The SPECTrum of Thallium-201 Imaging in Coronary Artery Disease

In this issue of the Journal a study using single photon emission computed tomography (SPECT) with thallium-201 reports an improvement in the noninvasive diagnostic accuracy of the detection of coronary artery disease (*1*). In our laboratory, conventional, as well as quantitative planar thallium imaging, is used alone or with exercise: (1) for screening high-risk patients for coronary artery disease; (2) for determining if nonspecific symptoms may be secondary to coronary artery disease; (3) in attempting to determine the severity or localization of coronary disease in patients with typical symptoms; (4) for ascertaining the viability of tissue distal to a severe stenosis with regard to potential candidacy for revascularization; (6) for determining the location and extent of irreversible damage in myocardial infarction and ischemic cardiomyopathy; and (6) (related to 4 and 5) for evaluating the success of intracoronary streptokinase administration in evolving myocardial infarction. In order to evaluate rationally the use of SPECT in cardiac diagnosis, it is important to examine first what can be reasonably expected from planar thallium imaging.

Stress test screening. Thallium-201 planar imaging using exercise as a provocative maneuver has become a useful adjunct in the diagnosis of coronary disease. Reports of thallium imaging during exercise demonstrate a sensitivity of 75–85% (*2–7*) with a specificity of 85–100%, compared with electrocardiographic stress testing with a sensitivity of approximately 65% (*2–5*). Thallium imaging, in combination with exercise electrocardiography, increases sensitivity to approximately 90% with a concomitant decrease in specificity to 80–85%. Exercise-thallium imaging may be especially helpful in those patients with resting ECG abnormalities (*2*), in patients receiving propranolol (*7*), or in those otherwise unable to reach a target heart rate. In critically evaluating these studies, however, one must keep in mind that the criteria for abnormality were fairly stringent, requiring a 50–70% luminal diameter narrowing to qualify as significant coronary stenosis. Patients with less critical stenoses of major vessels are subject to untoward events, including myocardial infarction, and could be missed by exercise-thallium testing as currently described.

Unfortunately, many patients with coronary disease have other illnesses that render them incapable of treadmill or bicycle exercise. Dipyridamole, a potent coronary vasodilator, reliably increases coronary blood flow in normal coronary arteries, producing relatively photopenic areas, which are supplied by stenotic arteries (*8–11*). It takes approximately a twofold increase or differential in coronary blood flow from a normal to a relatively ischemic zone to detect a significant change in a thallium image (*8*). Intravenous dipyridamole can produce coronary vasodilation sufficient to provide images comparable to those obtained at maximal exercise (*8*). Unfortunately, however, dipyridamole can also cause a "coronary-steal" phenomenon and angina pectoris if given in sufficient doses in the presence of critical coronary disease. Aminophyline may reverse this effect, however; aminophyline itself causes tachycardia, which may be contraindicated in patients with significant coronary disease. Dipyridamole thallium studies have shown similar sensitivity (93%) and specificity (72%) in comparison with combined ECG thallium studies (*11*). Despite promising results using dipyridamole as an adjunct in diagnosing coronary disease it is not approved by the FDA for that purpose and, hence, is unavailable for routine clinical use.

Identification of severity and location of coronary disease. For thallium scanning to be an effective tool, it should help identify the location and extent of coronary disease. Thallium scanning appears to be a poor method for differentiating ischemic from idiopathic cardiomyopathy. Large partial defects, which may demonstrate improved uptake on redistribution, are seen in idiopathic cardiomyopathy as well as in ischemic cardiomyopathy (*12*). Similarly, nonhomogeneous defects in cardiomyopathy may also appear in ischemic disease, whereas complete perfusion defects are more likely to be secondary to coronary disease (*13*). Thus, partial thallium defects, even with evidence for reperfusion, may not reliably indicate the presence of coronary disease, in patients with dilated hearts.

Planar thallium imaging is useful for detecting coronary disease but is much less reliable for determining the severity or location of coronary lesions (*13–17*). Left circumflex lesions are particu-

larly difficult to detect with planar thallium imaging even with exercise (*14,16*). Stenoses of 90% or greater in severity yield positive tests in 80% of patients whereas less severe stenoses (70–90%) are positive in only 39% of the cases (*14*). Patients with high-risk lesions, such as left main or severe three-vessel disease, are not clearly identified by thallium imaging (*15–17*). Quantification of the thallium images may improve the detection of regional disease (*18,31,32*). Stenosed vessels supplying noninfarcted myocardium are much less readily recognized than those supplying infarcted or partially infarcted myocardium (*19*). As one would expect, even with critical stenoses extensive collateralization to the involved artery results in poor sensitivity of the test as long as the artery supplying the collaterals is not significantly diseased (*20*).

