

The Saga of Scintigraphy in Acute Myocardial Infarction

Myocardial infarction, which causes much morbidity and mortality, is a major public-health problem. Holman et al. (1) first imaged acute myocardial infarcts with Tc-99m complexes (i.e., Tc-99m tetracycline). Subsequently, Bonte et al. (2,3) extensively studied and validated the imaging of acute myocardial infarction using Tc-99m-Sn(II)-pyrophosphate (Tc-99m PPI).

This editorial addresses two questions. First, what is the clinical utility of scintigraphy in acute myocardial infarction? Second, what is the future of gamma imaging of acute ischemic myocardial necrosis? These two questions are related to current knowledge of the pathophysiology of acute myocardial infarction.

To date, there is little understanding of why the bone-seeking Tc-99m ligand complex (Sn^{2+} -PPI) is sequestered by the myocardial cell injured in the ischemic process. It is also unclear how infarct scintigraphy fits in relation to skeletal tracer uptake (4). In fact, the notion that Tc-99m PPI uptake is associated with myocardial calcification (5) has been disputed (6). Similarly, the mechanisms whereby Tc-99m PPI distributes in the injured myocardial cell are unknown; an investigation reported that the Tc-99m chelate primarily forms nonmitochondrial polynuclear complexes with denatured macromolecules (7).

A fundamental, but often neglected, aspect of infarct scintigraphy is the peculiar dependence of the Tc-99m PPI uptake on coronary flow. The still uncontested data of Zaret et al. (8) demonstrated that: (a) maximal radiophosphate concentration occurs in ischemic regions where microsphere flow is 30% to 40% of normal; (b) in low-flow regions, myocardial Tc-99m PPI uptake is predominantly epicardial (7); (c) border zones (i.e., those regions forming the boundary between normal and deeply ischemic myocardium) do sequester radiophosphate (6,8). Two conclusions can thus be derived from these data. On the one hand, maximal radiophosphate uptake is not observable in the endocardial ischemic center of the infarcted heart (9). On the other hand, Tc-99m PPI uptake takes place in the less ischemic border zone (6,8). These purely biological findings are critical to any investigation aimed at the sizing of acute myocardial infarction. Furthermore, the above experimental data have been extended by clinical research. Patients with acute myocardial infarction appear to have larger infarct areas by Tc-99m PPI than by thallium-201 (10). In other words, Tc-99m PPI seems to distribute more preferentially to the border zone than does thallium-201.

It is intriguing that in contrast to Tc-99m PPI, antimyosin ($\text{F ab}'_2$) uptake in myocardial infarcts is inversely proportional to microsphere flow (11). The reasons for the unique antimyosin ($\text{F ab}'_2$) accumulation in the central core of infarcted zones are unknown, but plasma clearance of antibody and developing coronary collateral circulation are two postulated theories. An ideal radiopharmaceutical for cardiac infarct imaging must behave like antimyosin antibodies if the investigator wishes to size the area of necrosis with gamma imaging.

Infarct scintigraphy is a highly sensitive method of detecting acute transmural cardiac infarcts (12,13). Anterior infarcts are probably better identified than inferior infarcts (13). More data are needed on infarct scintigraphy in patients with infarct locations other than anterior.

Infarct scintigraphy is an insensitive method for the detection of acute nontransmural infarcts (14). Only a third of patients with subendocardial infarcts are abnormal on Tc-99m PPI imaging. This is unfortunate, as there is no difference in short-term mortality between patients with transmural and nontransmural cardiac infarcts (15), and many patients with subendocardial infarcts are missed by radiophosphate imaging.

A major problem with infarct scintigraphy is variable specificity. This is largely the result of either persistent blood-pool activity in the region of the heart (16), or radiophosphate myocardial uptake unrelated to acute myocardial infarction (13,17). Consequently, a scintigraphic diagnosis of acute myocardial infarction should require the presence of myocardial radioactivity in either

discrete or diffuse patterns, but with threshold intensity equal to that of bone (ribs or sternum). Since even the discrete pattern of Tc-99m PPI uptake may be nonspecific (17), other tracer procedures such as radionuclide ventriculography (18) or thallium-201 scintigraphy (19) may be used if the clinical situation is unclear.

At this time infarct scintigraphy is indicated for the patient in whom a diagnosis of acute transmural myocardial infarction is suspected but not established by clinical, enzymatic, and ECG criteria. These patients may have atypical chest pain, atypical ECG, intraventricular conduction defects, ventricular hypertrophy, or an acute cardiac infarct coexisting with previous myocardial infarcts (20).

Right-ventricular infarction occurs in 24% of patients with transmural infarction of the inferior wall of the left ventricle (21). Infarct scintigraphy, thallium-201 scintigraphy (19), or radionuclide ventriculography (22) have all been used in detecting right-ventricular infarction. Patients with this condition may present with evidence of cardiac tamponade and constrictive pericarditis (23), or they may present no evidence of right-ventricular dysfunction (24).

