kinetics of fluorine-18 misonidazole: a marker of hypoxia myocardial. *J Nucl Med* 1989;30:351–58.
9. Martin GV, Cerqueira M, Caldwell JH, Rasey JS, Embree L, Krohn KA. Fluromisonidazole: a metabolic marker of myocyte hypoxia. *Circ Res* 1990; 67:240–244.
10. Shelton ME, Dence CS, D-R Hwang, Herrero P, Welch MJ, Bergmann SR. In vivo delineation of myocardial hypoxia during coronary occlusion using florine-18 fluoromisonidazole and PET: a potential approach for identification of jeopardized myocardium. *J Am Coll Cardiol* 1990;16:477–85.
11. Martin GV, Caldwell JH, Graham MM, et al. Noninvasive detection of hypoxic myocardium using fluorine-18-fluoromisonidazole and PET. *J Nucl Med* 1992;33:2202–08.
12. Franko A. Misonidazole and other hypoxia markers: metabolism and applications. *Int J Radiat Oncol Biol Phys* 1986;12:1195–1202.
13. Mathias CJ, Welch MJ, Kilbourn MR, et al. Radiolabeled hypoxic cell sensitizers: tracers for assessment of ischemia. *Life Sci* 1987;41:199–206.
14. Koh W-J, Rasey JS, Evans ML, Grierson JR, Lewellen TK, Graham MM, Krohn KA, Griffin TW. Imaging of hypoxia in human tumor with [F-18]fluromisonidazole. *Int J Radiat Oncol Biol Phys* 1991;22:199–212.
15. Linder KE, Cyr J, Chan Y-W, Raju N, Ramalingam K, Nowotnik DP, Nunn AD. Chemistry of a Tc-PnAO-nitroimidazole complex that localizes in hypoxic tissue. *J Nucl Med* 1992;33(suppl):919.
16. Rumsey WL, Cyr JE, Narra RK. A novel ^{99m}Tc-laveled nitroheterocycle capable of identification of hypoxia in heart. *Biochem Biophys Res Commun* 1993;193:1239–46.
17. Edwards NC, Sinusas AJ, Bergin JD, Watson DD, Ruiz M, Beller GA. Influence of subendocardial ischemia on transmural myocardial function. *Am J Physiol* 1992;262:H568–H576.
18. Hartley CJ, Latson LA, Michael LH, Seidel CL, Lewis RM, Entman ML. Doppler measurement of myocardial thickening with a single epicardial transducer. *Am J Physiol* 1983;245:H1066–H1072.
19. Heymann MA, Payne BD, Hoffman JIE, Rudolph AM. Blood flow measurements with radionuclide-labeled particles. *Prog Cardiovasc Dis* 1977; 20:55–79.
20. Sinusas AJ, Watson DD, Cannon JM, Beller GA. Effect of ischemia and postischemic dysfunction on myocardial uptake of ^{99m}Tc-labeled methoxyisobutyl isonitrile and ^{201}Tl. *J Am Coll Cardiol* 1989;14:1785–1793.
21. Rumsey WL, Patel B, Linder KE. The effect of graded hypoxia on retention of ^{99m}Tc-nitroheterocycle in perfused rat heart. *J Nucl Med* 1994;35:18P.
22. Rumsey WL, Kuczynski B, Patel B, Linder KE. Detecting hypoxia in heart using phosporescence quenching and ^{99m}Tc-nitroimidazoles. *Adv Exp Med Biol* 1994:in press.
23. Dahlberg ST, Gilmore MP, Flood M, Leppo JA. Effect of hypoxia and low flow ischemia on the myocardial extraction of ^{99m}Tc-nitroimidazole. *Circulation* 1993;88(suppl):1339.
24. Uren NG, Marraccini P, Gistri R, De Silva R, Camici PG. Altered coronary vasodilator reserve and metabolism in myocardium subtended by normal arteries in patients with CAD. *J Am Coll Cardiol* 1993;22:650–8.
25. Ng CK, Sinusas AJ, Zaret BL, Soufer R. Kinetic analysis of ^{99m}Tc-labeled nitroimidazole (BMS181321) as a tracer of myocardial hypoxia. *Circulation* 1995:in press.

EDITORIAL

Value of Objective Assessment of New Radiopharmaceuticals

Clinical cardiovascular nuclear medicine and the industries that support and depend on it also depend on the following process:

1. An understanding of the important clinical problems, including scientific, medical and financial issues.
2. Identification of clinical information that is relevant to solving patients' problems.
3. Identification of clinical information that might be supplied uniquely or most efficiently by nuclear medicine methodology.
4. Development of methods to provide new information, including new radiopharmaceuticals, camera/computer systems of hardware and software, and new interventions to alter physiology for imaging of cardiovascular functions.
5. Independent, objective testing of the newly developed methodology.
6. Understanding that problems identified in this testing that will guide development of better final products (continuous quality improvement).
7. Expeditious governmental regulatory/approval process.

The study by Shi et al. (*1*) is an excellent example of a process which advances cardiovascular nuclear medicine. There has always been an interest in detecting myocardial ischemia directly and measuring its extent and severity quantitatively. Basic scientists have measured coronary venous lactate (*2*), tissue concentrations of lactate (*3*), high energy phosphates (*4*) and pH (*5*). Magnetic resonance spectroscopy (MRS) has made real strides in noninvasive imaging of these phenomena (*6*). Certain nitroimidazole compounds have been found to bind, in vitro, selectively to hypoxic cells (*7*). One of these compounds was labeled with ^{18}F for PET imaging (*8*). The fact that an agent binds selectively to hypoxic cells in vitro does not mean that the agent would necessarily be concentrated selectively in ischemic myocardium in vivo because uptake of an agent depends on its delivery by blood flow as well as on extraction from blood to tissue. For example, if the binding of an agent to ischemic cells is twice (2/1) its binding to normal cells (in vitro), but if blood flow is only one-fourth (¼) of normal in the ischemic region (in vivo), then uptake of the agent would be expected to be one-half (½) of normal in the ischemic region ($2/1 \times 1/4 = 1/2$). Such an agent might be imaged most effectively in conjunction with a blood flow tracer where the uptake of the agent relative to blood flow would be twice as great in ischemic as in normal myocardium ($1/2 \div 1/4 = 2/1$).