Detection of reversible ischemia. It is often difficult to determine when patients with left-ventricular dysfunction should be considered for revascularization surgery. The concept of reversible left-ventricular dysfunction distal to a severe stenosis is controversial. Nevertheless, experimental and clinical evidence suggest that thallium imaging may be useful in these patients. Since thallium activity is dependent on extraction and delivery rates as well as on washout rates, pertubation of these parameters by severe stenoses may produce useful information on tissue viability. Animal experiments have demonstrated that thallium activity in the myocardium supplied by a normal coronary artery gradually decreases over time after the initial distribution phase. In mildly ischemic areas, however, thallium activity increases over time (*21*) or possibly decreases in time at a much slower rate than areas supplied by a normal artery (*22–24*). The net effect is a resting thallium image demonstrating a relatively photopenic area that gradually resolves over time and several hours later achieves similar activity compared with normal regions. This principle has been evaluated in patients undergoing coronary bypass surgery. Rozanski reported that in 25 patients, 54% of 72 dyskinetic left-ventricular segments improved after bypass surgery. Ninety percent of those that improved had relative thallium defects that resolved at redistribution, and 76% of defects that did not demonstrate reperfusion remained functionally abnormal (*25*). Thus it appears that delayed redistribution of a significant thallium perfusion defect is an extremely good prognostic sign and may accurately identify those patients with reversible left ventricular dysfunction secondary to severe coronary stenosis.

Role of thallium imaging in myocardial infarction. Thallium-201 has been used both for the detection and quantification of myocardial infarction. Animal studies suggest that cellular uptake of thallium is dependent on metabolic integrity (i.e. reversible injury) (*26*). It is felt that an area with no uptake will not significantly increase in activity if the area in question is irreversibly damaged. Thus persistent areas with no uptake at redistribution imaging imply completed infarction (*27,28*), and the defect size correlates reasonably well with regional function abnormalities (*29*). Persistent defects are reported in up to 95% of patients with diagnostic electrocardiographic evidence for myocardial infarction (*29*). Thallium defects appear to decrease in size over time up to three months after myocardial infarction. This may indicate increased collateral blood flow into the ischemic zone surrounding the infarct and may contribute to decreased sensitivity in detecting patients with small myocardial infarctions (*30*).

Quantitative analysis of thallium imaging. Attempts have been made to improve the sensitivity and diagnostic accuracy of thallium imaging with digital image enhancement and quantitative analysis. Most investigators find that using quantitative techniques can improve the sensitivity of rest/exercise thallium imaging to 95% (*31–33*) with little decrease in specificity. This finding compares favorably with the combined sensitivity of visual interpretation of thallium images and the results of electrocardiographic stress testing. Quantitative analysis may also improve the ability to identify specific vessel involvement as well as the presence of three-vessel disease (*18,31,32*). Less severe stenoses might also be more readily identified by quantitative analysis (*31*). Nonetheless, three-vessel disease is still identified in only 78% to 86% of patients, and circumflex lesions are detected in only 63% of patients (*31,32*).

Single photon emission computed tomography. Two methods are available for thallium image analysis using tomographic techniques. The technical aspects of both multiple pinhole tomography and transaxial tomography are well outlined by Budinger (*34*). Of these two methods, transaxial tomography is by far the preferred technique, but statistical limitations, especially with the use of low-energy radionuclides such as thallium-201, limit its applicability in studies of the heart. Absolute quantification is theoretically not feasible for measurements such as flow analysis (*34*) in the heart. With seven-pinhole tomography true cross-sectional activity is not obtained, and defects ap-

pear to be propagated into adjacent slices where in fact they do not exist (*35,36*). Seven-pinhole tomography appears to have equivalent accuracy with planar thallium imaging in determining the presence of myocardial infarction (*36,37*).

