Sensitivity and Specificity of Quantitative Difference SPECT Analysis in Seizure Localization

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True ictal SPECT can accurately demonstrate perfusion increases in the epileptogenic area but often requires dedicated personnel waiting at the bedside to accomplish the injection. We investigated the value of perfusion changes as measured by ictal or immediate postictal SPECT in localizing the epileptogenic region in refractory partial epilepsy. **Methods:** Quantitative perfusion difference images were calculated by registering, normalizing and subtracting ictal (or immediate postictal) from interictal SPECT for 53 patients with refractory epilepsy. Perfusion difference SPECT results were compared with visually interpreted SPECT, scalp electroencephalography (EEG), MRI, PET and intracranial EEG. **Results:** In 43 patients (81%), discrete areas of increased perfusion (with ictal injections) or decreased perfusion (with postictal injections) were noted. Interictal scalp EEG was localizing in 28 patients (53%), ictal scalp EEG was localizing in 35 patients (66%) and intracranial EEG was localizing in 22 patients (85%) (of 26 patients who underwent invasive study). MRI was localizing in 34 patients (64%), PET was localizing in 32 of 45 patients (71%), interictal SPECT was localizing in 26 patients (49%) and peri-ictal SPECT (visual interpretation) was localizing in 30 patients (57%). By comparison with an intracranial EEG standard of localization, SPECT subtraction analysis had 86% sensitivity and 75% specificity. **Conclusion:** Our data provide evidence that SPECT perfusion difference analysis has higher sensitivity and specificity than any other noninvasive localizing criterion and can localize epileptogenic regions with accuracy comparable with that of intracranial EEG. To obtain these results, one must apply knowledge of the timing of the ictal injection relative to seizure occurrence.

Key Words: difference images; epilepsy; SPECT; ^{99m}Tc-hexamethyl propyleneamine oxime

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Focal increase in cerebral blood flow during partial seizures in animals and humans was first reported by Penfield in 1933 (*1*) and was repeatedly confirmed by others (*2–6*). SPECT, with its ability to demonstrate localized changes in cerebral blood flow during ictus, interictally and postictally, has been used for nearly two decades in the evaluation of epilepsy (*7–12*). The availability of SPECT imaging equipment with spatial resolution of 8–10 mm, the low cost of performing SPECT and the ability of SPECT to acquire ictal images make SPECT a unique technique in the presurgical investigation of refractory epilepsy. In addition, new radiotracers (*13–16*) have been developed to allow the labeled tracer to be injected within seconds of seizure onset and to enhance the ability of SPECT to delineate perfusion changes at the time of seizure activity and during brief ictal events (*17*). Furthermore, more sophisticated methods of SPECT interpretation have been introduced that have increased its diagnostic yield. Calculation of asymmetry indices between regions of interest (ROIs) and reference regions (semiquantitative analysis) has been performed by some investigators (*18–20*), and quantification of regions of greatest increase or greatest decrease after coregistration, normalization and subtraction of interictal and ictal images (quantitative analysis) has been reported (*21–23*). Moreover, coregistration of SPECT data onto MR images allows functional-anatomic correlation and enhances SPECT's localizing value (*21,22*).

More than 160 SPECT studies in epilepsy were published between 1993 and early 1997. Localizing SPECT results are verified by scalp electroencephalography (EEG) (*18–20,24–26*), MRI (*20,25*), PET (*27*), site of surgery and clinical outcome (*20,28*). In the great majority of these reports, SPECT findings were interpreted visually; there are also some reports of false localization (*27,28*). Lee et al. (*29*) raised questions regarding the reliability and accuracy of SPECT in differentiating the proven primary epileptogenic area from propagation sites.

In this study, we investigated the diagnostic value of blood flow changes (increases during ictus or decreases in the immediate postictal state) after applying our previously described subtraction analysis of ictal and interictal SPECT (*21,22*). These results were compared with overall surgical localization as judged by EEG, MRI and PET. In addition, we estimated sensitivity and specificity of the SPECT difference method as well as the presurgical methods of localization using intracranial EEG localization as a gold standard.

