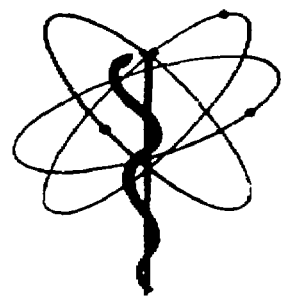
LABORATORY OF NUCLEAR MEDICINE AND RADIATION BIOLOGY

UNIVERSITY OF CALIFORNIA
900 VETERAN AVENUE
LOS ANGELES, CALIFORNIA



DOE CONTRACT DE-AM03-76-SF00012

LABORATORY OF NUCLEAR MEDICINE AND RADIATION BIOLOGY

900 Veteran Avenue

UNIVERSITY OF CALIFORNIA, LOS ANGELES, CALIFORNIA 90024

AND DEPARTMENT OF RADIOLOGICAL SCIENCES

UCLA SCHOOL OF MEDICINE, LOS ANGELES, CALIFORNIA 90024

These studies were supported by Contract #DE-AM03-76-SF00012 between the U.S. Department of Energy and the University of California

Prepared for the U.S. Department of Energy
under Contract #DE-AM03-76-SF-00012

EMISSION COMPUTED TOMOGRAPHY OF ^{18}F-FLUORO-DEOXYGLUCOSE AND ^{13}N-AMMONIA IN STROKE AND EPILEPSY.

David E. Kuhl, M.D.

INTERNATIONAL ATOMIC ENERGY AGENCY
in co-operation with the
WORLD HEALTH ORGANIZATION

INTERNATIONAL SYMPOSIUM
ON MEDICAL RADIONUCLIDE IMAGING

Heidelberg, Federal Republic of Germany, 1–5 September 1980

IAEA-SM-247/

EMISSION COMPUTED TOMOGRAPHY OF ^{18}F-FLUORODEOXYGLUCOSE AND ^{13}N-AMMONIA IN STROKE AND EPILEPSY.

KUHL, D.E., M.D., PHELPS, M.E., Ph.D., ENGEL, J. Jr., M.D.,Ph.D.
UCLA School of Medicine and Laboratory of Nuclear Medicine and Radiation Biology, Los Angeles, California 90024, USA.

This work was supported in part by: DOE Contract DE-AM03-76-SF00012 and USPHS Research Grants GM-24839, NS-15654, and NS-02808.

EMISSION COMPUTED TOMOGRAPHY OF ^{18}F-FLUORODEOXYGLUCOSE AND ^{13}N-AMMONIA IN STROKE AND EPILEPSY

The ECAT Positron Tomograph was used to scan normal control subjects, stroke patients at various times during recovery, and patients with partial epilepsy during EEG monitoring. ^{18}F-fluorodeoxyglucose (^{18}FDG) and ^{13}N-Ammonia ($^{13}NH_3$) were used as indicators of abnormalities in local cerebral glucose utilization ($LCMR_{glc}$) and relative perfusion, respectively.

In patients with stroke, mean $LCMR_{glc}$ in the contralateral hemisphere was moderately depressed during the first week, profoundly depressed in irreversible coma, and normal after clinical recovery. Local distributions of ^{18}FDG and $^{13}NH_3$ trapping reflected qualitatively the increases and decreases, as well as coupling and uncoupling, expected in stroke for local alterations in glucose utilization and perfusion. Hypometabolism, due to deactivation or minimal damage, was demonstrated with the ^{18}FDG scan in deep structures and broad zones of cerebral cortex which appeared normal on X-ray CT (XCT) and ^{99m}Tc pertechnetate scans.

In patients with partial epilepsy, who had unilateral or focal electrical abnormalities, interictal ^{18}FDG scan patterns clearly showed localized regions of decreased (20%-50%) $LCMR_{glc}$, which correlated anatomically with the eventual EEG localization. In most instances, these hypometabolic zones appeared normal on XCT and were unchanged on scans repeated on different days. In 5 of 6 patients who underwent anterior temporal lobectomy, the interictal ^{18}FDG scan correctly detected the pathologically confirmed lesion as a hypometabolic zone, and removal of the lesion site resulted in marked clinical improvement. In contrast, the ictal ^{18}FDG scan patterns clearly showed foci of increased (82%-130%) $LCMR_{glc}$ which correlated temporally and anatomically with ictal EEG spike foci and were within the zones of interictal hypometabolism.

