Present Status of the \(^{99m}\)Technetium Pyrophosphate Infarct Scintigram

IN 1973 Holman\(^1\) demonstrated that 24 hours after coronary occlusion myocardial infarcts in closed chest dogs could be visualized by scintigraphy using \(^{99m}\)technetium tetracycline. A short time later, Bonte\(^2\) presented similar results using \(^{99m}\)technetium pyrophosphate (\(^{99m}\)Tc-PYP). Two large clinical series of infarct scintigrams were then reported by Holman\(^3\) and by Willerson\(^4\) which stimulated interest in this potentially important diagnostic procedure.

Although the mechanism by which infarct imaging agents accumulate in damaged myocardium is not clear, it is clear that they concentrate selectively in acutely necrotic myocardium irrespective of the cause of the cardiac necrosis. Thus, a positive infarct scintigram identifies acutely damaged myocardium directly. This contrasts with other cardiac imaging techniques such as perfusion scintigrams with thallium 201\(^5\) or isotope ventriculograms\(^6\) which only permit an inferential diagnosis of acute infarction in some clinical situations by demonstrating localized perfusion deficits or segmental ventricular dysfunction.

This editorial assesses the clinical usefulness of the infarct scintigram in light of recent studies with emphasis on separating those clinical situations where the infarct scintigram provides important diagnostic information from those where it yields primarily confirmatory data. Studies not directly related to the clinical use of the infarct scintigram will not be included in this review.

Can infarct scintigraphy be easily performed and interpreted?

Infarct scintigrams of diagnostic quality can only be obtained if careful attention is given to the quality of the \(^{99m}\)Tc-PYP, the timing of the procedure, the quality of the image, and the experience of the reader. (Although many radionuclides can be used to obtain infarct scintigrams,\(^7\) none have been shown to be better for infarct imaging than \(^{99m}\)Tc-PYP, the radionuclide that has been used in most studies.)

Since the quality of \(^{99m}\)Tc-PYP prepared from commercially available kits is variable, the binding of \(^{99m}\)Tc to PYP and the amount of reduced-hydrolyzed \(^{99m}\)Tc in the preparation should be assessed with thin layer chromatography.\(^8\) Binding should exceed 95% and reduced-hydrolyzed \(^{99m}\)Tc should not exceed 2% of the total amount of radionuclide. Unbound \(^{99m}\)Tc will remain in the blood pool and cause false positive scintigrams (diffuse pattern) whereas reduced-hydrolyzed \(^{99m}\)Tc forms a colloid which accumulates in the liver.\(^9\) In addition, the rate at which bound \(^{99m}\)Tc-PYP clears from the blood pool should be assessed either by imaging the vascular pool in the thigh\(^10\) or by analysis of the blood concentration of \(^{99m}\)Tc-PYP at the time of cardiac scintigraphy, since relatively slow clearance of the radionuclide from the blood pool can also cause false positive scintigrams.\(^11\),\(^12\)

Furthermore, the test should be interpreted as technically inadequate if the ribs are not well delineated since this suggests that \(\textit{in vivo}\), the binding of \(^{99m}\)Tc-PYP was inadequate (under these conditions free \(^{99m}\)Tc will accumulate in the gut) or that there is delayed clearance of \(^{99m}\)Tc-PYP secondary to intrinsic renal disease or dehydration.\(^13\)

Since infarct scintigrams usually are negative within the first few hours following acute myocardial infarction\(^4\) scintigrams should not be obtained until at least 12 hours after the estimated time of acute infarction. Although this time estimate depends upon the clinical judgment of the referring physician, it should be considered at the time of scintigram interpretation. If an infarct scintigram obtained 12-24 hours following suspected acute myocardial infarction is negative, but nonetheless acute infarction is strongly suspected, repeating the procedure 48-72 hours following the acute event will yield a positive scintigram in some patients because the evolutionary patterns of scintigraphic abnormalities exhibit considerable temporal variation. Cardiac images should not be obtained until at least two hours after an i.v. \(^{99m}\)Tc-PYP has been administered and in patients with diffusely positive scintigrams, repeat imaging at a later time (4 hours after injection) may be helpful in excluding blood pool imaging.\(^11\),\(^12\)

Since the target to background ratio is relatively low in some positive infarct scintigrams, the contrast in the image should be maximized by obtaining scans with sufficient information density and by using high contrast film or computer image enhancement techniques.\(^14\) Also, in selected patients, particularly those who have had left radical mastectomy\(^15\) the effects of variable tissue attenuation on the infarct scintigram should be considered.

