Henry Ford Hospital Medical Journal

Volume 33
Number 2 *Medical Imaging 1985*

Article 14

6-1985

Current Concepts of Metabolic Functional Imaging with Positron Emitters

John W. Keyes Jr.

Henry Ford Hosp Med J
Vol 33, Nos 2 and 3, 1985

Current Concepts of Metabolic Functional Imaging with Positron Emitters

John W. Keyes, Jr, MD*

Positron emitting radionuclides have unique properties that make them nearly ideal as radioactive tracers for in vivo metabolic studies. Using positron emission tomographic (PET) scanning and positron-labeled radiopharmaceuticals, one can study local glucose metabolism in tissues, blood flow, oxygen utilization, protein synthesis, and many other functions noninvasively in normal subjects and patients who have various diseases. A review of some of these techniques and the relative advantages and problems associated with the PET approach is presented.

Developments in radiopharmaceutical science, nuclear medicine imaging technology, and computer modeling of biological processes have led to techniques that now permit the noninvasive measurement of basic physiologic processes within the human body. Determination of blood flow in tissues, local glucose metabolism in tissues, utilization of oxygen, efficiency of oxygen extraction from blood, and measurements of local receptor density and binding activity are all possible. The nuclear medicine techniques that make possible these determinations are designated the collective name of positron emission tomography (PET).

Requirements for Functional Imaging

To measure a physiologic process within the body (for example, local glucose metabolism in tissues), it is necessary to have a tag or tracer for glucose that can be accurately followed through the metabolic process. The ideal tracer must not disturb the measured physiologic process, must be safe, and should be measurable from outside the body for in vivo studies.

Commonly used positron radionuclides include positron emitting isotopes of carbon, oxygen, and nitrogen, which are the basic building-block atoms of organic molecules, and fluorine-18, which can be substituted for hydrogen in many organic molecules without significantly changing their biophysical behavior. These four radioisotopes provide positron emitting tags that can be synthesized into physiologically important substrates without altering the chemical or biophysical behavior of these substrates within the body. Thus, they meet the first criterion for an ideal tracer, not altering normal body biochemistry.

The positron mode of radioactive decay is unique among the radioactive tracers currently used for nuclear medicine imaging. The positron emitted during such decay represents an electron with a positive charge. Such a particle, unable to exist in normal matter, promptly undergoes what is called an annihilation reaction with a normal (negatively charged) electron. To satisfy the requirement for conservation of energy, two gamma rays are emitted as a result of this annihilation reaction. These gamma photons, which carry the energy equivalent of the rest-mass of two electrons, are given off in exactly 180° opposite directions from one another, providing an ideal format for external detection and localization. This pair of annihilation gamma rays are the means for easy, quantitative, noninvasive localization within the body.

When considering the use of radioactive tracers, safety usually refers to limiting patient radiation from the tracer. Positron-labeled tracers are usually safe for two reasons. First, because of the extremely short physical half-life of most positron emitters (Table) the radioactivity disappears from the body rapidly. Thus, total time of exposure is short, and the total integrated radiation dose is small. Second, because it is often possible to synthesize labeled compounds with high specific activities, only small amounts of labeled material must be administered to be detected.

The 180° opposed pair of annihilation photons provides ideal geometry for external localization and quantification of radiotracers within the body. The key to accurate external tracer imaging has been the development of positron emission tomographs, so-called PET scanners. The fact that a pair of gamma rays traveling in exactly opposite directions is emitted with each annihilation event is used to determine exactly the line along which the annihilation event occurred. Detectors placed on opposite sides of the body are directed toward each other and operated in what is known as the coincidence mode, wherein a radioactive decay event is not counted unless both detectors simultaneously detect a gamma ray. A ring of such detectors surrounding the body simultaneously measure the multiple lines of localization for many individual radioactive decay events. With this information and computer technology, a computed tomograph

Submitted for publication: February 18, 1985

Accepted for publication: May 17, 1985

* Catherine McAuley Health Center, Department of Radiology, Ann Arbor, MI 48106. Formerly Department of Diagnostic Radiology, Division of Nuclear Medicine, Henry Ford Hospital

Reprints not available

Table

Position Emitting Radionuclides in Current Use

Radionuclide	Physical Half-Life (minutes)
Oxygen-15	2.1
Carbon-11	20.4
Nitrogen-13	10.0
Fluorine-18	110.0
Gallium-68	68.5
Rubidium-81	274.8
Rubidium-82	1.3

of the distribution of radioactivity is calculated. The mathematics are exactly the same as those used in X-ray computed tomography, but the resulting tomogram shows the distribution of radioactivity rather than X-ray density. If the measurements are made properly and certain correction factors are applied, the resulting computed tomogram is a quantitatively accurate map of the distribution of radioactive tracer within a volume section of the body.