The in vivo ^{18}FDG-ECT method (1-6) for determination of the local cerebral metabolic rate for glucose ($LCMR_{glc}$) in individual brain structures is derived from the ^{14}C-DG autoradiographic method of Sokoloff et al (7). ^{18}FDG enters the brain rapidly, is phosphorylated by brain hexokinase, and the metabolic product, ^{18}FDG-6-PO4, remains fixed with little further metabolism. Calculations are based on a model of the biochemical behavior of deoxyglucose and glucose in the brain (2, 4, 5, 7). The time course of specific activity in cerebral capillary blood is estimated by measuring arterialized venous blood samples obtained while the blood

is clearing tracer, at times greater than 40 minutes there is measurement of local cerebral ^{18}F concentrations by ECT scan, and with knowledge of predetermined rate constants and lumped constant (LC) the operational equation allows calculation of $LCMR_{glc}$ corresponding to each zone of the tomographic image. The method measures exogenous glucose utilization, i.e., the glycolytic rate under the assumption there is no net glycogen accumulation or glycogenolysis. The method does not distinguish aerobic from anaerobic glycolysis. In the work reported here, ^{18}FDG scans were performed with the ECAT Positron Tomograph (8) (Ortec, Inc., Oak Ridge, TN) operated so that the spatial resolution was 1.7 cm within the image plane. For calculation of $LCMR_{glc}$, we used the operational equation developed by Huang et al (4) and validated by Phelps et al (5).

We chose $^{13}NH_3$ (9) as an indicator of relative cerebral perfusion because ammonia has a cerebral uptake that varies with capillary perfusion, a static cerebral distribution which is desirable for ECT scanning, a short physical half-life (10 minutes) which permits use prior to an ^{18}FDG scan without residual interference, and simple chemical preparation. We made no attempt to quantify $^{13}NH_3$ distributions in absolute units of cerebral blood flow. $^{13}NH_3$ was given by the intravenous route and ECAT (14) scans were begun several minutes after injection. The $^{13}NH_3$ scan preceded the ^{18}FDG scan by at least one hour, sufficient time to allow radioactive decay of 13N and avoid interference.

EFFECTS OF STROKE ON CEREBRAL METABOLISM AND PERFUSION.

We performed ECT scans of ^{18}FDG and $^{13}NH_3$ in normal control subjects and stroke patients at various times during recovery (3, 10). In normal subjects, mean CMR_{glc} was 5.28 ± 0.76mg/100g/min. In patients with stroke, mean CMR_{glc} in the contralateral hemisphere was moderately depressed during the first week, profoundly depressed in irreversible coma, and normal after clinical recovery. Quantification was restricted by incomplete understanding of tracer behavior in diseased brain, but relative local distributions of ^{18}FDG and $^{13}NH_3$ trapping reflected qualitatively the increases and decreases, as well as coupling and uncoupling, expected in stroke for local alterations in glucose utilization and perfusion. Early after cerebral vascular occlusion, there was a greater decrease in local $^{13}NH_3$ trapping than in ^{18}FDG trapping within the infarct, probably because of increased anaerobic glycolysis. Otherwise, ^{18}FDG was a more sensitive indicator of cerebral dysfunction than was $^{13}NH_3$. Hypometabolism, due to deactivation or minimal damage, was demonstrated with the ^{18}FDG scan in deep structures and broad zones of cerebral cortex which appeared normal on x-ray CT and ^{99m}Tc pertechnetate scans.

The relationship of local alterations in metabolism (D_{F-18}) and perfusion (D_{N-13}) in abnormal brain zones of these stroke patients are shown in Fig. 1. Data points falling on the dotted line represent metabolism = perfusion deficits, assuming the relationship of relative ^{13}N concentration to relative blood flow

was the same as we found in compressed dog brain. (A) In the first two days after stroke, perfusion is decreased more than glucose utilization within the infarct. (B) In the first two weeks, luxury perfusion appears at the infarct margins; local perfusion is increased but glucose utilization is not. (C) In old permanent infarcts that are obvious on x-ray CT scans, both glucose utilization and perfusion are markedly reduced. (D) In some ipsilateral tissues, there is less marked reduction in glucose utilization and perfusion, but no x-ray CT evidence of structural damage.

