Editorial Comment

Noninvasive Assessment of Myocardial Salvage After Coronary Reperfusion: A Perpetual Quest of Nuclear Cardiology*

GEORGE A. BELLER, MD, FACC

Charlottesville, Virginia

There is a pressing need to develop reliable noninvasive approaches for determination of the initial extent of myocardium at risk during acute myocardial infarction and for early assessment of the degree of salvage after reperfusion therapy. To be clinically useful, the method employed should not delay the institution of thrombolytic drug administration, should be easy to perform with conventional imaging technology available in the community hospital setting and should be able to provide information relevant to myocardial viability in addition to flow enhancement.

Thallium-201 imaging to assess coronary reperfusion. Myocardial perfusion imaging with thallium-201 has been utilized as a method for evaluating the efficacy of coronary reperfusion in acute myocardial infarction (1). When thallium-201 is injected intravenously during the occlusion phase (pretreatment), the degree of delayed redistribution after thrombolysis is proportional to the degree of flow restoration and, presumably, myocardial viability (2,3). Patients demonstrating successful thrombolysis had more thallium-201 redistribution and a smaller final thallium defect size in relation to prethrombolysis images than were observed in patients with a persistently occluded infarct-related vessel, who showed little change in defect size (4–6). Reduto et al. (4) found that the improvement in thallium-201 uptake on redistribution images correlated well with subsequent improvement in left ventricular ejection fraction.

There are some important limitations to the use of thallium-201 rest redistribution imaging in evaluating patients receiving thrombolytic therapy. First, the time that it takes to obtain pretreatment images may delay the institution of therapy up to 20 or 30 min. This delay is not feasible because

---

the earlier that reperfusion can be accomplished the greater chance there is for benefit in myocardial salvage. Second, if thallium-201 is administered for the first time too soon after reperfusion, the degree of salvage could be overestimated because the tracer is being administered during the phase of hyperemia. The result may be "excess" thallium uptake in the infarct zone (2,7,8). Third, lack of significant redistribution on 3 h to 4 h delayed images does not preclude residual myocardial viability. In patients who underwent intravenous streptokinase therapy, De Coster et al. (6) reported further improvement in thallium-201 uptake in the reperfused zone between the 4 h redistribution images and repeat studies performed at 4 days and 6 weeks. Furthermore, it has been estimated (9) that approximately 30% of persistent thallium defects observed on serial exercise scintigrams in patients with chronic coronary artery disease will show significantly improved early thallium uptake after revascularization. Some investigators (10,11) have advocated repeat imaging at 24 h to detect presence of "late" redistribution to better distinguish scar from ischemia.

Technetium-99m isonitriles: advantages over thallium. The technetium-99m isonitriles have emerged as a new class of perfusion agents that, because of superior physical characteristics, may be more optimal than thallium-201 for myocardial perfusion imaging. One of these agents, technetium-99m methoxy isobutyl isonitrile (MIBI) appears to be an appropriate agent to use clinically because of its low level of activity in lung and liver tissues (12). ^{99m}Tc-MIBI, unlike thallium-201, does not redistribute after transient ischemia and requires separate injections of the radionuclide to distinguish between reversible and irreversible myocardial injury. Its potential advantages over thallium-201 include 1) its 140 keV photon energy peak, which is optimal for gamma camera imaging and has produced higher quality images than those produced by thallium; 2) the shorter half-life and better dosimetry make it possible to administer a 10 to 15 times higher dose of the radiopharmaceutical than of thallium, yielding better images obtained in a shorter time period; 3) because of the high ^{99m}Tc-MIBI activity, one can combine perfusion imaging with assessment of right and left ventricular ejection fraction by first pass radionuclide angiography; 4) the high photon flux of ^{99m}Tc-MIBI permits electrocardiogram (ECG)-gated image acquisition, thereby allowing wall motion analysis from the cine display of the perfusion images; 5) because ^{99m}Tc-MIBI remains relatively fixed in myocardial cells after initial extraction without delayed redistribution, it provides information on regional blood flow and risk area at the time of its administration.

Thus, the radionuclide has potential to be superior to thallium-201 for assessment of hypoperfusion and viability in the setting of thrombolytic therapy. One can administer the

first dose of ^{99m}Tc-MIBI just before thrombolytic therapy. but can postpone imaging several hours after drug administration to obtain the pretreatment assessment of risk area, so as not to delay institution of thrombolysis. A second injection can then be performed after thrombolytic therapy to delineate the degree of improvement in flow and extent of myocardial salvage. Several experimental studies have been undertaken to validate this assumption (13,14).

