Epilepsia, **42**(12):1515–1522, 2001
Blackwell Science, Inc.

Disparity of Perfusion and Glucose Metabolism of Epileptogenic Zones in Temporal Lobe Epilepsy Demonstrated by SPM/SPAM Analysis on ^{15}O Water PET, [^{18}F]FDG-PET, and [^{99m}Tc]-HMPAO SPECT

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Summary: *Purpose:* To elucidate uncoupling of perfusion and metabolism and its significance in epilepsy, ^{15}O water and ^{18}F fluorodeoxyglucose (FDG) positron emission tomography (PET) and Tc-99m hexamethyl-propyleneamine-oxime (HMPAO) single-photon emission computed tomography (SPECT) were examined by SPM (statistical parametric mapping) and quantitation by using SPAM (statistical probabilistic anatomic map).

Methods: [^{15}O]water and [^{18}F]FDG-PET, and [^{99m}Tc]-HMPAO SPECT were performed in 25 patients (SPECT in 17 of 25) with medial temporal lobe epilepsy. For volume of interest (VOI) count analysis, the normalized counts using VOI based on SPAM templates of PET and SPECT were compared with those of the normal controls. Perfusion or metabolism was found abnormal if the Z score was >2 for each VOI. For SPM analysis, the differences between each patient's image and a group of normal control images (t statistic for $p < 0.01$) on a voxel-by-voxel basis were examined to find significant decreases in perfusion or metabolism.

Results: With SPAM VOI count analysis, areas of hypoperfusion were found in 13 patients in the epileptogenic temporal lobes by [^{15}O]water PET and areas of hypometabolism in 21 patients by [^{18}F]FDG-PET. With voxel-based SPM analysis, the epileptogenic zones were localized in 15 by [^{15}O]water PET and in 23 patients by [^{18}F]FDG-PET. The localization by [^{15}O]water PET was concordant with that of [^{18}F]FDG-PET. The areas of hypoperfusion on [^{15}O]water PET were absent or smaller than the areas of hypometabolism on [^{18}F]FDG-PET. Interictal [^{99m}Tc]-HMPAO SPECT revealed the hypoperfused zones in seven of 17 patients on visual assessment.

Conclusions: SPAM VOI count and SPM analysis of [^{15}O]water and [^{18}F]FDG-PET and [^{99m}Tc]-HMPAO SPECT revealed that in the same patients, the areas of hypoperfusion were concordant with but smaller than the areas of hypometabolism. Discordance of perfusion and metabolic abnormalities represents an uncoupling of perfusion and metabolism in the epileptogenic zones, and this might explain the lower diagnostic accuracy of perfusion imaging in temporal lobe epilepsy. **Key Words:** [^{15}O]water PET—[^{18}F]FDG-PET—Temporal lobe epilepsy—[^{99m}Tc]-HMPAO SPECT—Uncoupling.

During physiologic stimulation, blood flow is not tightly coupled to the oxidative metabolism in an activated cortex (1). In several pathologic conditions including epilepsy, there is evidence of an altered relation between blood flow and metabolism (2). In the epileptogenic zones, blood flow is uncoupled from the glucose metabolism on ^{15}O water and on ^{18}F fluorodeoxyglucose (FDG) positron emission tomography (PET) (3–6). In these studies, the regional cerebral glucose metabolic rates were lower than the regional cerebral blood flow in epileptogenic zones. This uncoupling was suggested to be the cause of the lower diagnostic value of interictal perfusion single-photon emission computed tomography (SPECT), which uses the uptake of [^{99m}Tc] agents to represent the regional cerebral blood flow.

Interictal perfusion SPECT was previously found to be useful for localizing the epileptogenic zones (7). However, recent meta-analysis revealed that the sensitivity of interictal perfusion SPECT was less than desirable (8). In a [^{15}O]water PET study (6) and a [^{99m}Tc]- hexamethyl-propyleneamine-oxime (HMPAO) SPECT study by the authors on the interictal blood flow (9), a sensitivity as low as 35% was revealed. In contrast, the sensitivity of

Revision accepted September 26, 2001.
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[^{18}F]FDG-PET was reported to be higher (7,9,10). Further understanding of the impact of the regional uncoupling between blood flow and metabolism on the localization of the epileptogenic zones is necessary.

