Thallium-201 and Technetium-99m-Sestamibi for Assessing Viable Myocardium

In the current era of thrombolytic therapy and interventional cardiology, the identification of viable myocardium in patients with coronary artery disease (CAD) and left ventricular dysfunction has emerged as a subject of intense clinical interest. In a large subset of patients with CAD, including those presenting with acute ischemic syndromes and those with chronic CAD, left ventricular performance may be impaired on the basis of regionally ischemic, stunned or hibernating mycocardium rather than myocardium that has been irreversibly damaged by recent or remote myocardial infarction (*1–5*). The ability to distinguish such viable from nonviable tissue in myocardial segments with severe disturbances in systolic wall motion has important management implications, since this differentiation would identify those high-risk patients in whom further invasive diagnostic procedures and therapeutic interventions would be warranted.

Among the available invasive and noninvasive modalities, nuclear cardiology techniques have achieved a preeminent position for the assessment of myocardial viability. This arises from the rather unique potential of scintigraphic methods to assess myocardial perfusion, cell membrane integrity and metabolic activity, thereby providing greater diagnostic precision regarding viability than can be achieved by assessment of regional anatomy or function alone. In particular, ^{201}Tl scintigraphy has evolved over the past decade and a half as an imaging modality that may be implemented not only in diagnosing CAD but also in assessing myocardial viability in patients with proven CAD. Since the myocardial uptake of ^{201}Tl is dependent both upon adequate perfusion to deliver the tracer and active transport of the tracer across an intact sarcolemma, thallium is superbly suited for determining tissue viability. On the other hand, the limitations of imaging ^{201}Tl are also well established, related primarily to its low-energy photons which are readily scattered and attenuated. These limitations have lead to considerable interest in the use of ^{99m}Tc-based perfusion agents.

Like ^{201}Tl, ^{99m}Tc-sestamibi and ^{99m}Tc-teboroxime are taken up by the myocardium in proportion to regional myocardial blood flow, and the available data indicate that the accuracy of both ^{99m}Tc-sestamibi and ^{99m}Tc-teboroxime in detecting CAD is equivalent to that of ^{201}Tl (*6,7*). However, there are only limited data regarding the use of either ^{99m}Tc-based agent for the detection of viable myocardium in patients with known CAD and left ventricular dysfunction. Technetium-99m-teboroxime demonstrates rapid washout from the myocardium (*6,7*) and the rate of regional washout appears to be directly related to regional myocardial blood flow (*8–10*). This suggests that ^{99m}Tc-teboroxime might be an interesting agent for the investigation of myocardial viability, but clinical data for this agent are scant and only preliminary data are available in humans (*11*).

More substantive data have been published for ^{99m}Tc-sestamibi. Although ^{99m}Tc-sestamibi exhibits only limited washout from normal or transiently ischemic myocardium (*6,7*), several investigators have demonstrated that the accumulation and retention of ^{99m}Tc-sestamibi in isolated perfused rat hearts or in occlusion-reperfusion models of acute ischemia in vivo is reduced in necrotic myocardium, even when coronary perfusion has been maintained or restored (*12–15*). These data, indicating that ^{99m}Tc-sestamibi is more than merely a perfusion marker but is also a marker of cellular viability, have fueled substantial interest and optimism in the use of this agent for assessing myocardial viability in patients with CAD (*16, 17*). However, in a recent issue of the *Journal*, Cuocolo et al. (*18*) demonstrate that the uptake of ^{99m}Tc-sestamibi at rest may significantly underestimate the frequency and magnitude of viable myocardium in patients with chronic CAD and left ventricular dysfunction, suggesting the possibility of important limitations in the clinical application of this agent to address viability in humans. The findings of Cuocolo et al. imply that exercise thallium imaging using a redistribution-reinjection protocol may provide viability information that is superior to that provided by ^{99m}Tc-sestamibi (*18*).

