The Prognostic Implications of Acute Myocardial Infarct Scintigraphy with $^{99m}$Tc-Pyrophosphate

B. Leonard Holman, M.D., Robert J. Chisholm, M.D., and Eugene Braunwald, M.D.

SUMMARY The predictive value of myocardial scintigraphy with $^{99m}$Tc-pyrophosphate was studied in 100 patients admitted to the coronary care unit with suspected acute myocardial infarction. None of the 21 patients with normal scintigrams had acute myocardial infarction by other criteria. Fifty-five percent of patients with diffuse uptake (pattern B), 73% of patients with focal uptake (pattern C) and all patients with intense focal uptake (pattern D) and massive uptake (pattern E) had acute infarction. The complication rate in the hospital and after discharge (mean followup: 6.1 months) for patients with pattern E was 88% compared to 42% for D, 30% for C, 36% for B and 10% for patients with normal scintigrams (A). For patients with acute infarction with patterns C, D and E, the complication rate rose with increasing size of the myocardial uptake of $^{99m}$Tc-pyrophosphate. In addition to its diagnostic potential, scintigraphy provides prognostic information which is useful for patient triage and for therapeutic decisions early in the evolution of the infarct.

PUMP FAILURE, the primary cause of in-hospital death in patients with acute myocardial infarction, reflects the extent of cellular necrosis. Recently, a scintigraphic technique has been developed using radiopharmaceuticals which sequester in acutely damaged myocardium. Since the extent of uptake of the radiotracer has correlated well with the size of infarction, acute infarct scintigraphy might be expected to have predictive value in assessing patients with acute myocardial infarction. In this study, we have correlated the diagnosis and complication rate of patients admitted to the coronary care unit with suspected acute infarction with the results of scintigraphy performed using $^{99m}$Tc-pyrophosphate.

Methods

One hundred patients admitted to the coronary care unit with the possible diagnosis of acute myocardial infarction were studied after informed consent had been obtained.
Scintigraphs of the chest were obtained 90 minutes after the injection of 10 mCi (5 mg) of \(^{99m}\text{Tc}\)-pyrophosphate using a portable Anger scintillation camera with a high resolution, low energy collimator and a pulse height analyzer window peaked symmetrically over the 140 keV photopeak of \(^{99m}\text{Tc}\). Scintigraphs were performed in the anterior, left anterior oblique and left lateral projections collecting 600,000 counts in each projection. The scintigraphic images were obtained on Polaroid film (type 52) and were interpreted independently by two observers without prior knowledge of the clinical diagnosis. In all cases, imaging was performed between one and six days after the onset of symptoms. Scintigraphy was performed between 24 and 48 hours after onset of symptoms in 44 patients, between 48 and 72 hours in 51 patients, between 72 and 96 hours in two patients and after 96 hours in three patients.

Routine chromatographic analysis and animal distribution studies were performed on each batch of \(^{99m}\text{Tc}\)-pyrophosphate. Batches demonstrating 3% or more of free \(^{99m}\text{Tc}\)-pertechnetate were not used for patient studies.

The scintigraphic patterns were divided into the following types (fig. 1): A) **normal** — myocardial uptake equal to that over right hemithorax (no identification of discrete cardiac silhouette); B) **diffuse** — myocardial uptake exceeding uptake over right hemithorax but less intense than the sternum and distributed over most or all of the myocardium; C) **focal** — discrete myocardial uptake less intense than the sternum; d) **focal** — discrete myocardial uptake involving less than 50% of the cardiac silhouette (as estimated from the admission chest radiograph) and equal to or more intense than the sternum; E) **massive** — increase in myocardial uptake involving 50% or more of the cardiac silhouette and equal to or more intense than the sternum.

