Improved Detection of Epileptic Foci with PET

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Objective: This study was conducted to determine the usefulness of a normal reference value database for the detection of areas of abnormal regional cerebral glucose metabolism. The results of this quantitative analysis were compared to a qualitative analysis based only on the detection of left/right asymmetry.

Methods: Ten patients with medically refractory partial complex epilepsy were studied. Metabolic rate images were generated from the patient's plasma glucose level, FDG clearance in serial arteriolized venous blood samples and PET images calibrated to a well counter.

Results: Using a threshold of greater than 20% left/right asymmetry, we found areas of hypometabolism in temporal regions of four patients. Using a threshold of 1.5 s.d. less than the mean normal value for a particular region, we found areas of hypometabolism in temporal regions of eight patients.

Conclusion: We found that when images were evaluated based on a laboratory normal value database, we were able to detect twice as many areas of hypometabolism.

Key Words: positron emission tomography (PET); epilepsy; fluorine-18-FDG

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A number of authors have documented the usefulness of PET scans with ^{18}F-fluoro-2-deoxy-D-glucose (FDG) in the presurgical evaluation of patients with medically refractory partial complex epilepsy (PCE) (*1–3*). However, because of the cyclical pattern of this disease (hypermetabolic in the ictal phases while hypometabolic in the interictal phase) and the performance characteristics of the available imaging instrumentation, areas of hypometabolism may only be detected in 57–81% of the patients with PCE.

The purpose of this study was to see if measured values for regional cerebral glucose metabolism ($rCMR_{glu}$) could be used to improve the detection of hypometabolic areas in patients with PCE. We have previously reported our laboratory normal values for $rCMR_{glu}$ in 30 brain regions based on studies of 39 patients studied under controlled behavioral conditions (*4*). In this paper we report on the use of these normal values to identify regions of abnormal $rCMR_{glu}$ in 10 patients with a history of PCE. This method of analysis was compared to a qualitative analysis based on the detection of left/right asymmetry in the resultant images.

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MATERIALS AND METHODS

PET Scanner

All scans were performed using a PETT VI system (*5*). The system has an average intrinsic in-plane geometrical resolution of 7.1 mm full width at half maximum (FWHM) and on-slice thickness or axial resolution at the center of each slice of 13.9 mm FWHM. The contribution of random coincidences before correction was found to be approximately 14% of the counts in an image of a 20-cm diameter phantom containing a uniformly distributed concentration of 1 μCi/cc. An automatic method of randoms correction, based on a calculated value derived from single count rates, was applied to all image data before analysis.

For this study, three of the available four rings of cesium fluoride (CsF) detectors were used to produce five simultaneous tomographic slices; three straight slices and two cross slices for a field of view of approximately 6.4 cm. To image the entire brain volume, the patients were scanned in two different positions offset by 2.8 cm. This results in eight unique images for analysis (Fig. 1). Measured attenuation correction factors for each position were obtained from transmission scans performed with a ^{68}Ge/^{68}Ga ring source prior to radiopharmaceutical administration.

Patients

Five male and five female patients were studied. Their ages ranged from 24 to 55 with a mean of 40.3 years. Five of the patients were on phenytoin and carbazepine therapy at the time of their scans. Two patients were taking carbazepine and primidone at the time of their scans. The remaining patients were taking carbazepine and divalproex sodium, carbazepine monotherapy or phenytoin at the time of their scans.

