myocardial infarction was made in 76 patients and was based on a typical history of chest pain, combined with either characteristic electrocardiographic changes or a rise in serum creatine kinase. The scintigraphic studies were not used to diagnose acute myocardial infarction. Nineteen of these 76 patients had a history of myocardial infarction. Fifteen patients lacked both diagnostic electrocardiographic and enzyme changes and were diagnosed as having unstable angina. As soon as possible after admission to the coronary care unit, thallium-201 myocardial perfusion scintigraphy was performed, followed immediately by technetium-99m gated blood pool scintigraphy. Scintigraphic studies were begun within 15 hours of the onset of chest pain in all cases (range 3–15 hours, mean ± SD 7 ± 4 hours).

In one patient, a gated blood pool scintigram was performed without a thallium study because thallium-201 was unavailable. In nine patients, gated blood pool studies either were not done because of arrhythmias or could not be analyzed because of technical problems. In no case was a study not performed because of hemodynamic deterioration or other change in patient status.

As part of routine treatment, most patients received oxygen by face mask, i.v. heparin to maintain a clotting time of 20–30 minutes (5000-U bolus and approximately 1000 U/hour), and continuous lidocaine infusion at an initial dose of 20 μg/kg/min, adjusted as necessary to suppress ventricular ectopic activity. Morphine and diuretics were given as clinically indicated. After the scintigrams, 19 patients received i.v. nitroglycerin for 48 hours as part of a separate prospective, randomized clinical trial. Invasive hemodynamic monitoring was not used in these or in the remaining patients except as clinically indicated.

The location of the acute myocardial infarction was defined electrocardiographically as anterior by primary ST-segment or T-wave changes or Q-wave development in leads 1, aV L, or V 1–V 6, or as inferior by changes in leads 2, 3 or aV F, or by abnormalities suggesting true posterior wall involvement. Transmural acute infarction was defined by evolution of abnormal Q waves with a duration ≥0.04 second and a depth ≥25% or the R wave in the same lead. Nontransmural infarction meant that ST-T changes occurred without Q-wave development. All patients had measurements of total serum creatine kinase activity on admission and every 4 hours thereafter using the Rosalki technique.

Patients were classified clinically according to the severity of left ventricular failure on admission. Two of the authors reviewed the recorded physical examination and read the admission chest radiographs (upright and usually portable) without knowledge of other clinical or laboratory results. Class I was defined as the absence of any signs of left ventricular failure. Class IIA included patients with basilar rales or ventricular gallop on auscultation, or an increase in upper lobe vascular or interstitial edema on a chest radiograph. Class IIB consisted of patients with alveolar infiltrates due to pulmonary edema, but without the clinical syndrome of acute pulmonary edema.

Cardiac Imaging

Thallium scintigraphy was performed 10 minutes after i.v. injection of 1.5–2.0 mCi of thallium-201 in the anterior and 40° and 60° left anterior oblique views using a Technicare Series 420 mobile scintillation camera with a low-energy, all-purpose, parallel-hole collimator, fitted with a cardiac shield. Images were acquired in 128 × 128 matrix format (Medical Data Systems Simultaneity System) for a total of 300K counts.

During the thallium study, stannous pyrophosphate was injected intravenously, followed by 20–25 mCi technetium-99m pertechnetate at the completion of the study for in vivo erythrocyte labeling. After 10 minutes, patients were imaged supine in the anterior and approximately 40° left anterior oblique positions (to best define the ventricular septum), using the same
camera-collimator system described above. Data were acquired in 32 × 32 matrix format with 1.9 × zoom and then software-interpolated to 64 × 64 with a commercial program. Acquisition was stopped when 250 K counts had been collected in at least one of the 14 frames over the cardiac cycle.