As an alternative method, the extent of myocardial uptake was determined in patients with clinical evidence of acute infarction and with scintiscans falling into patterns C, D and E. The area of \(^{99m}\text{Tc}\)-pyrophosphate uptake was determined by planimetry of the anterior, left anterior oblique and left lateral scintiscans and was analyzed without regard to heart size in the 40 patients with clinical evidence of acute infarction and with scintigraphic patterns C, D and E and who were studied between 24 and 72 hours after onset of symptoms. Scintigraphy was performed in 21 of these patients between 24 and 48 hours after onset of symptoms, in 19 patients between 48 and 72 hours and in three patients at 5-6 days. Because transient changes in the size of the radiotracer uptake could not be ruled out without earlier scintigraphy, the latter three patients were not sized by the planimetric method. For each patient, the scintigram with the largest area of myocardial uptake was used for analysis. In all but four patients the anterior scintigram had the largest area of tracer uptake. In four patients (all with lateral infarcts) the left anterior oblique scintigram was analyzed. Sizing was not possible in four patients due to overlying bone.

The reproducibility of the method was tested in the first ten patients studied with patterns C, D, or E. Two independent observers measured the area of \(^{99m}\text{Tc}\)-pyrophosphate uptake on the anterior scintiscan in each of the ten patients; the mean percent difference and the range were calculated.

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**Figure 1.** Scintigraphic classification of myocardial uptake of \(^{99m}\text{Tc}\)-pyrophosphate. A = normal; B = diffuse; C = focal, less intense than sternum; D = focal, equal or greater in intensity than sternum; E = massive.
To determine intra-observer reproducibility, one of the observers repeated the planimetry measurement one week after the first measurement. Again, the mean percent difference and range were calculated.

Acute myocardial infarction was considered present when at least three of the following criteria were satisfied: 1) chest pain consistent with myocardial ischemia lasting for more than one hour; 2) elevation of total serum creatine kinase (CK) of 50% or more above the upper limit of the normal range in the first three days of hospitalization; 3) detection of the MB isoenzyme of CK by electrophoretic assay of the patient's serum; 4) standard electrocardiographic criteria consistent with the diagnosis of acute myocardial infarction. Comparison between peak serum CK activity and area of $^{99m}$Tc-pyrophosphate uptake was by linear regression analysis. In all other data comparisons, statistical significance was determined by chi square analysis.

Unstable angina pectoris was defined as chest pain, ischemic in character, which was either of recent onset (less than one month) or which had increased in frequency, severity or duration in the month prior to admission. There was no electrocardiographic evidence of acute myocardial infarction, and the peak serum CK value in the three days following admission was less than 50% above the upper limit of normal. Complications were divided into those occurring in the hospital and those occurring following discharge. The inhospital complications included: 1) cardiogenic shock — systolic blood pressure less than 80 mm Hg persisting for more than two hours, oliguria (less than 20 ml/hour), clouding of consciousness, cool and clammy extremities, all in the absence of hypovolemia (left ventricular filling pressure exceeding 15 mm Hg); 2) serious ventricular arrhythmias (ventricular tachycardia or fibrillation); 3) extension of or new acute myocardial infarction subsequent to scintigraphy (as evidenced by subsequent elevation in serum CK activity and new electrocardiographic changes compatible with extension or reinfarction); and 4) death.

The complications occurring after discharge were: 1) cardiogenic shock, 2) new acute myocardial infarction, 3) development of unstable angina pectoris and 4) death attributable to coronary artery disease (either death resulting from a clinical ischemic syndrome or sudden death).

Patients with acute myocardial infarction were evaluated at the time of scintigraphy using the clinical classification described by Killip: I) no clinical signs of cardiac decompensation; II) heart failure; III) severe heart failure with pulmonary edema; IV) cardiogenic shock. Of the 59 patients with acute myocardial infarction, 33 were in class I, nine in class II, 10 in class III and seven in class IV.

In addition to the 59 patients with acute myocardial infarction, 30 had unstable angina pectoris, five had congestive heart failure, three had atypical chest pain, two had arrhythmias and one had syncope. There were eight deaths during the initial hospitalization, and 87 of the remaining 92 patients were followed for an average of 6.1 months, with a range of one to 24 months.

