

12. Koh W-J, Rasey JS, Evans ML, et al. Imaging of hypoxia in human tumors with [F18]-fluoromisonidazole. *Int J Radiat Oncol Biol Phys* 1991;22:199-212.
13. Biskupiak JE, Grierson JR, Rasey JS, Martin GV, Krohn KA. Synthesis of an (iodovinyl)misonidazole derivative for hypoxia imaging. *J Med Chem* 1991;34:2165-2168.
14. 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;251:H1044-H1055.
15. Heymann MA, Payne DB, Hoffman JIE, Rudolph AM. Blood flow measurements with radionuclide-labelled particles. *Prog Cardiovasc Dis* 1977;20:55-79.
16. King RB, Bassingthwaite JB, Hales JRS, Powell LB. Stability of heterogeneity of myocardial blood flow in normal awake baboons. *Circ Res* 1985;57:285-295.
17. Murray CE, Reimer KA, Hill ML, Yamasawa I, Jennings RB. Collateral blood flow and transmural location: independent determinants of ATP in ischemic canine myocardium [Abstract]. *Fed Proc* 1985;44:823.
18. Lowe JE, Reimer KA, Jennings RB. Evidence that ischemic cell death begins in the subendocardium independent of variations in collateral flow or wall tension. *Circulation* 1983;68:190-202.

## EDITORIAL

# Is Nuclear Medicine Viable and Can It Measure Viability?

Like the other imaging modalities, nuclear medicine is moving along the road towards being a discipline of prognosis rather than diagnosis. One way that this will be accomplished is by the development of new radiopharmaceuticals that will take us further from the morphologic imaging realm which the other imaging modalities do so well, into the area of functional imaging based upon the underlying biochemistry. Although PET radiopharmaceuticals have dominated the field of functional imaging based upon biochemistry in the past, new, single-photon based radiopharmaceuticals are being developed which challenge or even exceed PET's dominant position. One such example is the development and use of radiolabeled somatostatin analogues not just to identify tumor tissue, but more importantly, to predict the sensitivity of the tumor tissue to therapy using somatostatin itself (1). This situation, where a therapeutic drug is converted into a diagnostic drug, is unusual and in this case results in a highly specialized application. A more general desire is to develop a radiopharmaceutical that is able to indicate the (biochemical) functioning of a piece of tissue such as the oxygen sensing iodovinylmisonidazole (IVM) described by Martin et al. in this issue (2).

The functioning of a piece of tissue

is governed by the laws of supply and demand. Within limits, output can increase so long as the demands are met by an increase in supply of the necessary nutrients. For short periods of time, demand can exceed supply at the cost of producing a nutrient debt. As the supply is reduced, the maximum output is restricted and systems must be downregulated to maintain viability. Below some set point, which can be changed, this results in a cessation of output from the tissue. Further reductions in supply lead ultimately to cell death. When supply and demand are coupled and the tissue is stable, we can use perfusion, a crude measurement of supply, to assess the status of the tissue on a regional basis. In the case of the brain, we interpret the demand as that required by the expected normal neurological functioning. In the case of the myocardium, we interpret the demand as that required by the contractile function of the heart. When the normal functioning of the tissue is changed such that we cannot interpret what the demand is, perfusion becomes of less value and we need instead a measure of the potential for recovery (viability) of the tissue. Such is the case in ischemic myocardium or presentations of hibernating or stunned tissue (3).

The energy state of the cell is a measure of viability: This is, however, hard to obtain in a noninvasive manner, partly because of the variety of pathways the cell can use to produce its energy. A number of radiopharmaceuticals have been proposed

as viability markers which measure some aspect of the energy state of the myocardium (FDG, thallos ion, palmitate, acetate), but all have their deficiencies (4). Our understanding of the information content of a myocardial FDG image is, for instance, still far from complete (5,6) and even the conditions for obtaining one are still being refined (7,8). The assessment of viability is not, of course, only desirable for the myocardium but is relevant to patient management for all situations where ischemia is a component of the disease. This includes stroke, where delayed presentation and progression of the insult combine to make assessment of intervention options difficult, and oncology, where treatment is reliant on differences in metabolic rates and (undesirable) viability. Tissue oxygenation is an accessible common denominator to the cellular energy equation (9) and so a variety of methods for measuring tissue oxygen levels have been developed (10). The potential for using radiopharmaceuticals based upon the radiosensitizer, misonidazole, to depict hypoxic tissue in vivo noninvasively was recognized by Chapman in 1979 (11). The mechanism that causes trapping in hypoxic tissue relies on the competition between enzymatic reduction and ensuing reoxidation by molecular oxygen. Thus, nitroimidazoles are not retained in well oxygenated tissue because of efficient reoxidation of the species that lead to trapping. Nor are they retained in severely damaged tissue in which the

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enzymes necessary for the initial reduction have ceased to function.