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MATERIALS AND METHODS

Patient Population

Patients were selected from referrals to the Yale Epilepsy Program for presurgical evaluation for refractory localization-related epilepsy after meeting the following criteria: diagnosis of medically intractable partial seizures, completed continuous video-EEG monitoring and availability of both ictal and interictal SPECT study.

Patient Evaluation

Initial presurgical evaluation of epileptic patients included history, neurologic examination, neuropsychological assessment and long-term audiovisual (AV)-scalp EEG monitoring to record at least three habitual seizures. All patients underwent multiplanar MRI with quantitative measurements of the hippocampus, amygdala and temporal lobe according to a specific protocol. For those patients undergoing PET, 370 MBq (10 mCi) ^{18}F-labeled fluorodeoxyglucose were injected intravenously, with the patients' eyes open and the room lights dimmed. Images were acquired approximately 40 min after tracer administration. Twenty-one transverse images were reconstructed using a theoretical attenuation correction. The MR images used for anatomic localization of SPECT data were acquired as axial-oblique sections parallel to the temporal lobe through a field of view of 20 mm with 5 mm thickness, skipping 1.5 mm between slices.

In half of the patients, noninvasive evaluation methods yielded discordant results, so an intracranial EEG study was performed with various combinations of depth and subdural electrodes.

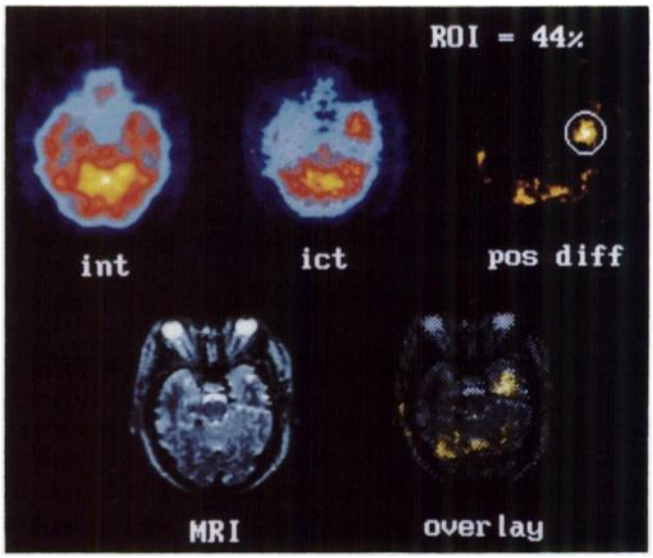

FIGURE 1. Selected slice from difference analysis in patient who was injected during clinical manifestations and EEG activity (int = interictal image; ict = ictal image; pos diff = positive difference image). Area of increased perfusion is demonstrated in left temporal lobe. Quantification of perfusion change (region of interest [ROI] analysis) shows 44% increase in perfusion. This area corresponds to region that was resected with excellent postoperative outcome at 12-mo follow-up. Pathology of resected tissue revealed hippocampal sclerosis. Positive difference superimposed onto corresponding MR image is shown in bottom right.

Interictal-Ictal SPECT Acquisition and Analysis

Interictal SPECT studies were performed in all patients after injections of 740 MBq (20 mCi) ^{99m}Tc-hexamethyl propyleneamine oxime (HMPAO) after a seizure-free period of at least 24 h. For ictal studies, patients received injections during seizure activity or immediately after cessation of clinical manifestations as documented by simultaneous continuous AV-EEG recording. SPECT acquisition and reconstruction were performed within 90 min after radiotracer injection using a three-head Picker PRISM 3000 camera (Picker International, Cleveland Heights, OH). The registering, normalizing, reslicing and calculating of difference images on the reconstructed images were performed on a Sun Spark 20 (Sun Microsystems, Inc., Palo Alto, CA) according to our previously reported protocol (*21,22*). Approximately 35 transverse slices were reconstructed for each SPECT acquisition using a standard Butterworth filter. The ictal SPECT image was registered to the interictal SPECT image using the automatic image registration algorithm (*30*). Using the same software, we also registered the MR image to the SPECT interictal volume. The total number of counts in both SPECT images was determined by summing all of the slices, and the total number of brain counts in the ictal image was normalized by a constant scaling factor to yield the same total counts as the interictal image. The two registered and normalized SPECT images were subtracted to yield negative and positive difference images, which were stored separately and were each overlaid onto the registered MR slices for anatomic localization (Figs. 1 and 2).

