부분적 간질에서 SPECT Subtraction을 이용한 발작 중 뇌혈류 변화에 대한 연구

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Ictal Cerebral Perfusion Patterns in Partial Epilepsy: SPECT Subtraction

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Abstract

Purpose: To investigate the various ictal perfusion patterns and find the relationships between clinical factors and different perfusion patterns. **Materials and Methods:** Interictal and ictal SPECT and SPECT subtraction were performed in 61 patients with partial epilepsy. Both positive images showing ictal hyperperfusion and negative images revealing ictal hypoperfusion were obtained by SPECT subtraction. The ictal perfusion patterns of subtracted SPECT were classified into focal hyperperfusion, hyperperfusion-plus, combined hyperperfusion-hypoperfusion, and focal hypoperfusion only. **Results:** The concordance rates with epileptic focus were 91.8% in combined analysis of ictal hyperperfusion and hypoperfusion images of subtracted SPECT, 85.2% in hyperperfusion images only of subtracted SPECT, and 68.9% in conventional ictal SPECT analysis. Ictal hypoperfusion occurred less frequently in temporal lobe epilepsy (TLE) than extratemporal lobe epilepsy. Mesial temporal hyperperfusion alone was seen only in mesial TLE while lateral temporal hyperperfusion alone was observed only in neocortical TLE. Hippocampal sclerosis had much lower incidence of ictal hypoperfusion than any other pathology. Some patients showed ictal hypoperfusion at epileptic focus with ictal hyperperfusion in the neighboring brain regions where ictal discharges propagated. **Conclusion:** Hypoperfusion as well as hyperperfusion in ictal SPECT should be considered for localizing epileptic focus. Although the mechanism of ictal hypoperfusion could be an intra-ictal early exhaustion of seizure focus or a steal phenomenon by the propagation of ictal discharges to adjacent brain areas, further study is needed to elucidate it. **(Korean J Nucl Med 2000;34:169-82)**

Key Words: SPECT subtraction, Partial epilepsy, Ictal perfusion pattern, Ictal hypoperfusion

Introduction

Both interictal and ictal SPECTs have been used successfully for localizing temporal lobe epilepsy (TLE), and have been reported to be less

sensitive but more specific in extratemporal lobe epilepsy (ELTE).[1] The low sensitivity of ictal SPECT in ETLE may be related to various clinical factors and technical limitations: (1) inhomogeneous and various perfusion patterns in brain regions, (2) difficult detection of subtle perfusion changes, (3) variability in radioisotope amount delivered to brain and injection time of radioisotope, (4) different slice levels and orientations arising from different patient positioning during the interictal and ictal SPECT scans, and (5) lack of a quantitative assessment of the difference between the interictal and ictal SPECT images, and other factors.

Recently, computer-aided methods to subtract interictal SPECT from ictal one and co-register subtracted SPECT image to MRI have been developed.[2] SPECT subtraction is considered as a useful tool for localizing seizure focus. However, interpretation of ictal and subtracted SPECT studies has many pitfalls. First, true ictal SPECT studies are often difficult to obtain because the completion of radioisotope injection during clinical seizures is not easy especially in short duration seizures of extratemporal origin. Second, the perfusion changes of the epileptogenic zone during periictal period are not known exactly yet. The seizure semiology at the time of injection represents only the seizure discharges occurring at the symptomatogenic zone, which can be either epileptogenic area or neighboring brain region. The time of injection, duration of seizures, propagation speed and pathway of ictal EEG discharges, and changing types of clinical seizures can affect perfusion patterns of epileptogenic zones during periictal period. Therefore, the real perfusion changes in the epileptogenic zone is not simple.

This study was aimed (1) to classify the various ictal perfusion patterns in subtraction SPECT, (2) to determine whether the detection of ictal focal hypoperfusion as well as hyperperfusion in subtraction SPECT improves the seizure localization, (3) to clarify the contributing clinical factors to determining ictal perfusion patterns, and (4) to compare the sensitivities of seizure localization in subtraction SPECT-MRI co-registration, conventional visual inspection of interictal and ictal SPECT, MRI and interictal FDG-PET (^{18}F-fluorodeoxyglucose positron emission tomography).

Material and Methods

1. Patients

Sixty-one patients with intractable epilepsy were included. All patients underwent the precise presurgical evaluation including clinical examination, long-term video-EEG monitoring, brain MRI, FDG-PET, interictal and ictal SPECT studies, and SPECT subtraction. All subjects had epilepsy surgery from 1995 to 1998.