Because new radiopharmaceutical agents are so important to cardiovascular nuclear medicine, there must be an efficient, rapid process that can assess the potential clinical value of the new agent relative to other agents or modalities. First, in the above example, a perfusion tracer would show up to twofold greater contrast (1/4) compared to a tracer that binds selectively

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For correspondence or reprints contact: Randolph E. Patterson, MD, Carlyle Fraser Heart Center, Emory:Crawford Long Hospital, 550 Peachtree St., NE, Atlanta, GA 30365.

to ischemic cells (at a 2/1 ratio). The clinical question being addressed must be understood and defined clearly. The new imaging agent would be of less value than a perfusion agent for identifying the presence of coronary artery obstruction (assuming a 2/1 ratio of uptake in ischemic/normal myocardium). On the other hand, a new radiopharmaceutical agent that binds selectively to ischemic myocardium might be very helpful to distinguish between viable/ischemic versus necrotic/infarcted myocardium, where both may show low blood flow.

The study by Shi et al. (*1*) provides an important assessment of the potential clinical value of a new ^{99m}Tc-labeled nitroimidazole (BMS181321). They used an elegant experimental model that is quite relevant to the clinical situation of myocardial ischemia: a dog with a partial coronary stenosis and stress-induced ischemia measured by coronary arterial pressure gradients (regional myocardial blood flow, wall thickening and regional coronary venous lactate concentrations). An experimental model of myocardial infarction would be a useful next step to assess detection of myocardial viability, but such models are much more difficult technically (and more expensive).

In the ischemia model, they proved the presence of ischemia during pacing by multiple reference methods, and they measured nitroimidazole concentration in tissue samples in vitro by SPECT imaging of the intact left ventricle ex vivo and by planar imaging in vivo. They showed the true relationship between nitroimidazole and blood flow by counting in vitro and in SPECT images ex vivo (both were 61%–65% greater than normal). The in vivo planar images were most helpful because they showed dramatically increased uptake of nitroimidazole in the liver compared to normal myocardium (323% greater than normal myocardium). Because of this liver activity, the authors conclude that "clinical myocardial imaging with BMS 181321 may be limited," but "use of ^{99m}Tc-labeled nitroimidazole compounds holds promise for positive imaging of ischemia" (*1*).

The authors deserve credit for their candor in pointing out the limitations of the current reality of BMS181321 (liver activity) as well as its advantages (increased uptake in ischemic myocardium). Only the in vivo imaging study of an instrumented, large animal could produce this clear-cut result. This result defines the current situation but does not destroy the vision of a positive imaging agent for myocardial ischemia. This article also defines a new problem for continuous quality improvement by radiochemistry research—the development of a compound with less liver activity during myocardial imaging. *The Journal of Nuclear Medicine* deserves credit for publishing what is, in a sense, a "negative result" (*9*), which clarifies the present reality of BMS181321. The company that developed BMS181321 deserves credit for supporting an objective, elegant but somewhat negative study of its agent. The company stands to gain further credibility and can also redirect its research efforts in this area (for example, modifying the agent to achieve less liver uptake or test a new agent).

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Randolph E. Patterson
Robert L. Eisner
Carlyle Fraser Heart Center
Emory:Crawford Long Hospital
Emory University School of Medicine
Atlanta, Georgia

REFERENCES

1. Shi CQX, Sinusas AJ, Dione DP, et al. Technetium-99m-nitroimidazole (BMS181321): a positive imaging agent for detection of myocardial ischemia. *J Nucl Med* 1995;36:1078–1086.
2. Opie LH. Effects of regional ischemia on metabolism of glucose and fatty acids. Relative rates of aerobic and anaerobic energy production during myocardial infarction and comparison with effects of anoxia. *Circ Res* 1976; 38(suppl I):52–68.
3. Dunn RB, Griggs DM Jr. Transmural gradients in ventricular tissue metabolites produced by stopping coronary blood flow in the dog. *Circ Res* 1975;37:438–445.
4. Allison TB, Ramey CA, Holsinger JW Jr. Transmural gradients of left ventricular tissue metabolites after circumflex ligation in dogs. *J Mol Cell Cardiol* 1977;9:837–852.
5. Watson RM, Markle DR, Ro YM, et al. Transmural pH gradient in canine myocardial ischemia. *Am J Physiol: Heart Circ Physiol* 1984; 15:H232–H238.
6. Yabe T, Mitsunami K, Okada M, et al. Detection of myocardial ischemia by 31P magnetic resonance spectroscopy during handgrip exercise. *Circ* 1994;89:1709–1716.
7. Martin GV, Caldwell JH, Rasey JS, et al. Enhanced binding of the hypoxia cell marker [^{3}H]fluromisonidazole in ischemic myocardium. *J Nucl Med* 1989;30:194–201.
8. Shelton ME, Dence CS, Hwang DR, et al. Myocardial kinetics of fluorine-18-misonidazole: a marker of hypoxia myocardial. *J Nucl Med* 1989;30:351–358.
9. Angell M. Negative studies. *N Engl J Med* 1989;321:464–466.