SPECT of the Brain and Heart—Future Directions

While single photon emission computed tomography (SPECT) has been with us for over a generation (*1*), its initial impact was slight. Recently SPECT has undergone a period of rapid growth. Nevertheless, if SPECT is to become an integral part of our clinical practice, there are several imperatives which must be met.

We Must Improve Spatial Resolution

We must maximize spatial resolution not only for technetium-99m but for other radionuclides as well. Iodine (^{123}I) and gallium-67 will continue to play important roles in the future of radiopharmaceutical development. Optimization of the rotating gamma camera must include improvements in software (reconstruction algorithms and attenuation corrections), system electronics, and detector and collimator design. For example, the quality of ^{123}I imaging has improved dramatically with the introduction of cast collimators, slant hole collimators (*2*), long bore collimators (*3*), and fan-beam collimators (*4*).

Gamma camera technology can be pushed only so far, however. While smaller community hospitals will continue to use the rotating gamma camera, patient volume will be great enough in most medical centers to justify special purpose instruments dedicated, for example, to brain imaging. Imaging systems with substantially greater crystal areas surrounding the target will result in high spatial and contrast resolution as well as greater sensitivity (*5*). While rotating gamma camera systems will be limited largely to radiotracers that are locked within the organ of interest, special purpose instruments will permit kinetic studies using radiotracers that have relatively short residence times within the brain. Rapid serial studies will also be possible, so that patients can be studied under a variety of pharmacologic and physiologic interventions.

We Must Develop a Spectrum of Radiopharmaceuticals

We already have a number of SPECT radiopharmaceuticals for evaluating brain function. Brain blood flow/metabolism can be studied with [^{123}I]IMP (*6*), [^{123}I]HIPDM (*7*), thallium-201 (^{201}Tl) DDC (*8*), [^{99m}Tc]HM-PAO (*9*) or [^{99m}Tc]ECD. Receptor function has been studied in the human using [^{123}I]IQNB, a muscarinic acetylcholine receptor antagonist (*10*) and promising animal studies have been performed using dopamine-1 and dopamine-2 antagonists (*11*).

We have already discovered that radiopharmaceutical development is not a straightforward progression from ^{123}I compounds to ^{99m}Tc compounds. In the brain, [^{123}I]IMP and [^{99m}Tc]HM-PAO do not measure the same thing. In patients with subacute strokes, [^{99m}Tc]HM-PAO follows perfusion and is associated with normal or increased uptake in the area of luxury perfusion while [^{123}I]IMP measures brain metabolism and is associated with decreased uptake in the same regions (*12*). In addition, positron emission tomography (PET) studies have shown us that we will learn far more from measuring both cerebral blood volume and cerebral perfusion than we will from perfusion alone (*13*). As a result, it is very likely that brain imaging will use a combination or even spectrum of radiotracers.

The development of single photon labeled receptor antagonists may very often follow leads derived from studies performed using position emission tomography (PET) technologies. It is far easier to synthesize new PET radiopharmaceuticals than single photon analogs. After

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these tracers have been screened using PET, the most promising approaches can be followed up by synthesizing appropriate single photon tracers. At the same time, there may very well be iodine containing pharmaceuticals which will lend themselves to single photon labeling more readily than positron labeling. Iodine-123 IQNB, a muscarinic acetylecholine antagonist is one such example. Studies in the human demonstrated muscarinic receptor binding as the principal mode for intracellular binding (*14*). Studies in patients with Alzheimer's disease demonstrated only mild reductions in receptor function in the face of more profound deficits in blood flow (*10*). These studies led to in vivo confirmation of etiologic hypotheses which could only be inferred by autopsy studies prior to the availability of SPECT imaging.

We Must Develop and Validate Techniques That Provide Diagnostically Unique and Important Information for Common Diseases

Too often, we get caught up in our search for technological improvements and innovations without exploring first the broader issues relating to the application and potential duplication of these technologies. An example of marrying our technology to a frequently occurring disease is neuroimaging in dementia. Alzheimer's disease is common, cannot be diagnosed at the time of initial clinical presentation in approximately half of the patients with the disease, and no technique short of brain biopsy provides clinically reliable diagnostic information in these patients.

Using clues derived from positron emission tomography studies, SPECT has been applied to patients with Alzheimer's disease with good initial success (*15–17*). Most patients with Alzheimer's disease have abnormal perfusion patterns even at the time of the initial clinical presentation. The abnormality is limited primarily to the associative cortex and is greatest in the posterior temporoparietal regions. In fact, the posterior temporoparietal regions are the only areas in which the severity of disease correlates inversely with [^{123}I]IMP uptake.