2. Interictal and ictal SPECT studies

Ethyl cysteinate dimer (ECD) labeled with ^{99m}Tc was injected intravenously for SPECT studies. Brain SPECT scan was performed within 90 min after the injection of radiotracer 925 MBq (25 mCi) ^{99m}Tc-ECD using a three-headed Triad XLT system (Trionix Research Laboratory, Twinsburg, OH) equipped with low-energy, high-resolution collimators. The transaxial system resolution of this camera is 6.9 mm full width at half maximum. Images were reconstructed by filtered backprojection using a Butterworth filter. Attenuation correction was performed using Chang's method (attenuation coefficient μ =0.12 cm^{-1})(Chang, 1987).[3]

Interictal injection of 925 MBq (25 mCi) ^{99m}Tc-ECD was performed in patients who had no documented seizure activity in the previous

24-hour period or more. For ictal studies, patients received injection of radiotracer during seizure activity or immediately after cessation of clinical seizures. The injection was considered as ictal when the radiotracer was injected during clinical or EEG seizure activity and postictal when injected after the seizure had ended. The patients were continuously monitored by a longterm video-EEG monitoring system during this phase. As soon as seizure activity was witnessed or alarmed by seizure button, the radiotracer was injected rapidly by trained EEG technician or nurse.

3. MRI imaging

The MRI scanning was performed with a GE Signa 1.5-Tesla scanner (GE Medical Systems, Milwaukee, WI, USA). SPGR(spoiled gradient recalled) volumetric MRI was scanned with the parameters of no gab, 1.6 mm thick, 124 slices, TR/TE=30/7, flip angle=45, 1 NEX, coronal. The voxel dimension was 0.875×0.875×1.6 mm.

FLAIR (fluid attenuated inversion recovery) was scanned with oblique coronal, 1.0 mm gap, 4.0 mm thickness, 32 slice, TR/TE=10002/127.5, 1 NEX, and axial images of FLAIR also was obtained with 2.0 mm gab, 5.0 mm thickness. T2 image was scanned with 0.3 mm gap, 3.0 mm thickness, 56 slice, TR/TE=5300/99, flip angle=90, 3 NEX, oblique coronal. T2 axial images was scanned too with 2.0 mm gab, 5.0 mm thickness.

4. Image Processing for SPECT subtraction

SPECT subtraction technique was processed on an off-line SUN Ultra 1 Creator workstation (Sun Microsystems, CA, USA) and with commercial software package, ANALYSE 7.5 (Biomedical Imaging Resource, Mayo Foundation, MN, USA).

All biomedical images were transferred from each scanner consoles to Unix workstation by 4 mm DAT device.

SPECT subtraction procedures consisted of the following processes.

1) Step-1

Ictal-interictal SPECT registration. Before subtracting each pixel value between two SPECT images, three-dimensional position of interictal SPECT was transformed to ictal SPECT. In all cases, RMSD (root mean square distance) was within 1 voxel. Correct registration is important to improve sensitivity of subtraction technique. And inaccurate registration may produce false perfusion difference.

2) Step-2

Radioisotope uptake level normalization. Different radioisotope uptake level was normalized because each patient has different uptake level of radioisotope. And normalization factor was calculated over the whole brain.[4]

3) Step-3

Ictal-transformed interictal SPECT subtraction. To get cerebral perfusion difference, ictal SPECT was subtracted by transformed and normalized interictal SPECT. Difference of radioisotope uptake level was calculated pixel by pixel subtraction. And subtracted SPECT was separately divided into positive (hyperperfusion) and negative (hypoperfusion) images.

4) Step-4

Noise erasing. To erase subtraction noise, standard deviation of each subtracted SPECT was calculated. Two SD were adjusted to erase noise. If no significant perfusion difference was observed after 2 SD thresholding, 1SD thresholding was performed.

5) Step-5

MRI-subtracted SPECT registration. The accurate anatomical localization of epileptogenic focus is important for successful epilepsy surgery.[2,4] For localization of difference images, we co-registered subtracted SPECT with SPGR MRI of the pati- ent's whole brain (Fig. 1). In most cases, the error ranges of SPECT-MRI registration were within 3 voxels.