Analysis of the Thallium-201 Scintigrams

Thallium scintigrams were scored objectively by a technologist using a computer-assisted technique called "circumferential profiles." Each view was independently analyzed after a single, nine-point, weighted smoothing without background subtraction. An ellipse was used to isolate the left ventricle from the rest of the image, and a computer-generated circumference was constructed around the outer edge of the left ventricle using an isocount criterion (usually about 50% of average activity in the ellipse) to provide a visual "best fit" to the outer edge of the left ventricle. Radii were then generated by the computer from the automatically determined image center to each point on the circumference (usually 75–125 radii). The average activity per pixel was calculated along each radius and normalized to the highest value, and a curve was displayed of normalized thallium activity vs angular location, starting from the radius oriented upward and proceeding counter clockwise. A defect score was then determined by computer by comparing the patient’s profile curve with normal limits obtained by averaging the curves of 13 normal volunteers from our previous study. The patient curve and normal curves were aligned on the radius corresponding to the apex. The lower limit of normal was defined as 2 standard deviations below the normal mean curve. A percent circumference defect was determined as the percent of radii with abnormally low activity. The defect score was calculated by integrating the area of the patient’s curve below normal (percent circumference defect multiplied by average reduction in activity for the abnormal radii). The score can also be calculated as the total reduction in activity divided by the total number of radii, or the average reduction in activity per radius. This method of computer scoring has acceptable intra- and interobserver reproducibility. Defect scores were summed for the three views to obtain a total defect score for each patient.

Analysis of Gated Blood Pool Scintigrams

Using a commercial computer program (MUGE), semiautomatic regions of interest were generated over the left ventricle for each frame in the cardiac cycle using a combined second derivative and count threshold algorithm. A background region was automatically generated lateral and inferior to the left ventricle in the end-systolic frame, five pixels wide and two pixels removed from the computer-generated left ventricular edge. From these regions of interest, a background-corrected left ventricular time-activity curve was obtained. Left ventricular ejection fraction was calculated as (LV end-diastolic counts – LV end systolic counts)/LV end-diastolic counts.

Regional wall motion was assessed visually in four left ventricular segments in each view. In the anterior view, two anterolateral segments and an apical and a distal inferior wall segment were analyzed; the inferobasal area could not be examined because of overlying right ventricle. In the left anterior oblique view, one septal, one inferoapical and two lateral wall segments were analyzed. Segments were judged to be normal, hypokinetic, akinetic or dyskinetic and received scores of 0–3, respectively. A total regional wall motion score was obtained by summing the scores of the eight individual segments.

Follow-up and Analysis of Data

Seventy-seven of 91 patients survived the first month after the acute event. They were each followed for 6 months and were cared for by their private physicians. Twenty-five patients were taking β blockers at the time of their 6-month follow-up. Three patients (two with unstable angina and one with subendocardial infarction) underwent coronary bypass surgery, all during their initial hospitalization. A t test was used to examine differences in means of continuous variables between survivors and nonsurvivors. Simple linear regression and the Spearman correlation coefficient procedure were used to test for relationships between pairs of continuous variables. The relationship of dichotomous variables was examined by the chi-square test. Values are given as mean ± SD.

Results

Characterization of Study Population

Of the 76 patients with an acute myocardial infarction, 19 (25%) were classified as having an anterior transmural, 21 (28%) an inferior transmural and 36 (51%) a nontransmural infarct. Nineteen (25%) had a history of myocardial infarction and 37 (49%) a history of angina. Nine patients were in class IIB left ventricular failure on admission and the remainder were in class I or IIA. Of the 15 patients who did not evolve an infarct and were diagnosed as having unstable angina, six (40%) had a history of infarction and 11 (73%) a history of angina. None were in class IIB on admission.

Clinical Outcome

Fourteen of the 91 patients (15%) died within 1 month after the ischemic event and 12 during the initial hospitalization; one patient died after 6 months (table 1). Twelve of the deaths appeared to be cardiac in origin, based on clinical findings and postmortem examinations where available. The other three deaths (patients 9, 12 and 14) were believed to be indirectly related to the ischemic event. One was due to a cerebrovascular accident; a recent thrombus occluding the carotid artery was found at necropsy. In the other two patients, the clinical record strongly implicated pulmo-
# Table 1. Characteristics of Nonsurvivors

<table>
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<tr>
<th>Pt</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Survival (days)</th>
<th>TI score</th>
<th>LVEF (%)</th>
<th>Prev MI</th>
<th>MI site</th>
<th>Transmural class</th>
<th>Admission clinic</th>
<th>Peak CK (IU/l)</th>
<th>Cause of death</th>
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<td>+</td>
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<td>+</td>
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<td>17.8</td>
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<td>+</td>
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<td>NA</td>
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<td>50</td>
<td>Pump failure</td>
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<td>+</td>
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*Value in parentheses indicates percent of left ventricle (LV) involved by infarction (old and new).