The subtraction images were interpreted according to our established protocol. At the time of difference-image interpretation, the time of injection with respect to time of seizure onset or cessation was not known. Three of the investigators in the epilepsy group viewed the positive and negative differences and by consensus determined a focus using the following criteria: the focus was in the gray matter, had a minimum size of 1 cm and was seen in the same area of the brain in three consecutive slices. The three largest areas of positive differences and the three largest areas of

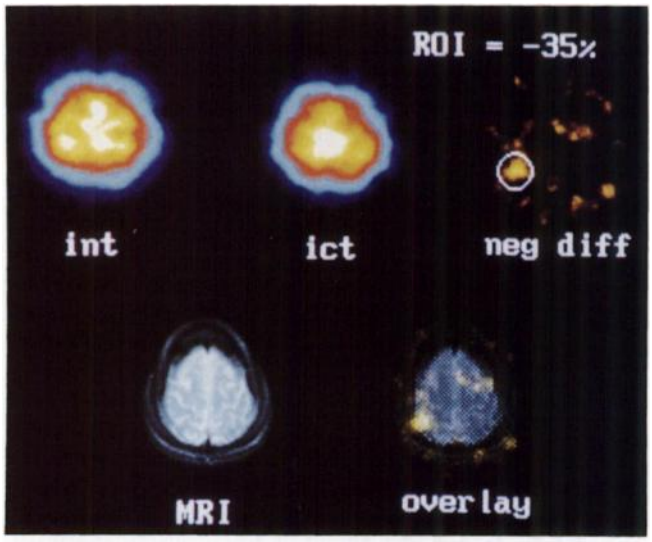

FIGURE 2. Selected slice from difference analysis in patient who was injected 77 s after seizure termination activity (int = interictal image; ict = ictal image; neg diff = negative difference image). Area of decreased perfusion (region of interest [ROI] = −35%) is revealed in right parietal lobe. This area corresponds to epileptogenic region, confirmed by interictal and ictal scalp EEG PET and neuropsychological assessment. Negative difference superimposed onto corresponding MR image is shown in bottom right.

negative differences were noted. If the focus selection criteria were not met, fewer than three foci, or none, were reported; if more than three areas were noted, the findings were reported as "diffuse changes." By drawing an ROI around each area, we calculated the percent change as the average of the most intense pixels in the area. Only areas with percent change higher than 20% were finally reported. As seen in Table 1, this usually resulted in one positive and/or one negative area being noted.

The resulting positive and negative images (demonstrating increases and decreases in blood flow, respectively, during ictus) were computed and displayed on the CeraSPECT workstation (Digital Scintigraphics, Inc., Waltham, MA). Selection of seizure focus as described was accomplished without additional reports of the patient's previous work-up, so a priori knowledge of the suspected epileptogenic area was not available. Analysis of ROIs yielded quantification of the percent change in perfusion. After identifying, drawing and quantifying ROIs, we selected the highest positive and/or negative region of perfusion change and reported it as the seizure focus. An example of an early ictal injection and the resulting positive difference focus is seen in Figure 1. In this case, the perfusion increase in the patient's left temporal lobe is obvious on the reconstructed transverse image. We have, however, documented examples of such ictal increases that were not discernible from the unsubtracted images (*21*). Figure 2 illustrates an example of a late injection that results in a difference image showing a negative change (decrease perfusion in the postictal state). Here, without registration, normalization and subtraction analysis, no differences were noted visually between the ictal and interictal images.

Time of ^{99m}Tc-HMPAO Injection

The time of clinical and EEG seizure onset and termination as well as the exact time of radioligand injection were determined by reviewing the videotapes obtained from the continuous video-EEG monitoring recordings. A syringe of ^{99m}Tc-pertechnetate and a Ceretec kit (Medi-Physics Inc., Amersham Healthcare, Arlington Heights, IL) were kept near the bedside. Typically, on first noting seizure onset, the technologist entered the patient's room, reconstituted the radiopharmaceutical by mixing the two containers within approximately 10 s and injected it into an established intravenous line. Approximately 1 of 8 patients was injected with stabilized ^{99m}Tc-HMPAO (which does not require reconstitution), when it was available because of other scheduled studies in the department.