Recently, statistical parametric mapping (SPM) (11–13) made it possible to display objectively the significantly hypoperfused or hypometabolic areas on a voxel-basis for both [^{15}O]water and [^{18}F]FDG-PET, and [^{99m}Tc]-HMPAO SPECT. Before this approach, a visual assessment and calculation were used of the counts in the regions of interest manually drawn on the individual images or templates (6), which required a high level of expertise and resulted in lower reproducibility because of variable partial volume effects. SPM with its user independence and objectivity were found to concord well with expert interpretation (14,15). Recently another objective VOI-drawing method was developed with statistical probabilistic anatomic maps (SPAM) based on the population magnetic resonance imaging (MRI) images of Evans et al. (16) and was successfully applied to interpret [^{18}F]FDG-PET images (17).

In this study, the differences of hypoperfusion and hypometabolism between [^{15}O]water, [^{18}F]FDG, and the [^{99m}Tc]-HMPAO images in the epileptogenic zones were investigated by voxel-based analysis by using SPM and automatic VOI count analysis with SPAM templates. A decrease in blood flow and glucose metabolism was measured in the temporal lobes ipsilateral and contralateral to the epileptogenic zones in patients with medial temporal lobe epilepsy. We tried to unravel the uncoupling of blood flow and metabolism in the epileptogenic zones and its clinical implication on [^{15}O]water and [^{18}F]FDG-PET, and [^{99m}Tc]-HMPAO SPECT.

MATERIALS AND METHODS

Subjects

Twenty-five patients were studied with intractable medial temporal lobe epilepsy (13 men and 12 women with an average age of 29 ± 8 years; Table 1). Diagnosis was confirmed by surgical outcome in 21 patients and by ictal EEG and MRI findings in the other four, who showed hippocampal sclerosis and/or atrophy. In 17 of 25 patients, [^{99m}Tc]-HMPAO SPECT was performed. Twenty-two age-matched controls (25 ± 6 years) were selected for [^{18}F]FDG-PET, 12 (24 ± 5 years) for [^{15}O]water PET, and 20 (23 ± 2 years) for [^{99m}Tc]-HMPAO SPECT.

Presurgical evaluation

The diagnosis was made by standard presurgical evaluation at Seoul National University Hospital; evaluation techniques included scalp video-EEG monitoring,

TABLE 1. *Patient characteristics and comparison of results by SPAM VOI count analysis and voxel-based SPM analysis on ^{15}O Water PET, ^{18}F FDG PET and ^{99m}Tc HMPAO SPECT*

No.	Age (yr)	Sex	Final Dx*	FDG		Water		HMPAO
				SPAM	SPM	SPAM	SPM	SPM
1	38	M	L	L	L	N	N	
2	19	M	L	L	L	R	N	
3	35	F	L	L	L	N	L	N
4	34	F	R	R	R	N	N	
5	25	F	L	L	L	N	N	L
6	23	F	L	L	L	L	L	
7	26	F	L	L	L	N	R	L
8	20	M	R	N	N	N	N	
9	16	M	L	L	L	L	L	N
10	19	F	L	L	L	L	L	R
11	27	F	R	R	R	N	R	N
12	17	M	R	N	R	R	R	L
13	27	F	L	L	L	N	N	N
14	32	M	L	B	B	L	B	N
15	46	M	L	L	L	L	B	L
16	40	M	R	R	R	R	R	N
17	41	M	L	L	L	L	L	N
18	38	M	L	L	L	L	N	
19	24	M	R	R	R	R	R	
20	31	M	L	N	L	L	L	N
21	30	F	R	R	R	R	R	N
22	38	F	R	R	R	L	R	N
23	23	F	L	L	L	N	L	N
24	27	M	R	R	R	N	R	N
25	20	M	R	R	R	R	R	

Final Dx, Final diagnosis was confirmed by surgical outcome (n = 21) or ictal EEG and MR findings (n = 4); Visual, result of visual interpretation; SPAM, result of SPAM VOI count analysis; SPM, result of voxel-based analysis; L, left; R, right; N, normal; B, Both; SPM, statistical parametric mapping; SPAM, statistical probabilistic anatomic map; VOI, volume of interest; MR, magnetic resonance.

brain MRI, interictal EEG, interictal and ictal SPECT, and PET. When results were inconclusive in four patients, additional intracranial EEG monitoring was performed.