Results

Table 1 indicates the incidence of acute myocardial infarction with each of the scintigraphic patterns. Of the 21 patients with normal scintigrams (pattern A), 14 had unstable angina pectoris, four were in congestive heart failure, one had a syncopal episode, one had arrhythmia and one had chest pain of noncardiac origin. Among the 22 patients with diffuse uptake (pattern B), 12 had acute infarction, eight had unstable angina pectoris, one patient was in congestive heart failure, and one had noncardiac chest pain. Of the 37 patients with focal uptake (pattern C), 27 had acute infarction, eight had unstable angina pectoris, one had alcoholic cardiomyopathy and one patient had a left ventricular aneurysm. All 12 patients with intense focal uptake (pattern D) and all eight patients with massive uptake (pattern E) had acute myocardial infarction.

Analyzing these results another way, all 59 patients with acute infarction had abnormal scans. Twenty of these patients had patterns D and E (not observed in patients without acute infarction) and the other 39 had patterns B and C. No patient with acute infarction presented with pattern A. Among the 30 patients with unstable angina pectoris, the scintigraphic patterns were normal (pattern A) in 14, exhibited diffuse uptake (pattern B) in eight and focal uptake (pattern C) in eight patients. Four patients without either unstable angina pectoris or acute infarction also had abnormal scans. One each of these patients had congestive heart failure (pattern B), chest pain of undetermined etiology (pattern B), alcoholic cardiomyopathy (pattern C) and left ventricular aneurysm (pattern C).

The predictive value of acute myocardial infarction scintigraphy is shown in figure 2. Patients with normal scintigrams (pattern A) had a complication rate of only 5% both in hospital and after discharge with no mortality (total morbidity rate: 10%). Patients with scintigraphic patterns B and

<table>
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<td>8 (22%)</td>
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<td>12 (100%)</td>
<td>0</td>
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<tr>
<td>E</td>
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Figure 2. Complication rates observed with various patterns of $^{99m}$Tc-pyrophosphate uptake (A = normal; B = diffuse; C = focal; less intense than sternum; D = intense focal; E = massive).
C did somewhat worse than patients with normal scintigrams but the differences were not significant (total morbidity rates: 36% and 30%, respectively). There was no difference in the complication rates in patients with these two patterns. Patients with pattern D had a complication rate of 42% after discharge, significantly higher than patients with patterns C and A. Patients with massive uptake (pattern E) had the highest complication rate of all groups (88% in hospital and 50% after discharge). The in-hospital complication rate was significantly greater than in patients with focal uptake (patterns C and D), diffuse uptake (pattern B) and normal scintigrams (pattern A). Similarly, the total complication rate (88%) and mortality rate (63%) in patients with massive uptake (pattern E) was significantly greater than in patients with focal uptake ($P < 0.01, P < 0.02$, respectively).

When both the clinical diagnosis and the scintigraphic pattern were considered, further predictive information was elicited. Patients without acute myocardial infarction by other clinical criteria but with abnormal scintigrams (patterns B and C) had a similar in-hospital complication rate compared to patients with normal scintigrams (pattern A). In the out-of-hospital period, the complication rate of those patients with abnormal scintigrams in the absence of acute myocardial infarction was somewhat greater than the complication rate in patients with normal scintigrams. The differences were not statistically significant, however.

There was a higher in-hospital complication rate in patients with clinical evidence of acute infarction and pattern B or C scintigrams than in patients without infarction but with similar scintigrams (26% vs 6%, $P < 0.05$) and in patients with normal scintigrams (26% vs 5%, $P < 0.05$). The reverse was observed after discharge. While only 6% of patients with acute infarcts and B or C scintigraphic patterns had complications after discharge, 26% of patients without infarction but with abnormal scintigrams (patterns B and C) had complications after discharge. The differences observed after discharge were not statistically significant, however.

In the ten patients in whom the reproducibility of measuring the area of uptake was studied, the mean absolute percent difference in measurements by one observer was 5.9% (range: 2.2–8.5%). The interobserver mean absolute percent difference was 7.1% (range: 2.1–15.1%).