The ECT scans consistently detected hypofunction in broad zones of remote cerebral cortex, striatum, and thalamus which appeared structurally intact on x-ray CT and normal on ^{99m}Tc pertechnetate scans. ^{18}FDG was a more sensitive indicator of this dysfunction than $^{13}NH_3$, as expected from the non-linear response of $^{13}NH_3$ trapping to changes in blood flow. The ECT study showed that more brain had been affected by stroke than was suggested by the other radiological studies (Fig. 2).

EFFECTS OF EPILEPSY ON CEREBRAL METABOLISM AND PERFUSION

In epilepsy, altered cerebral function is seldomly accompanied by changes in structure that are detectable by radiographic procedures. Diagnosis and classification of this altered function depends heavily on the use of electroencephalography (EEG) which records electrical activity associated with neuronal activity. EEG is extremely useful, but has limitations. It is often difficult to lateralize or to localize a seizure origin and to assess the severity and extent of underlying cerebral involvement. We report here the first measurements of cerebral metabolism and circulation by ECT resolved in three dimensions and performed concurrently with EEG recording of epileptic patients who were in the unperturbed interictal or spontaneous ictal state (11, 12).

In 12 of 15 patients who had unilateral or focal electrical abnormalities, interictal ^{18}FDG scan patterns clearly showed localized regions of decreased (20%-40%) $LCMR_{glc}$, which correlated anatomically with the eventual EEG localization. These hypometabolic zones appeared normal on x-ray CT in all but three patients and were unchanged on scans repeated on different days. In 5 of 6 patients who underwent anterior temporal lobectomy, the interictal ^{18}FDG scan correctly detected the pathologically confirmed lesion as a hypometabolic zone, and removal of the lesion site resulted in marked clinical improvement. In contrast, the ictal ^{18}FDG scan patterns clearly showed foci of increased (82%-130%) $LCMR_{glc}$ which correlated temporally and anatomically with ictal EEG spike foci and were within the zones of interictal hypometabolism (3 studies in 2 patients). $^{13}NH_3$ distributions paralleled ^{18}FDG increases and decreases in abnormal zones, but $^{13}NH_3$ differences were of lesser magnitude. When the relationship of $^{13}NH_3$ uptake to local blood flow found in dog brain was applied as a correction to patients' $^{13}NH_3$ scan

data, local alterations in perfusion and glucose utilization were usually matched both in interictal and ictal states (Fig. 3).

Interictal scan findings are illustrated in Fig. 4. This 4-year old girl has persistent right-sided tonic clonic seizures and right hemiparesis of three years' duration. The ^{18}FDG scans showed a marked reduction in cortical glucose utilization (-40%) over broad zones of the left cerebral hemisphere (arrow); there were corresponding, but lesser decreases in $^{13}NH_3$ concentration (not shown). Diffuse or multifocal EEG abnormalities were recorded in the left hemisphere, but the x-ray CT, cerebral arteriogram, and pneumoencephalogram were normal.

Six patients had anterior temporal lobectomies for intractable partial complex epilepsy; all showed pathological lesions in the resected temporal lobe specimen, and all had marked clinical improvement after surgery. Although preoperative x-ray CT showed none of these lesions, preoperative ^{18}FDG scans were abnormal in 5 of these patients; decreased $LCMR_{glc}$ coincided with the resection site and the extent of this metabolic deficit was larger than the extent of structural damage found at pathological evaluation.

We conclude that in the present state of development, this ECT method should aid in defining the location and extent of altered brain in the study of disordered function after stroke, for mapping response to therapeutic invention, and increasing understanding of how the human brain responds to stroke. In patients with partial epilepsy, the interictal ^{18}FDG scan is useful now in aiding localization of the dysfunctional cerebral zone most likely to be responsible for seizures in patients considered for temporal lobectomy. With further development, ECT may help in categorizing better the various forms of the disorder and in elucidating the basic mechanism of epilepsy in man.

REFERENCES

[1] Kuhl, D.E., Hoffman, E.J., Phelps, M.E., et al: Design and Application of the Mark IV Scanning System for Radionuclide Tomography of the Brain. (in) Medical Radionuclide Imaging. Vol. 1: International Atomic Energy Agency Symposium on Medical Radionuclide Imaging, Los Angeles, 1976, Vienna, IIAEA, 1977, pp 309-320.