The apparently discordant results of Cuocolo et al. in patients (*18*) and those of a number of other investigators in animal models (*12–15*) can be reconciled by examining the different mechanisms in CAD by which regional left ventricular function may be impaired in the absence of irreversible myocardial damage. Although "viability" is often used loosely to describe this situation, two distinct pathophysiologic processes (myocardial *stunning* and myocardial *hibernation*) may lead to the end-product of dysfunctional but viable myocardium. In both, the myocardial dysfunction is a potentially reversible process.

STUNNED MYOCARDIUM

Myocardial stunning results from severe acute ischemia followed by reperfusion, and the regional ventricular dysfunction associated with stunning represents the combined results of ischemic injury and reperfusion injury

Received Mar. 4, 1992; accepted Mar. 4, 1992.
For reprints contact: Robert O. Bonow, MD, Northwestern University Medical School, Wesley 524, 250 E. Superior St., Chicago, IL 60611.

(*2,5*). The common clinical setting in which stunned myocardium is observed is thrombolytic therapy or acute revascularization therapy for acute myocardial infarction. By definition, the myocardial dysfunction associated with stunning is completely reversible but may persist for days or weeks after reperfusion before resolving. Because coronary flow has been restored despite persistent myocardial dysfunction, stunned myocardium represents a flow-contraction "mismatch" (*5*). Although the mechanisms for myocardial stunning have not been fully determined, this is a well-demonstrated and reproducible phenomenon with excellent animal models.

On the basis of such animal models, one would anticipate that, in the setting of stunned myocardium, ^{99m}Tc-sestamibi would perform well as a viability marker, because flow is restored and sarcolemmal and mitochondrial processes necessary for cell viability (and for uptake and retention of ^{99m}Tc-sestamibi) are intact. Viable, but stunned, myocardium will retain ^{99m}Tc-sestamibi similar to the retention of ^{201}Tl (*13*). In contrast ^{99m}Tc-sestamibi is not retained by necrotic myocardium, despite its delivery and initial uptake (*12–15*). Li et al. demonstrated that the retention of ^{99m}Tc-sestamibi parallels indexes of viability (such as deoxyglucose uptake and histochemical staining) rather than myocardial blood flow (*13*). In keeping with the overall experience in animal models, clinical investigation has shown that ^{99m}Tc-sestamibi activity in patients within the first week after thrombolytic therapy for acute myocardial infarction is significantly related to late ejection fraction measurements (*19,20*).

HIBERNATING MYOCARDIUM

In contrast to stunned myocardium, in which contractile dysfunction persists despite restoration of flow, the term "hibernating" myocardium describes the regional ventricular dysfunction resulting from chronic reduction in coronary flow (*1,3,4*). Thus, hibernation represents a "match" between reduced perfusion and reduced contraction (*21*). As with stunned myocardium, the myocardial dysfunction associated with hibernation is a reversible phenomenon and will resolve after restoration of myocardial perfusion. The detection of such reversibly dysfunctional myocardium in patients with chronic CAD is clinically relevant, since ventricular function has the potential to improve, at times substantially, after revascularization procedures (*22–24*). Because the patients studied by Cuocolo et al. had chronic left ventricular dysfunction (*18*), the issue addressed in this study is the ability of ^{201}Tl versus ^{99m}Tc-sestamibi to distinguish hibernating from fibrotic myocardium.

Thallium-201 imaging has the potential to accurately make this distinction. Because flow is reduced in the hibernating state, the injection of ^{201}Tl at rest would be expected to demonstrate an initial perfusion defect; however, late imaging will show redistribution in the majority of viable territories (*25–29*). Exercise-thallium scintigraphy may also provide important information in this regard, although many regions of hibernating myocardium appear to have irreversible thallium defects on redistribution images. It has been shown that roughly 50% of regions with "irreversible" thallium defects will improve in function after revascularization (*30–32*). Thus, standard exercise-redistribution thallium scintigraphy may not provide satisfactory precision in differentiating between infarcted versus hibernating myocardium. These results may be improved upon considerably by thallium reinjection techniques, which demonstrate enhanced ^{201}Tl activity in up to 50% of regions with irreversible defects on redistribution images (*33–38*), an experience confirmed in the current study by Cuocolo et al. (*18*). We have recently shown that thallium reinjection after exercise-redistribution imaging provides data comparable to rest-redistribution imaging in patients with chronic ventricular dysfunction (*29*).

