Difference Images Calculated from Ictal and Interictal Technetium-99m-HMPAO SPECT Scans of Epilepsy

I. George Zubal, Susan S. Spencer, Khursheed Imam, John Seibyl, Eileen O. Smith, Gary Wisniewski and Paul B. Hoffer

Department of Diagnostic Radiology, Yale University, New Haven, Connecticut

Image processing techniques were applied to SPECT brain images to aid in the localization of epileptic foci. **Methods:** Ictal and interictal cerebral perfusion SPECT images were acquired from 12 epilepsy patients (6 temporal, 6 extratemporal) after injection of 20 mCi ^{99m}Tc-HMPAO. Each ictal scan was registered to the same patient's interictal scan. Normalization of the three-dimensional data was applied to account for global percent brain uptake and total injected activity. After registration, normalization and subtraction of the SPECT images and functional difference images were computed. Difference images were calculated, which give a quantitative measure of perfusion alterations during ictus. The resulting difference images were also registered with each patient's MRI scan which permits localization of perfusion changes onto anatomical structures. **Results:** Areas in the brain where significant perfusion increases occur correlate with areas confirmed to be seizure foci. Four of the six patients with known temporal lobe seizure foci exhibited significant perfusion increases on the difference images. These areas demonstrate a percent increase of perfusion larger than 40%. For the extratemporal seizure patients, four of the four confirmed seizure sites were diagnosed with difference images. Results on the remaining two patients were inconclusive. **Conclusion:** When compared to side-by-side visual interpretation of the ictal and interictal SPECT images, registration of SPECT and MR images together with calculated difference maps greatly enhances the ability to localize epileptic seizure foci. This offers the potential to locate epileptic seizure foci using a noninvasive, inexpensive imaging procedure and data processing algorithm.

Key Words: epilepsy; image fusion; SPECT perfusion; image registration

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Up to 50,000 people in the United States could benefit from surgical treatment for intractable epileptic seizures (*1*). Accurate preoperative localization of the seizure focus is essential for successful surgery. Epilepsy, defined as recurrent seizures, is a phenomenon of excessive neuronal excitability which can be seen in the electrencephalographic (EEG) signals recorded from affected patients. Localized EEG abnormalities at the start of the epileptic seizure are often considered the sine qua non for diagnosis and localization of the epileptogenic zone. However, EEG recording from the scalp may be unreliable and can provide erroneous localization. For this reason, further confirmation of this localization or additional demonstration of localized functional or structural abnormalities are used to further define a cortical area as the source of seizures. In 20%–50% of patients with uncontrolled seizures considered for surgical treatment, scalp EEG (even when supplemented with conventional imaging studies) provides insufficient localizing information and intracranial electrodes are implanted in intracerebral and subdural locations (*2,3*). These are used for chronic recording of up to 4 wk during which the electrical manifestations of spontaneous seizures can be better localized. Exact areas of placement of such electrodes are determined by other localizing information obtained from structural and functional studies.

It has been known for many years that cerebral blood flow (CBF) increases during both generalized and focal epileptic seizures (*4–6*). In 1939, Penfield et al. described increased regional CBF ictally in humans (*4*). In 1968, Plum et al. described increased mean CBF during experimental seizures in animals (*5*). Both PET and SPECT have demonstrated this phenomenon. In addition, PET has been used to demonstrate parallel changes in metabolism in the cerebral cortex. Interictal PET studies have consistently demonstrated that discrete foci of hypometabolism occur in approximately 70% of patients with complex partial seizures and that these sites may be seen in more than one brain region in the same patients (*7–9*). For unknown reasons, this finding appears to occur more commonly in the temporal lobes in patients with complex partial seizures than it does in patients with extratemporal onsets of seizure. Reports have been variable, but much fewer patients with frontal seizure onsets will demonstrate focal hypometabolism on interictal FDG-PET (*10,11*). Most of these patients have structural lesions seen on MRI. The areas of hypometabolism or hypoperfusion always appear to be

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For correspondence or reprints contact: I. George Zubal, PhD, Department of Diagnostic Radiology, Yale University School of Medicine, 333 Cedar St., Box 208042, New Haven, CT 06520-8042.

larger than the area of structural abnormality (*12,13*). There is a strong correlation between the area of hypometabolism identified by PET and the site of electrophysiological abnormality identified by a combination of electrophysiological data (*14*).