Data Analysis

Concordance of SPECT findings with the site of seizure onset was determined using the intracranial EEG data recorded during the ictus for which the injection was accomplished. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of SPECT subtraction analysis were calculated by using a 2 × 2 table.

Sensitivity of SPECT subtraction analysis represented the proportion (or percentage) of patients with SPECT findings coincident with the region that had documented ictal onset activity during intracranial EEG recording. Specificity represented the proportion of patients without localization in areas that indeed did not show any epileptiform activity. PPV represented the probability of recording ictal onset in the area of SPECT findings. NPV represented the probability of obtaining normal EEG activity given a negative SPECT study.

In patients who did not undergo intracranial study, SPECT results (by visual and quantitative interpretation) were called localizing when they were consistent with overall surgical localization judged by agreement of two or more noninvasive methods of presurgical evaluation combined (interictal scalp EEG, ictal scalp EEG, PET and volumetric MRI), without any conflicting localization on other studies.

RESULTS

Demographic and Clinical Data

Fifty-three patients (25 males, 28 females; mean age 33.2 ± 12.6 y; age range 13–57 y) met the selection criteria and were included in the study (Table 1). Twenty-eight patients were diagnosed with temporal lobe epilepsy (53%) and 25 patients (47%) were diagnosed with extratemporal epilepsy. Past medical history revealed no predisposing factors in 23 patients. A history of perinatal complications were reported by 9 patients, traumatic head injury was reported by 9 patients, febrile seizures were reported by 5 patients, central nervous system infection was reported by 5 patients and cerebrovascular events were reported by 2 patients. The great majority of the recorded seizures were complex partial seizures with or without secondarily generalizing seizures.

Presurgical Evaluation Results

MRI was performed in all patients and revealed hippocampal atrophy in 18 patients, no structural lesions in 16, hippocampal sclerosis in 5, abnormalities suggestive of developmental abnormalities in 4, changes resulting from prior surgery in 4, encephalomalacia in 3, infarct in 1, venous angioma in 1 and temporal lobe herniation in 1. Nine of the patients with preoperative MRI findings that were consistent with hippocampal atrophy or hippocampal sclerosis had mesial temporal sclerosis confirmed by pathology. In the patients who did not have surgery, we considered MRI to be positive if the clinical symptomatology, the EEG findings and PET image were suggestive of medial temporal lobe epilepsy. In all other cases, MRI findings were considered to be false-positive (Table 1).

Interictal scalp EEG was localizing in 28 patients (53%), nonlocalizing in 13 (24%) and unremarkable in 12 (23%). Ictal scalp EEG was localizing in 35 patients (66%) and was nonlocalizing in 18 (34%). Intracranial EEG was localizing in 22 of 26 patients who underwent an invasive study (85%). MRI was localizing in 34 patients (64%) and was nonlocalizing in 19 (36%). PET was localizing in 32 of 45 patients (71%).

SPECT Results and Comparative Sensitivity and Specificity of Neuroimaging Modalities

Injections were performed in 17 patients during clinical or EEG activity, at the end of the seizure in 8 patients and after seizure termination in 28 patients. Mean seizure duration was 82.9 ± 57.7 s. The mean delay from seizure onset to injection was 86.8 ± 41.1 s (range 22–220 s). The mean delay from seizure cessation to injection for postictal injections was 44.8 ± 28.6 s (range 10–100 s). Increase in perfusion was noted in all patients with ictal injections (n =

TABLE 1
Demographic Features of Patient Group and Epileptogenic Region Localization Data