That thallium reinjection methods are useful for assessing myocardial viability is substantiated by their high positive and negative predictive accuracies regarding improvement in regional ventricular function after revascularization (*33,36*). Moreover, the results of thallium reinjection provide viability information that is concordant with the presence or absence of preserved metabolic activity by PET in the majority of myocardial regions so studied (*29,39,40*). It should be noted that the number of patients included in such comparative studies to date is relatively small, and definitive conclusions regarding the comparative abilities of ^{201}Tl and PET imaging to characterize viable myocardium must await larger trials. In view of the improved imaging capabilities of PET, one would anticipate enhanced diagnostic information in at least a subset of patients.

In view of chronic hypoperfusion associated with hibernation, there are theoretical limitations in the use of ^{99m}Tc-sestamibi to identify viable myocardium in patients with chronic CAD. Resting ^{99m}Tc-sestamibi images would be expected to demonstrate a perfusion defect, but whether the underperfused myocardium is viable or not may be difficult to decipher. The experience with PET would forecast that coronary flow data alone would not accurately distinguish between viable and nonviable myocardium (*41*). Without additional redistribution data, the initial ^{99m}Tc-sestamibi defect alone may provide insufficient information. This hypothesis appears to be confirmed by the current findings of Cuocolo et al. (*18*), in which a large number (approximately 60%) of myocardial regions identified as viable by thallium reinjection were categorized as "nonviable" by a resting ^{99m}Tc-sestamibi image.

These data suggest that ^{99m}Tc-sestamibi may have promise as a viability marker in the setting of stunned myocardium after reperfusion therapy for acute myocardial infarction, but has inherent limitations in the setting of hibernating myocardium with sus-

tained reduction in myocardial blood flow. It is important to point out, however, that this conclusion must be considered tentative at present, because the available data are limited. First, Cuocolo et al. studied only 20 patients (*18*) and a larger patient series is required to confirm these results. Second, the accepted gold standard for myocardial viability—improved regional or global ventricular function after revascularization—was not evaluated, although thallium reinjection results (as noted above) have provided clinically acceptable predictive accuracies in other studies (*33*, *36*). Third, the ^{99m}Tc-sestamibi data were assessed using strictly qualitative, visual scoring methods. Quantitative count-based analyses might yield threshold values of regional ^{99m}Tc-sestamibi activity that would provide greater accuracy in assessing viability. This has been the experience of other investigators (*42*). Finally, there is evidence that ^{99m}Tc-sestamibi does redistribute in some regions with transient ischemia (*43*), and preliminary data in an animal model of sustained low-flow ischemia suggest that ^{99m}Tc-sestamibi may redistribute in a manner comparable to ^{201}Tl (*44*,*45*). This possibility needs to be explored in patients with chronic CAD and left ventricular dysfunction before firm conclusions can be made regarding the inability of ^{99m}Tc-sestamibi to accurately detect hibernating myocardium. Thus, we believe that the use of ^{99m}Tc-sestamibi for assessing viable myocardium remains an open issue that should lead to further interesting and exciting investigation in the future.

Robert O. Bonow
Vasken Dilsizian
Cardiology Branch
National Heart, Lung, and Blood Institute
Bethesda, Maryland