5. Interpretation of SPECT (interic- tal, ictal and subtracted SPECTs)

When interictal SPECT was subtracted from ictal SPECT, the brain region with positive values indicated hyperperfusion area and the region with negative values meant hypoperfusion area. Five different kinds of SPECT images were interpreted separately by two reviewers (H.W.L. and W.S.T.) who were blinded to clinical data, results of other
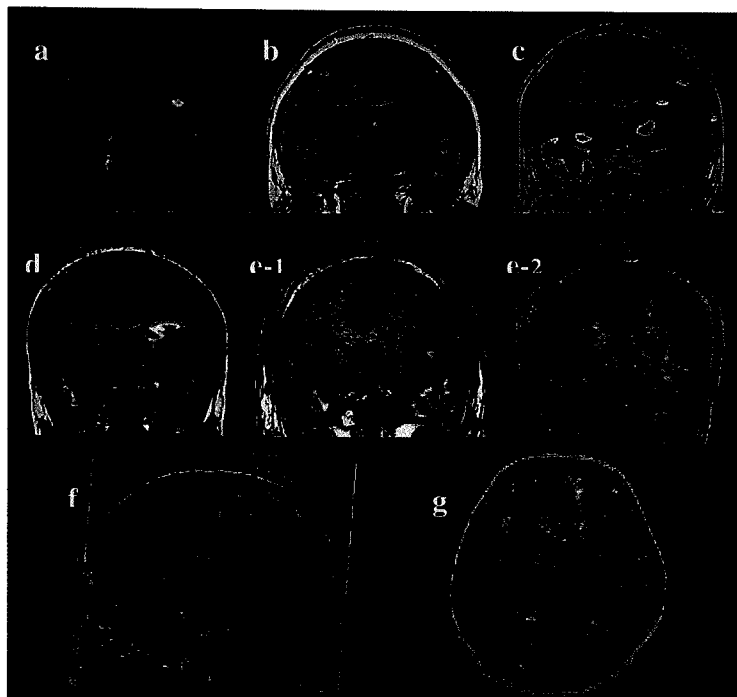
Fig. 1. Focal hyperperfusion of subtracted SPECT in TLE: (a) hyper- perfusion in only mesial temporal region of right mesial TLE, (b) hyperperfusion in lateral temporal region of a left neocortical TLE, and (c) hyperperfusion in both mesial and lateral temporal areas in a right mesial TLE. (d) is hyperperfusion-plus pattern of subtracted SPECT: bilateral temporal hyperperfusion with left predominance in a left neocortical TLE. (e-1 & e-2) are combined hyperperfusion-hypoperfusion pattern of subtracted SPECT [(e-1) is a positive image showing hyperperfusion in left anterior temporal region and (e-2) is a negative image showing hypo- perfusion in left posterior and basal lateral temporal cortex from the same interictal & ictal SPECT images]. (f, g) are perfusion patterns of subtracted SPECT in ETLE patients [(f) focal hyperperfusion in a right supplementary motor area seizure and (g) focal hypoperfusion in a left frontal lobe epilepsy.

tests, and surgical outcome. Five different sets of SPECT images were as follows: (1) interictal SPECT, (2) ictal SPECT, (3) hyperperfusion images of subtracted SPECT ("positive results of subtraction"), (4) hypoperfusion images of subtracted SPECT ("negative results of subtraction"), and (5) both hyperperfusion and hypoperfusion images of subtracted SPECT (hyperperfusion-hypoperfusion combined analysis). These five sets of SPECT images were presented to first two reviewers by one set at a time, in random order for the set and for the patient sequences, so that all reviewers were blinded to their previous interpretations to other sets. If the two reviewers disagreed, a third blinded reviewer was used (S.B.H). Agreement of the third reveiwer with one of the primary reviewers served as the final determination.

Reviewers localized the abnormality in each SPECT image to 1 of 16 sites (i.e. either right or left: frontal, frontotemporal, temporal, frontoparietal, temporoparietal, parietal, occipitoparietal, or occipital) or classified the image as nonlocalizing or nonlateralizing. The final decision of localization was reached by the agreement of all reviewers. If the three reviewers failed to reach an accord on localization after discussion, that image was considered nonlocalizing or nonlateralizing.

The concordance rates to the final epileptic focus proven by invasive EEG monitoring and epilepsy surgery were calculated in subtracted SPECT, conventional interictal/ictal SPECT, MRI and interictal FDG-PET studies. The various ictal perfusion patterns in subtracted SPECT were described, and we tested the relationship between the ictal perfusion patterns of subtracted SPECT and clinical factors such as locations of seizure foci (temporal versus extratemporal origins), types of tissue pathology (hippocampal sclerosis, cortical dysplasia and others), and injections times of

radioisotope.

6. Injection time of radiotracer for SPECT study

For determination of seizure length and injection timing, the seizure onset was taken as the time of earliest indication of a warning (verbalized or pushing the seizure button) or of abnormal movements, behavior, or impaired awareness. The end of a seizure was the time when ictal movements or behavior ceased. To confirm the ictal period, ictal EEG was interpreted simultaneously. The time of the injection was taken as the time when the plunger on the syringe containing the radiotracer was fully depressed. The exact time of injection was recorded by the EEG fellow or the staff. The time of injection in relation to seizure occurrence was determined with accuracy by playing back the videotape that had recorded clinical seizure with radioisotope injection and reviewing ictal EEG during that seizure.

Injection time of the radioisotope in each patient was normalized to seizure duration in order to accommodate seizures of different lengths. Therefore, the normalized % time (t) was calculated by [(tracer injection time − seizure end time)/total seizure duration] × 100, where the time and duration were measured in seconds. Thus positive % time values (t > 0) represent time after seizure cessation (postictal period) while negative % time (-100 < t < 0) represent time from seizure onset to seizure end (ictal period). For examples, t=-50% injection time means the injection performed at the midpoint of the seizure, t=-100 at seizure onset, and t=0 at seizure end.

