Posicam 6.5 BGO Positron Camera. *J Nucl Med* 1990;31:610–616.
129. Raylman RR, Hutchins GD, Schwaiger M, Paradise AH. The effect of axial sampling and motion on three-dimensional quantification of myocardial defects with positron emission tomography. *J Nucl Med* 1989;30: 892.
130. Bendriem B, Dewey SL, Schlyer DJ. Dependence on the recovery coefficient on axial sampling in multislice positron emission tomography. *J Nucl Med* 1989;30:892.
131. Gould KL, Goldstein RA, Mullani NA. Economic analysis of clinical positron emission tomography of the heart with rubidium-82. *J Nucl Med* 1989;30:707–717.
132. Gould KL. Goals, gold standards and accuracy of non-invasive myocardial perfusion imaging for identifying and assessing severity of coronary artery disease. *Current Opinion in Cardiology* 1989;4:834–844.
133. Gould KL, Mullani NA, Williams B. PET, PTCA and economic priorities. *Clin Cardiol* 1990;13:153–164.
134. Bodenheimer MM, Banka VS, Fooshee C, Hermann GA, Helfant RH. Relationship between regional myocardial perfusion and the presence, severity and reversibility of asynergy in patients with coronary heart disease. *Circulation* 1978;58:789–878.
135. Rozanski A, Berman DS, Gray R, et al. Use of thallium-201 redistribution scintigraphy in the preoperative differentiation of reversible and nonreversible myocardial asynergy. *Circulation* 1981;64:936–944.
136. Iskandrian AS, Hakki A-H, Kane SA, Goel IP, Mudth ED, Segal BL. Rest and redistribution thallium-201 myocardial scintigraphy to predict improvement in left ventricular function after coronary arterial bypass grafting. *Am J Cardiol* 1983;51:1312–1316.
137. Cloninger KG, DePuey EG, Garcia EV, et al. Incomplete redistribution in delayed thallium-201 single proton emission computed tomographic (SPECT) images: an overestimation of myocardial scarring. *J Am Coll Cardiol* 1988;12:955–963.
138. Galli M, Bencivelli W, Pardo NF, Tavazzi L. Underestimation of residual ischemia by thallium-201 scintigraphy after myocardial infarction. *Chest* 1988;94:876–878.
139. Tamaki N, Yonekura Y, Yamashita K, et al. Relation of left ventricular perfusion and wall motion with metabolic activity in persistent defects on ^{201}Tl tomography in healed myocardial infarction. *Am J Cardiol* 1988;62:202–208.
140. Brunken RC, Kottou S, Nienaber CA, et al. PET detection of viable tissue in myocardial segments with persistent defects at Tl-201 SPECT. *Radiology* 1989;172:65–73.
141. Tamaki N, Yonekura Y, Yamashita K, et al. Positron emission tomography using fluorine-18 deoxyglucose in evaluation of coronary artery bypass grafting. *Am J Cardiol* 1989;64:860–865.
142. Hill JL, Gettes LS. Effect of acute coronary artery occlusion on local myocardial extracellular K+ activity in swine. *Circulation* 1980;61:768–777.
143. Conrad GL, Rau EE, Shine KI. Creatine kinase release, potassium-42 content and mechanical performance in anoxic rabbit myocardium. *J Clin Invest* 1979;64:155–161.
144. Gould KL, Haynie M, Hess MJ, Yoshida K, Mullani NA, Smalling RW. Myocardial metabolism of fluorodeoxyglucose compared to cell membrane integrity for the potassium analog Rb-82 for assessing viability and infarct size in man by PET. *J Nucl Med* 1990:31:1–9.
145. Sease D, Garza D, Merhige ME, et al. Does myocardial uptake of F-18-Fluoro-deoxy-glucose by positron emission tomography reliably indicate myocardial viability in acute myocardial infarction? [Abstract]. *Circulation* 1989;80:II–378.
146. Pierard LA, DeLandsheere CM, Berthe C, Rigo P, Kulbertus HE. Identification of viable myocardium by echocardiography during dobutamine infusion in patients with myocardial infarction after thrombolytic therapy: comparison with positron emission tomography. *J Am Coll Cardiol* 1990;15:1021–31.
147. Bianco JA, Bakanauskas J, Carlson M, et al. Augmented uptake of 2-C-14-D-deoxyglucose in reversibly-injured myocardium. *Eur J Nucl Med* 1988;13:557–562.
148. Komatsumoto S, Greenberg JH, Hickey WF, Reivich M. Local cerebral glucose utilization in chronic middle cerebral artery occlusion in the cat. *J Cereb Blood Flow Metab* 1989;9:535–547.
149. Wijns W, Jacque AM, Leners N, et al. Accumulation of polymorphonuclear leukocytes in reperfused ischemic canine myocardium: relation with tissue viability assessed by fluorine-18-2-Deoxyglucose uptake. *J Nucl Med* 1988;29:1826–1832.
150. Mody F, Buxton D, Krivokapich J, Hansen H, Selin C, Schelbert H. Attenuated response of glucose metabolism in reperfused canine myocardium to changes in substrate levels. *J Am Coll Cardiol* 1990;15:80A.
151. Merhige ME, Ekas RD, Mossberg K, Taegtmeyer HT, Gould KL. Catechol stimulation, substrate competition and myocardial glucose uptake in conscious dogs assessed with positron emission tomography. *Circ Res* 1987;61(supp II):124–120.
152. Bonow RO, Bacharach SL, Cuocolo A, Dilsizian V. Myocardial viability in coronary artery disease and left ventricular dysfunction: thallium-201 reinjection vs fluorodeoxyglucose [Abstract]. *Circulation* 1989;80: (suppl) II–377.
153. Bonow RO, Dilsizian V, Cuocolo A, Bacharach SL. Myocardial viability in patients with chronic coronary artery disease and left ventricular dysfunction: thallium-201 reinjection versus ^{18}F-fluorodeoxyglucose. *Circulation* (In Press).