Infarct scintigraphy is a useful means of detecting acute myocardial infarction occurring after open-heart surgery (25). On the other hand, persistently abnormal Tc-99m PPI scans imply poor long-term prognosis and may be related to existing abnormalities of left-ventricular wall motion (13). Finally, in a puzzling recent report, Codini et al. showed that patients with acute massive transmural infarcts may have totally normal infarct scintigrams (26).

In this issue of the *Journal* Corbett et al. (27) describe a new computer-assisted method by which multigated Tc-99m PPI scintigrams and Tc-99m blood-pool ventriculograms are displayed simultaneously. Further, the dynamic overlays can be obtained in multiple projections. This technique, no doubt, will have applications in dual-radionuclide studies (such as the one used by these authors), or in radiotracer investigations requiring multiple sampling angles. However, the preliminary clinical series of twenty-one patients presented by Corbett et al. does not establish a clear-cut clinical indication for the method described (27). The authors do not report the interobserver variability that may have existed when they determined improved location or increased extent of radiophosphate uptake. Nor is the reader provided with an explanation as to why the combined tracer studies were performed in patients with typical myocardial infarction. Additionally, the clinical population consisted of patients with normal or markedly abnormal left-ventricular function, which renders analysis of results extremely difficult. There were only three patients with right-ventricular infarction. One can hardly evaluate the claim made by the authors that detection of right-ventricular infarction was more precise with the new method.

During the last 11 yr a major research effort has been directed toward the protection of ischemic myocardium (28). This research has provided investigators with a better understanding of the pathophysiology of acute myocardial infarction.

In the canine model of acute myocardial infarction, it has been established that: (a) the myocardial endocardial zone at the center of the infarct is most vulnerable to cell death (29); (b) coronary collateral circulation develops in the epicardial myocardial layer, and in particular, lateral to the ischemic zone (30); (c) there is most probably a border zone where myocardial cell salvage is possible by utilization of pharmacologic agents (30); and (d) there is great variability in the size of acute myocardial infarction in dogs that receive identical coronary artery occlusions (31). Experimentally, reperfusion within 3 hr of the occlusion results in greater dog survival than that of animals with permanent occlusions (31). Likewise, pharmacologic interventions can reduce the magnitude of acute cardiac necrosis in the epicardial and border zones (30).

These promising animal data have not as yet found human counterparts. In patients with an acute transmural myocardial infarction, recanalization of an occluded coronary artery by intracoronary infusion of streptokinase within 3 hr after the onset of symptoms did not prevent development of acute myocardial infarction in 24 of 30 patients (32). Similarly, none of the pharmacologic agents used for infarct size reduction has produced consistent and easily demonstrable salvage of myocardial cells (33).

Noninvasive gamma imaging would be most helpful in the setting of an acute myocardial infarction if it could measure the extent of the myocardium that can recover from injury (34). Tc-99m PPI cannot be used for infarct sizing, as there is a significant amount of radiophosphate uptake in the merely ischemic border zone (6-8,11). Likewise, thallium-201 scintigraphy is not optimal for infarct sizing, since perfusion defects in ischemic areas lead to overestimation of the extent

of infarction during the first 24 hr after the insult (19).

What is the utility of Tc-99m PPI scintigraphy in assessing the extent of an acute myocardial infarction? Total myocardial infarct size also depends on how many of the four major coronary arteries suffer from significant occlusion (35). Moreover, in patients dying from myocardial infarction, there is an inverse relation between the percentages of old and new cardiac infarcts (35). Finally, left-ventricular performance, as evaluated by the global ejection fraction, is inversely related to the size of the infarcted area (36,37). From the foregoing it is difficult to define the role of infarct scintigraphy in measuring the extension of an acute myocardial infarction. Even accepting that a significant new infarct can be imaged in a patient with an old myocardial infarct, one still cannot discriminate between accumulation of radiophosphate in ischemic and infarcted regions. On the other hand, radionuclide cineangiography, using the first-pass (18,38-40) or the multigated blood-pool (41) methods, allows assessment of biventricular global and regional cardiac performance, and it is an important prognostic indicator in patients who have sustained an acute myocardial infarction (39).

As with any other area of nuclear medicine, progress in the imaging of acute myocardial infarction will result from development of better radioindicators and advances in instrumentation.

An ideal radiopharmaceutical must assess metabolic pathways that are disabled by the ischemic insult. Since fats are an essential cardiac fuel, C-11 palmitate imaging with emission transaxial tomography (42) deserves intensive trials in patients with cardiac infarcts. Although positron tomography is cumbersome, several academic centers in this country are now in an excellent position to conduct this "all the way" research approach.

During the last year there has been renewed interest in the application of single-photon tomography with Tc-99m PPI for the sizing of myocardial infarcts (43,44). Whether this technique, which really tracks the border zone (45), will have wide clinical utility remains to be seen. Certainly, advances in single-photon tomography could be greatly accelerated by the development of newer radiopharmaceuticals.

J. A. BIANCO

West Roxbury Veterans Administration Hospital
West Roxbury, Massachusetts

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