[2] Reivich, M., Kuhl, D.E., Wolf, A. et al: The ^{18}F-Fluorodeoxyglucose Method for the Measurement of Local Cerebral Glucose Utilization in Man. Circ.Res. 44:127-137, 1979.

[3] Kuhl, D.E., Phelps, M.E., Hoffman, E.J., et al: Initial Clinical Experience with ^{18}F-2-Deoxy-Glucose for Determination of Local Cerebral Glucose Utilization by Emission Computed Tomography. (in) Ingvar,D.H., Lassen, N. (eds.):

Cerebral Function, Metabolism, and Circulation. A CBF Symposium in Copenhagen, Denmark, June 1977. Acta Neurol. Scand. Suppl. 64, Vol. 56, Copenhagen, Munksgaard, 1977, pp. 192-193.

[4] Huang, S.C., Phelps, M.E., Hoffman, E.J., et al: Non-Invasive Determination of Local Cerebral Metabolic Rate of Glucose in Normal Man with (F-18)2-Fluoro-2-Deoxyglucose and Emission Computed Tomography: Theory and Results. Am. J. Physiol. 238:E69-E82, 1980.

[5] Phelps, M.E., Huang, S.C., Hoffman, E.J., et al: Tomographic Measurement of Local Cerebral Glucose Metabolic Rate in Man with 2-^{18}F-Fluoro-2-Deoxy-D-Glucose: Validation of Method. Ann. Neurol. 6:371-388, 1979.

[6] Reivich, M., Kuhl, D.E., Wolf, A., et al: Measurement of Local Cerebral Glucose Metabolism in Man with ^{18}-F-2-Fluoro-2-Deoxy-D-Glucose, (in) Ingvar, D.H., Lasson, N. (eds.): Cerebral Function, Metabolism and Circulation, a CBF Symposium in Copenhagen, Denmark, June 1977. Acta Neurol. Scand. Suppl. 64, Vol. 56, Copenhagen, Munksgaard, 1977, pp 190-191.

[7] Sokoloff, L., Reivich, M., Kennedy, C., et al: The (^{14}C) Deoxyglucose Method for the Measurement of Local Cerebral Glucose Utilization: Theory, Procedure, and Normal Values in the Conscious and Anesthesized Albino Rat. J. Neurochem. 28: 897-916, 1977.

[8] Phelps, M.E., Hoffman, E.J., Huan, S.C., et al: ECAT: A New Computerized Tomographic Imaging System for Positron-Emitting Radiopharmaceuticals: J. Nucl. Med. 19:635-647, 1978.

[9] Phelps, M.E., Hoffman, E.J., Kayband, C.: Factors which Affect Cerebral Uptake and Retention of $^{13}NH_3$. Stroke 8:694-702,1977.

[10] Kuhl, D.E., Phelps, M.E., Kowell, A.P., 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. 8:47-60, 1980.

[11] Kuhl, D.E., Engel, J., Phelps, M.E., et al: Patterns of Local Cerebral Metabolism and Perfusion in Partial Epilepsy by Emission Computed Tomography of ^{18}F-Fluorodeoxyglucose and ^{13}N-Ammonia. (in) Gotoh, F., Nagei, H., Tayaki, Y. (eds.) Cerebral Blood Flow and Metabolism. Acta Neurol. Scand. Suppl. 72, Vol. 60, Copenhagen, Munksgaard, 1979, pp 538-539.

[12] Kuhl, D.E., Engel, J., Phelps, M.E., and Selin, C.: Epileptic Patterns of Local Cerebral Metabolism and Perfusion in Man Determined by Emission Computed Tomography of ^{18}FDG and $^{13}NH_3$. Ann. Neurol. (in press).

LEGENDS

Fig. 1: Relationships of alterations in local metabolism (D_{F-18}) and relative perfusion (D_{N-13}) in abnormal brain zones of stroke patients. From Kuhl et al [10].

Fig. 2: Scans made two months after sudden transaction of the left internal carotid artery by a knife wound. Although both the ^{18}FDG and x-ray CT scans show the focal infarct in the left frontal lobe, only the ^{18}FDG scan shows the diffuse hypometabolism throughout the entire left hemisphere, a permanent result of the left hemispheric ischemia. From Kuhl et al [10].

