PET Imaging in Neurology

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This is the third article of the four-part series on PET imaging. Upon completion of this article, the reader should be able to (1) identify the radiotracers used in neuro-PET imaging, (2) be aware of the technical considerations, and (3) understand the practical applications of neuro-PET imaging.

Positron emission tomography (PET) imaging, a relatively noninvasive physiologic imaging technique, makes it possible to observe metabolic and biochemical changes in the human brain as it performs its basic and specific task-depended functions. Historically, not unlike first applications of computed tomography, PET imaging was used early on for examining the brain. PET has slowly evolved from a research tool to a clinically applicable diagnostic imaging modality and has been expanded into extracranial areas. The spectrum of PET imaging now includes important applications in cardiology and oncology. The history, the technical aspects of radiotracer production, instrumentation, and an overview of the utility of PET have been described in the first article (*1*) of this series on PET.

This article will focus on PET applications in patients with complex partial epilepsy, cerebrovascular disease, dementia, and brain tumors. The use of PET for examining patients with mental functional illnesses is being developed at several PET research centers and will be discussed briefly.

A description of useful parameters that can be evaluated by PET brain studies, the appropriate radiotracers and technical aspects of "neuro-PET" are described first. Examples of practical PET in neurology are given in the second half of this article.

NEURO-PET TECHNOLOGY

Radiotracers for Neuro-PET Studies

The biochemical and physiologic parameters that can be examined and/or measured by PET are listed in Table 1. Cerebral blood flow (CBF) and the cerebral metabolic rate of glucose, global or local, (lcMRGlu) are the most commonly examined. There is a strong relationship between brain function, CBF, and metabolism. The tracer kinetic models for CBF and lcMRGlu have been established and validated (*2*, *3*) and both parameters can be measured by state of the art PET instrumentation. Cerebral blood flow PET studies can be performed with $H_2{}^{15}O$ after i.v. bolus injection (*4*) or $C^{15}O_2$ inhalation and PET at steady state conditions (*2*). The latter method is technically more complex than the bolus method and the radiation dose from the gas to the trachea may be a limiting factor. CBF studies also often used nitrogen-13 labeled ammonia.

Cerebral glucose metabolism can be assessed by [^{18}F]-2-deoxyglucose (FDG) or [^{11}C]-2-deoxyglucose. Fluorine-18-FDG is the preferred agent because of its more convenient half-life (110 min compared to 20 min for ^{11}C). When using glucose for static imaging, data acquisition typically starts 40-45 min postinjection. Although ^{11}C-glucose is more physiologic than [^{18}F]FDG, it enters complex metabolic pathways immediately after injection, thus making analysis of PET images more difficult.

Regional oxygen metabolism is measured by determining the cerebral extraction of inhaled $^{15}O_2$ gas, the total arterial oxygen content, and CBF. The logistics of this method are complex and, therefore, measuring O_2 metabolism is not a routine PET application.

Other parameters that can be determined are amino acid transport and protein synthesis. Amino acids that have been used to study transport are L-methionine, L-leucine, DL-tryptophan, L-valine, L-glutamine, L-glutamate and several other natural amino acids and unnatural amino acids such as aminocyclobutanecarboxylic acid or aminocyclohexanecarboxylic acid. Amino acid analogs are most suitable in measuring transport because they cannot be metabolized. Natural amino acids enter metabolic pathways and are incorporated into protein and are, therefore, suitable to measure the rate of protein synthesis. L-leucine, L-phenylalanine, and L-methylmethionine, all labeled with ^{11}C, have been used for this purpose.

Measuring the pH in selected regions of the brain by using ^{11}C-dimethyloxazolidinedione (DMO) is a research application and provides no clinical utility at the present time. Finally, there are radioligands for PET neuroreceptor studies

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TABLE 1. PET Assessment of Neurologic Disorders

1. Energy
2. Blood flow
3. Receptor analysis
4. pH
5. Metabolism
6. AA transport
7. Protein synthesis

that are currently used in research, which may eventually lead to clinical applications. Some of these radiotracers and their corresponding neuroreceptors are shown in Table 2.