Transaxial tomography in combination with intravenous dipyridamole has been used to evaluate patients for coronary disease. There was a 10% improvement in sensitivity using SPECT compared with planar imaging if quantitative analysis of the SPECT images was performed (*38*). The results of qualitative analysis of SPECT images were no different from the results with qualitative analysis of planar images (*38*). One recent study found no difference in sensitivity between planar and emission computed tomography in the detection of coronary disease; however, location of disease and estimation of severity was better using emission computed tomography (*39*).

Transaxial tomography is reported to be better than planar thallium imaging in detecting myocardial infarction especially in patients with inferior or nontransmural infarction (*36,37,40*). Quantitative analysis of emission computed tomography images in animal models suggests that a reasonable correlation exists between infarct size determined by tomographic imaging and actual measurements (*41*). Quantification of regional myocardial blood flow was not possible in intact dogs. Qualitative interpretation of these images, however, correlates reasonably well with quantitative flow measurements (*42*).

In the article by Kirsch et al. in this issue of the Journal (*1*), analysis of SPECT was compared with planar images in patients with coronary disease without myocardial infarction, in patients with myocardial infarction, and in control patients. The patients with coronary disease without myocardial infarction had relatively severe disease with 33 of 40 patients having greater than 75% or complete coronary occlusion. More than half the patients had significant wall-motion abnormalities. Images were obtained without intervention at rest. Using emission tomography the sensitivity was 87% in the noninfarct group compared with 58% using planar imaging techniques. Myocardial infarction was correctly identified in 93% compared with 68% using planar imaging. The disparity in sensitivity between this report and others (*36,37,40,39*) may represent differences in the patient populations, but it may also represent differences in efficiency and accuracy of the imaging equipment used as well as the skill of the interpreters. Certainly without intervention one would not expect a superior detection of patients with coronary disease due to the limitations of thallium-201 imaging (*8*). Quantitative analysis of planar thallium images may well produce results as good as those reported by Kirsch's group (*32–33*).

It would appear that sensitivity in detecting coronary disease using emission computed tomography is approximately 10% better than that with planar imaging, but this small advantage is still subject to question (*38,39*). Quantitative analysis of planar images, however, may produce similar sensitivity and specificity to tomographic techniques in detecting coronary disease (*32,33*). SPECT does appear to be better for localizing disease and assessing severity of disease especially in the inferior and posterolateral circulations (*39*). Emission computed tomography may be better than planar imaging for detecting myocardial infarction especially in patients with inferior or nontransmural infarcts (*37,40*). Relative quantification of infarct size may be possible (*40*); however, quantitative flow analysis in the myocardium appears out of the reach of SPECT technology (*34,42*).

Although commercial cameras equipped with computers necessary for quantitative analysis may cost in the range of $150,000, an additional $30,000 must be expended for upgrading these cameras to perform transaxial computed tomography. Cameras designed specifically for transaxial tomography cost approximately $230,000. Using the available information, it would appear that quantitative analysis of planar thallium images, a process most camera-dedicated computing systems are capable of, will produce results comparable to those of SPECT. One wonders then if the additional cost of a SPECT system is compensated for by the ability to detect smaller areas of myocardial ischemia or infarction on the posterior wall of the left ventricle. Since absolute quantitative infarct sizing and flow analysis are not possible with current SPECT technology, it appears at the present time that SPECT offers little additional benefit compared with planar thallium imaging.