REFERENCES

1. Rahimtoola SH. Coronary bypass surgery for chronic angina—1981: a perspective. *Circulation* 1982;65:225–241.
2. Braunwald E, Kloner RA. The stunned myocardium: prolonged, postischemic ventricular dysfunction. *Circulation* 1982;66:1146–1149.
3. Braunwald E, Rutherford JD. Reversible ischemic left ventricular dysfunction: evidence for "hibernating" myocardium. *J Am Coll Cardiol* 1986;8:1467–1470.
4. Rahimtoola SH. The hibernating myocardium. *Am Heart J* 1989;117:211–213.
5. Bolli R. Mechanism of myocardial stunning. *Circulation* 1990;82:723–738.
6. Leppo JA, DePuey EG, Johnson LL. A review of cardiac imaging with sestamibi and teboroxime. *J Nucl Med* 1991;32:2012–2022.
7. Maddahi J, Kiat H, Berman DS. Myocardial perfusion imaging with technetium-99m-labeled agents. *Am J Cardiol* 1991;67: 27D–34D.
8. Stewart RE, Schwaiger M, Hutchins GD, et al. Myocardial cliearance kinetics of technetium-99m-SQ30217: a marker of regional myocardial blood flow. *J Nucl Med* 1990;31: 1183–1190.
9. Stewart RE, Heyl B, O'Rourke RA, Blumhardt R, Miller DD. Demonstration of differential post-stenotic myocardial technetium-99m-teboroxime clearance kinetics after experimental ischemia and hyperemic stress. *J Nucl Med* 1991;32:2000–2008.
10. Gewirtz H. Differential myocardial washout of technetium-99m-teboroxime: mechanism and significance. *J Nucl Med* 1991;32:2009–2011.
11. Hendel RC, Dahlberg ST, Parker M, McSherry BA, Weinstein H, Leppo JA. Comparative assessment of myocardial viability with thallium-201 and Tc-99m-teboroxime planar imaging [Abstract]. *Circulation* 1991;84:II-90.
12. Beanlands RSB, Dawood F, Wen WH, et al. Are the kinetics of technetium-99m methoxyisobutyl isonitrile affected by cell metabolism and viability? *Circulation* 1990;82:1802–1814.
13. Li QS, Matsumura K, Dannals R, Becker LC. Radionuclide markers of viability in reperfused myocardium: comparison between ^{18}F-2-deoxyglucose, ^{201}Tl, and ^{99m}Tc-sestamibi [Abstract]. *Circulation* 1990;82:III–542.
14. Edwards NC, Ruiz M, Watson DD, Beller GA. Does Tc-99m sestamibi given immediately after coronary reperfusion reflect viability? [Abstract]. *Circulation* 1990;82:III–542.
15. Freeman I, Grunwald AM, Hoory S, Bodenheimer MM. Effect of coronary occlusion and myocardial viability on myocardial activity of technetium-99m-sestamibi. *J Nucl Med* 1991; 32:292–298.
16. Machac J. Technetium-99m isonitrile: a perfusion or a viability agent? *J Am Coll Cardiol* 1989;14:1685–1688.
17. Liu P. Technetium-99m-sestamibi: another window on myocardial viability? *J Nucl Med* 1991;32:298–299.
18. Cuocolo A, Pace L, Ricciardelli B, Chiariello M, Trimarco B, Salvatore M. Identification of viable myocardium in patients with chronic coronary artery disease: comparison of thallium-201 scintigraphy with reinjection and technetium-99m methoxyisobutyl isonitrile. *J Nucl Med* 1992;33:505–511.
19. Gibbons RJ, Verani MS, Behrenbeck T, et al. Feasibility of tomographic technetium-99m-hexakis-2-methoxy-2-methylpropyl-isonitrile imaging for the assessment of myocardial area at risk and the effect of acute treatment in myocardial infarction. *Circulation* 1989;80: 1277–1286.
20. Christian TF, Behrenbeck T, Pellikka PA, et al. Mismatches of left ventricular function and perfusion with Tc-99m-isonitrile following reperfusion therapy for acute myocarial infarctions: identification of myocardial stunning and hyperkinesia. *J Am Coll Cardiol* 1990;16: 1632–1638.
21. Ross J Jr. Myocardial perfusion-contraction matching: implications for coronary artery disease and hibernation. *Circulation* 1991;83: 1076–1083.
22. Rozanski A, Bernard D, Gray R, et al Preoperative prediction of reversible myocardial asynergy by postexercise radionuclide ventriculography. *N Engl J Med* 1982;307:212–213.
23. Brundage BH, Massie BM, Botvinick EH. Improved regional ventricular function after successful surgical revascularization. *J Am Coll Cardiol* 1984;3:902–908.
24. Dilsizian V, Bonow RO, Cannon RO, et al. The effect of coronary artery bypass grafting on left ventricular systolic function at rest: evidence for preoperative sublinical myocardial ischemia. *Am J Cardiol* 1988;61:1248–1254.
25. Berger BC, Watson DD, Burwell LR, et al. Redistribution of thallium at rest in patients with stable and unstable angina and the effect of coronary artery bypass surgery. *Circulation* 1979;60:1114–1125.
26. Iskandrian AS, Hakki A, Kane SA, et al. Rest and redistribution thallium-201 myocardial scintigraphy to predict improvement in left ventricular function after coronary artery bypass grafting. *Am J Cardiol* 1983;51: 1312–1316.
27. Mori T, Miniamiji K, Kurogane H. Ogawa K, Yoshida Y. Rest-injected thallium-201 imaging for assessing viability of severe asynergic regions. *J Nucl Med* 1991;32:1718–1724.
28. Ragosta M, Beller GA, Watson DD, Kaul S, Gimple LW. Can resting thallium-201 imaging predict improvement after revascularization in patients with severely reduced left ventricular function? [Abstract]. *Circulation* 1991; 84 (suppl II);II–89.
29. Dilsizian V, Bacharach SL, Perrone-Filardi P, Arrighi JA, Maurea S, Bonow RO. Concordance and discordance between rest-redistribution thallium imaging and thallium reinjection after stress-redistribution imaging: comparison with metabolic activity by PET [Abstract]. *Circulation* 1991;84 (suppl II):II–89.
30. Rozanaki A, Berman D, Gray R, et al. Use of thallium-201 redistribution scintigraphy in the preoperative differentiation of reversible myocardial asynergy. *Circulation* 1981;64: 936–944.
31. Gibson RS, Watson DD, Taylor GJ, et al. Prospective assessment of regional myocardial perfusion before and after coronary revascularization surgery by quantitative thallium-201 scintigraphy. *J Am Coll Cardiol* 1983;1: 804–815.
32. Liu P, Kiess MC, Okada RD, et al. The persistent defect on exercise thallium imaging and its fate after myocardial revascularization: does it represent scar or ischemia? *Am Heart J* 1985; 110:996–1001.
33. Dilsizian V, Rocco TP, Freedman NMT, Leon MB, Bonow RO. Enhanced detection of ischemic but viable myocardium by the reinjection of thallium after stress-redistribution imaging. *N Engl J Med* 1990;66:158–163.
34. Rocco TP, Dilsizian V, McKusick KA, Fisch-