Patient Preparation for Neuro-PET Studies

When using PET to study neurologic disorders, we want to recognize or measure focal, regional, or global differences in blood flow, metabolism, or more specific neurochemical relationships between the various regions of the brain. A group at the University of California at Los Angeles has shown that activation of visual, auditory, cognitive, sensory, motor, and memory areas of the brain results in increased glucose uptake in the respective regions (*5*). The sensitivity of the brain in receiving and processing information poses a problem and makes the task of neuro-PET imaging more difficult. The external environmental conditions (noise, temperature, lighting, patient discomfort) superimpose complex metabolic patterns upon the specific response pattern that we want to examine. Patched eyes, plugged ears or open eyes and ears are recommended resting conditions. At our institution, we use patched eyes and plugged ears.

The patient preparation protocol is as follows:

1. NPO for 4 hr prior to PET scan.
2. Patient well hydrated.
3. Move patient to quiet waiting/prep area 15 to 30 min before PET scan.
4. Start i.v. 1 × 20 gauge intracath (do not use scalp vein set).
5. Start slow i.v. drip of normal saline.
6. Keep patient comfortable and calm until moved into the scanning room.
7. Avoid the use of sedation, if possible.

Performing a PET Brain Scan

The patient is placed on the scanner table and moved into the gantry so that the head is positioned with the orbitomeatal line (OM line) parallel to the "coincidence lines" of the detectors. A transmission scan using an external germanium-68 source is made to collect data for attenuation correction. Following the transmission scan the radiotracer is injected and emission scanning is started either immediately or 45 min (FDG) postinjection. The distribution of the radiotracers is recorded by the detectors for computer-aided reconstruction of activity distribution images. If the metabolic rate of glucose is to be measured, multiple arterial blood samples have to be drawn to obtain the input functions for the tracer kinetic model: [^{18}F]FDG and glucose in the blood. The final image on the computer screen is a display of the metabolic rate of glucose within the structures of the brain. Our protocol and time line for a quantitative FDG brain scan is shown in Figure 1.

TABLE 2. Applications of Cyclotron-Produced Radiopharmaceuticals in Neuro-PET

Isotope	Radiopharmaceutical	Application
^{11}C	^{11}CO	Blood volume
	Methionine	Protein synthesis
	Glucose	Glucose metabolism
	Methyl-D-Glucose	Glucose transport
	Etorphine	Opiate receptor mapping
	Flunitrazepam	Benzodiazepine receptor mapping
	L-dopa	Dopamine receptor mapping
	Pimozide	Dopamine receptor mapping
^{13}N	Ammonia	Blood flow
^{15}O	$H_2{}^{15}O$	Blood flow
	$C^{15}O_2$	Blood flow, oxygen metabolism
	$C^{15}O$	Blood volume
	$^{15}O_2$	Oxygen metabolism
^{18}F	Deoxyglucose	Glucose metabolism
	Antipyrine	Blood flow
	Dopa	Dopamine receptor mapping
	Haloperidol	Dopamine receptor mapping
	Spiroperidol	Dopamine receptor mapping

Quantitation of PET Data

Measuring the metabolic rate of glucose or CBF requires validated tracer kinetic models, and input functions from arterial blood samples for solving mathematical equations. This is time-consuming and labor-intensive for the nuclear medicine technologist and the staff in the image processing laboratory.

The question is, how much quantitation is necessary for clinical PET imaging and to what extent are measurements in absolute quantities (μmole/min/unit) needed? Of course, strict tracer kinetic methods need to be followed if precise measurements of biochemical processes are required in research designed to advance the understanding of the biology and function of the brain. For practical PET imaging aimed at solving clinical problems, less complex analytical procedures should be adequate. Methods simpler than the autoradiographic approach by Sokoloff (*6*), such as the graphic method by Patlak (*7*) or even simpler dynamic methods that purely analyze activity concentration ratios, should be sufficient for clinical PET studies.