Magnetic resonance imaging

Standard MRI (1.5 T; spatial resolution, 1.0 × 1.0 mm; matrix, 256 × 256 mm; field of view, 25 cm; Siemens, U.S.A.) was performed with a conventional spin-echo T_1-weighted sagittal and T_2-weighted axial and coronal sequences. The T_2-weighted fast spin-echo sequences with 3-mm-thick sections and the T_1-weighted 3D magnetization were prepared, and rapid acquisition with gradient-echo sequences with 1.5-mm-thick sections was obtained in the oblique coronal plane of the temporal lobes perpendicular to the long axis of the hippocampus.

On sagittal, coronal, and transverse MRIs, no neocortical lesions were found. Two of the patients were normal on MRI, and the other 23 patients showed hippocampal sclerosis and/or atrophy.

Interictal [^{15}O]water positron emission tomography

The [^{15}O]water PET was acquired during the interictal phase by using an ECAT-Exact47 PET scanner (spatial resolution, 6.1 × 6.1 × 4.3 mm; CTI/ Siemens). A transmission scan was acquired for 20 min by using triple ^{68}Ge rod sources. A volume of 370–925 MBq of [^{15}O]water was injected intravenously, and the emission scans were acquired for 2 min with 5 s intervals. The resting scans obtained by summing the images of 60-s duration after [^{15}O]water activity reached plateau were used. The transaxial images were reconstructed by using a Shepp-Logan filter (cutoff frequency, 0.3 cycles/pixel) and corrected for attenuation by using the attenuation map obtained from the transmission images.

Interictal [^{18}F]fluorodeoxyglucose positron emission tomography

The [^{18}F]FDG-PET was acquired during the interictal phase by using an ECAT-Exact47 PET scanner (spatial resolution, 6.1 × 6.1 × 4.3 mm; CTI/Siemens). A transmission scan was acquired for 20 min by using triple [^{68}Ge] rod sources. Then 370 MBq of [^{18}F]FDG was injected intravenously after 6 h of fasting with the patients' eyes closed in a quiet, dimly lit room. Any unnecessary communication and activity during the 30-to 40-min postinjection period were discouraged. An emission scan was acquired for 20 min with the 2-D acquisition mode. The transaxial images were reconstructed by using a Shepp-Logan filter (cutoff frequency, 0.35 cycles/pixel) and corrected for attenuation by using the attenuation map obtained from the transmission images. The transaxial images were realigned to yield both sagittal and coronal images. The section thickness was 3.2 mm.

Interictal [^{99m}Tc]-HMPAO SPECT

The [^{99m}Tc]-HMPAO was reconstituted and stabilized with $CoCl_2$. Then 1,110 MBq of [^{99m}Tc]-HMPAO was injected during the interictal period ≥72 h after the previous ictal study. Ten minutes after the injection, an interictal SPECT was performed. The interictal SPECT images were acquired with a triple-head Prism3000 SPECT camera (Picker International, OH, U.S.A.) with a low-energy high-resolution fan-beam collimator. One hundred twenty images were acquired for 20 s each by using the step-and-shoot method with an interval of 3 degrees and a 128 × 128 matrix. The transaxial images were reconstructed by using a filtered backprojection with a Metz filter (× = 1.5~2.0). The attenuation was corrected with Chang's method. Transaxial images were realigned to yield both sagittal and coronal images. Section thickness was 5 mm.

Analysis of image by visual analysis, SPAM count analysis, and voxel-based SPM analysis

Three imaging methods were analyzed by three different analysis methods, which yielded nine data. However, [^{15}O]water PET was not of high enough quality to be analyzed by visual interpretation, and [^{99m}Tc]-HMPAO SPAM data showed much variation, so that the definition of normal range was not easy. Excluding these two combinations of imaging and analysis methods, the other seven data were presented.

Visual-image interpretation of [^{18}F]FDG-PET and [^{99m}Tc]-HMPAO SPECT

The cerebral cortex was divided into the occipital lobe, medial temporal lobe, lateral temporal lobe, frontal lobe, and parietal lobes. Two nuclear physicians assessed the regional metabolism and perfusion on the [^{18}F]FDG-PET and on [^{99m}Tc]-HMPAO SPECT. On the [^{18}F]-FDG interictal PET, the most hypometabolic region was determined to be the epileptogenic zone. On the interictal [^{99m}Tc]-HMPAO SPECT, the most hypoperfused region was considered to be the epileptogenic zone. The [^{15}O]water PET was not used for visual assessment.