7. Statistical analysis

McNemar's chi-square test for paired proportions was used to compare the proportion of patients localized by subtracted SPECT-MRI

co-registration with the proportion localized by traditional visual inspection of interictal-ictal SPECT, MRI and PET studies. Chi-square test was used to compare categorical data and Fisher's exact test was used for dichotomous variables to compare the numbers of various perfusion patterns in different seizure foci and different pathological groups. One-way analysis of variance (ANOVA) was used to compare the means of injection time among the four groups of ictal perfusion patterns. The significance level was set at p<0.05 for all tests.

Results

1. Clinical features

1) Demographics

Of the total 61 patients, thirty-five patients were males and twenty-six were females. The patients' ages ranged from 1 to 48 years (mean= 24 ± 9.9 yr). The mean age of seizure onset was 12 ± 8.1 years, and the mean duration of seizure history was 12 ± 7.4 years.

The final epilepsy classifications were 27 (44.3%) mesial TLE, 16 (26.4%) neocortical TLE, and 18 (29.5%) ETLE. Thirty-two (52.5%) had lesions on MRI and other 29 (47.5%) had no lesion. MRI of Mesial TLE patients showed hippocampal sclerosis in 20 and no lesion in 7. Ten of 16 neocortical TLE and six of 18 ETLE patients had lesion on MRI (Table 1).

2) Postsurgical outcome and pathology

All patients had surgery after presurgical evaluation including longterm video-EEG monitoring, MRI, interictal/ictal SPECT, FDG-PET, and intracranial EEG recording if necessary.

Mean postoperative follow-up period was 18 ± 10.3 months. Forty-seven patients (77.0%) were seizure free (class I). Ten patients (16.4%) were almost seizure-free except rare disabling seizures since surgery (class II). Four patients (6.6%) had worthwhile reduction of seizures (class III).

The tissue pathology was abnormal in all patients. Hippocampal sclerosis was found in 24 patients (39.4%), gliosis and/or cortical dyslamination in 20 patients (32.8%), cortical dysplasia in 15 patients (24.6%), oligodendroglioma and oligoastrocytoma in one patient (1.6%) respectively.

2. The concordance rates of seizure localization to the final epileptogenic focus: interictal and ictal SPECT, subtraction SPECT, MRI and interictal FDG-PET

The concordance rates of seizure localization were 41.0% (25/61) by interictal SPECT and 68.9% (42/61) by ictal SPECT. The concordance rates by SPECT subtraction were hyperperfusion image (52/61, 85.2%) or hypoperfusion image

Table 1. Epilepsy Syndrome Classification of the Patients (N=61)

	Nonlesional (%)	Lesional (%)	Total
TLE	17 (27.9)	26 (42.6)	43 (70.5)
Mesial TLE	7 (11.5)	20 (32.8)	27 (44.3)
Neocortical TLE	10 (16.4)	6 (9.8)	16 (26.4)
ETLE	12 (19.7)	6 (9.8)	18 (29.5)
Total	29 (47.5)	32 (52.5)	61 (100.0)

TLE, temporal lobe epilepsy; ETLE, extratemporal lobe epilepsy

(14/61, 23.0%) and combined analysis of hyper-perfusion-hypoperfusion images (56/61, 91.8%) (Table 2). The concordance rates of subtraction SPECT for both neocortical TLE and ETLE were significantly higher than those of interictal and ictal SPECT (p<0.05 by McNemar's chi-square test).

MRI was performed in 61 patients and FDG-PET in 51 patients. The comparison of concordance rates was performed in these 51 patients, who had all MRI, PET and SPECT studies. The concordance rates to epileptic focus were 57.7% (30/51) by MRI, 63.5% (33/51) by PET, 84.6%

(44/51) by hyperperfusion image of subtraction SPECT and 90.4% (47/51) by hyperperfusion-hypoperfusion combined analysis of subtraction SPECT (Table 3). The seizure localization rate of subtraction SPECT was significantly higher than those of MRI and PET studies (p<0.01 by McNemar's chi-square test).

3. Patterns of ictal perfusion changes in subtraction SPECT

The ictal perfusion patterns of subtraction SPECT images were classified as follows: (1) focal hyperperfusion, (2) hyperperfusion-plus, (3)

Table 2. The Concordance Rates of Seizure Localization in Interictal & Ictal SPECT, Hyperperfusion Images, Hypoperfusion Images and Combined Analysis of Hyperperfusion-hypoperfusion Images in Subtraction SPECT-MRI Co-registration (N=61)

Subgroup (n)	Conventional PECT (%)		Subtraction SPECT (%)		
	Interictal	Ictal	Hyperperfusion	Hypoperfusion	Combined
MTLE (27)	15 (55.6)	22 (81.5)	24 (88.9)	2 (7.4)	24 (88.9)
NTLE (16)*	4 (25.0)	8 (50.0)	14 (87.5)	4 (25.0)	15 (93.8)
ETLE (18)*	6 (33.3)	12 (66.7)	14 (77.8)	8 (44.4)	17 (94.4)
Total (61)*	25 (41.0)	42 (68.9)	52 (85.2)	14 (23.0)	56 (91.8)

MTLE, mesial TLE; NTLE, neocortical TLE; ETLE, extratemporal lobe epilepsy.
* p<0.05 by McNemar's chi-square test; The seizure localization concordance rates of combined analysis by subtraction SPECT were significantly higher than the conventional interpretation of interictal and ictal SPECT in NTLE and ETLE, not in MTLE.