Abbreviations: TI = thallium; LVEF = left ventricular ejection fraction; MI = myocardial infarction; Ant = anterior; Inf = inferior; CABG = coronary artery bypass graft; DVT = deep-vein thrombosis; LAD = left anterior descending coronary artery; RCA = right coronary artery; ITM = inferior transmural infarct; ATM = anterior transmural infarct; LMCA = left main coronary artery; LCx = left circumflex coronary artery; NA = not applicable.
nary emboli as the cause of death, and a venogram demonstrated massive deep-vein thrombosis in one case. These three deaths were included in all analyses unless stated otherwise.

**Thallium Scintigraphy**

Seventy-four percent of the patients demonstrated a perfusion defect (18 of 19 with anterior transmural, 20 of 20 with inferior transmural and 22 of 36 with nontransmural infarcts, and seven of 15 with unstable angina). Nonsurvivors had a significantly higher mean defect score than survivors, 9.2 ± 7.4 vs 2.3 ± 3.4 (p < 0.001) (fig. 1). As in our previous study, a defect score of 7.0 provided the best discrimination between survivors and nonsurvivors. Nine of the 15 nonsurvivors (60%) had a defect score of 7 or greater and 70 of the 75 survivors (93%) had a score of less than 7. Excluding the three noncardiac deaths, the thallium score was 7 or higher in nine of 12 nonsurvivors (75%). Compared with the overall mortality rate of 15% at 1 month, mortality was 57% in the subgroup of 14 patients with a defect score of 7 or higher and 8% in the 76 patients with a score of less than 7. Values at 6 months were similar, with an overall mortality rate of 16%, compared with 64% and 8% in the high- and low-risk thallium subgroups.

A score of 7 generally corresponded to a moderate reduction of thallium uptake involving 40% of the left ventricle in two views or a severe reduction involving 60% in a single view. Figure 2 shows the relationship between defect score and the percent of left ventricular circumference involved, expressed as either the maximum in any one view or the sum of all three views. A defect score of less than 1 was associated with maximum and total circumference defects of up to 10% and 20%, respectively. For scores of 7 or greater, the maximum circumference defect ranged from 36% to 60% (mean 48 ± 8%), and 12 of 14 were more than 40%. As with defect score, the percent circumference defect was significantly greater in nonsurvivors than survivors (maximum circumference defect 38 ± 17% vs 21 ± 17%, p < 0.001; total circumference defect 83 ± 45% vs 36 ± 35%, p < 0.001).

**Gated Cardiac Blood Pool Scintigraphy**

Eighty-seven percent of the patients had a left ventricular regional wall motion abnormality (15 of 15 patients with anterior transmural, 18 of 20 with inferior transmural and 27 of 32 with nontransmural infarcts, and 11 of 15 with unstable angina), and 65% had at least one akinetic or dyskinetic segment (15 of 15 with anterior transmural, 15 of 20 with inferior transmural and 17 of 32 with nontransmural infarcts, and six of 15 with unstable angina). Only 42% had an abnormal global left ventricular ejection fraction, defined as less than 55% (11 of 15 with anterior transmural, seven of 20 with inferior transmural and 15 of 32 with nontransmural infarcts, and one of 14 with unstable angina).

Figure 3 shows the left ventricular ejection fraction for survivors and nonsurvivors. Mean ejection fraction was significantly lower in nonsurvivors, 44.4% vs 59.4% (p < 0.01). An ejection fraction of 35% pro-
vided the best discrimination between the two groups. Sixty-four of 68 survivors (94%) had an ejection fraction above this level, and six of 14 nonsurvivors (43%) had an ejection fraction of 35% or less. Excluding the three noncardiac deaths, ejection fraction was 35% or less in six of 11 nonsurvivors (55%). The mortality rate at 1 month was 50% in the subgroup of 10 patients who had an ejection fraction of 35% or less, compared with only 11% in the 72 patients with an ejection fraction above 35%. The corresponding values at 6 months were 60% and 11%, respectively.