SPAM VOI count analysis on [^{15}O]water PET and [^{18}F]FDG-PET

The SPAM images of Montreal Neurological Institute were applied to calculate objectively the PET counts in certain VOIs (17). The SPAM consisted of 98 VOI images including the cortical VOIs of both hemispheres. Each image consisted of the probabilities (0~1) that belong to specific regions.

The [^{15}O]water or [^{18}F]FDG-PET images were normalized for the global counts and normalized spatially to the average brain MRI atlas of the International Consortium of Brain Mapping (ICBM) by using SPM 99 (Wellcome Department of Cognitive Neurology, University of London, U.K.). Affine transformations were performed

to determine the 12 optimal parameters needed to register the individual brain on the template. SPAM probability-weighted mean counts were obtained for seven VOIs of the temporal lobes by using the probabilistic brain atlas of VOIs: the amygdala; hippocampal formation; parahippocampal gyrus; superior, middle, and inferior temporal gyri; and uncal gyrus. Mean count of each VOI was calculated by dividing the probability-weighted count sum of all the voxels in the VOI by the sum of probability sum of the VOI. Compared with the count distribution of each VOI of the normal controls, the VOI Z values of the patients were calculated. A Z value ≤ 2 was considered to represent a significantly decreased count of the VOI.

The number of VOIs with significantly decreased perfusion or metabolism was counted for both temporal lobes. A particular temporal lobe was determined to be hypoperfused or hypometabolic when one or more VOIs showed significantly decreased perfusion or metabolism. Thereafter, epileptogenic zones were lateralized to the temporal lobe having the larger numbers of these significantly hypoperfused or hypometabolic VOIs.

Voxel-based SPM analysis on [^{15}O]water PET, [^{18}F]FDG-PET, and [^{99m}Tc]-HMPAO SPECT

The differences between a [^{15}O]water, [^{18}F]FDG, or [^{99m}Tc]-HMPAO scan of each patient and those of the controls were statistically analyzed by using the SPM 99 package (Wellcome Department of Cognitive Neurology) implemented on a Matlab (Mathworks Inc., U.S.A.) (15). Subtle differences between the transformed image and the template were removed by a nonlinear registration method by using the weighted sum of the predefined smooth basis functions used in a discrete cosine transformation. Spatially normalized images were then smoothed by convolution with an isotropic gaussian kernel with 16-mm FWHM.

The effect of global difference was removed by normalizing the count of each voxel to the global count of the cortical area by using proportional scaling in SPM. A significant decrease in the regional metabolism was estimated by comparing the respective PET or SPECT images with those from normal controls by using *t* statistics at every voxel. The voxels with uncorrected p values 0.01 with the extent of 100 voxel-cluster were considered significant. The *t* values were then transformed into Z values. Numbers of significantly decreased voxels in the epileptogenic temporal lobes were counted and used to represent the size of the hypoperfused or hypometabolic areas.

Ictal EEG studies and surgical outcome

In all the patients, a video-monitored EEG was acquired. The left or right temporal lobe was found to be epileptogenic in 21 patients on ictal EEG. In the other four patients, the ictal EEG was ambiguous or bilateral. In 21 patients, an anterior temporal lobectomy was performed. The surgical outcome was in Engel class I in 20 patients and class III in the remaining patient after an average follow-up period of 38 (±8) months. The other four patients are awaiting surgery.

Statistical analysis

A χ^2 test was performed to compare the sensitivity of the SPAM and SPM analysis of interictal [^{15}O]water PET, [^{18}F]FDG-PET, and the [^{99m}Tc]-HMPAO SPECT.

RESULTS

SPAM VOI count analysis on interictal [^{15}O]water PET

On quantification of the [^{15}O]water PET, nine patients showed a lower perfusion in the left temporal lobes and six patients in the right temporal lobes (Table 1). Remaining 10 patients were normal. The quantified [^{15}O]water uptakes of the temporal lobe VOIs were correct in 13 of 25 patients (Fig. 1). An average of 0.9 (±1.1) VOIs among the seven temporal lobe VOIs showed decreased perfusion. In two of the patients with decreased perfusion, perfusion was decreased in one or three VOIs of contralateral temporal lobe on [^{15}O]water PET.