Table 3. Comparison of Seizure Localization Concordance Rates between MRI, Interictal FDG-PET and Subtraction SPECT (n=52)

	Concordant (%)	Nonconcordant/nonlocalizing (%)
MRI	30 (57.7)	22 (42.3)
FDG-PET	33 (63.5)	19 (36.5)
Subtraction SPECT		
Hyperperfusion image	44 (84.6)	8 (15.4)
Hypoperfusion image	7 (13.5)	45 (86.5)
Combined analysis*	47 (90.4)	5 (9.6)

* p<0.01 by McNemar's chi-square test; The seizure localization concordance rate of combined analysis by subtraction SPECT was significantly higher than that of MRI or interictal FDG-PET.

combined hyperperfusion-hypoperfusion, (4) focal hypoperfusion only, and (5) nonlocalized or non-lateralized (Table 4). Focal hyperperfusion was defined as only increased blood flow observed in epileptic focus. Hyperperfusion-plus was defined as hyperperfusion seen in epileptic focus and adjacent cortical regions. Combined hyperper-fusion-hypoperfusion means hypoperfusion area as well as hyperperfusion area observed in epileptic focus at the same subtraction SPECT image. Focal hypoperfusion implies only decreased perfusion without hyperperfusion area seen in the epileptic focus.

In TLE patients, focal hyperperfusion pattern was found in 24/43 (55.8%) cases. Focal hyper-perfusion in TLE could be subdivided as follows (Table 5); (1) ipsilateral mesial temporal only (Fig. 1a), (2) ipsilateral lateral temporal only (Fig. 1b), and (3) ipsilateral mesial and lateral temporal hyperperfusion (Fig. 1c). Hyperperfusion-plus in TLE sometimes showed ipsilateral temporal and adjacent frontal or even parietal hyperperfusion, but more commonly appeared as bilateral temporal hyperperfusion with ipsilateral temporal predomi-nance which was found in 9/43 (21.0%) cases. The most common perfusion pattern of TLE was focal hyperperfusion of both ipsilateral mesial and lateral temporal regions in 17/43 (39.6%), [11/27 (40.8%) in mesial TLE and 6/16 (37.5%) in neocortical TLE]. Focal hyperperfusion in mesial

Table 4. Ictal Perfusion Patterns of Subtraction SPECT and Locations of Epileptic Focus (Temporal and Extratemporal Origins)(N=61)

	TLE (%)	ETLE (%)
Focal hyperperfusion	24 (55.8)	8 (44.4)
Hyperperfusion-plus	9 (21.0)	1 (5.6)
Combined hyperperfusion-hypoperfusion*	5 (11.6)	5 (27.8)
Focal hypoperfusion*	1 (2.3)	3 (16.6)
Nonconcordant/nonlocalizing	4 (9.3)	1 (5.6)

TLE, temporal lobe epilepsy (n=43); ETLE, extratemporal lobe epilepsy (n=18)
* $p<0.05$ by Fisher's exact test; The number of combined hyperperfusion-hypoperfusion and focal hypoperfusion was significantly higher in ETLE than TLE group.

Table 5. Patterns of Ictal Perfusion Changes in Mesial and Neocortical TLE Patients

	Mesial TLE (%, n=27)	Neocortical TLE (%, n=16)
Mesial temporal hyperperfusion*	9 (33.3)	0 (0.0)
Lateral temporal hyperperfusion*	0 (0.0)	4 (25.0)
Mesial and lateral temporal Hyperperfusion	11 (40.8)	6 (37.5)
Bilateral temporal hyperperfusion	4 (14.8)	4 (25.0)
Hypoperfusion only	0 (0.0)	1 (6.3)
Nonconcordant/nonlocalizing	3 (11.1)	1 (6.3)

* $p<0.05$ by Fisher's exact test; Mesial temporal hyperperfusion alone was found only in mesial TLE and lateral temporal hyperperfusion only in neocortical TLE, while the incidences of other ictal perfusion patterns were not significantly different between mesial TLE and neocortical TLE.