Alzheimer's disease is not the ideal example of marrying SPECT with clinical needs. For diagnostic tests to be clinically useful, the technology must not only provide accurate information about the disease but it must also affect patient outcome. SPECT functional imaging is useful in diagnosing treatable or benign conditions such as depression or vascular dementia and reduces the emotional and financial impact of misdiagnosis during the early course of Alzheimer's disease, but the test does not impact on patient outcome in the majority of patients with Alzheimer's disease because there is as yet no adequate therapy.

A test that has provided unique information and also impacts heavily on patient outcome is myocardial perfusion imaging in suspected coronary artery disease. Here we have a clinically accepted technique which has provided us with a rich lode of clinical information over the past decade.

Unfortunately as we attempt to transfer this technology from planar imaging to SPECT, we find that ^{201}Tl, a most satisfactory imaging agent for planar imaging, is not satisfactory for SPECT because of its (a) low photon flux, (b) low photon energy, and (c) redistribution. To improve spatial resolution and to permit combining planar and SPECT imaging in a more efficient manner, ^{99m}Tc-labeled agents which remain in the myocardium are preferable. The isonitriles have a number of family members which are most promising candidates (*18–20*). Technetium-99m MIBI is an isonitrile with high myocardial uptake, binding primarily within the cytosol of the myocardial cell. Myocardial uptake is similar to that of ^{201}Tl over a wide range of flows and does not wash out of ischemic or normal myocardium. With little or no hepatic or pulmonary uptake, the agent is ideal for SPECT imaging. The isonitriles open up new opportunities because injection can be performed at sites distant from the nuclear medicine clinical unit and because imaging of transient physiologic events can be performed after the time of injection.

We Must Develop and Validate Reliable Quantitative Techniques

Quantitative SPECT has been suggested for measuring tissue volume and tracer activity. Absolute measures of tracer activity levels are extremely difficult to measure accurately with existing instrumentation, particularly in the myocardium. Spatial resolution is insufficient, partial volume effects are large and attenuation corrections are difficult.

On the other hand measures of tissue volume can be performed with reasonable accuracy.

Using infarct avid agents such as [^{99m}Tc]pyrophosphate, we have shown that measurement of infarct size correlates directly with patient prognosis (*21*). With infarcts >40 g by SPECT, patient morbidity was >85% while the morbidity was <29% with infarcts <40 grams. Measurements with ^{99m}Tc-labeled perfusion tracers should allow us to closely measure and monitor the extent of transient ischemia by comparing pre- and poststress studies and by measuring the volume of normally perfused myocardium.

Quantitative techniques are also essential for reducing the information overkill associated with SPECT. With standard SPECT techniques we are looking at two, not three, dimensional images. Integration of two dimensional cross-sectional images reconstructed in multiple planes is an extremely difficult task for the human brain. It is much easier for the eye-brain complex to interpret a single reconstructed three dimensional image, preferably, as a cine display. The bull's-eye plot is a successful example of data compression ideally suited for SPECT myocardial perfusion imaging with either ^{201}Tl or ^{99m}Tc isonitriles (*22*). The three dimensional surface map is another useful method. Surface images are created by projecting three dimensional isocontour surfaces within the transaxial slice space onto a viewing plane. In practice, the three-dimensional surface map provides a cinematic display of organ tracer distribution. When applied to perfusion brain imaging in Alzheimer's disease, for example, we are able to clearly define the geographical distribution of the deficits, facilitating recognition of the disease as one affecting the associative areas of the brain. High uptake in the primary cortex including the primary motor and sensory strip along the central fissure, occipital lobe, and cerebellum is far more clearly defined with this method than with two dimensional cross-sectional imaging techniques.

CONCLUSION

There are several reasons why progress in SPECT technology has lagged behind that in other cross-sectional imaging modalities such as computed tomography and magnetic resonance.

1. Industry has been unwilling to commit resources into SPECT on the same scale as CT or MR. Indeed the latter two cross-sectional techniques have drained intellectual and financial resources from SPECT.
2. For almost two decades, SPECT played only a marginal role complementing planar imaging. Until the 1980s, no radiopharmaceutical required SPECT for diagnostic imaging.
3. Finally, research dollars allocated for emission tomography have been monopolized by positron emission tomography.

Over the past four or five years we have seen some changes which make me reasonably optimistic that the imperatives that I have discussed will be met and that SPECT will play an important and rapidly expanding role in clinical nuclear medicine. The development of tracers for brain and heart imaging which require tomography has forced industry to pay more attention to SPECT. A number of independent approaches to special purpose neuro-instrumentation, if pursued actively, could lead to substantial improvements in image quality. The widespread availability of rotating gamma cameras will encourage the development of high volume diagnostic techniques using SPECT rather than the far more expensive and less available PET technologies. Finally as single photon radiodiagnostics emerge with unique roles as diagnostic agents and physiologic markers, we will see a more balanced distribution of research dollars into critically important PET oriented research efforts and into the increasingly unique applications of SPECT imaging.