Finally, the infarct scintigram should be interpreted by a knowledgeable observer familiar with the various evolu-

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tionary patterns of infarct scintigraphic abnormalities (see below).

Some of the unfavorable results with infarct scintigraphy that have been reported are probably due to inadequate imaging techniques. Infarct scintigrams should not be used as a diagnostic tool unless the quality of the radiopharmaceutical and the quality of the imaging procedure are carefully controlled.

What is the sensitivity of the infarct scintigram?

Studies in dogs suggest that only infarcts larger than 3 gm (2-4% of left ventricular mass) can be detected with 99mTc-PYP infarct scintigrams. (The size of a typical clinical infarct is > 10% of left ventricular mass.) Since the resolution of cardiac imaging procedures is probably better in dogs than in man, infarcts even larger than 2-4% of left ventricular mass may not be detectable in patients with the infarct scintigram. Detection will be a particular problem when the infarct is located in the true posterior wall which is far removed from the camera in all projections.

Infarct scintigrams are more sensitive than the electrocardiogram for the diagnosis of acute infarction, particularly if the electrocardiogram contains pre-existing abnormalities such as left bundle branch block. Measurements of serum enzymes and isoenzyme levels, such as MB-CPK, obtained at the appropriate time are at least as sensitive as the infarct scintigram for the detection of acute myocardial infarction.

What is the specificity of the infarct scintigram?

The specificity depends upon the type of scintigraph pattern which is observed. The scintigraphic patterns are classified on the basis of their location and intensity. If the scintigraphic abnormality can be localized to a given segment of the left ventricle, such as the anterior wall, it is classified as a localized or regional abnormality. If the increased cardiac uptake of 99mTc-PYP cannot be localized, the scintigraphic abnormality is classified as diffuse. Quantitation of intensity for either the localized or diffuse pattern is based upon a comparison between the intensity of the cardiac scintigraphic uptake and the concentration of 99mTc-PYP in bone which normally accumulates this radio-nuclide. Abnormalities that are less than, equal to, or greater than bone uptake are classified as 2+, 3+, and 4+, respectively. Equivocal uptake is classified as 1+. Concerning the specificity of the diffuse pattern, three large studies have shown that even with carefully prepared 99mTc-PYP and injection technique, 1+ and 2+ diffuse cardiac scintigraphic uptake will be seen in 13-35% of patients who presumably have no cardiac abnormalities. The high incidence of faintly positive diffuse scintigraphic abnormalities in patients with normal hearts probably reflects an inability to separate blood pool imaging from nonlocalized uptake of 99mTc-PYP in damaged myocardium. Serial imaging, computer subtraction techniques, quality control of the radiopharmaceutical and determinations of the concentration of 99mTc-PYP in blood, should make it possible to separate these two scintigraphic patterns more reliably in the future. Diffuse scintigraphic abnormalities of 3+ intensity occur in less than 3% of patients with normal hearts. Thus, if the 1+ and 2+ diffuse abnormality on the infarct scintigram is discounted, then the specificity of the diffuse pattern is > 97%. Diffuse scintigraphic abnormalities have been reported in a large variety of cardiac conditions besides acute myocardial infarction. However, the interpretation of these abnormalities, particularly if they are of 2+ or less intensity, is usually difficult because similar abnormalities are seen in patients with presumably normal hearts.

Concerning the specificity of the localized uptake, such abnormalities occur almost exclusively in patients with heart disease, although not necessarily acute myocardial infarction. The following conditions have been associated with positive localized abnormalities on the infarct scintigram: acute myocardial infarction that involves transmural or sub-endocardial portions of the left ventricle, old myocardial infarctions with or without a ventricular aneurysm, continuing low grade myocardial necrosis, or relatively large infarcts less than six months old, valvar calcification, invasion of the left ventricular wall by carcinoma, myocardial contusion, and repeated high energy cardioversions. In addition, it is likely that other conditions associated with myocardial necrosis such as myocarditis, myocardial abscess, penetrating cardiac trauma, and aneurysm, may also yield localized scintigraphic abnormalities on infarct scintigrams. Thus, from a practical standpoint, a positive localized infarct scintigraphic abnormality almost always implies the patient has a condition associated with cardiac necrosis. Characteristics of both localized and diffuse scintigraphic abnormalities in most instances give no clues to the cause of the cardiac necrosis. Consequently, the infarct scintigram will be of limited diagnostic assistance in patients who on clinical grounds have any or several of the above possibilities. For example, consider a patient who had a large myocardial infarction three months ago and now has an episode of prolonged chest pain. A positive infarct scintigram in such a patient could represent any of the following: 1) recurrent acute myocardial infarction; 2) low grade continuing myocardial necrosis in an area of previous infarction; 3) a ventricular aneurysm secondary to a previous infarct; or 4) increased calcium accumulation in a quiescent old infarction. Thus, in this situation, the infarct scintigram does not provide accurate information concerning the age of the scintigraphic abnormality in days, weeks, or months.