EDITORIAL

The Clinical Role of Positron Emission Tomography for Cardiology in the 1990s and Beyond

Although positron emission tomography (PET) has been performed in patients for more than 15 years, it has only recently begun to emerge as a diagnostic modality for use by clinicians. Implementation of clinical PET has been delayed by several factors, including the high cost of required equipment ($5–7 million with camera, cyclotron and supporting equipment), absence of U.S. Food and Drug Administration (FDA) approval, the lack of widespread reimbursement from federal and private insurers, and the paucity of large clinical trials (including outcome data) from multiple sites. Some solutions to these limitations appear to be near. The entry of major manufacturers into PET imaging should decrease the price of cameras due to increased competition. Other recent changes are joint ventures between clinical and/or research centers with radiopharmaceutical groups that share a cyclotron. By sharing or leasing the cyclotron, the capital equipment and operating costs should be reduced while making PET tracers available to sites with cameras but without cyclotrons. The regulatory barriers are also starting to resolve. In November 1989, the FDA issued a position statement on PET radiopharmaceuticals indicating that PET centers could continue to operate even though New Drug Applications

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For reprints contact: Richard A. Goldstein, MD, Director, Nuclear Cardiology, Cardiology Division Room 1.246, The University of Texas Medical School at Houston, 6431 Fannin, Houston, TX 77030.

(NDAs) were not yet approved. Subsequently, rubidium-82 generator use for clinical purposes was approved in December 1989. The issues related to reimbursement are now being reviewed by the Office of Health Technology Assessment (OHTA) at Health Care Financial Administration (HCFA) for Medicare coverage and independently by members of Health Insurance Association of America (HIAA). This editorial reviews the advantages and limitations of PET imaging as a diagnostic modality and discusses whether these enhancements justify the higher cost of equipment and ensuing charges for clinical studies.