Whatever method is to be applied to answer a specific diagnostic question in clinical neuro-PET imaging, the nuclear medicine technologist will have to perform various analyses such as (a) comparing average counts per pixel from one region of interest (ROI) to another, (b) producing sequential activity distribution profiles through serial tomographic images of a PET study, or (c) calculating differential absorp-

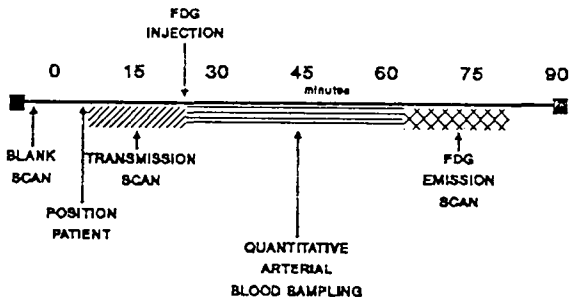


FIG. 1. Protocol and time-line for a quantitative FDG brain scan.

tion ratios (DAR) for ROIs of dynamic PET studies (*8*). Processing of PET data adds, albeit not insignificantly, to the workload of the nuclear medicine PET technologist.

PRACTICAL PET APPLICATIONS FOR NEUROLOGIC DISORDERS

Neurologic disorders for which PET has been of diagnostic value are complex partial epilepsy, cerebrovascular disease (strokes), dementia, and brain tumors. Typical examples for PET scan findings/patterns obtained with [^{18}F]FDG, $^{13}NH_3$, $H_2{}^{15}O$ and ^{11}C-aminocyclobutanecarboxylic acid (ACBC) for these different neurologic problems are presented in the subsequent portion of this paper.

Complex Partial Epilepsy

According to the council report of the American Medical Association (*9*), approximately 800,000 epileptics in the U.S. are resistant to drug therapy and some of them would benefit from surgery if the epileptogenic focus could be accurately identified. CT and magnetic resonance imaging (MRI) usually do not show any abnormalities. If they do, depth electrodes can be used to confirm the focus. This, however, requires a surgical procedure. PET can help identify epileptogenic foci if CT and MRI are normal.

Dr. Jerome Engel, Jr. and colleagues were the first to use PET in selecting patients for surgical treatment of partial epilepsy (*10*). They have shown that CBF and glucose metabolism is increased in the epileptogenic focus during seizures and decreased interictally. The sensitivity of PET to locate epileptogenic foci is ~70%, and even greater if increased opiate receptor density is found by using ^{11}C-Carfentanil (*11*).

An example of significant interictal suppression of FDG uptake in the right temporal lobe of a patient with partial epilepsy is shown in Figure 2.

Figure 3 shows an FDG-PET scan that was done while the patient had a major seizure. The seizure started in the right arm, extended into the right leg and eventually involved the entire left side of the body. The scan shows focal activity in both frontal lobes.

This demonstrates one of the disadvantages of FDG-PET imaging. Data collection typically starts at 45 min postinjection. The final PET image shows a summation of all metabolic events that occurred between injection of FDG and the end of data collection. The image in Figure 3 shows one focus in each frontal lobe, and one cannot tell in which hemisphere

FIG. 2. Partial epilepsy. Interictally decreased glucose utilization in right temporal lobe.

the epileptic seizure started. The relative decrease of activity in the left frontal lobe which triggered the seizure early may indicate that peak activity had already passed.

Nevertheless, FDG-PET imaging can corroborate the localization of epileptogenic foci, especially with computer assisted anatomical correlation to CT, MRI, single-photon emission computed tomography (SPECT) and electroencephalograph information. By superimposing images from different modalities (and with further improvement of the spatial resolution of PET) an epileptic focus can be delineated with great precision for surgical treatment.