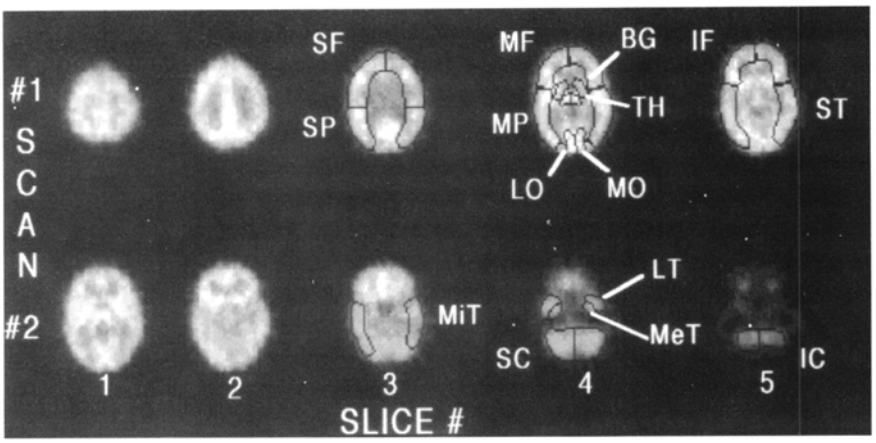

FIGURE 1. Fluorine-18-FDG images for analysis. Shown are the two scan positions and the ROIs used for quantitative analysis. Note that scan 1, slices 4 and 5 are identical to scan 2, slices 1 and 2. Key: SF = superior frontal; SP = superior parietal; MF = mid frontal; MP = mid parietal; LO = lateral occipital; MO = mesial occipital; TH = thalamic; BG = basal ganglia; IF = inferior frontal; ST = superior temporal; MiT = mid temporal; LT = lateral temporal; MeT = mesial temporal; SC = superior cerebellum; and IC = inferior cerebellum.

Patient Preparation

Patients signed informed consent forms prior to participation in this study, and all PET procedures were approved by the University of Chicago Hospitals' Institutional Review Board. All patients were instructed not to eat anything or drink beverages containing glucose or caffeine for at least four hours prior to the scan. A thermoplastic facemask was prepared for each patient and was used to minimize patient movement and facilitate repositioning.

Each patient had an intravenous catheter placed in the proximal forearm or dorsum of the hand. The forearm and hand were then wrapped in a heating pad to increase the surface temperature of the skin to approximately 44°C. This method of arteriolizing venous blood has been shown to be effective and eliminates the need for arterial catheterization (*6*). The patient's arm was heated for approximately 20 min prior to injection and remained in the pad until blood sampling was completed at approximately 70 min postinjection. Serial blood samples were obtained from this arm to measure ^{18}F concentration and plasma glucose levels. A second venous catheter was inserted in the opposite arm for radiopharmaceutical administration.

Controlled Task Condition

We have previously reported a study of seven normal right-handed subjects that demonstrated the importance of controlling a subject's behavioral state during the FDG uptake period. In that study we found that a simple visual monitoring task, performed with eyes open and ears uncovered, produces a more controlled, stable and reproducible patient condition than that obtained when patients were injected while awake but with their eyes covered and ears plugged (*7*).

Patients in this study performed a modified version of the Raven's Progressive Matrices (*8*) during the FDG uptake period. A computer monitor was positioned such that the patient could see the screen while positioned in the scanner. Each patient was presented a pattern with a missing piece. Using a mouse, controlled by the hand of the arm not being used for blood sampling, the patient positioned the cursor over the piece that would complete the pattern. The attention, motor and sensory demands for this task resemble those of the visual monitoring task performed by the patients used to determine average $rCMR_{glu}$ values. (This particular task was used for these patients because they were actually part of a two-scan protocol, which will be reported separately, in which the cognitive demand for the second scan was increased significantly by making the problem set more difficult to solve.)

Data Analysis

Metabolic rate images were generated using the method of Sokoloff (*9*), as modified by Huang (*10*) and Hutchins (*11*) from the patient's plasma glucose level, the time activity curve for FDG clearance from the serial blood samples and PET images in cps/pixel calibrated to well counter cps/ml (*6*). The metabolic rate images from the ten patients in this study and five normal patients were evaluated by an experienced nuclear medicine physician who had no knowledge of patient identity or clinical history. Each image was evaluated for the presence of areas of hypometabolism and classified as definitely abnormal, probably abnormal, possibly normal, probably normal or definitely normal.

For the measurement of regional metabolic rates, 15 regions of interest (ROIs) were drawn for each hemisphere corresponding to the frontal, parietal, temporal and occipital cortices as well as the basal ganglia, thalamus and cerebellum (Fig. 1). Relatively large ROIs were drawn for reproducible placement on all PET scans as well as to avoid partial volume effects by remaining well above the spatial resolution limit of the PETT VI (*12*). Average CMR_{glu} per pixel, standard deviation and total number of pixels were determined for each region.

RESULTS

Table 1 shows our average normal CMR_{glu} and standard deviation for each of the 30 regions and each patient's $rCMR_{glu}$ for these regions. Underlined values in Table 1 are the regions that were found to have a left/right asymetry of greater than 20% regardless of measured metabolic rate. This qualitative analysis corresponds well with areas identified as definitely abnormal when the metabolic rate images were interpreted without ROI information.