Patient no.	Sex	Age (y)	Scalp EEG	Intracranial EEG	MRI	PET	Injection time from seizure onset (s)	Visual SPECT	% Positive difference	% Negative difference
1	F	50	L T	Not done	L Hc S	Bi T	nc (pi)	Normal	—	L T = 50
2	F	37	L T	Not done	L Hc S	Normal	75 (pi)	L T	—	L T = 45
3	M	24	Nloc	R P-T	Bi Hc A	R P-T	nc (pi)	R P	R F = 58 R O = 30	R Post T = 41, LF = 30
4	F	17	L T	Not done	Bi Hc A	Bi T	97 (end)	L T	L ant T = 54	—
5	M	37	R H (R F)	Not done	R F D	R F	152 (pi)	R F-T	—	R F = 60
6	F	43	R T	Not done	R Hc S	R T	90 (pi)	R T	—	R T = 45
7	M	33	Nloc	Nloc	Normal	Not done	nc (i)	L P	R F-T = 43 L P = 42	—
8	M	33	R T	Not done	Normal	R T > L T	120 (pi)	R P	—	R T = 47
9	F	14	Nloc	Not done	Bi Hc A	L T-O	94 (pi)	L T	R F-T = 70	—
10	M	26	Nloc	Not done	L Hc A	Normal	85 (pi)	L T	LT-P = 30	L F-P-T = 25
11	M	43	R T	R T-O	R T herniation	Normal	94 (i)	R T	R T-O = 50	—
12	M	27	Nloc	Not done	Normal	Bi F	nc (i)	L T-P	Bi T = 50	—
13	F	48	L F-T	Not done	L F (res)	L F	110 (pi)	Normal	—	L F = 25
14	F	32	R T	Nloc	R Hc A	Not done	60 (pi)	R T	R T = 41	—
15	M	22	Nloc	Not done	R P (res)	R P	60 (pi)	R P	R P = 70	—
16	F	21	Nloc	L F	Normal	R P-O	80 (pi)	L T	—	L F = 47
17	F	31	R F	Not done	Normal	Normal	27 (pi)	R T	R F = 47	—
18	F	24	L T	Bi T	Normal	R T-F	128 (i)	L T	L T = 40	R T = 40
19	M	28	Bi F (R > L)	Not done	Normal	Not done	54 (i)	R F-P	R F = 34	—
20	M	56	L T	Not done	Normal	Normal	40 (i)	L T	L T = 84	—
21	M	53	L T	Not done	L F-P encephalomalacia	Not done	87 (end)	L F-P	—	L T = 28
22	F	50	L T	Not done	L Hc S	L T	nc (end)	R T	L T = 44	—
23	F	32	Nloc	Not done	Normal	R T	120 (pi)	L T	—	R T = 30
24	M	38	L T	L T	Normal	L T	nc (end)	Normal	—	L T = 32
25	F	21	Nloc	L sup P	Normal	Normal	51 (pi)	L T	—	L P = 44
26	M	36	L T and R T	Not done	L T encephalomalacia	L T > R T	60 (pi)	L T	L T = 74	R T = 42
27	F	41	L T	Not done	Bi Hc A	Bi T	47 (i)	L T	L T = 56	—
28	M	42	R T	Not done	R Hc A	R T	67 (i)	R T	R T = 42	—
29	F	18	R H	Not done	R T D	Bi T	104 (end)	Normal	—	R F-T = 47
30	F	17	R P	Not done	Normal	R P	77 (pi)	L P	—	R F = 30
31	F	18	Nloc	L P-O	L H encephalomalacia	L T-P	85 (i)	L T-P	LF-P-O = 35	—
32	M	13	Bi F (R > L)	Not done	Normal	R F-T	95 (pi)	R T	R F = 40	—
33	F	47	Nloc	Not done	Normal	R T	22 (pi)	Normal	L F = RF = 30	—
34	F	23	Nloc	Nloc	L Hc A	Normal	75 (end)	Normal	R H = 35	—
35	M	36	RT	Not done	R Hc A	R T	112 (pi)	L T	—	R T = 35
36	F	55	LT	Not done	L Hc A	LT	89 (pi)	LT	—	L T = 92
37	F	32	L T	L T	L Hc A	Not done	45 (i)	L T	L T = 76	—
38	M	33	L T	L T	L Hc A	L T	220 (pi)	L T	—	L T = 76
39	M	21	L O	L O	L O infarct	L O	120 (pi)	L F-P	—	L O = 20
40	M	47	Nloc	R SMA	Normal	Not done	nc (i)	Normal	R SMA = 99	—
41	M	57	L F	L SMA	R Hc A	Not done	40 (pi)	L F	—	L SMA = 27
42	F	28	L T	Not done	L Hc A	L T	87 (i)	L T	L T = 76	—
43	F	50	L T	L T	L Hc S	L T	100 (end)	L T	—	L T = 73
44	F	23	Nloc	R F-T	R F (res)	R F-T	nc (pi)	R F-T	—	R F-T = 34
45	F	25	Nloc	L T	L Hc A	Not done	155 (pi)	R T	—	L T = 30
46	F	16	Nloc	R T-O	R heterotopias	R T	40 (i)	R T-O	R T-O = 60	—
47	F	48	L F-T	L T	R T angioma	L T	94 (i)	L T	L T = 75	—
48	M	52	Bi F	R T	Bi Hc A	R T	nc (i)	R T	R T = 35	—
49	M	28	Nloc	R T-O	R T-O dysplasia	R O	189 (pi)	L T P	—	L T = 91 R T = 55
50	M	18	L T	L T-O	L T-O (res)	L T-O	65 (i)	R T	L T-O = 50	—
51	M	17	Nloc	Nloc	Normal	L P-T	50 (i)	L F-P	R P = 36 L P = 30	R H
52	M	38	L T	L T	L Hc A	L T	57 (end)	L T	L T = 44	—
53	F	45	Nloc	R T-O	L Hc A	R T	135 (pi)	R T	—	L F-P = 25