PHYSIOLOGIC ASSESSMENT OF CORONARY HEART DISEASE

The final arbitrator for the diagnosis of coronary disease has been the presence of a visually determined stenosis of >50% diameter narrowing based on coronary arteriography (*1*). The use of arteriography as the "gold standard" has recently been challenged by several investigators that point out significant inter- and intraobserver variability, the eccentricity of most coronary lesions, and the difficulty in relying on percent narrowing when the "normal" part of the vessel, the denominator in percent narrowing, may itself be diffusely diseased (*2–4*). An additional problem with the use of a 50% stenosis as the definition of a significant coronary artery lesion is the implication that patients with lesser degrees of stenosis do not have physiologically important disease. The basis for the selection of a 50% diameter cutoff point is derived from animal studies using fixed stenosis of variable severity (*5*). Lesions with >50% stenosis are associated with a decrease in maximal flow with vasodilation (i.e., decreased coronary flow reserve). Since the diagnosis of a functionally significant lesion is based on the inability to increase flow under stress conditions, it would seem preferable to determine the presence and extent of disease on the basis of noninvasive, direct measurements of regional perfusion at rest and during high flow states (exercise or pharmacologic). This type of approach would be similar to the earlier animal experiments that formed the foundation for defining severity of stenosis in terms of anatomy and physiologic limitations in increasing myocardial perfusion in response to stress.

Perfusion Imaging with Single-Photon Emitters

Myocardial perfusion imaging with thallium-201 is well established as a means for diagnosing coronary heart disease (*6–10*). Initial studies showed a high sensitivity and specificity but more recently, the observed specificity has decreased (*11–12*). One explanation for these changes is referral bias. For example, if one begins to rely on a test for decisions about the need for arteriography, there is a bias to do invasive testing only on abnormal thallium studies and not in patients with normal ^{201}Tl scintigrams. Thus, specificity falls since patients with false-positives have arteriography, whereas most patients who are true-negatives do not. The same evolution would be expected for any test relying on a binary decision (positive/negative). Thallium-201 is inherently limited to this type of analysis since the absence of attenuation correction precludes true quantitation of activity.

Two new technetium-99m-based perfusion agents have recently been approved by the FDA: teboroxime (Cardiotec) and sestamibi (Cardiolite) (*13–16*). The higher photon decay energy of ^{99m}Tc should decrease attenuation artifacts. However, published studies have not clearly demonstrated an improvement in diagnostic accuracy with these tracers over that obtainable with ^{201}Tl.

In theory, advances in camera technology might allow attenuation correction to be performed with SPECT to obtain true quantitation. However, such technical improvements are likely to increase the price of SPECT systems substantially.

Perfusion Imaging with PET

Several investigators have developed models with PET to measure regional perfusion in absolute terms using rubidium-82, oxygen-15-water, and nitrogen-13-ammonia (*17–19*). However, coronary blood flow estimates by PET have not been directly compared to anatomic measurements of stenosis severity obtained with quantitative arteriography (QCA). Relative perfusion reserve (stress to rest in a defect divided by a comparable measure for a normal segment) has been studied in patients who have undergone QCA (*20*). In these studies, relative perfusion reserve was normal until the stenosis exceeded 50% in diameter and then decreased with more severe stenosis. Following angioplasty, changes in perfusion reserve parallel arteriographic changes in stenosis severity (*21*). These results are concordant with animal studies relating anatomy and coronary flow reserve (*22*).

Although the measurement of myocardial perfusion per se should theoretically improve our ability to assess coronary disease, it is important to the clinician and insurer to know whether these differences will justify the attendant higher cost of PET by reducing or eliminating more expensive procedures and/or decreasing morbidity and mortality. When PET has been evaluated using sensitivity and specificity, the results have been promising.

In an early study, Schelbert reported a sensitivity of 97% and a specificity of 100% for PET stress perfusion imaging with ^{13}N-ammonia in 32 patients with disease and 13 controls (*23*). Similar results were obtained by Yokenura et al. (*24*). Demer and colleagues compared ^{13}N-ammonia or ^{82}Rb rest/dipyridamole stress images to QCA and found a good correlation between coronary flow reserve (CFR), estimated from arteriography and vis-

ually interpreted PET (*25*). Recently, Go et al. compared thallium SPECT and ^{82}Rb PET directly to arteriography in 202 patients, 133 of whom had neither prior coronary artery bypass procedures nor angioplasty (*26*). They reported a statistically significant increase in the sensitivity of PET of 95% (compared with 79% for SPECT) but no change in specificity (82% compared with 76% for PET and SPECT, respectively). In contrast, Stewart et al. from Michigan reported a higher specificity and similar sensitivity with PET/SPECT in patients compared with quantitative coronary arteriography (*27*).