Cerebrovascular Disease (Stroke)

Cerebral oxygen metabolism is closely linked to glucose metabolism and the affected area in strokes can be easily delineated by $^{13}NH_3$ CBF or [^{18}F]FDG scans. Monitoring CBF and glucose metabolism can be useful in assessing prognosis, treatment, and planning rehabilitation of the patients. Figure 4 shows matching perfusion defects ($^{13}NH_3$) and hypometabolism (FDG) in a cerebral vascular accident involving the right middle cerebral artery.

Matched decreased blood flow and metabolism in the presence of compensatory increase in oxygen extraction in the affected region indicates tissue viability. In this situation the

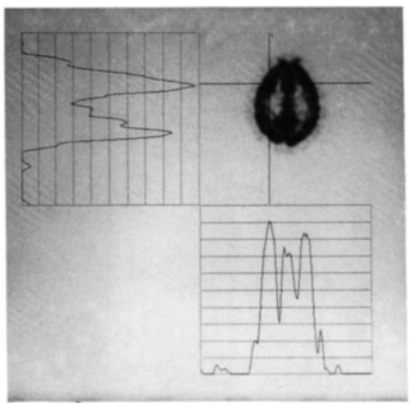


FIG. 3. Bi-focal epileptogenic foci during seizure. Horizontal and sagittal activity distribution profiles through the foci show relative increase of activity in the right frontal lobe.

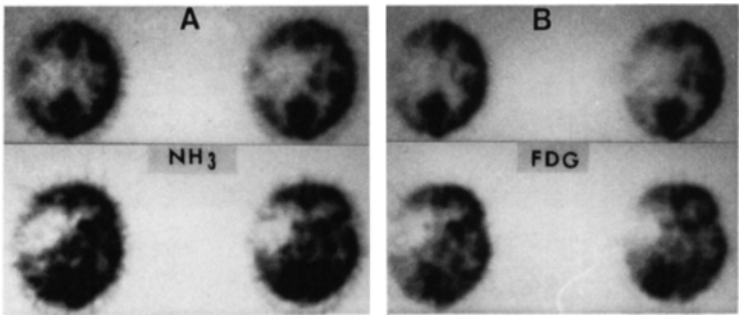


FIG. 4. (A) $^{13}NH_3$-ammonia and (B) [^{18}F] FDG scans of patient with stroke involving right middle cerebral artery.

patient might benefit from an internal-external carotid artery bypass or endarterectomy. Instead of using a CBF and metabolism study, a CBF study before and after i.v. injection of Diamox can help to determine whether an endarterectomy is likely to be of benefit to the patient. Diamox dilates the vascular system and increases CBF in normal subjects. In patients with significant carotid artery occlusion and angiographically demonstrated collateral blood supply, absence of the Diamox effect indicates that physiologic compensatory mechanisms are operating at their maximum and further improvement from collateral blood flow cannot be expected. This is the type of patient that should benefit from an endarterectomy. This test was developed for CT in conjunction with stable xenon (*10*). We have adapted the method for PET imaging using ^{15}O-labeled water. The 2-min half-life of ^{15}O allows the pre- and post-Diamox CBF studies to be completed in less than 1 hr.

A Diamox $H_2{}^{15}O$ PET study before and after endarterectomy is presented in Figure 5. Figure 5A shows CBF in a 64-yr-old man with a >95% stenosis of the left common carotid artery. A perfusion defect in the left parietal and posterior parietal lobe did not change after Diamox administration. The time-activity curves in Figure 5B confirm this interpretation. The results of endarterectomy in Figure 5C show improvement of CBF and restoration of the Diamox response. This type of PET study might prove extremely useful for the evaluation of stroke patients.