The present study. In this issue of the Journal, Wackers and his colleagues (15) from several collaborating institutions have successfully applied serial ^{99m}Tc-MIBI imaging in patients with acute myocardial infarction undergoing thrombolytic therapy. Area at risk was determined from initial images delineating the perfusion pattern before initiation of thrombolytic therapy. There was no delay in instituting prompt therapy because these pretreatment images were processed several hours after administration of recombinant tissue-type plasminogen activator (rt-PA). Because of the lack of redistribution of ^{99m}Tc-MIBI, these images should accurately reflect the area at risk. Patients with a patent infarct artery had a significantly greater decrease in defect size on repeat images performed 18 to 48 h after thrombolytic therapy than did patients with persistently occluded vessels.

Some additional interesting observations were made in this study. First, the size of the area at risk varied markedly among the patients in this study, and there was no obvious relation between extent of underlying coronary artery disease or presence of coronary collateral flow and the area at risk. Second, 7 of the 23 patients receiving rt-PA had no change in defect size from the immediate to the follow-up study, a finding that should not necessarily imply failure to achieve reflow. If a high grade residual stenosis was present after clot lysis, causing a persistent diminution in resting flow, this might contribute to the residual defect size. When ^{99m}Tc-MIBI is administered in this setting, uptake will be reduced in the irreversibly injured region as well as in the hypoperfused peri-infarction zone. This reduction would yield a defect after reperfusion that was *larger* than the extent of necrotic myocardium. Thus, the presence of a severe residual stenosis would contribute to underestimation with ^{99m}Tc-MIBI of degree of viability. If thallium-201 is administered under such circumstances after reperfusion, there would be an initial defect encompassing both the necrotic and ischemic zones. Delayed imaging 2 to 4 h later would show rest thallium redistribution in the myocardial region that remained underperfused because of the residual stenosis but was, in fact, salvaged by reflow through the previously occluded vessel.

Third, there was only an average 36% reduction in relative defect size after thrombolytic therapy in this group of patients treated within 4 h of onset of chest pain. This does not seem like a great change, but it must be enough to correlate with improved survival and enhanced left ventric-

ular function, as reported in multiple series of patients receiving thrombolytic therapy in this time frame. However, as previously observed with thallium-201 studies (6), certain patients in this study showed further reduction in ^{99m}Tc-MIBI defect size at days 6 to 14. Hence, ultimate degree of salvage may be underestimated on early post-thrombolytic images. Could this continuing improvement in MIBI uptake be attributed to further increase in nutrient coronary blood flow, reversal of ischemic alterations in MIBI intracellular extraction, or both? Further investigation is warranted in this regard. Sinusas et al. (16) showed that ischemia alone, or postischemic dysfunction ("stunning"), did not affect myocardial uptake of ^{99m}Tc-MIBI.

Clinical implications. Wackers and co-workers (15) found that a relative decrease by >30% in the size of the ^{99m}Tc-MIBI perfusion defect predicted patency of the infarct-related artery providing evidence obtained noninvasively of the efficacy of treatment. This is an important observation because we have few reliable non-angiographic methods to predict successful reperfusion. ^{99m}Tc-MIBI imaging could become a useful technique to incorporate in future clinical research trials assessing efficacy of pharmacologic approaches for reperfusion.

Finally, how might serial myocardial perfusion imaging with ^{99m}Tc-MIBI be incorporated in the acute management of myocardial infarction to better select patients receiving thrombolytic therapy for early coronary angiography? First, a "split dose" technique for serial ^{99m}Tc-MIBI imaging 2 h apart will have to be developed. This might involve computer subtraction of the pretreatment ^{99m}Tc-MIBI activity (because it will not have decayed) from the posttreatment images obtained only several hours instead of 18 to 48 h later, as performed in the study by Wackers et al. (15). If the area at risk is small on the pretreatment images, then it wouldn't matter what the posttreatment images demonstrated because the patient would be in a low risk category. This pattern might be observed in a significant number of patients with inferior infarction. If the area at risk on the prethrombolytic images was large and a significant reduction in defect size was seen on repeat posttreatment images, then adequate reperfusion had probably occurred and early angiography would not be required. In contrast, if the area at risk was large initially and remained unchanged on repeat imaging after completion of the thrombolytic protocol, it could be inferred that infarct vessel patency had not been restored. Wackers et al. (15) found an inverse relation between left ventricular ejection fraction at hospital discharge and the size of the ^{99m}Tc-MIBI myocardial perfusion defect prior to treatment. Thus, early angiography with a view toward angioplasty to establish reflow and enhance myocardial salvage could benefit patients who fail to show a reduction of a large perfusion defect with thrombolytic therapy alone. This might truly be considered a "rescue angioplasty."