Left ventricular ejection fraction was correlated with both regional wall motion score, reflecting the total score of hypokinetic, akinetic and dyskinetic left ventricular segments, and with the number of akinetic/dyskinetic segments (r = 0.75 and 0.67, respectively). Mean values for regional wall motion score and number of akinetic/dyskinetic segments were higher in nonsurvivors than survivors (regional wall motion score, 9.9 ± 4.1 vs 5.5 ± 4.4, p < 0.001; number of akinetic/dyskinetic segments, 3.4 ± 1.7 vs 1.8 ± 1.9, p = 0.003).

All patients were imaged within 15 hours of the onset of symptoms. Because hemodynamics as well as thallium perfusion defect size and ejection fraction may change during the acute phase of infarction, the results were analyzed to determine if the time of scintigraphy and ejection fraction or defect size were related. No significant association was found: Of 51 patients imaged within 6 hours of symptoms, 18% had thallium defect scores of 7 or greater and 11% had ejection fractions of 35% or less. Of the 40 patients imaged between 6 and 15 hours, 13% had high defect scores and 9% low ejection fractions (NS).

Relation Between Thallium and Blood Pool Scintigraphy

In most patients there was a concordance between thallium perfusion defects and akinetic or dyskinetic left ventricular segments. Both findings were present in 59% of patients (15 of 16 with anterior transmural, 15 of 20 with inferior transmural and 14 of 31 with nontransmural infarcts, and four of 15 with unstable angina) and both were absent in 20% (0 of 36 with transmural and 10 of 31 with nontransmural infarcts, and six of 15 with unstable angina). In 12 patients, a thallium defect was present without an akinetic left ventricular segment (five with inferior transmural infarcts, two with extensive right ventricular involvement, four with nontransmural infarcts and three with unstable angina); in six patients, regional akinesis was seen without a thallium defect (one with an anterior transmural infarct, three with nontransmural infarcts and two with unstable angina).

Figure 4 shows the relation between thallium defect score and left ventricular ejection fraction for patients who underwent both studies. Large defect scores were generally associated with reduced ejection fractions and low scores with normal ejection fractions, although there was considerable scatter in the middle range. Linear regression analysis provided the equation: EF = 63.4 - 1.8 (TI score) (r = 0.55, p < 0.001). Patients with high-risk thallium scores had ejection fractions of 19–62%. Six patients had ejection fractions of 35% or less, four patients had ejection fractions of 36–50% and three patients values greater than 50%. In contrast, only 15 of 68 patients (22%) with low-risk defect scores had ejection fractions of less than 50%.

The mortality rate was highest in patients who had concordant high-risk scintigrams and lowest in those who had concordant low-risk studies (fig. 5). Of the six patients with a thallium defect score of 7 or greater.

![Figure 3](http://circ.ahajournals.org/lookup/suppl/doi:10.1161/01.CIR.107.11.1277/-/DC1/fig3.jpg)

**Figure 3.** Left ventricular ejection fractions for survivors and nonsurvivors. The dashed line, representing the best discriminating value, is drawn at 35%. Open circles represent patients with a previous infarct and solid circles patients without a prior infarct.

![Figure 4](http://circ.ahajournals.org/lookup/suppl/doi:10.1161/01.CIR.107.11.1277/-/DC1/fig4.jpg)

**Figure 4.** Relation between thallium defect score and left ventricular ejection fraction. A low thallium score is associated with a normal ejection fraction and a large thallium score with a reduced ejection fraction, but there is considerable scatter (EF = 63.4 - 1.8 (TI score), r = 0.55).
and ejection fraction of 35% or less, five died, compared with five of 64 (8%) who had a thallium score of less than 7 and ejection fraction of more than 35%. When the studies gave discordant results, the mortality was intermediate: three of seven (43%) with high-risk thallium and low-risk ejection fraction and one of four (25%) with low-risk thallium and high-risk ejection fraction. Neither type of scintigraphic study identified the three patients who suffered noncardiac death; thallium scores were 0.6, 2.3 and 5.8 and ejection fractions were 63%, 67% and 54%, respectively.

Among the nonsurvivors, the mode of death appeared to differ, depending on the results of the early scintigraphic studies (table 1). Of five patients with concordant high-risk thallium score and ejection fraction who died, four of the deaths were early and related to pump failure, while one patient died unwitnessed at 6 months. Of three deaths in the group with a high-risk thallium score and a low-risk ejection fraction, two were related to recurrent ischemic episodes and one was due to left ventricular free wall rupture (this patient had an ejection fraction of 39% and demonstrated left ventricular failure before death). One patient with low-risk thallium score and high-risk ejection fraction died unwitnessed 1 day after discharge from the hospital. Of five deaths in the group with concordant low-risk thallium and ejection fraction, one was related to recurrent ischemia with acute heart failure (autopsy showed extensive subendocardial infarction), one occurred the evening after bypass surgery, two were related to probable pulmonary emboli and one was caused by a stroke (probably embolic).