Modern PET scanners simultaneously produce multiple, contiguous tomographic images. In effect, such multisection PET scanners provide a three-dimensional image of the distribution of radioactive tracer within a given part of the body. Thus, using an appropriately selected positron-labeled radiopharmaceutical and a modern, multisection PET scanner, maps are constructed of the distribution and time-course of the metabolism of physiologic substrates within the body.

Finally, the use of positron technology to study in vivo processes requires a computerized mathematical model of the metabolism of a given physiologic substrate. For example, the tracer ^{18}F-fluoro-2-deoxy-D-glucose (FDG) is a positron-labeled analog of glucose. After intravenous administration of the tracer, its distribution within the body is related to the local rate of glucose metabolism by specific tissues. The ratio of the absolute tracer uptake of a specific tissue and the actual rate of glucose metabolism within that tissue is not one to one, however. Detailed knowledge of how the tracer is metabolized and localized within the tissue is necessary to evaluate results of the study. Knowledge of the exact process permits construction of a mathematical model and a computer program that will convert the initial PET scan of FDG detected within the tissue into a map of local glucose metabolism.

Currently, models are available for accurately measuring local tissue glucose metabolism rates (1,2), blood flow within specific tissues (3-5), oxygen utilization within specific tissues (4,5), and the extraction fraction of oxygen from blood circulation through a given organ or area of an organ (4). A great deal of work now underway is designed to measure local tissue receptors for a variety of biochemical messengers (6,7). Similarly, investigators are trying to develop accurate models for parameters such as blood-brain barrier permeability and local rates of protein synthesis (8).

Applications of PET Scanning

Every physiologic/metabolic process is potentially amenable to investigation using PET techniques, provided a suitable tracer can be synthesized in a short enough period of time. Methods for studying a large number of physiologic processes have already been developed and applied to many normal and pathologic conditions. A large percentage of PET research has focused on normal and abnormal central nervous system (CNS) function. A few selected examples serve to introduce the beauty and depth of these techniques.

Cerebral glucose metabolism rate

When administered intravenously, the tracer FDG enters the metabolized pool of glucose and is taken up by cells that are actively metabolizing glucose. Once within the cell, FDG is phosphorylated but cannot progress further in the metabolic pathway for glucose. In essence, the labeled compound becomes trapped in the cell. By obtaining a PET scan after the administration of FDG, the local rate of glucose metabolism can be calculated using an appropriate computer model, and the result can be presented as a functional image, a quantitative map of the rate of glucose metabolism in the tissue (1).

Figure 1 is an example of such a functional image of glucose metabolism in the normal human brain. Images are shown at four levels. The darker the area, the greater the local