The morbidity and mortality of patients with acute myocardial infarction and with focal (C and D) and massive (E) patterns varied directly with the area of $^{99m}$Tc-pyrophosphate uptake as determined by planimetry of the anterior view (fig. 3). It was noted that all patients in whom the area of myocardial uptake was less than 16 cm$^2$ on the anterior projection suffered no complications in both the early and late follow-up periods. Patients with moderate uptake (16–40 cm$^2$) had a total complication rate of 68%, significantly greater than patients with uptake less than 16 cm$^2$. The mortality rate was 12% in this group. When the uptake was greater than 40 cm$^2$, the total complication rate was 67%. Six of the seven patients with complications died of pump failure.

When the correlation between area of tracer uptake and complication rate was analyzed with respect to infarct location (table 2), the predictive value was approximately equivalent for anterior and inferior infarcts. While no patients with anterior and inferior infarcts and tracer uptake of less than 16 cm$^2$ had complications, 67% of patients with anterior and 72% of patients with inferior infarcts and tracer uptake between 16 and 40 cm$^2$ had complications. Four of the six patients with lateral infarcts had less than 16 cm$^2$ of uptake; none of these patients had complications.

The correlation between peak serum CK activity and the area of $^{99m}$Tc-pyrophosphate uptake was poor ($r = 0.39$).

The predictive value of other prognostic indices was also assessed. Of the 36 patients with transmural infarcts by electrocardiographic criteria, 15 (43%) had complications and nine (26%) died; of the 24 patients without transmural infarcts, nine (38%) had complications and three (13%) died. These differences were not statistically significant.

Peak serum CK activity provided a predictive index of in-hospital complications comparable to scintigraphy. While the patients with pattern E scintigrams had higher complication and mortality rates than the patients with CK activity greater than seven times the upper limit of normal (88% vs 57% and 50% vs 22%), the differences were not significant. Scintigraphy provided more information than serum CK activity with regard to complications after discharge, however (figs. 2 and 4).
The predictive value of the area of $^{99m}$Tc-pyrophosphate uptake (fig. 3) was greater than the predictive value of peak serum CK activity for total complications and those occurring after discharge. Thus, the total mortality rate was higher in patients with large (larger than 40 cm²) areas of tracer uptake than in patients with CK levels greater than seven times the upper limit of normal (75% vs 21%, $P < 0.05$). While there was a significantly higher total complication rate in patients with moderate uptake (16-40 cm²) than in those with small uptake (less than 16 cm²) (75% vs 0%), there was no significant difference between moderate and low peak serum CK levels (39% vs 33%).

When prognosis was correlated with Killip classification in patients with acute myocardial infarction, the in-hospital and total complication rates were significantly greater for patients in class III (pulmonary edema) than in class II (heart failure without pulmonary edema) and class I (no heart failure) (fig. 5). The in-hospital mortality was significantly greater in class IV (cardiogenic shock) than in class III ($P < 0.05$). There was no difference in the complication rates between classes I and II.

When the extent of $^{99m}$Tc-pyrophosphate uptake was measured in the 26 patients in Killip classes I and II with scintigraphic patterns C, D and E, there was a significant difference between the total complication rate in the eight patients with tracer uptake of less than 16 cm² (0%) and the 18 patients with uptake of 16 cm² or greater (50%) ($P < 0.05$).

**Discussion**

In experimental models of acute myocardial infarction, increased concentrations of $^{99m}$Tc-pyrophosphate are limited for the most part to necrotic, irreversibly ischemic myocardium. In clinical studies, however, myocardial uptake of $^{99m}$Tc-pyrophosphate has been observed in conditions other than acute infarction, including unstable angina pectoris, ventricular aneurysm, congestive heart failure, and cardiomyopathy. This lack of specificity of the test in the diagnosis of infarction has led to concern regarding its role in the diagnostic process. Attempts to find the proper role for this procedure by determining its diagnostic accuracy are hampered by the limitations inherent in those other diagnostic techniques which have been used to corroborate the scintigraphic diagnosis.