**Prediction of Mortality from Clinical and Scintigraphic Variables**

Taken singly, only two clinical variables were significantly associated with 1-month mortality: transmural infarction ($\chi^2 = 11.71, p < 0.001$) and peak serum creatine kinase $> 1000$ IU/l ($\chi^2 = 4.21, p < 0.038$). Results for 6-month mortality were virtually identical, except that a history of myocardial infarction reached borderline significance ($p < 0.065, \chi^2 = 3.32$). Other clinical variables, including age, sex, admission clinical class, location of infarction and treatment with i.v. nitroglycerin, were not significantly associated with mortality at either 1 month or 6 months.

The scintigraphic variables were more strongly associated with mortality than the clinical ones. As dichotomous measures, thallium defect score of 7 or greater and left ventricular ejection fraction of 35% or less were both highly significant against 1-month mortality ($\chi^2 = 21.83, p < 0.001; \chi^2 = 9.95, p < 0.002$, respectively). For 6-month mortality, the association was even stronger (thallium defect score, $\chi^2 = 27.07$; ejection fraction, $\chi^2 = 14.82$). The chi-square value for thallium defect score was higher than that for ejection fraction in both of these analyses. With thallium scintigraphy, percent circumference defect values were associated with mortality at 1 and 6 months, although the chi-square values were lower than with defect score. For this reason, further analyses were done using the thallium defect score rather than the circumference variables. With blood pool scintigraphy, regional wall motion score and number of akinetic/dyskinetic segments were not significantly associated with 1- or 6-month mortality.

The sensitivity and specificity of the scintigraphic variables for predicting mortality are shown in table 2 for the whole patient population and two subgroups. When patients with unstable angina were excluded, sensitivity and specificity for both thallium score of 7 or greater and ejection fraction of 35% or less fell slightly. Among patients with their first acute infarct, sensitivity was considerably reduced, although few died. The association between ejection fraction and mortality was not statistically significant in the first infarct subgroup.

To test the ability of scintigraphic and clinical variables to additively predict mortality, stepwise logistic analysis\(^\text{11}\) was applied to the whole patient population using those variables identified in the univariate analyses as being significant at the 0.05 level. This level of significance was considered appropriate to avoid type II errors known to be associated with small data sets. The stepwise logistic procedure may be viewed as an
Table 2. Prediction of 6-month Mortality by Scintigraphic Variables in Patient Subgroups

<table>
<thead>
<tr>
<th></th>
<th>Thallium score ≥ 7</th>
<th>Ejection fraction ≤ 35%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>All patients</td>
<td>60% (9/15)</td>
<td>93% (70/75)</td>
</tr>
<tr>
<td>Patients with acute</td>
<td>57% (8/14)</td>
<td>90% (55/61)</td>
</tr>
<tr>
<td>infarction*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with first</td>
<td>38% (3/8)</td>
<td>90% (43/48)</td>
</tr>
<tr>
<td>acute infarction</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Patients with unstable angina excluded.
†Refers to statistical significance of association between variable and mortality by chi-square or Fisher exact test.

Analog to stepwise multiple regression, but more appropriate for the dichotomous outcome of survival. Both logistic and multiple stepwise regression analyses select a "best" subset of variables and generate a prediction equation. The logistic regression predictivity equation estimates the probability of death, \( P(d) \), for a given subject based on the selected variables. Analyses were done with different groups of variables, including clinical only, scintigraphic only, and clinical plus scintigraphic. A probability cut point of 0.5 was then used to predict whether an individual would live or die.