Visual assessment and SPAM VOI count analysis on interictal [^{18}F]FDG-PET

Among 25 patients, 14 patients showed left temporal hypometabolism, and nine showed right temporal hypometabolism on visual assessment. The remaining two patients were normal on [^{18}F]FDG-PET.

On quantification of the [^{18}F]FDG uptakes of the VOIs in the temporal lobes, 13 patients showed signifi-

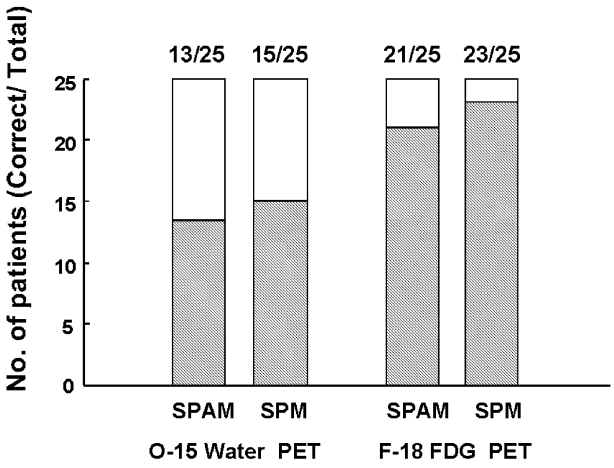


FIG. 1. Number of patients with correct localization of epileptogenic zones by statistical probabilistic anatomic map (SPAM) volume of interest (VOI) count analysis and voxel-based statistical parametric mapping (SPM) analysis on [^{15}O]water positron emission tomography (PET) and [^{18}F]fluorodeoxyglucose (FDG)-PET. Sensitivity of SPAM or SPM analysis results of [^{18}F]FDG-PET was superior to that of [^{15}O]water PET. No difference was found between SPAM and SPM analyses.

cant hypometabolism in left temporal lobes, eight in the right temporal lobes, and one in both temporal lobes (Table 1). Remaining three patients were normal. The quantified FDG uptakes of the temporal lobe VOIs were correct in 21 of 25 patients (Fig. 1). An average of 3.6 (±2.5) VOIs showed decreased metabolism among the seven VOIs in the temporal lobe. In nine of the 21 patients with unilateral hypometabolism, the metabolism was lower in one to three VOIs of the contralateral temporal lobes, but to a lesser extent.

On comparison of visual interpretation and SPAM VOI count analysis, 23 were concordant. In the remaining two patients, visual interpretation was correct, but SPAM analysis yielded normal or bilateral results (Table 1, cases 8 and 14). In the three among those concordant 23 patients, two patients were normal on both analysis methods, and in the other three, localization of epileptogenic zones was undetermined on visual interpretation between medial temporal lobe and adjacent lobes.

Voxel-based SPM analysis on [^{15}O]water and [^{18}F]FDG-PET

The epileptogenic zones were correctly localized in the temporal lobes on SPM analysis of the [^{15}O]water PET in 15 patients (Fig. 1). Two patients showed bilateral hypoperfusion, and seven were normal. The size of areas with decreased perfusion ranged from 0 to 4,753 voxels in the epileptogenic temporal lobes (mean ± SD, 521 ± 989).

Epileptogenic zones were correctly localized in the temporal lobes by SPM analysis of the [^{18}F]FDG-PET by revealing areas of hypometabolism in 23 patients (Fig. 1). One patient showed bilateral hypometabolism, and another was normal. The size of areas with decreased metabolism ranged from 0 to 5,789 voxels in the temporal lobes (mean ± SD, 2,481 ± 1,597).