temporal region alone was found in 9/27 (33.3%) of mesial TLE and focal lateral temporal hyperperfusion in 4/16 (25.0%) of neocortical TLE. Bilateral temporal hyperperfusion was found in both mesial and neocortical TLE patients (Fig. 1c), in 4/27 (14.8%) and 4/16 (25.0%) respectively. Combined hyperperfusion-hypoperfusion pattern was observed in 5/43 (11.6%) cases; 2/27 (7.4%) in mesial TLE and 3/16 (18.7%) in neocortical TLE. One of these patients with combined hyperperfusion-hypoperfusion pattern was illustrated (Fig. 1e). He was a 24-year-old man with frequent complex partial seizures or secondarily generalized seizures for more than 17 years. The brain MRI revealed cortical dysplasia in the left posterior lateral and basal temporal cortex. The EEG showed initial ictal rhythm on the left posterior lateral temporal region and propagation of ictal EEG discharge to the anterior temporal area. The radioisotope injection was performed 32 seconds before clinical seizure end and the EEG discharge showed build-up in the bilateral anterior temporal regions with left side predominance at that time. On subtracted SPECT, ictal hypoperfusion was found at the left posterior temporal cortex while ictal hyperperfusion was seen at the left anterior temporal region. In TLE, only one patient (2.3%) who had neocortical TLE showed focal hypoperfusion without hyperperfusion at epileptic focus despite radioisotope being injected during ictal period.

In ETLE, focal hyperperfusion (Fig. 1f) was observed in 8/18 (44.4%), hyperperfusion-plus in 1/18 (5.6%), combined hyperperfusion-hypoperfusion in 5/18 (27.8%). Focal hypoperfusion with radiotracer injected during ictal period was seen in 3/18 (16.6%) cases, one of whom was illustrated at Fig. 1g.

Overall 4 of 61 patients (6.6%) showed only focal hypoperfusion in epileptic foci. One of them was neocortical TLE and the remaining three were ETLE. No mesial TLE patient showed focal hypoperfusion in subtracted SPECT.

4. Clinical factors related to ictal perfusion patterns of subtracted SPECT

Locations of seizure foci (temporal and extratemporal origins), types of tissue pathology (hippocampal sclerosis, cortical dysplasia and others), and injection times of radioisotope were tested in their relationship with ictal perfusion patterns.

The numbers of patients showing hypoperfusion area in epileptic foci (either focal hypoperfusion or combined hyperperfusion-hypoperfusion patterns) were significantly higher in ETLE than TLE patients (p<0.05 by Fisher's exact test) (Table 4).

In regard to the tissue pathology, ictal hypoperfusion pattern of subtracted SPECT was seen significantly less frequently in patients with hippocampal sclerosis than in the patients with other pathology such as cortical dysplasia, gliosis and cortical dyslamination (p<0.05 by chi-square test) (Table 6). Only one patient with hippocampal sclerosis showed ictal hypoperfusion with hyperperfusion in subtraction SPECT.

The ictal perfusion patterns were not significantly related to the injection time of radioisotope (p>0.05 by ANOVA test)(Fig. 2). Sometimes unexpected coupling of perfusion pattern and injection time was found. Four patients (6.6%) who had the tracer injection postictally showed focal hyperperfusion at seizure focus. Another four cases (6.6%) who had the injection during the early ictal period showed only focal hypoperfusion of subtraction SPECT in epileptic focus. Seven patients (11.5%) who had the injection during ictal period revealed combined hyperperfusion-hypoperfusion pattern.

Table 6. Ictal Perfusion Patterns of Subtraction SPECT in Different Pathology (HS, CD and others)

	HS (%, n=24)	CD (%, n=15)	Others (%, n=20)
Focal hyperperfusion	15 (62.5)	9 (60.0)	7 (35.0)
Hyperperfusion-plus	6 (25.0)	1 (6.7)	2 (10.0)
Combined hyperperfusion-hypoperfusion*	1 (4.2)	4 (26.7)	5 (25.0)
Focal hypoperfusion*	0 (0.0)	1 (6.7)	3 (15.0)
Nonconcordant/nonlocalizing	2 (8.3)	0 (0.0)	3 (15.0)

HS, hippocampal sclerosis; CD, cortical dysplasia; Others, gliosis/cortical dyslamination.
* p<0.05 by chi-square test; The incidences of combined hyperperfusion-hypoperfusion and focal hypoperfusion were significantly lower in HS than CD and others.
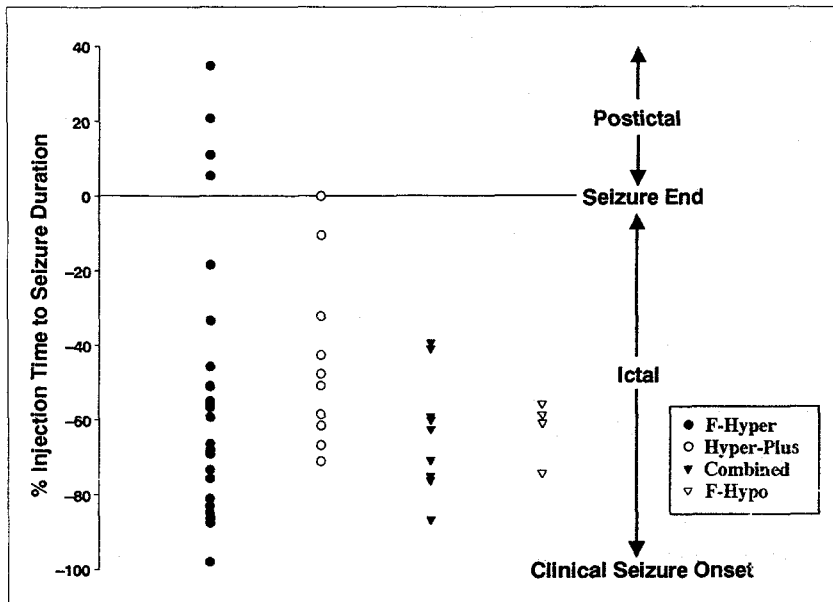
Fig. 2. The ictal perfusion patterns of subtracted SPECT versus the injection time of radiotracer. The % injection time means the percentage of total seizure duration ("100" is the seizure onset time and "0" is seizure end time). Negative value indicates ictal period while positive value means postictal period. F-Hyper: Focal hyperperfusion, Hyper-plus: Hyperperfusion-plusr, Combined: Combined hyperperfusion-hypoperfusion, Hypo: focal hypoperfusion