We have found that myocardial scintigraphy with $^{99m}$Tc-pyrophosphate is a sensitive, but not always specific, indicator of acute infarction. All patients with the clinical diagnosis of infarction had abnormal scintigrams. This finding is of particular diagnostic significance in patients with normal scintigrams, since it provides strong evidence against the diagnosis of myocardial infarction, and in patients with scintigraphic patterns D and E, which strongly supports the diagnosis of acute infarction. A definitive diagnosis could not be made from the scintigrams in patients with diffuse (B) or focal (C) uptake since 45% of the former and 27% of the latter did not have other evidence of infarction. While most of the patients with focal uptake and no evidence of acute infarction had unstable angina pectoris, it was not possible, in the absence of previous scintigraphy, to determine the number of patients with persistently abnormal scintiscans due to previous infarction or ventricular aneurysm. The low specificity found with diffuse uptake may reflect persistence of blood pool activity or myocardial uptake in patients with an acute ischemic event but without other clinical evidence of irreversible damage. Delayed scintigraphy (three hours postinjection) may have increased the specificity of the test for acute infarction by discriminating between persistent blood pool activity and myocardial uptake.

While the diagnostic significance of myocardial scintigraphy with $^{99m}$Tc-pyrophosphate is at times unclear, this study has demonstrated that the scintigraphic pattern of myocardial uptake provides clues to the patient’s future course, both in-hospital and long term. Those patients with normal scintiscans (pattern A) had very few complications
while in the hospital. Conversely, massive intense uptake (pattern E) always signaled acute myocardial infarction and was usually accompanied by serious complications either in hospital or during the subsequent period.

If we add clinical information as it becomes available, the prognostic information derived from scintigraphy is increased. Thus, in those patients with clinical evidence of acute infarction and with focal and massive uptake (patterns C, D and E), the complication rate, particularly during hospitalization, was directly related to the area of uptake. In fact, patients with clinical evidence of infarction and small foci of $^{99m}$Tc-pyrophosphate myocardial uptake (less than 16 cm$^2$) had complication rates comparable to those of patients without acute infarction. While $^{99m}$Tc-pyrophosphate uptake is not as accurate an index of infarct size in inferior as in anterior infarction, 16, 18 the extent of tracer uptake was found to be of predictive value in both groups of patients.

A number of other indices of acute infarct scintigraphy appear to have prognostic value. A high incidence of ischemic complications has been observed in patients with focal myocardial uptake of $^{99m}$Tc-pyrophosphate persisting for more than six weeks after infarction. 20 Similarly, the incidence of left ventricular failure has correlated well with the extent of $^{99m}$Tc-pyrophosphate uptake in patients with acute infarction. 21

Clinical classifications of patients with acute myocardial infarction can be sensitive predictors of patients at high risk. In this study, patients classified as Killip III and IV had a complication rate of greater than 90%. Clinical classification was of only limited value in patients classified as Killip I and II (71% of the patients with acute infarction).

Acute infarct scintigraphy added prognostic value to the clinical classification, particularly in patients without heart failure and in those with failure but without pulmonary edema. Patients classified as Killip classes I or II and with focal uptakes of 16 cm$^2$ or greater had a considerably higher complication rate than those in comparable clinical classes but with myocardial uptakes less than 16 cm$^2$.

Acute infarct scintigraphy with $^{99m}$Tc-pyrophosphate was of greater value than peak serum CK activity for predicting the total number of complications, particularly in patients with clinical evidence of infarction and with focal or massive tracer uptake. The tests were comparable indicators of hospital complications. The more accurate appraisal of late complications by scintigraphy may result from overestimation of the size of the acute infarct because of uptake in previous infarction of aneurysm, that is, in patients with acute necrosis superimposed on extensive previous damage. These patients would be expected to have a higher complication rate than patients without previous necrosis. Serum CK levels would not differentiate patients with or without previous infarction.