EEG = electroencephalogram; L = left; T = temporal; Hc = hippocampus; S = sclerosis; Bi = bilateral; nc = not clear; pi = postictal; Nloc = nonlocalizing; R = right; P = parietal; A = atrophy; F = frontal; O = occipital; post = posterior; ant = anterior; H = hemisphere; D = developmental abnormality; i = ictal; res = resection; sup = superior; SMA = supplementary motor area.

17), and decrease inperfusion was noted in most patients with postictal injections (19 of 28) or with injections at the end of seizure (5 of 8) (Table 1).

SPECT by quantitative subtraction analysis was localizing to a single region of a single lobe in 43 patients (81%). Quantitative SPECT showed correct lateralization in 2 patients (4%), and it was multifocal in the remaining 8 patients (15%). In 3 of the 8 patients with multifocal findings, the injection of radioagent was performed during a secondarily generalized seizure, and discrete ROIs and decreases in perfusion were seen.

The ^{99m}Tc-HMPAO injection was ictal in 15 of 43 patients with localizing quantitative SPECT, at the end of clinical seizure activity in 7 patients and after seizure termination in 21 patients. Quantitative SPECT analysis revealed localized increased perfusion greater than 30% (range 30%–90%) in all patients (100%) with ictal injection (n = 15; e.g., patient in Figure 1). Localized decreases in perfusion greater than 20% (range 20%–90%) were seen in 17 of 21 patients (81%) with postictal injection (e.g., patient in Figure 2); in the other 4 patients, increases in perfusion were noted. When injection was performed at the end of clinical seizure activity (n = 7), 3 patients had increased and 4 had decreased perfusion. Increases in blood flow failed to localize the epileptogenic area in 4 of the 26 patients who exhibited increases, and, similarly, decreases in blood flow failed to localize the epileptogenic region in 3 of the 24 patients who exhibited decreases. In the 4 patients who had increases in blood flow that failed to localize the epileptogenic area, increases in blood flow were noted in multiple cerebral regions. The EEG was localizing in 2 of these patients and was nonlocalizing in the others. For the 3 patients who had decreases in blood flow that failed to localize the epileptogenic area, decreased perfusion was noted in the hemisphere contralateral to scalp EEG localization in 1 of the patients, which was consistent with seizure semiology. The remaining 2 patients had intracranial studies, and perfusion decreases were noted in the contralateral hemisphere of EEG localization.

Interictal SPECT by visual interpretation was localizing in 26 patients (49%), and peri-ictal SPECT (visual analysis) was localizing in 30 patients (57%). In 18 patients, ictal and interictal SPECT were localizing to the same region.