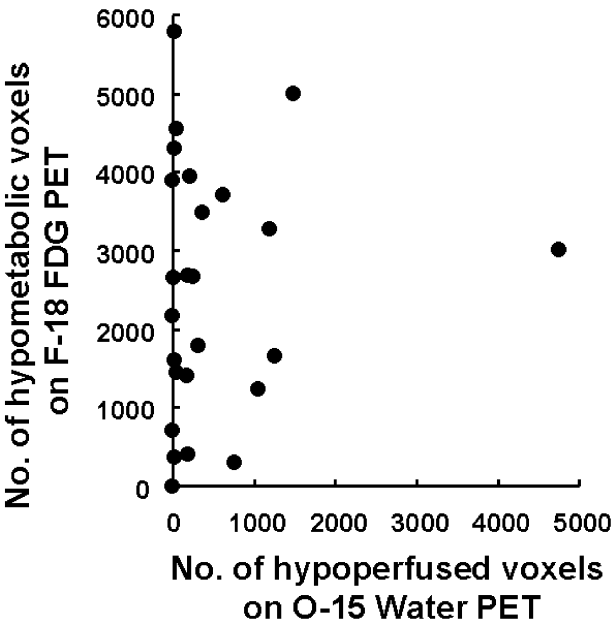
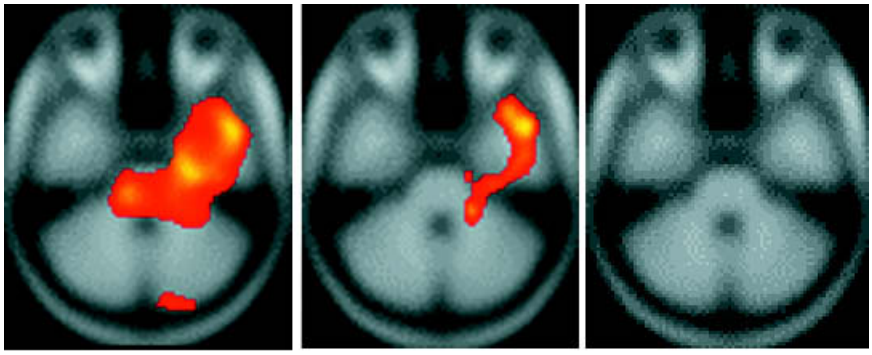


FIG. 2. Number of hypoperfused voxels and hypometabolic voxels on [^{15}O]water positron emission tomography (PET) and [^{18}F]fluorodeoxyglucose (FDG)-PET in the epileptogenic temporal lobes. Numbers of hypoperfused or hypometabolic voxels (uncorrected p values <0.01) were counted by voxel-based statistical parametric mapping (SPM) analysis. Each data point represents voxel number per epileptogenic whole temporal lobe per patient. Numbers of hypometabolic voxels tended to be much larger than those of hypoperfused voxels. In 10 patients, hypoperfused voxels were absent or nearly absent.

Figure 2 shows a scattergram of numbers of hypoperfused voxels in the epileptogenic temporal lobes found by SPM analysis on [^{15}O]water and [^{18}F]FDG-PET. Hypoperfused voxels were absent in four patients or were <50 in six patients (Fig. 2). The hypoperfused voxels were fewer than hypometabolic voxel in 11 patients but more numerous in the other two patients. In the remain-



	FDG	Water	HMPAO
No of voxel decreased by SPM	3707	628	0
No of area decreased by SPAM	6	3	0

FIG. 3. This patient showed partial uncoupling between metabolism and perfusion in the epileptogenic zone. Both [^{18}F]fluorodeoxyglucose (FDG)-positron emission tomography (PET) and [^{15}O]water PET revealed that this patient had left temporal lobe epilepsy, which was proven by surgical outcome (patient 9). Extent of the hypometabolic area was larger than that of the hypoperfused area. Statistical parametric mapping (SPM) analysis of [^{99m}Tc]-hexamethylpropyleneamine-oxime (HMPAO) PET did not show any area of hypoperfusion. Statistical probabilistic anatomic map (SPAM) volume of interest (VOI) count analysis revealed that [^{18}F]FDG uptake was decreased in six VOIs, and perfusion was decreased in three VOIs in the left temporal lobe.

ing two patients, the numbers of hypoperfused voxels were similar to those of hypometabolic ones. In these 15 patients with decreased perfusion and metabolism, the laterality of hypoperfusion shown on [^{15}]O water PET was concordant with that of hypometabolism on the [^{18}F]FDG-PET (Fig. 3). Figure 4 is an example of hypometabolic but not hypoperfused epileptogenic temporal lobe.

Visual assessment and voxel-based SPM analysis on interictal [^{99m}Tc]- HMPAO SPECT

In seven of 17 patients, areas of decreased perfusion were found on interictal [^{99m}Tc]-HMPAO SPECT by visual assessment. The other 10 patients were normal.

