Editorial: "Hot Spot" Imaging Agents for Acute Myocardial Infarction

Indium-111 Fab antimyosin antibody (AMAB) is the latest and possibly the greatest character in the line of infarct-avid, "hot spot" imaging agents (*1*), specifically designed to label acutely infarcted myocardium. Most of its predecessors were summarily dismissed from the clinical scene or focused on other applications due to inappropriate physical characteristics related to their prolonged half-life or suboptimal energy of emission (*2*), nonspecific localization in extracardiac structures causing interpretive ambiguities (*3,4*), temporal factors causing delay in localization (*3*), or blood-flow dependence bringing irregularity in uptake unrelated to infarct density (*5*). The current "player," technetium-99m (stannous) pyrophosphate (PYP), now makes infrequent appearances, often in "bit" parts, in spite of enthusiastic early reviews based on a sound, simple, inexpensive, and widely available method (*6*). In this issue of the *Journal*, Tamaki and coworkers present data seemingly indicating persistent AMAB image positivity at a time remote from the acute event (*7*). The implications of this finding to the utility of AMAB imaging must be considered in the light of current clinical needs, the objectives, capabilities, and history of infarct-avid agents, particularly PYP.

When initially introduced in the early 1970s, an agent was sought which would facilitate infarct diagnosis and CCU triage. Catheterization of the infarct patient was dangerous and contraindicated. Thrombolytic therapy was unheard of, and its theoretical basis in occlusion of the infarct-related vessel, was still nearly ten years away (*8*). Of course, instrumentation of the coronary arteries any time soon after infarction would be dangerous and generally hard to justify while the differentiation of scar from viable myocardium was thought a straight-forward if not simple issue. The critical question initially served by infarct-avid agents, similar to that raised in reference to myocardial specific enzymes, would address the issue of whether the patient with chest pain had suffered an infarction. A negative response would move the patient out of the CCU proving cost-effective (*9*). To serve this purpose, in addition to diagnostic accuracy, the agent would need to demonstrate peak sensitivity early after the event. Additionally, imaging methods sometimes presented valuable localizing information (*10*), and contained data related to infarct size, which was more of theoretical value at that time (*11*).

Received Oct. 5, 1989; revision accepted Oct. 5, 1989.
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The early and careful pathologic studies of Reimer, Jennings and coworkers (*12*), would soon support the concept of myocardium at ischemic risk (*13*). Later studies documented the relationship between myocardium at risk and prognosis both in and outside the infarct setting (*14*). Now, infarct sizing is a more practical concern, as the main thrust in treatment of ischemic heart disease lies in the "salvage" of myocardium at ischemic risk. Today, admission to the CCU is less often directed at passive strategies to monitor and support the infarct patient than to more active measures to preserve ischemic myocardium. Diagnostic tools to serve this purpose are now available and require not only rapid, accurate infarct diagnosis, but the accurate identification and differentiation of normal, potentially ischemic, actively ischemic, and irreversibly infarcted myocardium, the latter, both acute and remote. Further, this capability must be manifest in patients with "stable" coronary syndromes, as well as in unstable angina, in the setting of acute infarction and with reperfusion interventions. Such refined assessment, and particularly the differentiation of viable myocardium from scar, is now necessary in order to appropriately utilize the wide range of currently available therapy in a clinically appropriate, cost-effective manner. This explains the recent increase in interest in perfusion scintigraphy and the application of scintigraphic methods to patients undergoing reperfusion (*15*), to those who cannot undergo dynamic exercise (*16*), and to the definition of "culprit" angioplasty (*17*). It has also spurred the development of new imaging methods (*16*) and agents (*1,7,18*) as well as the current interest in PET technology. Infarct-avid agents could provide a piece of the ischemic "puzzle." Unlike the indirect and nonspecific nature of perfusion and segmental wall motion abnormalities, their uptake must be specific for the acute event.

Pyrophosphate has been most recently applied to this purpose. The agent complexes with amorphous phosphates, chrystalline hydroxyapetite or other macromolecules, likely by chemisorption (*19*). Everything about its localization in myocardium mimic its localization in bone, including its dependence on regional perfusion (*5,20*). Although its ^{99m}Tc label is optimal, and may be imaged soon after administration, its uptake by myocardium is optimal, only 1–3 days after the event, likely owing to the maturation of the localizing process (*21*). Yet, associated skeletal labeling and the problem of nonspecific blood-pool labeling (*22*) may be somewhat mitigated by their recognition and by the application