REFERENCES

1. Kuhl DE, Edwards RQ. Image separation radioisotope scanning. *Radiology* 1963; 80:653–662.
2. Polak JF, Holman BL, Moretti J-L, Eisner RL, Lister-James J, English RJ. I-123 HIPDM brain imaging using a rotating gamma camera equipped with a slant-hole collimator. *J Nucl Med* 1984; 25:495–498.
3. Mueller SP, Polak JF, Kijewski MF, Holman BL. Collimator selection for SPECT brain imaging: The advantage of high resolution. *J Nucl Med* 1986; 27:1729–1738.
4. Tsui BMW, Gullberg GT, Edgerton ER, Gilland DR, Perry JR, McCartney WH. Design and clinical utility of a fan beam collimator for SPECT imaging of the head. *J Nucl Med* 1986; 27:810–819.

5. Hill TC, Costello P, Gramm HF, Lovett R, McNeil BJ, Treves S. Early clinical experience with a radionuclide emission computed tomographic brain imaging system. *Radiology* 1978; 128:803.
6. Holman BL, Lee RGL, Hill TC, et al. Cerebral perfusion imaging with I-123 labeled amines. *Arch Neurol* 1984; 41:1060–1063.
7. Kung HF, Tramposch KM, Blau M. A new brain perfusion imaging agent: I-123 HIPDM (N, N, N′-trimethyl-N′-2-hydroxy-3-methyl-5-iodobenzyl-1, 3-propanediamine). *J Nucl Med* 1983; 24:66–72.
8. deBruine JF, van Royen EA, Vyth A, de Jong JMB, van der Schoot JB. Thallium-201 diethyldithiocarbamate: an alternative to iodine-123 N-isopropyl-p-iodoamphetamine. *J Nucl Med* 1985; 26:925–30.
9. Ell PJ, Hocknell JML, Jarritt PH, et al. A Tc-99m-labelled radiotracer for the investigation of cerebral vascular disease. *Nucl Med Commun* 1985; 6:437–441.
10. Holman BL, Gibson RE, Hill TC, Eckelman WC, Albert M, Reba RC. Muscarinic acetylcholine receptors in Alzheimer's disease: in vivo imaging with iodine-123-labeled-3-quinuclidinyl-4-iodobenzilate and emission tomography. *JAMA* 1986; 254:3063–3066.
11. Kung HF, Billings JB, Guo Y-Z. In vivo biodistribution of SKF-103108A: a potential D-1 receptor site specific imaging agent. *J Nucl Med* 1986; 27:906.
12. Moretti JL, Cesaro P, Cinotti L, Defer G, Raynaud C, Ducassou D. Tomoscintigraphy and subacute strokes: Comparative application with HMPAO Tc-99m and IMP I-123. *J Nucl Med* 1987; 28:623.
13. Frackowiak RSJ, Pathophysiology of human cerebral ischemia: studies with positron tomography and 0-15. In: Sokoloff L, ed. *Brain imaging and brain function.* New York: Raven Press, 1985:139–160.
14. Eckelman WC, Reba RC, Rzeszotarski WJ, et al. External imaging of cerebral muscarinic acetylcholine receptors. *Science* 1984; 223:291–293.
15. Holman BL. Perfusion and receptor SPECT in the dementias-George Taplin Memorial Lecture. *J Nucl Med* 1986; 27:855–860.
16. Sharp P, Gremmell H, Cherryman G, Besson J, Crawford J, Smith F. Application of iodine-123-labelled isopropylamphetamine imaging to the study of dementia. *J Nucl Med* 1986; 27:761–768.
17. Cohen MB, Graham LS, Lake R, et al. Diagnosis of Alzheimer's disease and multiple infarct dementia by tomographic imaging of iodine-123 IMP. *J Nucl Med* 1986; 27:769–774.
18. Holman BL, Jones AG, Lister-James J, et al. A new Tc-99m-labeled myocardial imaging agent, hexakis (t-butylisonitrile) technetium (I) [Tc-99m TBI]: initial experience in the human. *J Nucl Med* 1984; 25:1350–1355.
19. Holman BL, Sporn V, Jones AG, et al. Myocardial imaging with technetium-99m CPI: initial experience in the human. *J Nucl Med* 1987; 28:13–18.
20. Sia STB, Holman BL. Dynamic myocardial imaging in ischemic heart disease: use of technetium-99m isonitriles. *Am J Cardiac Imaging* 1987; 1:125–131.
21. Holman BL, Goldhaber SZ, Kirsch C-M, et al. Measurement of infarct size using single photon emission computed tomography and Tc-99m-pyrophosphate: a description of the method and a comparison with patient prognosis. *Am J Cardiol* 1982; 50:503–511.
22. Garcia EV, Ezquerra NF, DePuey EG, et al. An artificial intelligence approach to interpreting thallium-201 3-dimensional myocardial distributions. *J Nucl Med* 1986; 27:1005.

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