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REFERENCES

1. KIRSCH C-M, DOLIWA R, BÜELL U, et al: Detection of severe coronary heart disease with Tl-201: Comparison of resting single photon emission tomography with invasive arteriography. *J Nucl Med:* 24 761-767, 1983
2. BAILEY IK, GRIFFITH LSC, ROULEAU J, et al: Thallium-201 myocardial perfusion imaging at rest and during exercise, comparative sensitivity to electrocardiography in coronary artery disease. *Circulation* 55:79-87, 1977
3. RITCHIE JL, TROBAUGH GB, HAMILTON GW, et al: Myocardial imaging with thallium-201 at rest and during exercise. Comparison with coronary arteriography and resting and stress electrocardiography. *Circulation* 56: 66-71, 1977
4. MCCARTHY DM, BLOOD DK, SCIACCA RR, et al: Single dose myocardial perfusion imaging with thallium-201: Application in patients with non diagnostic electrocardiographic stress tests. *Am J Cardiol* 43:899-906, 1979
5. BODENHEIMER MM, BANKA VS, FOOSHEE CM, et al: Comparative sensitivity of the exercise electrocardiogram, thallium imaging and stress radionuclide angiography to detect the presence and severity of coronary heart disease. *Circulation* 60:1270-1277, 1979
6. CALDWELL JH, HAMILTON GW, SORENSEN SG, et al: The detection of coronary artery disease with radionuclide techniques: A comparison of rest-exercise thallium imaging and ejection fraction response. *Circulation* 61:610-619, 1980
7. ISKANDRIAN AS, SEGAL BL: Value of exercise thallium-201 imaging in patients with diagnostic and nondiagnostic electrocardiograms. *Am J Cardiol* 48:233-238, 1981
8. GOULD KL: Noninvasive assessment of coronary stenosis by myocardial perfusion imaging during pharmacologic coronary vasodilation I physiologic basis and experimental validation. *Am J Cardiol* 41:267-278, 1978
9. GOULD KL, WESTCOTT RJ, ALBRO PC, HAMILTON GW: Noninvasive assessment of coronary stenosis by myocardial imaging during pharmacologic coronary vasodilatation. Clinical methodology and feasibility. *Am J Cardiol* 41:279-287, 1978
10. BÜELL U, STRAUER BE, BÜRGER S, et al: Effects of physical stress and pharmacologically induced coronary vasodilation on myocardial and nonmyocardial ^{201}thallium-uptake. *Eur. J Nucl Med* 3:19-27, 1978
11. BENDERSKY R, OKADA RD, BOUCHER CA, et al: Comparison of intravenous dipyridamole thallium imaging with exercise radionuclide angiography. *J Am Coll Cardiol* 1(2):602, 1983 (abst)
12. DUNN RF, UREN RF, SADICK N, et al: Comparison of thallium-201 scanning in idiopathic dilated cardiomyopathy and severe coronary artery disease. *Circulation* 66:804-810, 1982
13. MCKILLOP JH, MURRAY RG, TURNER JG, et al: Can the extent of coronary artery disease be predicted from thallium-201 myocardial images. *J Nucl Med* 20:715-719, 1979
14. MASSIE BM, BOTVINICK EH, BRUNDAGE BH: Correlation of thallium-201 scintigrams with coronary anatomy: factors affecting region by region sensitivity. *Am J Cardiol* 44:616-622, 1979
15. DASH H, MASSIE BM, BOTVINICK EH, BRUNDAGE BH: The noninvasive identification of left main and three-vessel coronary artery disease by myocardial stress perfusion scintigraphy and treadmill exercise electrocardiography. *Circulation* 60:276-284, 1979
16. RIGO P, BAILEY IK, GRIFFITH SC, et al: Value and limitations of segmental analysis of stress thallium myocardial imaging for localization of coronary artery disease. *Circulation* 61:973-981, 1980
17. HÖR G, KANEMOTO N: ^{201}Tl-myocardial scintigraphy: Current status in coronary artery disease results of sensitivity/specificity in 3092 patients and clinical recommendations. *Nucl Med* 20:136-147, 1981
18. GIBSON RS, TAYLOR GJ, WATSON DD, et al: Predicting the extent and location of coronary artery disease during the early postinfarction period by quantitative thallium-201 scintigraphy. *Am J Cardiol* 47:1010-1019, 1981
19. RIGO P, BAILEY IK, GRIFFITH LSC, et al: Stress thallium-201 myocardial scintigraphy for the detection of individual coronary arterial lesions in patients with and without previous myocardial infarction. *Am J Cardiol* 48:209-216, 1981
20. RIGO P, BECKER LC, GRIFFITH LSC, et al: Influence of coronary collateral vessels on the results of thallium-201 myocardial stress imaging. *Am J Cardiol* 44:452-458, 1979
21. POHOST GM, OKADA RD, O'KEEFE DD, et al: Thallium redistribution in dogs with severe coronary artery stenosis of fixed caliber. *Circ Res* 48:439-446, 1981
22. GRUNWALD AM, WATSON DD, HOLZGREFE HH, et al: Myocardial thallium-201 kinetics in normal and ischemic myocardium. *Circulation* 64:610-618, 1981
23. OKADA RD, LEPPO JA, STRAUS HW, et al: Mechanisms and time course for the disappearance of thallium-201 defects at rest in dogs. *Am J Cardiol* 49:699-706, 1982
24. BERGMANN SR, HACK SN, SOBEL BE: "Redistribution" of myocardial thallium-201 without reperfusion: Implications regarding absolute quantification of perfusion. *Am J Cardiol* 49:1691-1698
25. ROZANSKI A, BERMAN DS, GRAY R, et al: Use of thallium-201 redistribution scintigraphy in the pre-operative differentiation of reversible and nonreversible myocardial asynergy. *Circulation* 64:936-944, 1981
26. GOLDHABER SZ, NEWELL JB, ALPERT NM, et al: Effects of ischemic like insult on myocardial thallium-201 accumulation. *Circulation* 67:778-786, 1983
27. POHOST GM, ZIR LM, MOORE RH, et al: Differentiation of transiently ischemic from infarcted myocardium by serial imaging after a single dose of thallium-201. *Circulation* 55:294-302, 1977
28. SMITHERMAN TC, OSBORN RC, NARAHARA KA: Serial myocardial scintigraphy after a single dose of thallium-201 in men after acute myocardial infarction. *Am J Cardiol* 42:177-182, 1978