Fig. 3: Relationship of altered relative perfusion (D_{N-13}) and metabolism (D_{MR}) in abnormal brain zones during interictal and ictal states. The dotted curve is the predicted locus of tissue data where change in LCBF and $LCMR_{glc}$ would be matched. From Kuhl et al [12].

Fig. 4: Interictal ^{18}FDG scan demonstrates marked reduction in cortical glucose utilization over broad zones of the left cerebral hemisphere (arrow). Diffuse or multifocal EEG abnormalities were recorded in the left hemisphere, but the x-ray CT, cerebral arteriogram, and pneumoencephalogram were normal. From Kuhl et al [12].

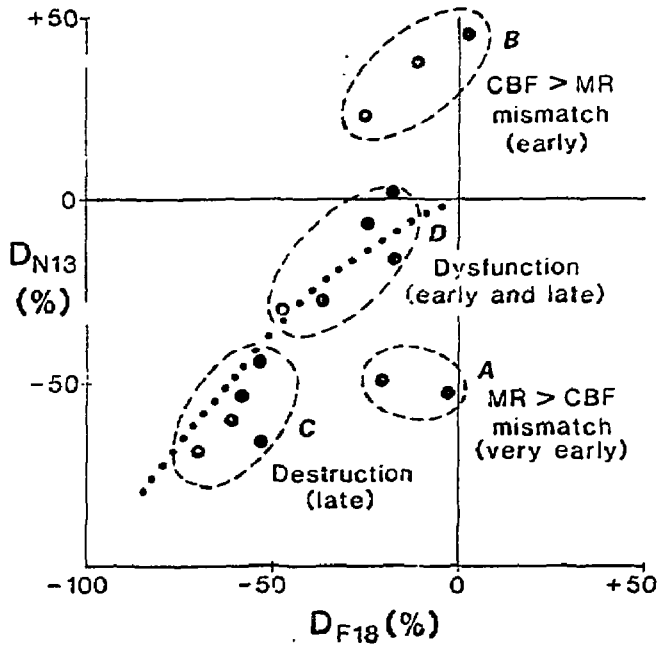


Figure 1

(Original photograph is with original type copy of text)

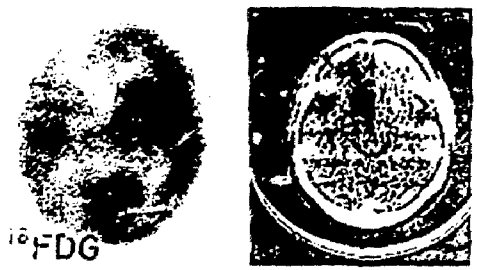


Figure 2

(Original photograph is with original type copy of text)

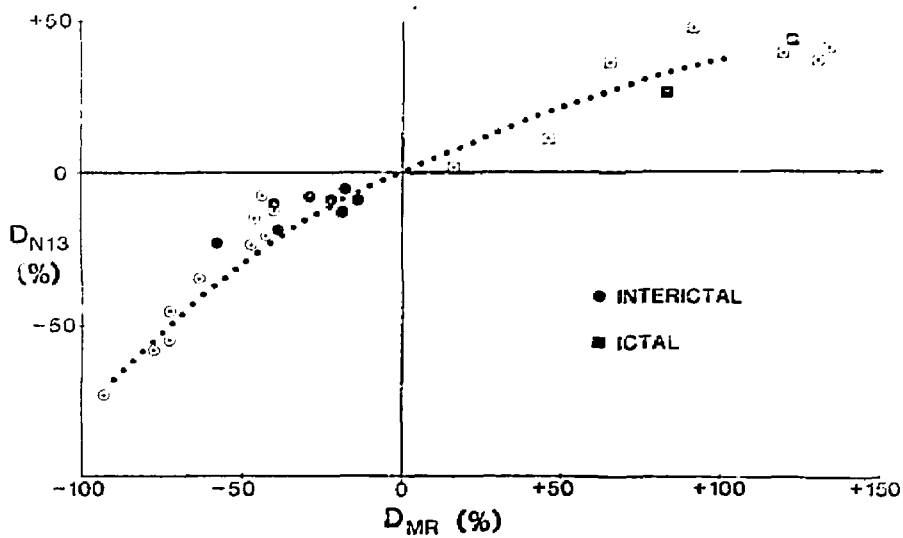


Figure 3

(Original photograph is with original type copy of text)

Figure 4

(Original photograph is with original type copy of text)