man AJ, Boucher CA, Strauss HW. Comparison of thallium redistribution with rest "reinjection" imaging for detection of viable myocardium. *Am J Cardiol* 1990;66:158–163.
35. Tamaki N, Ohtani H, Yonekura Y, et al. Significance of fill-in after thallium-201 reinjection following delayed imaging: comparison with regional wall motion and angiographic findings. *J Nucl Med* 1990;31:1617–1623.
36. Ohtani H, Tamaki N, Yonekura Y, et al. Value of thallium-201 reinjection after delayed SPECT imaging for predicting reversible ischemia after coronary artery bypass grafting. *Am J Cardiol* 1990;66:394–399.
37. Kayden DS, Sigal S, Soufer R, Mattera J, Zaret BL, Wackers FThJ. Thallium-201 for assessment of myocardial viability: quantitative comparison of 24-hour redistribution imaging with imaging after reinjection at rest. *J Am Coll Cardiol* 1991;18:1480–1486.
38. Dilsizian V, Freedman NMT, Bacharach SL, Perrone-Filardi P, Bonow RO. Regional thallium uptake in irreversible defects: magnitude of change in thallium activity after reinjection distinguishes viable from nonviable myocardium. *Circulation* 1992;85:627–634.
39. Bonow RO, Dilsizian V, Cuocolo A, Bacharach SL. Identification of viable myocardium in patients with chronic coronary artery disease and left ventricular dysfunction: comparison of thallium-201 with reinjection and PET imaging with ^{18}F-fluorodeoxyglucose. *Circulation* 1991; 83:26–37.
40. Tamaki N, Ohtani H, Yamashita K, et al. Metabolic activity in the areas of new fill-in after thallium-201 reinjection: comparison with positron emission tomography using fluorine-18-deoxyglucose. *J Nucl Med* 1991;32: 673–678.
41. Tillisch JH, Brunken R, Marshall R, et al. Reversibility of cardiac wall-motion abnormalities predicted by positron tomography. *N Engl J Med* 1986;314:884–888.
42. Rocco TP, Dilsizian V, Strauss HW, Boucher CA. Technetium-99m isonitrile myocardial uptake at rest. II. Relation to clinical markers of potential viability. *J Am Coll Cardiol* 1989;14: 1678–1684.
43. Taillefer R, Primeau M, Costi P, Lambert R, Leveille J, Latour Y. Technetium-99m-sestamibi myocardial perfusion imaging in detection of coronary artery disease: comparison between initial (1-hour) and delayed (3-hour) postexercise images. *J Nucl Med* 1991;32:1961–1965.
44. Sinusas AJ, Bergin JD, Edwards NC, Watson DD, Ruiz M, Beller GA. Technetium-99m isonitrile and thallium-201 activity are comparable following 3 hours of low flow ischemia [Abstract]. *J Am Coll Cardiol* 1990;15:8A.
45. Sinusas AJ, Bergin JD, Edwards NC, et al. Comparison of Tc-99m methoxyisobutyl isonitrile and Tl-201 uptake during low flow ischemia [Abstract]. *J Nucl Med* 1990;31:713.