The Position of PET Today

The major advantage of PET over SPECT is the ability to correct for differences in attenuation that would be expected to improve interpretation by minimizing artifacts. Another advantage is the ability to complete studies in 1–1.50 hr as opposed to 4–6 hr for ^{201}Tl and ^{99m}Tc-sestamibi. Does quantification make a significant difference in selecting patients for intervention? Theoretically it should. Given the variability of interpretation of arteriography and the attenuation problems with ^{201}Tl and ^{99m}Tc, PET is a strong candidate for use as a decision end point for determining the need for arteriography and whether a lesion would require revascularization. Such studies would be expected to be particularly helpful in patients most likely to have either diaphragmatic or breast tissue attenuation artifacts with ^{201}Tl or ^{99m}Tc radionuclides.

ASSESSMENT OF MYOCARDIAL VIABILITY USING RADIONUCLIDE TRACERS

One of the areas that PET is beginning to have major impact on in clinical decision-making is the determination of myocardial viability with 2-fluoro 2-deoxyglucose (FDG) (*28*). The premise is that only a viable, metabolically active myocardium takes up glucose. With myocardial ischemia, uptake of glucose is enhanced because of a diminished oxygen supply that increases anaerobic metabolism. FDG is extracted similarly to its normal circulating physiological counterpart. However, after it is phosphorylated and trapped in the cell, it is not broken down further. Tillisch et al. found that the presence of FDG in myocardium, normalized for differences in delivery, predicted improvement in regional left ventricular function following surgical revascularization. Patients without FDG uptake had no significant change in wall motion (*29*). These observations have been used as a clinical basis for differentiating potentially reversible ischemic disease (i.e., "hibernating" myocardium) from extensive myocardial scar in patients with severe left ventricular dysfunction who are being considered for coronary artery revascularization procedures or cardiac transplantation.

Do ^{201}Tl redistribution scans provide similar information? Thallium redistribution imaging for viability is based on differences in flow-dependent washout between normal, ischemic and infarcted regions (*30*). In experimental animals, viability is usually present in myocardium with flow greater than 0.6 ml/min/g and absent in regions with flow less than 0.4 ml/min/g (*31*). Regions with intermediate flows are not clearly separated into live or dead tissue simply on the basis of flow or ^{201}Tl uptake.

A study by Brunken et al. found that 58% of fixed thallium defects (irreversibly injured) were viable by FDG (*32*). Tamaki obtained similar results with 40% of persistent thallium defects displaying FDG activity (*33*). Recent studies have suggested that reinjection of thallium at 4 hr increases the number of segments classified as viable (*34*). Thallium redistribution studies would be expected to be least reliable in regions of intermediate flow where differences between viable and necrotic tissue activity may be borderline. Interpretation of FDG uptake in such regions may be facilitated by the quantitative properties of PET imaging and the presence of a "hot spot" to read as opposed to a "cold spot" for thallium.

Several other approaches to the PET assessment of viability have undergone preliminary testing, including the use of labeled fatty acids (carbon-11-palmitate), aerobic metabolites (carbon-11-acetate and pyruvate) and differential washout of rubidium-82 (*35–38*). Further clinical validation of these tracers must be performed before they can be considerable acceptable markers of viability in patients.

FUTURE DIRECTIONS

The quantitative properties of PET and the wide range of possible tracers using carbon-11, nitrogen-13, and fluorine-18 should expand the use of PET as the technology becomes more widely available. PET should be useful as a research and clinical tool for evaluating interrelations between hormones and their receptors and in the determination of cellular abnormalities associated with the development of cardiomyopathies, arrhythmias, atherosclerosis, and thrombosis. Another potential role for PET may be in the evaluation of unstable coronary artery plaques and in identifying progression and regression of atherosclerotic lesions. PET may also be used to study end organ pharmacokinetics directly rather than relying on blood levels of cardiac drugs. These new areas should represent some of the largest growth areas for PET's clinical applications.