29. NIESS GS, LOGIC JR, RUSSELL RO, et al: Usefulness and limitations of thallium-201 myocardial scintigraphy in delineating location and size of prior myocardial infarction. *Circulation* 59:1010–1019, 1979
30. BUDA AJ, DUBBIN JD, MACDONALD K, et al: Spontaneous changes in thallium-201 myocardial perfusion imaging after myocardial infarction. *Am J Cardiol* 50:1272–1278, 1982
31. MADDAHI J, GARCIA EV, BERMAN DS, et al: Improved noninvasive assessment of coronary artery disease by quantitative analysis of regional stress myocardial distribution and washout of thallium-201. *Circulation* 64:924–935, 1981
32. BERGER BC, WATSON DD, TAYLOR GJ, et al: Quantitative thallium-201 exercise scintigraphy for detection of coronary artery disease. *J Nucl Med* 22:585–593, 1981
33. FARIS JV, BURT RW, GRAHAM MC, et al: Thallium-201 myocardial scintigraphy: Improved sensitivity, specificity and predictive accuracy by application of a statistical image analysis algorithm. *Am J Cardiol* 49: 733–742, 1982
34. BUDINGER TF: Physical attributes of single-photon tomography. *J Nucl Med* 21:579–592, 1980
35. WILLIAMS DL, RITCHIE JL, HARP GD, et al: In vivo simulation of thallium-201 myocardial scintigraphy by seven-pinhole emission tomography. *J Nucl Med* 21:821–828, 1980
36. TAMAKI N, MUKAI T, ISHII Y, et al: Clinical evaluation of thallium-201 emission myocardial tomography using a rotating gamma camera: Comparison with seven-pinhole tomography. *J Nucl Med* 22:849–855, 1981.
37. MAUBLANT J, CASSAGNES J, LE JUNE JJ, et al: A comparison between conventional scintigraphy and emission tomography with thallium-201 in the detection of myocardial infarction. Concise communication. *J Nucl Med* 23:204–208, 1983
38. FRANCISCO DA, COLLINS SM, GO RT, et al: Tomographic thallium-201 myocardial perfusion scintigrams after maximal coronary artery vasodilation with intravenous dipyridamole. Comparison of qualitative and quantitative approaches. *Circulation* 66:370–379, 1983
39. PRIGENT F, FRIEDMAN J, MADDAHI J, et al: Comparison of rotational tomography with planar imaging for thallium-201 stress myocardial scintigraphy. *N Nucl Med* 24:P18, 1983 (abst)
40. RITCHIE JL, WILLIAMS DL, HARP G, et al: Transaxial tomography with thallium-201 for detecting remote myocardial infarction. *Am J Cardiol* 50:1236–1241, 1982
41. CALDWELL JH, RITCHIE JL, HARP GW, et al: Quantitation of myocardial perfusion defects by single photon emission tomography. *Circulation* 66-II:149, 1982
42. CALDWELL JH, WILLIAMS DL, HAMILTON GW, et al: Regional distribution of myocardial blood flow measured by single-photon emission tomography: Comparison with in vitro counting. *J Nucl Med* 23:490–495, 1982