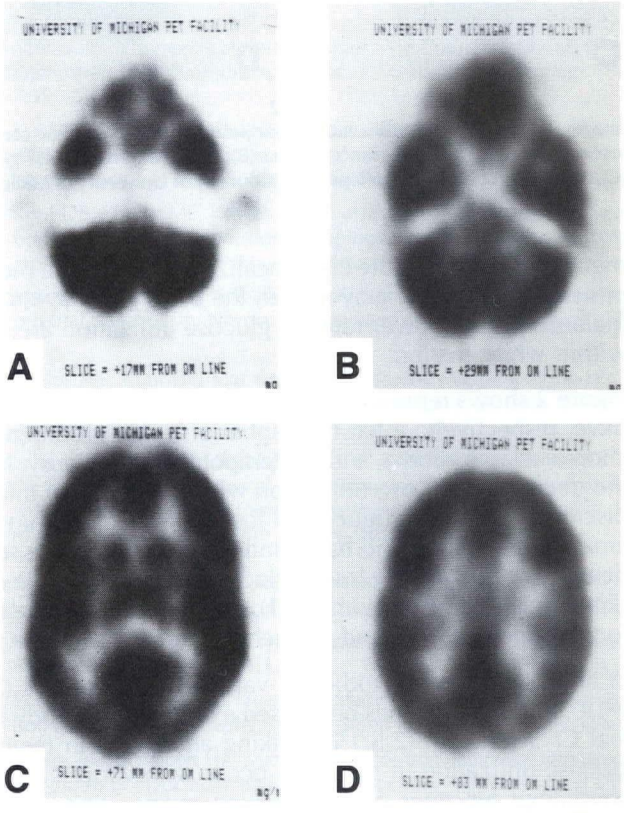

Fig 1

Computer processed functional images depicting glucose metabolic rate in healthy 26-year-old male volunteer. Scale is in mg of glucose metabolized per minute per 100 g of tissue. Sections are contiguous; A = lowest, D = highest. (Courtesy of University of Michigan.)

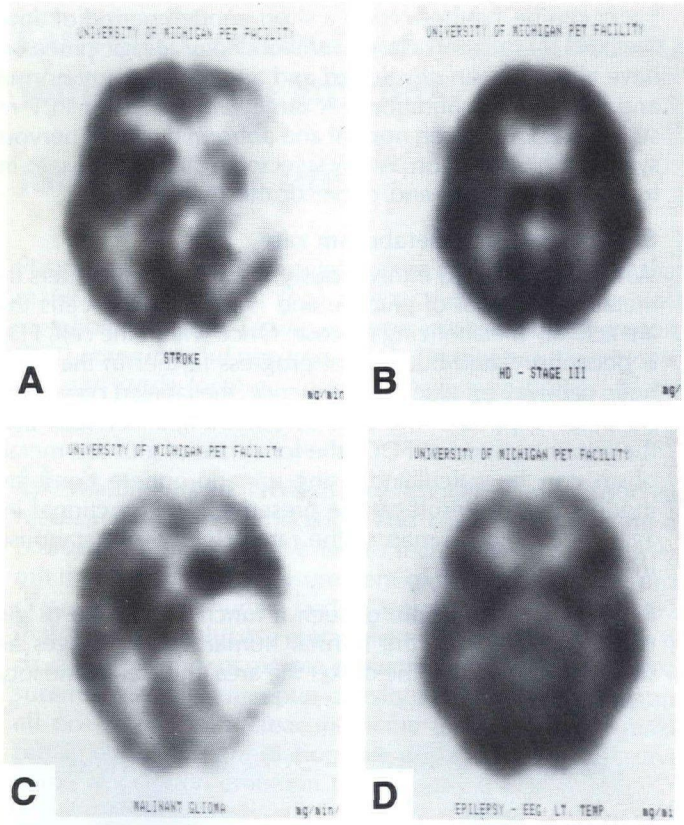

Fig 2
Images of glucose metabolism rate in four patients with left middle cerebral artery infarct (A), Huntington's chorea (B), left temporoparietal glioma (C), and left temporal lobe epilepsy (D). (Courtesy of University of Michigan.)

metabolic rate. Note the clear localization of glucose metabolism in the cerebral gray matter, the basal ganglia, and the thalamus; much lower rates of glucose utilization are seen within white matter.

Figure 2 shows representative sections of four patients who have, respectively, a left hemispheric stroke, Huntington's chorea, a large glioma, and left temporal lobe epilepsy. Note the decreased glucose utilization within the area of infarct, disclosing the tissue injury and loss of function within this area. In the patient who has Huntington's chorea, the study demonstrated a striking loss of glucose in the area of the caudate nuclei (compare with Fig 1), concordant with the anatomic abnormality found in such patients.

In addition to many studies of various CNS diseases (2-4, 9-14), PET scanning has been used extensively to study normal CNS function (2,5,15). Striking alterations in regional glucose utilization in the brain occur with various normal physiologic functions such as listening, memorizing, and seeing (15,16). For example, Mazziotta and coworkers (15) demonstrated changes in lateralization of function related to hearing that depended on whether the individual was listening to music or speech.