Table 3 lists the variables selected and the mortality prediction achieved for each analysis. Using clinical predictors only, no variable was significant after selection of transmural infarction and no participants were classified as having greater than a 0.5 chance of dying. Addition of scintigraphic predictors helped considerably, and the best results were achieved using a combination of thallium defect score (7 or greater vs less than 7), ejection fraction (35% or less vs greater than 35%) and transmural infarction (transmural vs nontransmural or no infarction). With this set of variables, 11 patients were calculated to have a 50% or greater chance of dying, eight of whom actually died, and 70 patients had less than a 50% chance of death, 64 of whom lived. Thallium defect score was always selected as the most significant variable when available, but ejection fraction and transmural infarction were additive to the application. Application of this analysis to the subgroup of patients evolving acute infarction (unstable angina excluded) produced similar results, except that ejection fraction was no longer significant (\( \chi^2 = 11.72 \), \( \chi^2 \) for transmural = 4.70).

With this set of variables, nine patients were calculated to have a 50% or greater chance of dying, six of whom actually died, and 58 patients had less than a 50% chance of death, 51 of whom lived.

The stepwise logit analysis could also be used to separate groups with a high, medium and low risk of death. Combining the two scintigraphic variables, we found that concordant high-risk or low-risk scintigrams correctly identified groups with a high or low risk of death, while discordant results identified the middle-risk group (table 4, fig. 5).

The results from the multiple logit analysis can also be viewed as a continuous scale of probability in which the choice of a cut point is dependent on the projected use of the data. Figure 6 shows the results using the best combination of clinical and scintigraphic variables. The predicted probability of death was 87% when thallium defect score was 7 or greater, ejection fraction was 35% or less and the infarct was transmural. When only two of the variables were in the high-risk category, the probability of death was intermediate, 40–60%, while a single high-risk variable was associated with a 10–20% probability. When all three variables were low risk, the probability of death was only 3%.

Discussion

Our results indicate that thallium perfusion imaging and scintigraphic ventriculography performed within 15 hours of the onset of symptoms are useful for predicting mortality in patients with acute myocardial infarction admitted in clinical class I or II. A large thallium defect, i.e., a computer score of 7 or greater, identified a high-risk subgroup with 6-month mortality of 64%, while defect scores less than 7 were associated

Table 3. Stepwise Multiple Logistic Analyses

<table>
<thead>
<tr>
<th>Variables used in analyses</th>
<th>Variables selected</th>
<th>No. of pts actually classified dead</th>
<th>No. of pts actually alive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical and scintigraphic</td>
<td>Ti (16.67), transmural (5.06), EF (2.81)</td>
<td>11</td>
<td>64 (91%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8 (73%)</td>
<td>70</td>
</tr>
<tr>
<td>Clinical only</td>
<td>Transmural (9.77)</td>
<td>0</td>
<td>91</td>
</tr>
<tr>
<td>Scintigraphic only</td>
<td>Ti (16.67), EF (3.27)</td>
<td>6</td>
<td>75</td>
</tr>
<tr>
<td>Thallium and clinical</td>
<td>Ti (20.87), transmural (5.37)</td>
<td>10</td>
<td>72 (90%)</td>
</tr>
<tr>
<td>EF and Clinical</td>
<td>EF (11.26), transmural (5.75)</td>
<td>7</td>
<td>65 (87%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 (57%)</td>
<td>75</td>
</tr>
</tbody>
</table>

Under variables selected, values in parentheses are stepwise chi-square (based on 1 degree of freedom) reflecting statistical significance over and above previously selected variables.

Abbreviations: Ti = thallium; EF = ejection fraction.


Table 4. Identification of High-, Medium- and Low-risk Groups by Scintigraphy

<table>
<thead>
<tr>
<th>Thallium scintigraphic result</th>
<th>p (d) observed</th>
<th>p (d) predicted from logit equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defect score ≥ 7, EF ≥ 35%</td>
<td>83%</td>
<td>80.6%</td>
</tr>
<tr>
<td>Defect score ≥ 7, EF &gt; 35%</td>
<td>43%</td>
<td>45.2%</td>
</tr>
<tr>
<td>Defect score &lt; 7, EF ≥ 35%</td>
<td>25%</td>
<td>29.1%</td>
</tr>
<tr>
<td>Defect score &lt; 7, EF &gt; 35%</td>
<td>8%</td>
<td>7.6%</td>
</tr>
</tbody>
</table>

Abbreviations: EF = ejection fraction; p (d) = probability of death within 6 months of ischemic event (see figure 5).

with a mortality of only 8%. Similarly, patients with left ventricular ejection fraction of 35% or less had a 60% 6-month mortality, compared with 11% in those with ejection fractions greater than 35%.