Discussion

Our study showed that subtraction SPECT improved the localization rate (91.8%) of epileptic focus and provided us the accurate anatomical orientation of ictal perfusion changes through SPECT-MRI co-registration. SPECT subtraction technique could separate the boundary of brain region with significant perfusion changes from unchanged underlying brain. In addition to ictal hyperperfusion, new finding "ictal hypoperfusion" of subtraction ictal SPECT improved further the seizure localization of ictal SPECT. In mesial

TLE, subtraction SPECT had higher sensitivity of seizure localization than the ictal SPECT but no statistical significance was observed. In neocortical TLE and ETLE, however, the seizure localization rate of subtraction SPECT was significantly higher than the conventional visual analysis of ictal SPECT. With the improvement of SPECT subtraction technique, the value of hypoperfusion at epileptic focus has been suggested only in postictal SPECT scans.[19,20] They reported that the use of SISCOM (subtraction SPECT coregistered to MRI) to detect focal cerebral hypoperfusion in addition to focal hyperperfusion improved the sensitivity and specificity of postictal SPECT in intractable partial epilepsy. In their postictal SPECT study, significantly higher proportions of the hyperperfusion SISCOM images (65.7%), the hypoperfusion SISCOM images (74.3%), and the combined hyperperfusion-hypoperfusion SISCOM evaluation (82.9%) were localizing than were the conventional method of side-by-side comparison of unsubtracted images (31.4%; p<0.0001).[20]

Our study was the first attempt to sort the ictal perfusion patterns by subtraction SPECT-MRI co-registration and relate them to clinical factors in both TLE and ETLE. For postictal hyperperfusion shown in 4 patients of our study, several explanations can be possible. A recent study showed ictal mesial temporal hyperperfusion persisted into the postictal period in some cases. This observation is consistent with the postictal hyperperfusions previously reported in a larger series of patients, in which depth electrode EEG studies showed total cessation of ictal activity at the time of HMPAO injection.[21,22] Two factors may underlie the ictal and postictal mesial temporal hyperperfusion.[7] Experimentally, the extracellular cations (H^+ and K^+) responsible for the peri-ictal increases in cerebral microflow take some minutes to decline after the end of the seizure.[23] Secondly, peri-ictal regional CBF may be coupled to increased non-oxidative glucose metabolism, which reflects hippocampal metabolic activity in physiological neural activation in humans[24] and experimental hippocampal seizures.[25]

Four patients showed focal hypoperfusion at epileptic focus even though radiotracer was injected in early ictal period. Subtraction SPECT of another 10 patients revealed hypoperfusion area well as hyperperfusion area during ictal period. This ictal hypoperfusion phenomenon has been neglected because only ictal hyperperfusion was focused and subtraction technique was not available. The ictal perfusion patterns of the patient in Fig. 3 provide some information upon the mechanism of ictal hypoperfusion. The initial seizure onset zone (posterior temporal area) showed hypoperfusion in subtraction SPECT whereas the zone with later build-up of ictal discharges (anterior temporal region) had hyperperfusion. From this observation, ictal hypoperfusion at epileptic focus can be from "intra-ictal early exhaustion of an initial seizure focus" or "steal phenomenon" of neighboring brain regions where ictal discharges propagated to. The ictal SPECT represents the perfusion status of the brain when radiotracer was injected. During epileptic seizures, regional cerebral blood flow continues to change. Ictal perfusion patterns may be related to many clinical factors (the speed of ictal propagation to adjacent brain regions, the intensity of ictal discharges, the area of brain with active ictal discharges at the time of injection, the energy status of different brain regions including epileptic focus, and the metabolic state of epileptic focus when radioisotope reached the brain tissue). Therefore, the interpretation of only ictal hyperperfusion can't understand correctly the whole pictures of ictal perfusion changes.