Conclusions. From both experimental data and the early clinical experience reported by Wackers and colleagues (15), it appears that serial ^{99m}Tc-MIBI imaging may accurately reflect the risk area at the time of coronary occlusion and noninvasively determine degree of reflow and extent of myocardial salvage after thrombolytic therapy. Although the value and limitations of this new perfusion imaging approach need to be more precisely delineated in further prospective studies with larger numbers of patients, this initial experience is certainly encouraging.

References

1. Beller GA. Role of myocardial perfusion imaging in evaluating thrombolytic therapy for acute myocardial infarction. J Am Coll Cardiol 1987;9:661–8.

2. Granato JE, Watson DD, Flanagan TL, Gascho JA, Beller GA. Myocardial thallium-201 kinetics during coronary occlusion and reperfusion: influence of method of reflow and timing of thallium-201 administration. Circulation 1986;73:150–60.

3. Granato JE, Watson DD, Flanagan TL, Beller GA. Myocardial thallium-201 kinetics and regional flow alterations with 3 hours of coronary occlusion and either rapid reperfusion through a totally patent vessel or slow reperfusion through a critical stenosis. J Am Coll Cardiol 1987; 9:109–18.

4. Reduto LA, Freund GC, Gaeta JM, et al. Coronary artery reperfusion in acute myocardial infarction: beneficial effects of intracoronary streptokinase on left ventricular salvage and performance. Am Heart J 1981; 102:1168–75.

5. Simoons ML, Wijns W, Balakumaran K, et al. The effect of intracoronary thrombolysis with streptokinase on myocardial thallium distribution and left ventricular function by blood pool scintigraphy. Eur Heart J 1982; 3:433–40.

6. De Coster PM, Melin JA, Detry JMR, Brasseur LA, Beckers C, Col J. Coronary artery reperfusion in acute myocardial infarction: assessment by pre- and postintervention thallium-201 myocardial perfusion imaging. Am J Cardiol 1985;55:889–95.

7. Forman R, Kirk ES. Thallium-201 accumulation during reperfusion of ischemic myocardium: dependence on regional blood flow rather than viability. Am J Cardiol 1984;54:659–63.

8. Melin JA, Becker LC, Bulkley BH. Differences in thallium-201 uptake in reperfused and nonreperfused myocardial infarction. Circ Res 1983; 53:414–9.

9. Gibson RS, Taylor GJ, Watson DD, et al. Prospective assessment of regional myocardial perfusion before and after coronary revascularization surgery by quantitative thallium-201 scintigraphy. J Am Coll Cardiol 1983;1:804–15.

10. Cloninger KG, DePuey EG, Garcia EV, et al. Incomplete redistribution in delayed thallium-201 single photon emission computed tomographic (SPECT) images: an overestimation of myocardial scarring. J Am Coll Cardiol 1988;12:955–63.

11. Kiat H, Berman DS, Maddahi J, et al. Late reversibility of tomographic myocardial thallium-201 defects: an accurate marker of myocardial viability. J Am Coll Cardiol 1988;12:1456–63.

12. Wackers FJTh, Berman DS, Maddahi J, et al. Technetium-99m hexakis 2-methoxyisobutyl isonitrile: human biodistribution, dosimetry, safety, and preliminary comparison to thallium-201 for myocardial perfusion imaging. J Nucl Med 1989;30:301–11.

13. Verani MS, Jeroudi MO, Mahmarian JJ, et al. Quantification of myocardial infarction during coronary occlusion and myocardial salvage after reperfusion using cardiac imaging with technetium-99m hexakis 2-methoxyisobutyl isonitrile. J Am Coll Cardiol 1988;12:1573–81.

14. Sinusas A, Weber K, Watson D, et al. The assessment of ischemia during occlusion and reperfusion using methoxy-isobutyl isonitrile (abstr). J Am Coll Cardiol 1989;13:29A.

15. Wackers FJTh, Gibbons RJ, Verani MS, et al. Serial quantitative planar technetium-99m-isonitrile imaging in acute myocardial infarction: efficacy for noninvasive assessment of thrombolytic therapy. J Am Coll Cardiol 1989;14:861–73.

16. Sinusas AJ, Watson DD, Beller GA. Effect of ischemia and postischemic dysfunction on myocardial uptake of Tc-99m–labeled methoxy-isobutyl isonitrile and thallium-201. J Am Coll Cardiol, in press.