Cerebral blood flow

A number of methods have been developed to measure cerebral blood flow using PET methods (3-5). Figure 3 is a representative example of a functional map of cerebral blood flow in a normal individual. The tracer was oxygen-15 labeled water. As expected in this normal subject, the local cerebral blood flow rather closely paralleled the local cerebral metabolic rate for glucose (Fig 1). This parallelism does not exist in many disease states; physiologic/metabolic imbalances have been documented in such states as acute stroke, luxury-perfusion syndrome, misery-perfusion syndrome, and neoplasm (3,4).

Other applications

Much excellent work relating PET methods to heart and myocardial metabolism has been accomplished. Because the heart normally uses free fatty acids as a primary substrate for energy metabolism, carbon-11 labeled palmitic acid is an excellent tracer for determination of myocardial metabolism. Schon et al produced functional images of local myocardial fatty acid metabolic rate and have studied a wide variety of cardiac conditions with this technique (17).

Problems and Predictions

The ability to make such elegant measurements of various

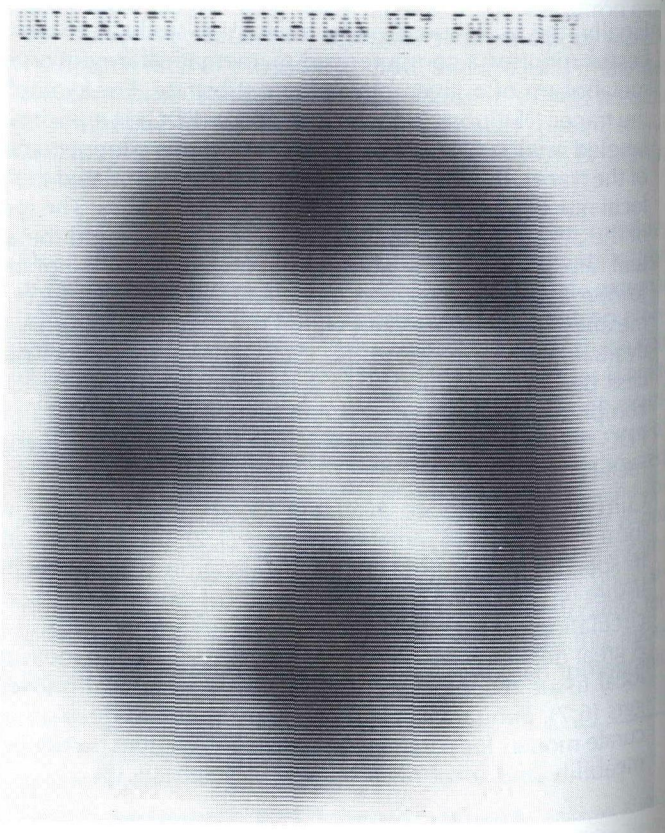

Fig 3
Functional image of cerebral blood flow in normal subject. Calculated using ^{15}O-H_2O method. (Courtesy of University of Michigan.)

physiologic processes within the body is bought at a price, however. The physical half-life of the various positron emitting radioisotopes is quite short (Table). Fluorine-18, for example, has a physical half-life of less than two hours, and oxygen-15, a half-life of only two minutes. Elaborate and technologically complex solutions are required in order to use tracers that have such an evanescent existence. Typically, a fully equipped radiosynthetic chemistry laboratory is needed immediately adjacent to the scanning site. Most positron emitting radionuclides are produced using cyclotrons that are small enough to be installed and operated physically close to a medical research facility. A large number of positron research sites developed around the world in recent years have on-site cyclotrons for the local, immediate production of the tracer radioisotopes that they use. However, in their present state of development, these machines are not suitable for routine clinical production of radionuclides.

Metabolic research using positron-labeled radiotracers requires a relatively elaborate and technically complex underpinning. An on-site cyclotron, a specially tailored radiochemistry and radiopharmaceutical synthetic facility, a PET scanner, and relatively sophisticated computing and image processing facilities are all necessary to conduct such research successfully. Work is currently underway in many centers to simplify, miniaturize, and automate many of these procedures; it may be possible in the future to incorporate positron technology into general patient care, at least at large tertiary care centers. For the present, this approach to medical imaging and physiologic research remains a highly specialized, albeit extremely elegant and productive, means of examining the human body.

Acknowledgment

The author thanks Mrs Andrea Harper for her editorial assistance.