In such patients, the interpretation of the scintigraphic abnormality should not be based on the scintigram alone, since it could provide confusing information to the uninitiated. Rather, the infarct scintigraphic abnormality should be interpreted in light of the patient’s history and other findings. Although a single positive infarct scintigram is not diagnostic of acute myocardial infarction in all patients, serial infarct scintigrams which reveal typical evolutionary changes in the scintigraphic abnormality, are strongly suggestive of acute myocardial infarction.

If a patient with a documented myocardial infarction has a persistently positive infarct scintigram weeks or months following the acute infarction in the absence of suspected reinfarction, the persistent scintigraphic abnormality is of prognostic significance. Such abnormalities suggest that the previous infarction was probably large and that the involved area is presently either akinetic or dyskinetic. As might be expected such patients have a high incidence of persistent angina and congestive heart failure.

Many old myocardial infarctions unassociated with ven-
Can infarct scintigrams localize the site of the myocardial infarction?

Diffuse scintigraphic abnormalities which occur in most patients with subendocardial infarct\cite{9,26} do not localize these infarctions because the apparent distribution of the scintigraphic abnormality almost certainly extends beyond the predominantly involved region. Acute transmural infarctions, however, can be localized with infarct scintigraphy because such infarcts are associated with localized scintigraphic abnormalities in 90% of cases.\cite{9,10} If the electrocardiogram fails to localize an acute myocardial infarction because of pre-existing abnormalities such as left bundle branch block, then the infarct scintigram provides a non-invasive way of localizing the site of acute infarction in some patients. A recent study by Sharpe et al.\cite{25} suggests that in patients with inferior wall myocardial infarction, a left anterior oblique infarct scintigram will identify a subgroup of patients who have associated infarction of the right as well as left ventricle. This diagnosis is important in patients who have hypotension secondary to inferior infarction because hypotension in this clinical setting should be treated with volume expansion.\cite{28}

Can the infarct scintigram be used to determine the size of an acute myocardial infarction?

Three experimental studies\cite{15,16,29} suggest that the size of an acute myocardial infarction does correlate ($r > 0.8$) with the size of the scintigraphic abnormality. These studies, however, have been performed in dogs with anterior transmural myocardial infarction associated with a localized scintigraphic abnormality. In other studies, in which the size of inferior or subendocardial infarctions estimated by serum enzymes was compared with the size of scintigraphic abnormalities, results have been less encouraging.\cite{20}

Several problems make quantitation of infarct size with scintigrams difficult. First, the uptake of $^{99m}$Tc-PYP is not linearly related to the extent of necrosis because its concentration in necrotic myocardium is flow dependent.\cite{31-34} Second, the resolution of the imaging equipment is limiting, particularly in certain regions of the heart such as the true posterior wall, which are far removed from the camera in all projections. Third, since the geometry of the infarction is complex,\cite{26} three dimensional imaging techniques will be needed to delineate precisely the volume of an infarct. Thus, although large and small infarcts are associated with scintigraphic abnormalities of different sizes, it is unlikely that the size of an acute myocardial infarction can be determined quantitatively with an infarct scintigram.

Can infarct scintigrams diagnose extension of an acute myocardial infarction?

Since the progression and regression of scintigraphic abnormalities in patients with uncomplicated myocardial infarction is variable,\cite{4,9,25} normal evolutionary changes in the scintigraphic abnormalities observed on repeated infarct scintigrams usually cannot be separated from changes in the scintigraphic pattern secondary to infarct extension. Infarct scintigrams usually will be negative during the first 12 hours following an infarction.\cite{4} During the following 36 hours, abnormalities on the infarct scintigram often become more prominent in the absence of clinically suspected infarct extension\cite{17} probably because calcium deposition and coronary flow in the infarcted area are increasing.\cite{52,56,57} Later in the course of myocardial infarction for periods varying from five or six days to six months or longer, patients who initially had regional abnormalities on an acute infarct scintigram will display localized scintigraphic patterns (25%), diffuse abnormalities (27%), or have negative scintigrams (48%).\cite{9} Hence it is unlikely that small infarct extensions can be diagnosed accurately by repeated infarct scintigrams. If serial infarct scintigrams are done, however, certain sequential abnormalities are very suggestive of infarct extension. These include the following: a marked increase in the size of a scintigraphic abnormality compared to the scintigraphic abnormality observed 3-4 days following the acute infarction; reappearance of a scintigraphic abnormality that had previously cleared; or appearance of a regional scintigraphic abnormality in an area that was previously normal. When such sequential changes on infarct scintigrams are observed, other clinical evidence of infarct extension should be sought.