Hypoperfused zones were found in the temporal lobes by voxel-based SPM analysis of the [^{99m}Tc]-HMPAO SPECT in five patients, among whom three were correct and the other two were incorrect compared with the final diagnosis. The other 12 patients did not reveal any areas of hypoperfusion in the temporal lobes (Fig. 3).

Comparison of sensitivity of SPAM or SPM analysis on [^{15}O]water PET, [^{18}F]FDG-PET, and [^{99m}Tc]-HMPAO SPECT

On the SPAM analysis [^{18}F]FDG PET yielded better sensitivity than [^{15}O]water PET to find epileptogenic zones ($p = 0.01$; Fig. 1). On the SPM analysis, [^{18}F]FDG-PET yielded better sensitivity than did [^{15}O]water PET or [^{99m}Tc]-HMPAO SPECT ($p = 0.008$). However, there was no difference between SPAM and SPM analyses of either [^{18}F]FDG-PET or [^{15}O]water PET.

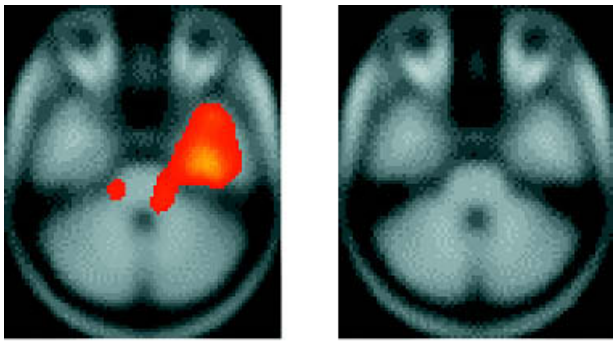
DISCUSSION

Gaillard et al. (3) performed simultaneous imaging of [^{15}O]water PET and [^{18}F]FDG-PET. They found that ratio of the local cerebral glucose metabolic rate to the regional cerebral blood flow was lower in the inferior lateral temporal cortex with the template region of interest (ROI) method. Template ROI was superior to ROI manually drawn on individual images. In our study, the subjectivity of drawing an ROI was overcome by a SPAM-based VOI template. As the VOI is derived from a population-based MRI template, the counts of the seven VOIs of each temporal lobe could be calculated reproducibly. Rather than comparing asymmetric indices, the counts of the VOI of each temporal lobe was compared with those of normal controls. After defining the normal range of normalized counts, the hypoperfused or hypometabolic areas were determined by using Z values on the [^{15}O]water or [^{18}F]FDG-PET by SPAM VOI count analysis.

SPM, which had been used for brain activation studies, also can be used for locating areas with significant hypometabolism or hypoperfusion compared with normal controls. Compared with the [^{18}F]FDG images of the age-matched normal controls, the hypometabolic areas recognized by visual assessment was detected by SPM analysis on the [^{18}F]FDG-PET (14,15). Assessment of the hypoperfused areas was difficult visually on the [^{15}O]water PET. However, by using SPM, a voxel-based quantification of the regional blood flow was possible on [^{15}O]water PET. The area of decreased perfusion was determined by using [^{99m}Tc]-HMPAO SPECT in the same way.

This voxel-based SPM analysis supported the earlier SPAM VOI analysis results. In contrast to the SPAM VOI analysis, in SPM, the variation of counts was calculated on a voxel basis. Although SPM analysis yielded areas of hypoperfusion or hypometabolism similar to those of SPAM VOI analysis, not only were the areas of hypometabolism wider than the areas of hypoperfusion, but also the epileptogenic zones were found more often by [^{18}F]FDG-PET than by [^{15}O]water PET. Both reproducible and objective SPAM VOI and voxel-based SPM methods corroborated our visual observations and the previous reports (3,5,6,18). Zubal et al. (19) recently described a method for using interictal SPECT/PET ratio images to demonstrate epileptogenic foci. Because spatial normalization between two different imaging methods can be readily performed, this ratio image might be another good approach to demonstrate uncoupling on a voxel basis.