SPECT quantitative analysis (increased or decreased flow) was in agreement with localizing interictal scalp EEG in 26 of 28 patients (Table 2), with localizing ictal scalp EEG in 32 of 35 patients (Table 3), with localizing MRI in 30 of 34 patients (Table 4) and with localizing PET in 27 of 32 patients (Table 5). Furthermore, the SPECT quantitative method provided correct localization in 17 patients with inconclusive interictal scalp EEG (Table 2), in 11 patients with nonlocalizing ictal scalp EEG (Table 3), in 13 patients with nonlocalizing MRI (Table 4) and in 9 patients with unremarkable or unlocalized PET (Table 5).

Sensitivity of quantitative SPECT analysis was 86% as determined by a standard of intracranial EEG localization for both temporal and extratemporal epilepsy, whereas specificity was 75%, and PPV and NPV were 95% and 50%, respectively (Table 6). In addition, sensitivity, specificity, PPV and NPV were calculated on the basis of invasive EEG localization for interictal and peri-ictal SPECT (visual interpretation), MRI and PET, as shown in Table 6. Quantitative SPECT analysis demonstrated a unique combination of high sensitivity (86%) and specificity (75%). Although some other diagnostic studies (SPECT-visual analysis, MRI) demonstrated the same specificity, they had considerably lower sensitivity (Table 6).

TABLE 2
Quantitative Difference SPECT and Interictal Scalp EEG (n = 53)

SPECT (diff) localization	No. of patients
Consistent with localized ii EEG	26 (49%)
Inconsistent with localized ii EEG	2 (4%)
Localized SPECT and unlocalized ii EEG	17 of 25 (68%)
Unlocalized SPECT and unlocalized ii EEG	8 of 25 (32%)

EEG = electroencephalography; diff = difference analysis; ii = interictal.

Surgery, Follow-up and Pathology

Anterior medial temporal resection or extratemporal resection to normal tissue margins guided by preoperative electrophysiology was performed in 24 patients. Follow-up ranged from 12 to 30 mo (mean 17 ± 5.4 mo). Postoperative outcome was based on Engel's classification (*31*). Thirteen patients were seizure free since surgery (class IA), 1 patient had generalized convulsions associated with antiepileptic drug withdrawal (class ID), 3 patients had worthwhile seizure improvement after surgery (class IIIA) and 7 patients were classified as having no significant seizure reduction (class IV) (usually associated with limited resection because of functional tissue).

Pathology revealed hippocampal sclerosis in 9 patients, cortical dysplasia in 2 patients, heterotopia in 3 patients, lesions consistent with old hemorrhage in 1 patient, infarct in 1 patient, inflammatory changes in 1 patient, tumor in 2 patients, profound gliosis in 1 patient, mild gliosis in 3 patients and normal tissue in 1 patient.

TABLE 3
Quantitative Difference SPECT and Ictal Scalp EEG (n = 53)

SPECT (diff) localization	No. of patients
Consistent with localized i EEG	32 (60%)
Inconsistent with localized i EEG	3 (6%)
Localized SPECT and unlocalized i EEG	11 of 18 (61%)
Unlocalized SPECT and unlocalized i EEG	7 of 18 (39%)

EEG = electroencephalography; diff = difference analysis; i = ictal.

TABLE 4
Quantitative Difference SPECT and MRI (n = 53)

SPECT (diff) localization	No. of patients
Consistent with localized MRI	30 (57%)
Inconsistent with localized MRI	4 (7%)
Localized SPECT and unlocalized MRI	13 of 19 (68%)
Unlocalized SPECT and unlocalized MRI	6 of 19 (32%)

diff = difference analysis.

DISCUSSION

Changes in blood flow as measured by SPECT have been extensively used for almost two decades to help localize the epileptogenic area. Based on pooled data from literature and judged by a standard of EEG localization, Spencer (*32*) determined that the diagnostic sensitivity of interictal SPECT was 66%, and specificity was 68% for temporal lobe epilepsy and 60% and 93%, respectively, for extratemporal epilepsy. In that same study, sensitivity of ictal SPECT was 90%, and specificity was 77% for temporal epilepsy and 81% and 93%, respectively, for extratemporal epilepsy. Devous et al. (*33*) in their meta-analysis study estimated that the sensitivity of SPECT in localizing the epileptogenic focus relative to diagnostic evaluation in temporal lobe epilepsy was 44% for interictal, 75% for postictal and 97% for ictal studies. Even though our patient group consisted of 50% extratemporal epilepsy patients, we observed a sensitivity of 73% for visual interpretation of our peri-ictal studies when we used depth electrodes as our comparison standard.