The 20% asymmetry threshold used for the qualitative analysis represents approximately a 1.5 s.d. of the mean whole

TABLE 1
Regional Glucose Metabolism (mg/100 gm/min)

Region of interest			Normal subjects $\bar{X}$ Value	SD	Patient values 1	2	3	4	5	6	7	8	9	10
Left	Frontal	Sup	7.91	1.30	7.70	8.40	6.75	6.07	**3.91**	7.18	6.15	9.14	6.56	6.61
Right	Frontal	Sup	7.74	1.32	7.55	8.01	6.64	5.96	**3.92**	7.07	4.78	8.79	6.59	6.10
Left	Parietal	Sup	8.05	1.14	7.45	8.91	6.97	6.76	**4.38**	7.28	**6.03**	9.31	6.73	7.08
Right	Parietal	Sup	7.47	1.36	7.50	7.94	6.69	6.02	**4.17**	6.91	3.98	8.58	6.75	6.56
Left	Frontal	Mid	8.00	1.18	7.09	7.87	7.01	**6.04**	**5.75**	7.03	NS	8.53	6.35	**5.99**
Right	Frontal	Mid	7.69	1.17	6.72	7.61	6.67	**5.79**	**5.14**	7.22	NS	8.69	6.81	**5.84**
Left	Parietal	Mid	7.86	1.24	7.53	7.90	6.88	6.30	6.23	6.58	NS	8.38	6.33	6.62
Right	Parietal	Mid	7.54	1.15	6.98	7.56	6.55	**5.66**	**5.47**	6.73	NS	7.81	6.88	**5.81**
Left	Frontal	Inf	7.98	1.21	7.47	7.95	6.68	6.41	**6.16**	6.58	**6.13**	7.86	6.89	**5.64**
Right	Frontal	Inf	7.65	1.13	6.83	7.40	6.57	6.07	**5.14**	6.56	4.32	7.84	6.76	**5.44**
Left	Temporal	Sup	7.75	1.08	7.63	8.49	7.00	6.56	6.78	7.18	**5.97**	7.83	6.46	**5.97**
Right	Temporal	Sup	7.52	1.06	7.04	7.90	7.02	6.03	**5.86**	7.10	4.02	7.49	6.82	**5.61**
Left	Basal Nuc		9.08	1.41	9.05	10.29	8.42	8.10	7.09	7.65	7.01	9.81	7.76	7.02
Right	Basal Nuc		8.68	1.34	7.99	9.88	8.26	7.11	**6.20**	7.57	4.58	9.26	8.42	6.91
Left	Thalamic		8.56	1.30	7.45	9.56	7.99	8.01	7.34	7.07	**6.10**	8.68	7.30	7.10
Right	Thalamic		8.25	1.24	7.35	8.95	8.10	7.62	7.45	7.08	5.07	8.14	7.32	6.66
Left	Occipital	Mesial	9.27	1.54	8.92	9.34	8.70	7.01	7.43	8.26	**6.06**	10.19	7.40	7.26
Right	Occipital	Mesial	9.16	1.60	8.91	9.64	8.79	6.92	6.97	8.28	**5.71**	10.11	8.14	7.18
Left	Occipital	Lateral	7.27	1.23	8.44	7.88	6.92	6.87	6.91	7.46	**5.15**	7.82	7.04	6.67
Right	Occipital	Lateral	7.07	1.34	7.73	7.81	7.06	6.38	6.37	7.38	3.81	7.97	7.23	6.32
Left	Temporal	Mid	7.21	1.09	6.57	7.72	5.99	6.33	6.00	5.82	6.02	7.11	5.81	**5.55**
Right	Temporal	Mid	7.06	1.08	6.43	7.08	6.29	5.97	**5.39**	5.62	4.37	6.27	5.83	**5.06**
Left	Temporal	Mes	6.47	1.02	5.83	6.88	**4.75**	5.67	6.27	5.50	NS	5.92	**4.68**	**4.83**
Right	Temporal	Mes	6.21	0.93	5.39	5.91	5.56	4.63	4.96	4.52	NS	5.14	**4.68**	**4.52**
Left	Temporal	Lat	6.38	0.98	5.52	6.59	4.96	5.30	6.03	**4.73**	**4.25**	5.64	**4.79**	**4.56**
Right	Temporal	Lat	6.34	0.92	5.44	6.11	5.55	**4.92**	4.66	**4.40**	**3.65**	**4.91**	**4.70**	**4.15**
Left	Cerebellum	Sup	7.50	1.13	6.09	7.36	6.83	6.78	7.04	6.58	**5.55**	7.38	**5.58**	**4.67**
Right	Cerebellum	Sup	7.35	1.15	5.83	7.07	6.71	6.46	7.48	6.31	**5.19**	7.23	**5.79**	**4.59**
Left	Cerebellum	Inf	6.57	1.08	5.44	NS	5.73	5.54	5.56	5.52	**4.13**	5.71	**4.51**	**4.08**
Right	Cerebellum	Inf	6.50	1.02	5.50	NS	5.95	5.82	5.52	5.64	**4.64**	5.66	**4.41**	**4.31**
Whole Brain			7.56	1.02	6.98	7.85	6.67	6.15	5.73	6.54	5.21	7.90	6.40	5.75