Other techniques have been developed to estimate the magnitude of ischemic necrosis in patients with acute myocardial infarction. Creatine kinase and MB-creatine kinase release curves have been suggested as useful in this regard, 22 but their reliability depends on early contact with the patient and serial blood samples are required for assay. Scintigraphy has the advantage that only a single study is required which can be performed at any time between the first and at least the third day after onset of symptoms. Precordial ST-segment and QRS complex mapping may be helpful in assessing the efficacy of interventions designed to reduce the size of anterior infarcts but these methods are not useful for measuring infarct size. 23-25

The primary usefulness of acute myocardial infarct scintigraphy may be its ability to isolate 1) those patients at low risk during their in-hospital course, potentially reducing their hospital stay, and 2) those high risk patients who may benefit from more intensive medical or surgical management. Furthermore, the scintigraphic classification described in this study provides diagnostic and predictive information which may be useful in the evaluation of medical and surgical therapies aimed at limiting infarct size. 26

References

Evaluation of Left Ventricular Function
(Ejection Fraction and Segmental Wall Motion)
by Single Pass Radioisotope Angiography

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SUMMARY Changes in ejection fraction (EF) and segmental wall motion (SWM) have been shown to be sensitive indicators of left ventricular (LV) function. This information is only obtainable by contrast angiography or gated blood pool scans. Gated studies assume a fixed geometry for the LV for EF determinations, are lengthy and limited primarily to the LAO projection. We correlated contrast and Tc-99m pertechnetate angiograms by single pass radioisotope angiography (immediately preceding the contrast study) in 12 patients. EF was calculated from the LV time/activity curve and values ranged from 0.21 to 0.72. Angiographic correlation yielded \( r = 0.97 \). Regional LV wall motion was evaluated by dividing a summed cardiac cycle into 16 frames and dynamically and sequentially displaying these frames. Regional wall motion evaluation of four LV quadrants correlated well with angiography (\( r = 0.97 \)). For quantitation these images were divided into four anterior and four inferior segments and the areas of respective segments were compared and expressed as a shortening fraction. SWM compared favorably with angiographic determinations (\( r \) ranged from 0.70 to 0.99). Thus, single pass radioisotopic determinations of EF and SWM in the RAO projection correlate well with the angiographic values and provide essential quantitative information on LV function otherwise unobtainable at the bedside.

THE ABILITY TO monitor hemodynamics in a critically ill patient, at the bedside, has increased our understanding of the pathophysiology of heart disease and the effects of therapeutic interventions on myocardial performance. Indices of left ventricular function which are usually measured include pulmonary artery wedge pressure, arterial pressure and cardiac output. However, none of these parameters are dependent entirely upon the absolute level of left ventricular function. They are affected by changes in ventricular compliance and/or fluctuations of the central volume. Therefore, measurements of these parameters of left ventricular function are often confusing and may even be misleading.

Ejection fraction has been reported to be a sensitive indicator of left ventricular function but it can also be misleading since it varies with changes in both afterload and preload, independent of changes in left ventricular function. Segmental wall motion has been shown to be one of the most sensitive indicators of left ventricular function but until recently has only been obtainable during cardiac catheterization.

Gated cardiac blood pool scans have been shown to be useful in determining ejection fraction and qualitatively evaluating regional wall motion. These studies are limited by assuming a fixed geometry for the left ventricular ejection fraction calculation, and by requiring lengthy acquisition times and a stable cardiac rhythm. They also are limited primarily to the left anterior oblique projection. The technique of single pass radioisotope angiography provides rapid bedside determination of ejection fraction and quantitation of segmental wall motion in the critically ill patient.

Methods and Materials

Twelve patients, age 27 to 67 (mean 51) years, were studied. Three patients had valvular heart disease, and nine patients had symptomatic coronary artery disease. All patients required cardiac catheterization for diagnosis and evaluation of coronary artery disease and/or evaluation of myocardial function.

The studies were performed in the cardiac catheterization laboratory. Using standard techniques a Swan-Ganz catheter was positioned in the right pulmonary artery and another catheter in the body of the left ventricle. The patient was placed in the 30° right anterior oblique projection. Twenty-five microliters of Technetium-99m (2 ml of sodium pertechnetate) was placed in an extension tube connected to the distal lumen of the Swan-Ganz catheter. Ten milliliters of 5% dextrose solution was then rapidly injected through the extension tubing to achieve a bolus injection of the Tc-99m pertechnetate.

Imaging was accomplished using an Ohio Nuclear por-
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