The most common perfusion pattern of mesial and neocortical TLE was focal hyperperfusion of both ipsilateral mesial and lateral temporal regions. Focal hyperperfusion in mesial temporal region was observed only in mesial TLE and focal lateral temporal hyperperfusion was seen only in neocortical TLE. This observation could be an important finding to differentiate neocortical from mesial TLE. Previous study also reported some differences of perfusion patterns on ictal SPECT in subgroups of TLE.[12] They observed that TLE with hippocampal sclerosis or foreign-tissue lesion in mesial temporal lobe showed ictal hyperperfusion in the ipsilateral mesial and lateral temporal regions. TLE with foreign-tissue lesion in lateral temporal lobe had ictal hyperperfusion in bilateral temporal lobes with ipsilateral predo-minance. They reported ictal hyperperfusion was restricted to the ipsilateral anteromesial temporal region in TLE with normal temporal lobe and good surgical outcome.

The ictal perfusion patterns were not signi-ficantly related to the injection times in this study. Determination of ictal perfusion patterns appeared to be more related to the location of seizure foci and tissue pathology than the injection time of radiotracer.

The previous studies showed that immediately after the cessation of seizure activity, cerebral perfusion at the epileptogenic site returns to baseline level and then enters a hypoperfusion state for several seconds.[19,20] A similar postictal switch (from hyperperfusion to hypoperfusion) of CBF has been reported in temporal lobe epilepsy.[7,22] They injected a radiotracer between 0 and 60 seconds after the end of temporal lobe seizures. Although focal temporal hyperperfusion was best seen with ictal injection of radiotracer, focal hyperperfusion which usually restricted to the anteromesial temporal region also was found

with the injection performed in the first few postictal minutes. In contrast, hypoperfusion of adjacent lateral temporal cortex might persist for up to 10 to 20 minutes after the cessation of clinical seizures.[20] The sequence of periictal per-fusion changes in TLE can be summarized as a significant relative increase in mesial and lateral temporal lobe blood flow during the seizure, followed by a reduction in perfusion of the epi-leptogenic hemisphere especially lateral temporal cortex with relative preservation of mesial tem-poral blood flow in the immediate postictal state. Also, it was suggested that postictal blood flow changes gradually return to normal within 10 to 30 minutes.[7] The timing of perfusion switch after extratemporal lobe seizures has been less well studied, but anecdotal information suggests that it may be earlier than it is after temporal lobe seizures.[26]

In summary, subtracted SPECT-MRI co-registration revealed that ictal perfusion changes during partial seizures were various and showed hypoperfusion as well as hyperperfusion during ictal period. Using SPECT subtraction technique and careful interpretation of SPECT with other clinical features are recommended for more accurate localization of epileptic focus.

요　　약

목적: Ictal SPECT의 간질 병소를 찾는 민감도와 정확도는 각 연구마다 다르다. 발작 중에 발생할 수 있는 여러 가지 형태의 뇌혈류변화를 알아보고 이와 관련된 임상 요인들을 찾아보기 위하여 본 연구를 수행하였다. 대상 및 방법: 간질 수술을 받을 61명의 부분적 간질 환자들에서 interictal SPECT와 ictal SPECT를 시행한 후 두 영상을 차감하여 subtraction SPECT (sub-SPECT)영상을 구하였다. Sub-SPECT에서 보인 발작 중 뇌혈류변화의 형태는 1) 국소 뇌혈류증가(focal hyperperfusion), 2) 뇌

혈류증가 플러스(hyperperfusion-plus), 3) 국소 뇌
혈류감소(focal hypoperfusion), 그리고, 4) 혈류증
가-감소 복합형(combined hyperperfusion-hypoper-
fusion)의 4가지로 나누었다. 각 형태 별로 간질초
점 (epielptic focus)과의 일치율 (concordance rate)
을 산출하였다. **결과**: Conventional ictal SPECT
분석법의 간질촛점 진단율은 68.9%이었고, sub-
SPECT의 진단율은 뇌혈류증가 만을 분석하였을
때는 85.2%이었고, 뇌혈류 증가 및 감소를 모두 평
가하였을 때는 91.8%이었다. 발작 중 국소 뇌혈류
감소는 측두엽외 간질에 비하여, 측두엽 간질에서
더 드물게 관찰되었다. 내측 측두엽에서만 발생한
뇌혈류증가는 내측 측두엽간질에서만 관찰되었고,
외측 측두엽에서만 발생한 뇌혈류증가는 신피질 측
두엽간질에서만 관찰되었다. 해마 경화를 동반한
측두엽간질은 다른 병리소견에 비하여 발작 중 뇌
혈류감소 현상을 매우 적게 보였다. **결론**: Ictal
SPECT를 분석할 때는 뇌혈류증가 뿐만 아니라 뇌
혈류감소 현상도 유심히 보아야 하며, 발작 중 국소
뇌혈류감소의 기전으로 간질초점의 발작 중 초기
에너지고갈 (intra-ictal early exhaustion) 또는 간질
초점 주변부로의 발작파 전파에 의한 steal 현상 등
을 생각할 수 있지만 앞으로 규명하여야 할 과제이
다.

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