NS = Not Sampled

Boldface values: regions <1.5 s.d. from mean value.

Underscored values: regions <20% contralateral side.

brain metabolic rate in our normal population. For the quantitative analysis in this study, a region was identified as hypometabolic if the measured metabolic rate was more than 1.5 s.d. less than the normal value for that region. The regions found to be hypometabolic based on a qualitative analysis were found to be abnormal on a quantitative analysis as well. The additional abnormal regions identified using our normal reference values are shown in bold type in Table 1.

DISCUSSION

Based on a study of 241 patients with PCE reported by Henry, et al. (*13*) the detection of an area of hypometabolism in 4 of 10 patients based on a left/right asymmetry or qualitative analysis, is approximately what would be expected from a scanner with the performance characteristics of the PETT VI. However, this qualitative analysis would miss regions of temporal lobe hypometabolism in four other patients as shown in Table 1, including Patients 3 and 8, each having only a single abnormal region. By using measured metabolic rate data, we were able to detect areas of hypometabolism in the temporal lobes of 8 of 10 patients. This is a slightly better percentage than Henry reported for qualitative evaluations of scans performed using tomographs with better performance characteristics than the PETT VI.

Patients 4, 5, 7, and 10 were all twice as old as the mean age of the patients in our normal population. This may account for the bilateral frontal and parietal abnormalities identified in the quantitative analysis of their studies. Kuhl (*14*) and Azari (*15*) have reported age-related reductions in measured metabolic rates for glucose consumption, with the frontal and parietal lobes being slightly more reduced than other brain regions.

To date, 7 of the 10 patients in this study have undergone anterior temporal lobectomy for their partial complex epilepsy. The selection of the surgical site was based on video-EEG recordings with scalp electrodes, sub-dural electrode grids, neuropsychological testing and MRI findings. Table 2 shows

TABLE 2
Agreement of PET Scan Findings

Patient	Surgery	Scan abnormality
1	L	none
2	R	none
3	L	**Left**
4	R	Right
5	L	Right
6	Not done	Right
7	R	Right
8	R	**Right**
9	Not done	**Bilateral**
10	Not done	**Bilateral**

that qualitative analysis (shown in normal type) correctly identified the eventual surgical site in only 2 of these 7 cases. Using quantitative analysis, the eventual site of surgery was correctly identified in 2 additional cases (shown in bold type in Table 2). In addition, neuropsychological testing on Patient 9 pointed to moderately severe bilateral temporal lobe dysfunction.

We recognize that the 1.5 s.d. threshold used in this study could result in a false positive study in approximately 6% of the cases analyzed using this technique. However, as shown in Table 2, there is a good agreement between the quantitative analysis of the PET scan data and the eventual surgical site. It is possible that, if these studies were performed with a tomograph having better performance characteristics, a statistically more significant threshold could have been used.

CONCLUSION

We believe that this study demonstrates an important, but occasionally overlooked, basic principle of nuclear medicine. In nuclear medicine we study physiology and function. Function may be inferred from looking at a picture. However, to truly evaluate function it is necessary to be able to compare values measured in a particular patient to established normal population values obtained under standardized conditions, for your methodology and laboratory.

The apparent bilateral frontal lobe abnormalities identified in the four older patients in this study point out the importance, as with other quantitative nuclear medicine procedures, of establishing normal values based on the characteristics of the patient population you plan to study. In this study of patients with partial complex epilepsy, twice as many areas of hypometabolism were identified using normal reference values for glucose metabolism than would have been detected based on an analysis of the pictures of function alone.

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