The development and testing of radiolabeled nitroimidazoles as probes of oxygen tension in tissues *in vivo* has occurred in both PET and SPECT, with  $^{18}\text{F}$  or radioiodine-labeled compounds being most common. The target tissues have mostly been the myocardium or tumors, with much less attention centered on the brain. Recently some of the compounds have been tested in humans, for instance, FMISO in the myocardium and in tumors (12–15) and IAZA in tumors (16).

The paper by Martin et al. in this issue of the *Journal* (2) describes the characteristics of IVM, the latest of a long line of radiohalogenated misomidazole derivatives, as a marker for hypoxia. The authors describe the results of studies performed in two canine models, one with “simple” stenosis and the other with a lesser degree of stenosis coupled with increased demand. In using the first model, they found increased retention of IVM-derived radioactivity in areas with reduced blood supply. The authors establish that retention is in areas of viable tissue by using sonomicrometry to show that there is a return of contractile function in this tissue. This goes some way towards countering the criticisms of Goldstein (4) that hypoxia localizing agents have not been shown to predict return of function. Uptake was significantly higher in the endocardium than in the epicardium, despite the latter region having lower average flows, presumably a manifestation of the increased demand of endocardial tissue which could not be met by increasing flow. The results of the second model confirm that increased demand in the presence of limited supply also produces hypoxia which can be detected using IVM. These results place IVM firmly in the camp of compounds that can localize in hypoxic tissue *in vivo*. They further establish that the tissue that retains IVM more than normal tissue is viable but jeopardized. Although not addressed in this paper, other studies *in vitro* have shown that

infarcted tissue cannot retain nitroimidazoles because trapping requires the presence of functioning reducing enzymes.

No images are presented in this paper, so it remains to be seen if the selective retention of IVM is sufficient for this purpose. When FMISO was used in similar canine models, both Shelton et al. (12) and Martin et al. (13) found that images of the ischemic/hypoxic tissue in the myocardium are not easy to obtain, especially soon after injection. The myocardium appears to be a more difficult target than tumors because good images of tumors have been obtained using FMISO (14, 15) or IAZA (16) at 1–2 hr postinjection. Part of the problem is generic to the current group of nitroimidazoles and is a result of having to wait for the radioactivity delivered to the normal myocardial tissue to clear to sufficiently low levels, a process which takes a few hours. Because there is little or no retention of radioactivity in the normal myocardial tissue, reading the nitroimidazole images does have the problem of accurately placing the defect within the myocardium. This is similar to the problems of pyrophosphate or antimyosin imaging but is perhaps more critical, because with nitroimidazoles one is trying to identify viable tissue which may change and therefore need to be followed for some time rather than dead tissue, identified by infarct-avid agents, which does not change. Shelton et al. (12) developed an image manipulation technique using independently measured regional blood flow to improve their images.

The extended time necessary to acquire the desired images is a limitation pointed out by Goldstein (4) which precludes the use of FMISO in the acute cardiac ischemia patient. A cyclotron-derived radiolabel generally makes this difficult, and so a technetium-labeled agent is desirable [some progress has been made in this direction (17)]. Thus, none of these agents is ideal for the management of the acute ischemia patient, however, the long residence time in hypoxic tissue of nitroimidazoles does give one the

options of injecting before interventions are started and imaging later, similar to protocols proposed for MIBI. For these purposes, the longer-lived radioiodine-labeled IVM or IAZA and technetium compounds have some advantages over the  $^{18}\text{F}$ -labeled compounds.

What then is the importance of the paper by Martin et al.? First, the development of new single-photon radiopharmaceuticals is the life-blood of clinical nuclear medicine. Recent commentaries on the future of nuclear medicine in this journal (18–21) have concentrated too much on training, manpower and political issues and have omitted the need for new radiopharmaceuticals as factors of importance. Without new agents, the future of the field is bleak, as progress will be dependent upon extracting new life from existing agents. There is no doubt that this can be done. The use of the thallous ion to measure tumor viability is a good example (22). There is, however, a limit to the extractable net worth yet to be discovered in existing agents. Nitroimidazoles may constitute a new marketable class of compounds that can help nuclear medicine do what no other imaging modality can do and thus attract more practitioners (not just physicians) into the field. New classes of compounds take tremendous time and effort to identify and market, and the development of IVM and IAZA represents steps along the way.

Second, the development of IVM, IAZA and technetium-labeled nitroimidazoles clearly demonstrates that SPECT has a role to play in the assessment of viability in the same way that the radioiodine-labeled receptor binders such as CIT (23) and somatostatin analogues (1) have shown that PET does not have sole ownership of the measurement (quantitative or qualitative) of receptors *in vivo*.

Third, the development of the radioiodine-labeled nitroimidazoles has taken significant time and effort by a number of groups. The two compounds that have progressed the farthest do not have the same characteristics (24) and further development is

planned. Conversion to technetium-labeled compounds is occurring, but marketing will not come quickly nor inexpensively because of the tremendous effort it takes to develop new classes of compounds.