Ictal SPECT provides better localization when compared with the interictal studies (*22,33*). Ictal SPECT findings may lead to false localization when they are not also correlated with time of injection in relation to seizure occurrence.

We analyzed ictal and postictal SPECT results on 53 patients in the context of their presurgical evaluation for refractory epilepsy, using our previously described quantitative subtraction method (*21,22*). SPECT quantitative analysis yielded localizing data, judged by overall surgical localization, in 43 patients (81%); it was inconclusive in the remainder. Fifteen patients were injected during clinical manifestations, and 28 patients were injected at the end of or after seizure termination. All patients with ictal injections (n = 15) exhibited increases in blood flow in the epileptogenic area, and most of the patients (n = 17) with late injections (n = 21) showed decreases. Overall, increases were localizing in 84% and decreases were localizing in 87% of patients with those findings. In fact, our results show that hypoperfusion in the epileptogenic area (seen when injection of radiotracer is performed just after seizure cessation) is at least as accurate as hyperperfusion (seen with injection during the actual ictus). Thus, "late" injections, performed within 100 s of seizure termination, demonstrate localized reductions in perfusion relative to interictal state that accurately delineate the epileptogenic region. These results also support a model of transition from hyperperfusion (during ictus) to excessive hypoperfusion (during the immediate postictal state) to persistent interictal hypoperfusion (*22*).

TABLE 5
Quantitative Difference SPECT and PET (n = 45)

SPECT (diff) localization	No. of patients
Consistent with localized PET	27 (60%)
Inconsistent with localized PET	5 (11%)
Localized SPECT and unlocalized PET	9 of 13 (69%)
Unlocalized SPECT and unlocalized PET	4 of 13 (31%)

diff = difference analysis.

TABLE 6
Comparative Sensitivity and Specificity of Neuroimaging Methods in Patient Group by Intracranial EEG Standard (n = 26)

Method	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
SPECT (diff)	86	75	95	50
SPECT (ii, visual)	50	75	91	22
SPECT (i, visual)	73	75	93	30
MRI	60	75	93	25
PET (n = 20)	78	50	93	25

EEG = electroencephalography; PPV = positive predictive value; NPV = negative predictive value; diff = difference analysis; ii = interictal; i = ictal.

As seen previously, SPECT quantitative results were strongly concordant with interictal scalp EEG, ictal scalp EEG and with PET when both were localizing. Interictal SPECT, on the other hand, had lower sensitivity and specificity than all the other studies (Table 6). Interictal SPECT has been reported to be localizing in 48% (*26*) to 53% (*24*) of patients with temporal lobe epilepsy and to be of limited value in extratemporal epilepsy (*34*). Our data provide additional strong evidence that interictal SPECT yields limited localizing information.

CONCLUSION

Our findings suggest that quantitative subtraction analysis of interictal and ictal or postictal SPECT is a highly sensitive and specific method of localization as judged by intracranial EEG localization. Admittedly, total brain counts may not be the optimal method for normalizing the two SPECT scans. However, we believe it is a simple and effective method for the majority of cases we have studied, because the epileptogenic area appears to be a well-defined local area where neuronal activity and perfusion change significantly compared with the rest of the brain. Indeed, in the case where large areas of the brain are involved in seizures, total counts may not be a good normalization method, and we have

indeed investigated the use of an area on the cerebellum and in the white matter as a measure of the required normalization between the two SPECT images. We investigated a group of 20 patients using this alternate method and found quite poor results compared with total counts normalizations. But, despite the normalization methods, the results are consistent with scalp EEG, MRI and PET when they are localizing and when quantitative difference images accurately define the epileptogenic region when other methods fail. Systematic application and careful interpretation are required to further refine the role of SPECT quantification in epilepsy localization.

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