Richard A. Goldstein
James T. Willerson
University of Texas Health Science Center
Houston, Texas

REFERENCES

1. Klocke FJ. Measurements of coronary flow reserve: defining pathophysiology versus making clinical decisions about patient care. *Circulation* 1987;76:1183–1189.
2. Marcus ML, Skorton DJ, Johnson MR, et al. Visual estimates of percent diameter stenosis:

"a battered gold standard." *J Am Coll Cardiol* 1988;11:882–885.
3. Gould KL. Percent coronary stenosis: battered gold standard, pernicious relic or clinical practicality? *J Am Coll Cardiol* 1988;11:886–888.
4. Vogel RA. Assessing stenosis significance by coronary arteriography: are the best variables good enough? *J Am Coll Cardiol* 1988;12:692–693.
5. Gould KL, Lipscomb K. Effects of coronary stenosis on coronary flow reserve and resistance. *Am J Cardiol* 1974;34:48–55.
6. Ritchie JL, Zaret BL, Strauss HW, et al. Myocardial imaging with thallium-201: a multicenter study in patients with angina pectoris or myocardial infarction. *Am J Cardiol* 1978;42:345–350.
7. 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* 1981;64:924–935.
8. Turner DA, Battle WE, Deshmukh H, et al. The predictive value of myocardial perfusion scintigraphy after stress in patients without previous myocardial infarction. *J Nucl Med* 1978;19:249–255.
9. 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.
10. DePasquale EE, Nody AC, DePuey EG, et al. Quantitative rotational thallium-201 tomography for identifying and localizing coronary artery disease. *Circulation* 1987;77:316–327.
11. Iskandrian AS, Heo J, Kong B, et al. Effect of exercise level on the ability of thallium-201 tomographic imaging in detecting coronary artery disease: analysis of 461 patients. *J Am Coll Cardiol* 1989;14:1477–1486.
12. Diamond GA. How accurate is SPECT thallium scintigraphy? *J Am Coll Cardiol* 1990;16:1017–1021.
13. Seldin DW, Johnson LJ, Blood DK, et al. Myocardial perfusion imaging with technetium-99m-SQ30217: comparison with thallium-201 and coronary anatomy. *J Nucl Med* 1989;30:312–319.
14. Stewart RE, Schwaiger M, Jutchins GD, et al. Myocardial clearance of technetium-99m-SQ30217: a marker of regional myocardial blood flow. *J Nucl Med* 1990;31:1183–1190.
15. Kahn JK, McGhie I, Akers MS, et al. Quantitative rotational tomography with ^{201}Tl and ^{99m}Tc-2-methoxy-isobutyl-isonitrile. A direct comparison in normal individuals and patients with coronary artery disease. *Circulation* 1989;79:1282–1293.
16. Kiat H, Maddahi J, Roy L, et al. Comparison of technetium-99m-methoxy-isobutyl-isonitrile and thallium-201 evaluation of coronary artery disease by planar and tomographic methods. *Am Heart J* 1989;117:1–11.
17. Shah A, Schelbert HR, Schwaiger M, et al. Measurement of regional myocardial blood flow with N-13-ammonia and positron emission tomography in intact dogs. *J Am Coll Cardiol* 1985;5:92–100.
18. Bergmann SR, Fox KAA, Rand AL, et al. Quantification of regional myocardial blood flow in vivo with $H_2{}^{15}O$. *Circulation* 1984;70:724–733.
19. Herrero P, Markham J, Shelton ME, et al. Noninvasive quantification of regional myocardial perfusion with rubidium-82 and positron emission tomography. Exploration of a mathematical model. *Circulation* 1990;82:1377–1386.
20. Goldstein RA, Kirkeeide RL, Demer LL, et al. Relation between geometric dimensions of coronary stenosis and myocardial perfusion reserve in man. *J Clin Invest* 1987;79:1473–1478.
21. Goldstein RA, Kirkeeide RL, Smalling RW, et al. Changes in myocardial perfusion reserve after PTCA: noninvasive assessment with positron tomography. *J Nucl Med* 1987;28:1262–1267.