Finally, the development of viability indicating compounds will exercise the minds of the regulators and the regulated as to how to design clinical trials that will show not only *efficacy* (Do the compounds allow the prediction of viability?) but also, given this new economic climate, *efficiency* (Do the compounds provide a prediction of viability by nuclear medicine procedures less expensive than other (imaging) modalities?) These two yardsticks of efficacy and efficiency are now being asked of nuclear medicine. Therefore, new radiopharmaceuticals are one of the major factors in determining the future viability of nuclear medicine.

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## REFERENCES

- Larson S. Receptors on tumors studied with radionuclide scintigraphy. *J Nucl Med* 1991;32:1189-1191.
- Martin GV, Biskupiak JE, Caldwell JH, Rasey JS, Krohn KA. Characterization of iodovinylmisonidazole as a marker for myocardial hypoxia. *J Nucl Med* 1993;34:918-924.
- Opie LH. *Stunning, hibernation and calcium in myocardial ischemia and reperfusion*. Boston: Kluwer; 1992.
- Goldstein RA. Wanted: dead or alive—the search for markers of myocardial viability. *J Am Coll Cardiol* 1990;16:486-488.
- Kalf V, Schwaiger M, Nguyen N, McClanahan TB, Gallagher KP. The relationship between myocardial blood flow and glucose uptake in ischemic canine myocardium determined with fluorine-18-deoxyglucose. *J Nucl Med* 1992;33:1346-1353.
- Opie LH, Camici PG. Myocardial blood flow, deoxyglucose uptake and myocyte viability in ischemia. *J Nucl Med* 1992;33:1353-1356.
- Schelbert HR. Euglycemic hyperinsulinemic clamp and oral glucose load is stimulating myocardial glucose utilization during positron emission tomography. *J Nucl Med* 1992;33:1263-1266.
- Tamaki N. Myocardial FDG PET studies with the fasting, oral glucose loading or insulin clamp methods. *J Nucl Med* 1992;33:1263-1268.
- Connett RJ, Honig CG, Gayeski EJ, Brooks GA. Defining hypoxia: a system's view of  $\dot{V}O_2$ , glycolysis, energetics, and intracellular  $PO_2$ . *J Appl Physiol* 1990;68:833-842.
- Vanderkooi JM, Erecinska M, Silver IA. Oxygen in mammalian tissue: methods of measurement and affinities of various reactions. *Am J Physiol* 1991;260:C1131-C1150.
- Chapman JD. Hypoxic sensitizers—implications for radiation therapy. *N Engl J Med* 1979;301:1429-1432.
- Shelton ME, Dence CS, Hwang D-R, Herrero P, Welch MJ, Bergmann SE. In vivo delineation of myocardial hypoxia during coronary occlusion using fluorine-18 fluoromisonidazole and positron emission tomography: a potential approach for identification of jeopardized myocardium. *J Am Coll Cardiol* 1990;16:477-485.
- Martin GV, Caldwell JH, Graham MM et al. Noninvasive detection of hypoxic myocardium using fluorine-18-fluoromisonidazole and positron emission tomography. *J Nucl Med* 1992;33:2202-2208.
- Koh W-J, Rasey JS, Evans ML, et al. Imaging of hypoxia in human tumors with [ $F-18$ ]fluoromisonidazole. *Int J Radiat Oncol Biol Phys* 1991;22:199-212.
- Valk PE, Mathis CA, Prados MD, Gilbert JC, Budinger TF. Hypoxia in human gliomas: demonstration by PET with fluorine-18-fluoromisonidazole. *J Nucl Med* 1992;33:2133-2137.
- Parliament MB, Chapman JD, Urtasun RC, et al. Non-invasive assessment of human tumour hypoxia with I-123-iodoazomycin arabinoside: preliminary report of a clinical study. *Br J Cancer* 1992;65:90-95.
- DiRocco RD, Kuczyński BL, Pirro JP, et al. Imaging ischemic tissue at risk of infarction during stroke. *J Cereb Blood Flow Metab* 1993: in press.
- Maynard CD. Medical imaging in the nineties: new directions for nuclear medicine. *J Nucl Med* 1993;34:157-164.
- Wagner HN Jr. The new molecular medicine. *J Nucl Med* 1993;34:165-166.
- Holman BL. We are training our future. *J Nucl Med* 1993;34:167-168.
- Ell PJ. The future of nuclear medicine: a perspective from Europe. *J Nucl Med* 1993;34:169-170.
- Mountz JM, Raymond PA, McHeever PE, et al. Specific localization of thallium-201 in human high-grade astrocytoma by microautoradiography. *Cancer Res* 1989;49:4053-4056.
- Neumeyer JL, Wang S, Milius RA, et al. [ $^{123}I$ ]-2 $\beta$ -carbomethoxy-3 $\beta$ -(4-iodophenyl)tropane: high-affinity SPECT radiotracer of monoamine reuptake sites in the brain. *J Med Chem* 1991;34:3144-3146.
- Biskupiak JE, Krohn KA. Second generation hypoxia imaging agents. *J Nucl Med* 1993;34:411-413.