of specific imaging procedures (*23*) or related agents (*24*). Rarely seen in other conditions (*25*), myocardial labeling in myocarditis, transplant rejection, or coronary disease generally relates to necrosis. Although claims of nonspecific myocardial labeling in ischemic rather than infarcted tissue have been presented, they are often ambiguous. These have been based largely on staining methods separating histochemical not histopathologic differences, ambiguities related to persistent blood-pool labeling, and sometimes flawed comparisons of projected PYP area with that of other radiotracers (*26–28*). Its detrimental persistence late after an event has been observed (*29*). This finding can be confused with extramyocardial uptake and its frequency is likely low (*30*). Further, pathologic studies of persistent image positivity document specific localization in necrotic myocardium (*31,32*). The agent has demonstrated value for diagnosis where other infarct indicators are nonspecific or unavailable, as postcardiac surgery (*21,33*), in the presence of LBBB, days after the event, or postcardioversion (*21,34,35*). It has demonstrated an ability to image right ventricular infarction (*10*) and has been well correlated with infarct size and prognosis (*11,36,37*).

Most important and most detrimental is the biphasic relationship of the agent with blood flow (*38*). Here, in part due to a reduced plasma half-time, localization falls at low flow rates. This has been shown to reduce PYP uptake in the central, most dense, least perfused regions of infarction, and enhance labeling in the peripheral, best perfused regions. The latter is likely responsible for the relationship between successful reperfusion and early, prominent PYP uptake post-thrombolysis (*39*). However, the dependence on perfusion is also responsible for differential PYP uptake in infarction (*40*) and the lack of relationship between intensity of PYP labeling and infarct density.

Loss of sarcolemmal integrity with cell death permits access of AMAB to exposed myocardium (*41*). The mechanism of AMAB localization should optimize diagnostic specificity for acute infarction (*41*). A prolonged plasma half-life permits its localization, independent of regional flow, and should permit a more direct relationship between infarct density and tracer concentration (radioactivity). Although improved in several respects compared to prior "hot spot" agents, AMAB appears imperfect. In addition to a potential hypersensitivity reaction especially on repeated dosage, AMAB requires 48–72 hr following administration to localize in myocardium, presents significant extracardiac uptake, and currently utilizes a suboptimal radiolabel, reducing image resolution and limiting dosage (*1*). These features may limit its utility as a diagnostic agent and may hamper its specific localizing and sizing capabilities, important for prognosis.

The current manuscript presents evidence that prolonged AMAB localization may occur, late after infarction, and in the absence of apparent ongoing necrosis, reducing its diagnostic specificity for the acute event (*7*). Rather than a beneficial trait, as concluded by the authors, these claims, if confirmed, cloud the picture of ischemic tissue typing, preventing differentiation of acute from remote events. Due to the specific mechanism of localization, brief but not prolonged localization of the agent postinfarction would be understandable but has neither been previously sought nor seen (*43*). Owing to the selective nature of the patient population, the lack of clinical detail, the generally close temporal proximity of studies to a documented event, the inability to exclude related ongoing interventing necrosis, and the subjective interpretation of images, this manuscript neither proves the claim nor defines the extent of the problem. Similar claims of late nonspecific PYP localization received great early notoriety but has been shown to be rare (*31*), or truly related to ongoing, clinically unrecognized necrosis (*32*). Ironic is the lack of prolonged PYP image positivity in the current study.

Now the CCU is as much needed for patients with extensive viable myocardium at ischemic risk, as for postinfarct monitoring and treatment. The accurate categorization of the spectrum of ischemia-related pathology must be defined. Separation of normal, from viable, metabolically active, reversibly ischemic, from nonreversibly infarcted myocardium, is critical. Such a separation may be partially, but acceptably accomplished with intervention applied to a single agent, possibly related to perfusion or metabolism, or more likely with use of multiple tracers to specifically identify, locate and size the ischemic components and their relationship to ventricular function. Whether the appropriate radiolabel for ischemia and viability is thallium-201, the new technetium-based perfusion agents, flourine-18-deoxyglucose, or a combination of these, is now unclear. Perhaps different agents should be selected in specific relation to the clinical setting. While identification of the ischemic component is clinically most crucial and most widely applicable, postinfarction, the total picture, including differentiation of acute from remote infarction, is optimal. The appropriate radiotracer for necrosis is also not clear. Perhaps neither PYP nor AMAB are optimal. Perhaps one or both are acceptable. Current progress in magnetic resonance research promises the possibility of "hot spot" infarct imaging of yet another form (*44,45*).

Yet, the principles are established. The needs are clear. The renewed interest in infarct-avid agents brought by studies such as this, should stimulate an objective reconsideration of these agents and what we expect of them. Only a careful, complete, and open-minded evaluation of the facts will establish the appropriate agent. We cannot accept circumstantial evidence

but embark on more definitive studies to resolve ambiguities in localization characteristics. Given their relative advantages, we must look ahead and continuously seek the optimal specific scintigraphic indicators to define the "ischemic spectrum" and their practical clinical interaction with nonscintigraphic markers.

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