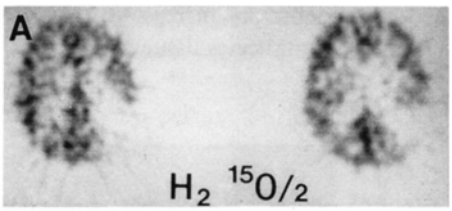
Dementias

PET imaging has also revealed a characteristic regional glucose utilization pattern in Alzheimer's disease (AD). The disease process involves the parietal lobes with extension into the temporal and occipital lobes and, to a lesser extent, in the frontal lobe (*11*). In pseudodementia of depressed elderly persons, the pattern is close to normal and in multiple infarct dementia randomly scattered areas of decreased glucose uptake are seen. In severe cases of AD, glucose utilization in the affected regions of the brain is suppressed by as much as 60% of normal age-matched control persons.

PET imaging with [^{18}F]FDG is not diagnostic for AD. The diagnosis of AD still requires biopsy or autopsy specimens, but can demonstrate metabolic patterns compatible to or untypical of AD. Figure 6A shows multiple hypometabolic areas (holes) in a three-dimensional surface volume image of a patient with AD examined at our institution's PET center. For comparison, a normal brain in three-dimensional view is shown in Figure 6B.

Brain Tumors

PET imaging has been successfully applied as a clinical tool for grading brain tumors, monitoring their response to treat-



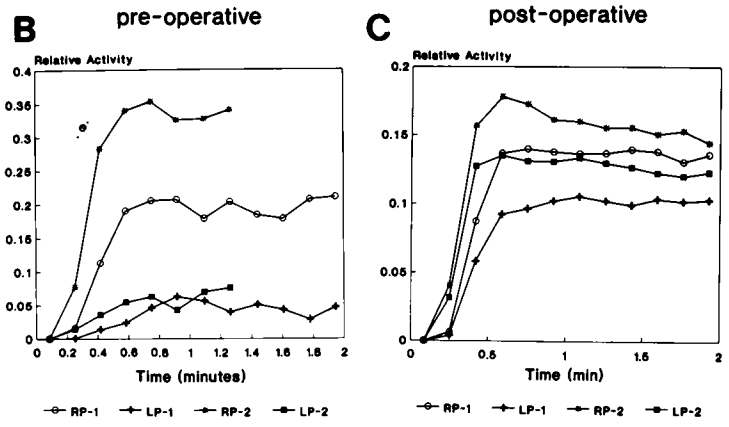


FIG. 5. (A) Oxygen-15-water CBF study. Two adjacent slices show large perfusion defect in left parietal lobe unchanged after 1 g of Diamox i.v. (B) Preoperative relative activity (counts/pixel-sec) in ROIs of the right and left parietal lobe. RP-1 = right parietal lobe before Diamox; RP-2 = right parietal lobe after Diamox; LP-1 = left parietal lobe before Diamox; and LP-2 = left parietal lobe after Diamox. There was no response to Diamox in LP. (C) Postoperative. Time-activity curves postendarterectomy demonstrating improved CBF and restoration of Diamox response in the previously affected left temporal lobe.

ment, and to differentiate between recurrent tumors and radiation necrosis. Two radiotracers suitable for this purpose are [^{18}F]FDG and ^{11}C-L-methionine. Di Chiro et al. have set a standard by showing that [^{18}F]FDG uptake is related to the metabolic activity and grade of brain tumors (*12–14*). Researchers in some PET centers in Europe claim that ^{11}C-L-methionine may be a more sensitive indicator for brain tumor proliferation than [^{18}F]FDG (*15–18*). The signal-to-noise ratio in PET images obtained with ^{11}C-L-methionine can be increased by blocking L-methionine uptake by normal brain using unlabeled phenylalanine. At our institution, we have started to use ^{11}C-ACBC, an amino acid analog in place of ^{11}C-L-methionine. Carbon-11-ACBC is taken up by tumor tissue but not by normal brain, and tumor-associated amino acid uptake is seen more clearly.