The results with early thallium imaging confirm our previous findings in a retrospectively gathered series of clinical class I and II patients with acute myocardial infarction.\(^6\) In that study, scintigraphically identified high-risk patients had a 6-month mortality of 62%, compared with 7% for low-risk patients. Despite the similarity in results, there are certain differences between the two studies. In the retrospective study, the predictive ability of the defect score was maximized because the high/low-risk dividing line was chosen after examination of the end-point mortality data. It was, therefore, of crucial importance to confirm the true value of this dividing line in a separate series of patients obtained prospectively and consecutively, and in which the discriminating defect score was applied without reference to the end point data. Because of the differences in study design, the patient populations in the two studies were somewhat different: Patients in the earlier study all had documented acute myocardial infarction, while in the current study we also included patients with suspected infarction. (Fifteen of 91 failed to evolve an acute infarct.) Patients who had chest pain but not infarction probably represent a subgroup with a lower short-term mortality rate, and their inclusion tends to slightly improve the apparent specificity and overall accuracy of the mortality prediction (table 2). However, their inclusion also results in a more relevant patient population, for patients must be imaged as early as possible, before laboratory confirmation of infarction is available, to maximize the value of admission scintigraphy for early risk stratification and patient management.

Several reports have supported the usefulness of ejection fraction measurements within the first few days of acute myocardial infarction.\(^8, 9, 14-17\) Ejection fraction has been inversely correlated with clinical class and is lower, on the average, in patients who die or develop other complications, e.g., heart failure or persistent angina. In the study of Rigo et al.\(^12\) five of 15 patients with an ejection fraction of 35% or less died, compared with one of 23 with an ejection fraction of more than 35%. Similarly, Schelbert et al.\(^15\) reported that six of 32 patients with ejection fractions of less than 52% within the first 5 days died, compared with none of 18 patients with a normal ejection fraction. Battler et al.\(^16\) found that an ejection fraction of less than 52% in the first 4 days did not predict 30-day mortality but was associated with a higher mortality at 1 year (24% vs 10%). Shah et al.\(^8\) studied the prognostic significance of ejection fractions measured within the first 24 hours, and have found that patients who die or develop complications tend to have lower ejection fractions. Of 56 patients admitted with their first transmural infarction, six of 11 patients with ejection fractions of 30% or less died, compared with one of 45 with ejection fractions greater than 30%. Fewer reports have appeared concerning the prognostic significance of early thallium imaging. Perez-Gonzalez et al.\(^17\) found that the extent of thallium defect within the first 10 days of infarction differed among asymptomatic survivors, survivors with heart failure and nonsurvivors. Mueller et al.\(^18\) reported that the mean thallium defect size was larger and left ventricular ejection fraction lower in a subgroup of clinical class I or II infarct patients demonstrating complex serum creatine kinase MB curves (multiple peaks or plateau) and a higher complication rate.

The timing of scintigraphic studies relative to the onset of infarction may have an important bearing on their predictive ability or on the precise cutoff points used to classify patients into high- and low-risk groups. Thallium defect size tends to decrease over time\(^19\) due to a reduction in ischemia that follows improved collateral flow, reopening of the occluded artery or stabilization of hemodynamic status. The rate at
which defects can improve in the first several hours after infarction is unknown. Similarly, left ventricular ejection fraction changes in most patients over the first few days, usually improving, but frequently getting worse. These changes probably depend on the severity of ischemia, intensity of catecholamine drive, loading conditions on the left ventricle, and changes in left ventricular geometry. Our patients were studied a mean of 7 hours (range 3–15 hours) after the onset of infarction, but if they had been imaged even earlier, the cutoff values of 7.0 for thallium score and 35% for ejection fraction might have been different.

Although left ventricular regional wall motion abnormalities were present in 87% of our patients (90% of those with documented infarction), only 42% (49% of infarct patients) had left ventricular ejection fractions of less than 55%. Most studies have found a higher percentage of acute infarct patients, 70–75%, to have abnormal ejection fractions, although patients were studied within the first few days and not necessarily as soon as possible after admission. A recent study, which may be more comparable to ours in that patients underwent imaging a mean of 8 hours after the onset of chest pain, found that only 55% of Killip class I and II patients had an ejection fraction of 50% or less. Normal or high ejection fractions during the early phase of acute infarction may be due to high circulating catecholamine levels, which may cause increased contraction of noninfarcted ventricular segments and preserve global left ventricular function.