Can the infarct scintigram discriminate between myocardial infarction and myocardial ischemia?

There is convincing experimental evidence that uptake of $^{99m}$Tc-PYP is not increased in ischemic, nonnecrotic myocardium.\cite{18,26,28} In contrast, when myocardium from animals\cite{16,22,23,28} or man\cite{25} which contains high concentrations of $^{99m}$Tc-PYP is examined histologically, evidence of myocardial necrosis is almost uniformly observed. Thus, the infarct scintigram can discriminate between myocardial ischemia and myocardial infarction if the limitations concerning its sensitivity and specificity discussed above are given consideration.

In what other conditions is the infarct scintigram helpful?

There are two important diagnoses which sometimes are difficult to support without the assistance of a positive infarct scintigram: myocardial contusion and myocardial infarction following cardiac surgery. The electrocardiogram in both of these conditions may be nonspecific\cite{19,26,39} and the serum cardiac enzymes are altered by skeletal muscle trauma.\cite{19,26,39,40} There is convincing experimental data that myocardial contusion secondary to blunt trauma causes myocardial necrosis and that $^{99m}$Tc-PYP accumulates in the involved area.\cite{41} Furthermore, clinical studies\cite{39,47} suggest that $^{99m}$Tc-PYP scintigrams are helpful in patients suspected of having myocardial contusion.

Experience with infarct scintigrams following coronary bypass surgery is also encouraging\cite{19,39,40} but two precautions should be observed. First, for a postoperative infarct scintigram to be of value, a preoperative scintigram must be available for comparison because a significant number of patients going to bypass surgery will have positive infarct scintigrams preoperatively.\cite{42} Second, because MB-CPK is elevated in uncomplicated cardiac surgery\cite{29} and electrocardiographic abnormalities may be nonspecific, one cannot always be certain that a positive postoperative infarct
scintigam always represents new acute infarction. Repeated intraoperative defibrillations with energies that exceed 10 watt/sec can cause scintigraphic abnormalities. Also, 99mTc-PYP may accumulate at the site of aneurysm resection. Thus, positive infarct scintigrams following coronary bypass surgery should be interpreted in light of the entire clinical picture.

In summary, when does a positive infarct scintigram provide important diagnostic information?

Right ventricular infarction and myocardial contusion usually cannot be diagnosed without a positive infarct scintigram. However, the diagnosis of right ventricular infarction is only of clinical significance in patients with inferior wall myocardial infarction who are hemodynamically unstable. In addition, in selected patients suspected of having acute myocardial infarction in whom a reliable history cannot be obtained or the usual diagnostic tests may not be helpful (myocardial infarction in patients with left bundle branch block or a permanent pacemaker, infarcts between 3 and 10 days old, patients with equivocal evidence of infarction, or myocardial infarction following cardiac surgery) an infarct scintigram may contribute important diagnostic information. Although a single positive infarct scintigram may not be diagnostic of acute infarction in all patients, evolving scintigraphic abnormalities observed on serial infarct scintigrams provide strong support to the diagnosis of acute infarction in most instances. In contrast to the selected patients in whom infarct scintigrams will provide useful information, in the average patient with classical enzyme and electrocardiographic evidence of myocardial infarction, the infarct scintigram contributes confirmatory information which is not essential for the management of these patients.

What is the future of infarct imaging?

Results from three important new areas of investigation suggest that infarct imaging has a bright future. Two potential gamma emitting imaging agents (radiolabeled fragments of cardiac myosin specific antibodies and neutrally charged liposomies) have biological properties which could lead to improved infarct scintigrams. Both concentrate in necrotic myocardium in proportion to the extent of necrosis and are not flow limited like 99mTc-PYP. Progress is also being made in the instrumentation needed to obtain three dimensional images with gamma emitting radioisotopes. Experimental studies with the positron emitting radionuclide C-palmitate have yielded excellent quality three dimensional images of myocardial infarctions. When this technique is applied to man, it may permit accurate sizing of an acute myocardial infarction. Finally, advances in computerized axial tomography may provide another accurate method of identifying areas of myocardial infarction and regional myocardial edema. Work in these three areas is proceeding at an accelerating rate and there is reason to expect that within the next few years it will be possible to determine accurately the size and location of an acute myocardial infarction in man with a noninvasive imaging method.

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