The sensitivity of interictal-perfusion SPECT was recently questioned (9,20); however, it was not evident that



	FDG	Water
No of voxel decreased by SPM	95	0
No of area decreased by SPAM	7	0

FIG. 4. This patient showed total uncoupling between metabolism and perfusion in the epileptogenic zone. [^{18}F]fluorodeoxyglucose (FDG)-positron emission tomography (PET) alone indicated that the left temporal lobe was epileptogenic, but [^{15}O]water PET did not. Statistical probabilistic anatomic map (SPAM) volume of interest (VOI) count analysis revealed that [^{18}F]FDG uptake was decreased in all the seven VOIs of the left temporal lobe.

this was due to the properties of [^{99m}Tc] agents or rather the lower resolution of SPECT. In our study with statistical quantitative methods, [^{15}O]water PET could not yield sensitivity equivalent to that of [^{18}F]FDG-PET. Interictal perfusion SPECT and PET could not compete with [^{18}F]FDG-PET in finding epileptogenic zones.

Several investigators reported uncoupling of the blood flow and glucose metabolism in the epileptogenic zones in intractable epilepsy (3,5,6,18). Our study is the confirmation of these findings by new operator-independent methods: automatic SPAM VOI count analysis and voxel-based SPM analysis. Quantitation of hypoperfused or hypometabolic voxels in the ipsilateral epileptogenic temporal lobes with an arbitrary cutoff value of uncorrected $p = 0.01$ on SPM analysis revealed even an absence or much smaller extent of hypoperfused areas than of hypometabolic areas. Because of the uncoupling of blood flow and glucose metabolism in the epileptogenic cortex, interictal [^{15}O]water PET or [^{99m}Tc]-HMPAO SPECT is not useful and might be sometimes misleading.

Three possible mechanisms were proposed for this uncoupling. First, [^{18}F]FDG-PET represents a relatively long-term state in intractable epilepsy patients, but [^{15}O]water PET represents a short-term state. Because the interictal spike discharge is not infrequently accompanied by increased metabolism and perfusion (21), the increased perfusion might be observed on interictal perfusion studies. Second, as the ictal episodes are followed by an increased perfusion of variable duration in the epileptogenic zones, even tens of minutes (22) or hours (23) after ictus, an interictal [^{15}O]water PET or [^{99m}Tc]-HMPAO SPECT might represent the "aftereffect" of the previous ictus without subclinical ictal discharges. The decreased metabolism in the interictal period can be concealed by the overlying hyperperfusion at the epileptogenic zones. However, the postictal aftereffect on glucose metabolism also was reported (24). Third, the glucose metabolism might be further downregulated to prevent ictal propagation in the areas near the epileptogenic zones. This explains why the hypometabolic areas are wider than the hypoperfused areas. Possibly the lower brain glucose concentration associated with the downregulated glucose transport in the cerebral capillary membrane might be involved in the wider area of hypometabolism (25).

There has been a possibility and a recent suggestion that the decreased uptake of [^{18}F]FDG on the [^{18}F]FDG-PET does not represent decreased glucose metabolism. [^{18}F]FDG decrease, not glucose metabolism, might be characteristic of the epileptogenic zones (26). If the lumped constant was estimated by using dynamic [^{18}F]FDG-PET data, the lumped constants should be lower if this were the case. This interpretation awaits further evidence.

In conclusion, [^{15}O]water PET and [^{99m}Tc]-HMPAO SPECT showed an uncoupling of perfusion from glucose metabolism on [^{18}F]FDG-PET in the epileptogenic zones in temporal lobe epilepsy. When the user-independent SPAM VOI counts were compared on [^{15}O]water PET and [^{18}F]FDG-PET, the epileptogenic zones with an abnormal metabolism or perfusion could be located best by [^{18}F]FDG-PET. Voxel-based analysis using the SPM method yielded areas of decreased perfusion and metabolism and their uncoupling on [^{15}O]water PET, [^{18}F]FDG-PET, and [^{99m}Tc]-HMPAO SPECT in epileptogenic zones. Both the quantitative VOI-based and voxel-based methods corroborated the uncoupling in the epileptogenic zones in medial temporal lobe epilepsy.

Acknowledgment: This study was supported by Korean Ministry of Health and Welfare HMP 96-M-2-1039 and HMP-99-7-02-0003. We appreciate the support and collaboration of Dr. Alan Evans, who provided SPAM data from Montreal Neurological Institute.

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