In our study, global ejection fraction correlated only modestly with regional wall motion score and the number of akinetic or dyskinetic left ventricular segments, and was also more predictive of mortality than the regional indices. A probable deficiency in this analysis, however, was the lack of a steep left anterior oblique view of the left ventricle to visualize the posterior and inferobasal regions. Without this view or similar views, the extent of wall motion abnormality in patients with inferior infarcts tends to be underestimated because the involved region is poorly represented on the standard anterior and 40° left anterior oblique views, and is often obscured by the right ventricle. A left lateral view is a standard part of a gated blood pool study in our laboratory.

Although thallium defect score and ejection fraction were both useful for risk stratification, the thallium score was more sensitive for predicting nonsurvivors at a similar level of specificity. Thallium defect size appears to be predictive because it provides an estimate of the sum total of irreversible ischemic damage, both old and new, plus potentially reversible ischemic myocardium at risk for future infarction. While ejection fraction should also reflect the sum of injured and ischemic myocardium, it may be influenced to a greater extent by other variables, such as left ventricular preload and afterload, ventricular geometry and sympathetic drive. We found a rough inverse correlation between thallium score and ejection fraction (fig. 4), and nine of 13 patients with thallium score of 7 or higher had ejection fractions below 40%. However, three patients had normal ejection fractions. All had inferior wall infarction, which has been associated with less depression of left ventricular function than anterior wall infarction. For a given size of damage, anterior wall function may be more important for preservation of global function. Another patient, who had an ejection fraction of 48%, had a history of anterior infarction and was admitted with a small new ischemic event (peak creatine kinase of 206 IU/l). In this patient, time-related compensatory changes may have limited the global functional impairment resulting from the first infarct. In contrast, four patients with thallium scores less than 7 had ejection fractions of 35% or less. Theoretically, this situation could result from superimposed myocardial disease, diffuse depression of myocardial perfusion, or technical problems in thallium defect scoring related to high background activity or a dilated left ventricular cavity with thin ventricular walls. Of the four patients, one had a cardiomyopathic pattern on thallium scan, one had evidence of diffuse ischemia (ejection fraction increasing from 27% to 43% during hospitalization), one was diabetic with severe peripheral vascular disease (possible diffuse ischemia), and one was a heavy user of alcohol (possible superimposed myocardial disease).

The value of a reliable prognostic index for patients admitted with suspected or evident acute myocardial infarction is clear. Early, accurate classification of patients into high- and low-risk categories should permit improved and more selective medical care. Higher-risk patients could be closely monitored in the coronary care unit for longer periods of time, ambulated more slowly and followed more closely after hospital discharge. Lower-risk patients could be ambulated sooner and discharged from the hospital earlier. By using a multivariate approach, such as stepwise multiple logistic analysis, patients with a very low probability of death (e.g., < 3%) could be identified at the time of presentation and treated less expensively on a routine hospital floor or possibly at home (fig. 6).

A second important use for early risk stratification is to guide the application of new therapies designed to limit infarct size. Since such therapies must be begun as early as possible, before the majority of ischemic myocardium has progressed to necrosis, it is essential that prognosis be estimated at admission. Treatment could then be applied selectively to higher-risk patients, who most urgently need therapy and who, at the same time, provide the best population for evaluating the effectiveness of a new treatment. If the new treatment is invasive or provides significant risk, patients with the highest risk of death (e.g., > 85%) may be selected, thereby limiting the exposure of lower-risk patients to side effects. A note of caution may apply, however, to patients with previous myocardial infarction and a new ischemic event of uncertain magnitude. The scintigraphic tests cannot distinguish between old and new injury, and a patient who has survived a large prior infarct and now has a small area of ischemic myocardium is lumped with one who presents with a large area of fresh necrosis. Whether a high-risk scinti-
gram carries the same prognostic significance in these two types of patients is unclear. In our study, the presence of prior infarction did not modify the predictive value of the scintigraphic tests, but the numbers of patients were small and more information is needed in this important area.

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Comparison of early thallium-201 scintigraphy and gated blood pool imaging for predicting mortality in patients with acute myocardial infarction.

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