An example of a PET brain tumor study is shown in Figure 7, which shows a MRI, a [^{18}F]FDG, and a ^{11}C-ACBC scan with time-activity curves of a 42-yr-old man who was referred to us with the question of radiation necrosis versus recurrent glioblastoma 8 mo postoperatively and post-radiation therapy. The MRI scan (Fig. 7A) suggested the possibility of recurrent tumor. This suspicion was supported by the FDG-PET study (Fig. 7B), which shows decreased glucose utilization in the left parietal/occipital area with a focal hot spot medially and anteriorly to the hypometabolic region. The additional information from the amino acid PET study shown in Figures 7C-D heightened the suspicion for recurrent neoplasm and was confirmed by stereotactic biopsy. This is a good example for a practical clinical application of PET in oncology.

PET Applications in Neuropsychiatric Disorders

PET receptor binding studies can map dopamine receptors, opiate receptors, or benzodiazepene and muscarinic receptors in the brain. Ligands used for this purpose, labeled with ^{11}C or ^{18}F, are still under development and limited to a few special research centers.

Some possible useful information on psychiatric disorders can be obtained by determining the metabolic rate of glucose or blood flow in the brain. In spite of the difficulties with controlling the variables of the environment around and within the patient, some patterns and hemispheric asymmetry of glucose uptake or blood flow have been observed in patients with chronic mental illness. In schizophrenics, cerebral glucose utilization has been found to be fairly normal. Patients with affective unipolar or bipolar illness have shown global depression of the metabolic rate of glucose with some hypofrontality; and decreased blood flow in the hippocampus has been found in patients with anxiety disorders. Patients with compulsive obsessive disorders have been found to have increased FDG uptake in the orbital gyri and the caudate nucleus. However, metabolic or CBF studies rather nonspecifically show only the anatomy of function or dysfunction in the brain. What is needed are specific transmitters that help to map the pathways in conjunction with anatomical and chemical observations. At this time, no singular typical variable or radiotracer is available to define schizophrenia or manic depression. The problem with psychiatric illnesses is that the pathophysiology for traditional functional mental illness is yet to be delineated. The reason lies in the difficulty in measuring the pertinent physiology of the human brain that is well protected by the bones of the skull and shielded by the blood-brain barrier.

Routine PET procedures for mental illnesses are not available at this time but are likely to become available during this "decade of the brain."

CONCLUSION

PET imaging has emerged from the research sphere to the realm of clinical applications in intracranial and extracranial disease. Although several applications of PET imaging in neurologic disorders such as epilepsy, dementia, and brain tumors are now validated and accepted as clinically useful, PET's role in defining the pathophysiology of functional mental illnesses requires further investigation.

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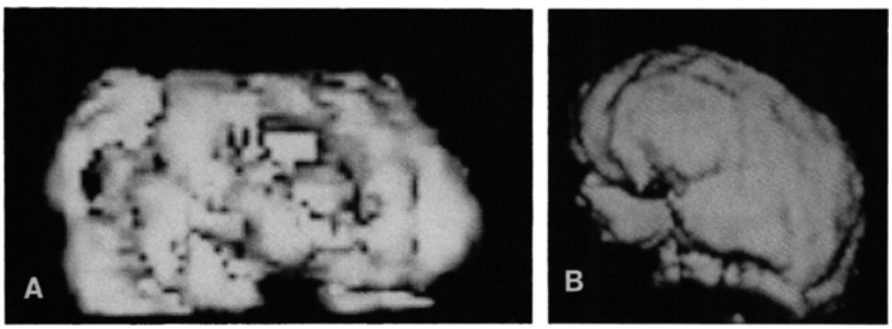

FIG. 6. (A) Surface volume FDG image of a patient with Alzheimer's disease showing multiple hypometabolic regions in the parietal, temporal and occipital lobe. (B) In contrast to Figure 6A the rotating volume image of a normal human brain showing a smooth surface and no defects.