References

1. Phelps ME, Huang SC, Hoffman TJ, et al. Tomographic measurement of local cerebral glucose metabolic rate in humans with (F-18) 2-fluoro-2-deoxy-D-glucose: Validation of method. Ann Neurol 1979; 6:371-88.
2. DiChiro G, Oldfield E, Bairamen D, et al. Metabolic imaging of the brain stem and spinal cord: Studies with positron emission tomography using ^{18}F-2-dexoyglucose in normal and pathological cases. J Comput Assist Tomogr 1983;7:937-45.
3. Ackerman RH, Subramanyam R, Correia JA, et al. Positron imaging of cerebral blood flow during continuous inhalation of $C^{15}O_2$. Stroke 1980; 11:45-9.
4. Baron JC, Bousser MG, Comar D, et al. Noninvasive tomographic study of cerebral blood flow and oxygen metabolism in vivo. Eur Neurol 1981; 20:273-84.
5. Frackowiak RSJ, Lenzi GL, Jones T, et al. Quantitative measurements of regional cerebral blood flow and oxygen metabolism in man using ^{15}O and positron emission tomography: Theory, procedures, and normal values. J Comput Assist Tomogr 1980;4:727-36.
6. Friedman AM, Huang C, Kulmala, HA, et al. The use of radiobrominated p-bromospiroperidal for x-ray imaging of dopamine receptors. Med Biol Eng Comput 1982;9:57-61.
7. McElvany KD, Katzenellenbogan JA, Shafer KE, et al. 16 (^{77}Br) bromoestradiol: Dosimetry and preliminary clinical studies. J Nucl Med 1982;23:425-30.
8. Bustany P, Sargent T, Saudubray JM, et al. Regional human brain uptake and protein incorporation of ^{11}C-L-methionine studied in vivo with PET. J Cereb Blood Flow Metab (Suppl) 1981;1:517-8.
9. Benson DF, Kuhl DE, Hawkins RA, et al. The fluorodeoxyglucose ^{18}F scan in Alzheimer's disease and multi-infarct dementia. Arch Neurol 1983;40;711-4.
10. deLeon MJ, George AE, Ferris SH, et al. Positron emission tomography and computed tomography assessments of the aging human brain. J Comput Assist Tomogr 1984;8:88-91.
11. Frackowiak RSJ, Pozzilli C, Legg NJ, et al. Regional cerebral oxygen supply and utilization in dementia. A clinical and physiological study with oxygen-15 and positron tomography. Brain 1981;104:753-78.
12. Friedland RP, Budinger TF, Ganz E, et al. Regional cerebral metabolic alterations in dementia of the Alzheimer type: Positron emission tomography with (^{18}F) fluorodeoxyglucose. J Comput Assist Tomogr 1983; 7:590-8.
13. Kuhl DE, Phelps ME, Kowell AP, et al. Effects of human aging on patterns of local cerebral glucose utilization determined by (^{18}F) fluorodeoxyglucose method. J Cereb Blood Flow Metab 1982;2:163-71.
14. Kuhl DE, Phelps ME, Kowell AP, et al. Effects of stroke on local cerebral metabolism and perfusion: Mapping by emission computed tomography of ^{18}FDG and $^{13}NH_3$. Ann Neurol 1980;8:47-60.
15. Mazziotta JC, Phelps ME, Miller J, et al. Tomographic mapping of human cerebral metabolism: Normal unstimulated state. Neurol 1981;31:503-16.
16. Phelps ME, Kuhl DE, Mazziotta JC. Metabolic mapping of the brain's response to visual stimulation: Studies in humans. Science 1981;211: 445-8.
17. Schon HR, Schelbert HR, Najafi A, et al. C-11 labeled palmitic acid for the noninvasive evaluation of regional myocardial fatty acid metabolism with positron computed tomography: I. Kinetics of C-11 palmitic acid in normal myocardium. Am Heart J 1982;103:532-47.

The following reviews are excellent sources for further information and include in-depth review of the current literature:

Beaney RP. Positron emission tomography in the study of human tumors. Semin Nucl Med 1984;14:324-41.

Phelps ME, Mazziotta JC, Huang SC. Study of cerebral function with positron computed tomography. J Cereb Blood Flow Metab 1982;2:113-62.

Phelps ME, Schelbert HR, Mazziotta JC. Positron computed tomography for studies of myocardial and cerebral function. Ann Intern Med 1983; 98:339-59.