(continued from page 776)

SELF-STUDY TEST ANSWERS

the joints of one hand and wrist, while sparing the opposite hand. Furthermore, the blood-pool image will demonstrate selectively greater hyperemia in the joint synovia, which is not seen in this patient.

Pseudogout or CPPD crystal deposition disease is predominantly an ailment of the large joints, such as the knee, usually afflicting one joint initially and rarely the interphalangeal joints. Blood-pool imaging will demonstrate the inflamed synovial vasculature, as in rheumatoid arthritis.

An arteriovenous fistula will lead to short-circuiting of the blood supply to the tissues distal to it, and would not cause the scintigraphic findings seen in this patient. The diffuse hyperperfusion and hyperemia of the entire hand is inconsistent with this diagnosis.

References

1. Holder LE, MacKinnon SE. Reflex sympathetic dystrophy in the hands: clinical and scintigraphic criteria. *Radiology* 1984;152:517–522.
2. Maurer AH, Holder LE, Espinola DA, Rupani HD, Wilgis EFS. Three-phase radionuclide scintigraphy of the hand. *Radiology* 1983;146:761–775.

ITEM 6: Scintigraphic Findings with Recent Fractures

ANSWER: E

Significant accumulation of ^{111}In leukocytes at the site of a healing fracture does not occur unless there is a complicating osteomyelitis. Mildly increased uptake of ^{111}In leukocytes has been reported to occur in association with callus formation or adjacent myositis ossificans. On bone scintigraphy, hyperperfusion, hyperemia, and marked uptake of ^{99m}Tc MDP on delayed images are typical with recent fracture. The accumulation of ^{67}Ga at new fracture sites is usually increased as well. The relative uptake of ^{67}Ga in the lesion can be as great as that of ^{99m}Tc MDP, and either congruent in distribution or less extensive. This seems to be a function of the amount of callus laid down.

References

1. Kim EE, Pjura GA, Lowry PA, Gobuty AH, Traina JF. Osteomyelitis complicating fracture: pitfalls of ^{111}In leukocyte scintigraphy. *AJR* 1987;148:927–930.
2. Schauwecker DS, Park H-M, Mock BH, et al. Evaluation of complicating osteomyelitis with Tc-99m MDP, In-111 granulocytes, and Ga-67 citrate. *J Nucl Med* 1984;25:849–853.

For further in-depth information, refer to the syllabus pages in Nuclear Medicine Self-Study I.