22. Gould KL, Schelbert HR, Phelps ME, et al. Noninvasive assessment of coronary stenosis with myocardial perfusion imaging during pharmacologic coronary vasodilation. V. Detection of 47 percent diameter stenosis with intravenous nitrogen-13-ammonia and emission-computed transaxial tomography in intact dogs. *Am J Cardiol* 1979;43:200–208.
23. Schelbert HR, Wisenberg G, Phelps ME, et al. Noninvasive assessment of coronary stenosis by myocardial imaging during pharmacologic coronary vasodilation. VI. Detection of coronary artery disease in man with intravenous NH_3 and positron computed tomography. *Am J Cardiol* 1982;49:1197–1207.
24. Yonekura Y, Tamaki N, Senda M, et al. Detection of coronary artery disease with ^{13}N-ammonia and high-resolution positron emission computed tomography. *Am Heart J* 1987;113:645–654.
25. Demer LL, Gould KL, Goldstein RA, et al. Diagnosis of coronary artery disease by positron emission tomography: comparison to quantitative coronary arteriography in 193 patients. *Circulation* 1989;79:825–835.
26. Go RT, Marwick TH, MacIntyre WJ, et al. A prospective comparison of rubidium-82 PET and thallium-201 SPECT myocardial perfusion imaging utilizing a single dipyridamole stress in the diagnosis of coronary artery disease. *J Nucl Med* 1990;31:1899–1905.
27. Stewart RE, Kalus ME, Molina E, et al. Rubidium-82 PET versus thallium-201 SPECT for the diagnosis of regional coronary artery disease [Abstract]. *Circulation* 1989;80:II–201.
28. Schwaiger M, Schelbert HR, Ellison D, et al. Sustained abnormalities in cardiac metabolism after transient ischemia in the chronic dog model. *J Am Coll Cardiol* 1985;6:336–347.
29. Tillisch J, Brunken R, Marshall R, et al. Reversibility of cardiac wall-motion abnormalities predicted by positron tomography. *N Engl J Med* 1986;314:884–888.
30. Grunwald AM, Watson DD, Holzgrefe HH Jr, et al. Myocardial thallium-201 kinetics in normal and ischemic myocardium. *Circulation* 1981;64:610–618.
31. Melin JA, Becker LC, Bulkley BH. Differences in thallium-201 uptake in reperfused and nonreperfused myocardial infarction. *Circ Res* 1983;53:414–419.
32. Brunken K, Schwaiger M, Grover-McKay M, et al. Positron emission tomography detects tissue metabolic activity in myocardial segments with persistent thallium perfusion defects. *J Am Coll Cardiol* 1987;10:557–567.
33. Tamaki N, Yonekura Y, Yamashita K, et al. Relation of left ventricular perfusion and wall motion with metabolic activity in persistent defects on thallium-201 tomography in healed myocardial infarction. *Am J Cardiol* 1988;62:202–208.
34. Dilsizian V, Swain J, Dextras R, et al. Prediction of viable myocardium by thallium reinjection at rest after stress-redistribution imaging: a pre- and postrevascularization study. [Abstract]. *Circulation* 1989;80(suppl II):III–366.
35. Lerch RA, Bergmann SR, Ambos HD, et al. Effect of flow-independent reduction of metabolism on regional myocardial clearance of ^{11}C-palmitate. *Circulation* 1982;65:731–738.
36. Armbrecht JJ, Buxton DB and Schelbert HR. Validation of [1-^{11}C]acetate as a tracer for noninvasive assessment of oxidative metabolism with positron emission tomography in normal, ischemic, postischemic, and hyperemic canine myocardium. *Circulation* 1990;81:1594–1605.
37. Goldstein RA, Klein MS, Sobel BE. Detection of myocardial ischemia before infarction, based on accumulation of labeled pyruvate. *J Nucl Med* 1980;21:1101–1104.
38. Goldstein RA. Kinetics of rubidium-82 after coronary occlusion and reperfusion. Assessment of patency and viability in open-chested dogs. *J Clin Invest* 1985;75:1131–1137.