SPECT has been used to image regional blood flow in epilepsy for over a decade and generally demonstrates hyperperfusion at the focus ictally and hypoperfusion interictally (*15*). The pharmacokinetics of ^{99m}Tc-HMPAO allow it to be effective for both ictal as well as interictal SPECT imaging of perfusion. HMPAO is a lipophilic compound that crosses the blood-brain barrier, is rapidly converted to a hydrophilic form and is trapped within cells. Extraction is complete within 2 min, at which time up to approximately 7% of the injected dose remains bound in tissue (*14*). Since it is stable within cells, scans can be obtained up to 6–8 hr after injection and still demonstrate the perfusion state during the seizure.

Studies relating perfusion defects imaged by SPECT cerebral blood flow agents in the baseline (interictal) state have been reported by several investigators with variable but not impressive yield (*16–19*). Others have reported higher yield of accurate localization of the epileptogenic region with perfusion alterations during the seizure (*20–23*). The interictal hypoperfusion might obscure increases during ictus, at least to visual inspection. By registering the ictal and interictal SPECT data and applying a normalization to account for variabilities in brain uptake and total injected activity, we calculated a functional image describing changes in brain perfusion during the ictus. This resulting difference image contains more information than can be perceived by viewing the reconstructed transverse slices alone.

MATERIALS AND METHODS

Twelve patients with intractable partial seizures (six temporal lobe, six extratemporal foci) received ictal and interictal injections of approximately 20 mCi of ^{99m}Tc-HMPAO. For ictal studies, patients received injections during EEG documented seizures; two patients were injected within 6 min after the onset of seizure but after cessation of epileptiform activity. Interictal injections of ^{99m}Tc-HMPAO were performed in patients who had no documented seizure activity in the previous 24 hr period. SPECT images were acquired within 90 min after injection using a three-headed Picker PRISM 3000 camera (Picker International, Cleveland Heights, OH). All patients received volumetric MRI scans for coregistration with the SPECT scans.

Projection data were acquired on the PRISM 3000 mounted with ultra high-resolution, parallel-hole collimators. Data were acquired over 40 min, during which the gantry makes a complete 360° orbit. A 128 × 128 matrix resolution was used with a 1.6 magnification factor. Transverse slices are reconstructed using a routine clinical filtered backprojection algorithm with Chang attenuation correction. The available reconstruction package allows prefiltering of the projection data using a selectable apodization filter whose cut-off frequency can be set to the position at which the image power spectrum is equal to the noise level in the projection images. Subsequently, approximately 30 to 40 transverse slices covering the whole brain were reconstructed using the ramp filter. All images were attenuation corrected using an attenuation coefficient which accounts for scattered events in the photopeak (0.11/cm). These reconstructed transverse images were transferred over the university/hospital ethernet network to the Imaging Science Research Laboratory where the registration, normalization, reslicing and calculation of difference images was carried out on a DEC-VAX 3500 (Digital Equipment Corporation, Maynard, MA).

The ictal perfusion scans and the MRI scan of each patient were registered to the patient's interictal perfusion scan using our computer registration program. The co-registered ictal and interictal perfusion scans were normalized according to total pixel counts in the brain and were subtracted from each other to obtain two sets of difference images. Positive difference images (showing increases during ictus compared to interictal) and negative difference images (showing decreases during ictus compared to interictal) were computed and displayed on the Ceraspect workstation (Digital Scintigraphics, Inc., Waltham, MA).

We had initially used the registration software made available from the University of Chicago (*24*). We have additionally investigated enhancements for this type of registration algorithm, whereby additional physiological landmarks (midplane and internal brain structures) can be used to improve the registration accuracy and reproducibility (*25,26*). Both of these available methods of coregistration are routinely used in our laboratory for evaluating clinical brain images. The complete image fusion process starting with reconstructed SPECT and MRI transverse images, resulting in coregistered difference images superimposed on the MR image, requires approximately 2 hr of combined CPU calculation and operator interactive data handling.

Some problems arise in trying to determine the difference between the ictal and interictal condition of the brain in epilepsy patients from image data. The SPECT images represent the distribution of radiopharmaceutical in the brain which is an indirect measure of perfusion. Ideally, areas of the brain not associated with the seizure focus would contain the same distribution of the radiopharmaceutical in both the ictal and interictal state, and the seizure focus would contain an elevated concentration of radiopharmaceutical, which would highlight its location. Due to extraneous influences, normal brain areas contain different concentrations of radiopharmaceutical in the ictal and interictal images. The radiopharmaceutical concentration is influenced by: (a) the total injected dose, which is not identical for both imaging sessions; (b) the time between preparation of dose and injection time, since the radiopharmaceutical undergoes a chemical decay process which is significant over minutes; (c) the general condition of the patient and; (d) uptake characteristics of the brain are not consistent since imaging sessions are conducted on separate days. We have assumed that the total brain uptake should vary only insignificantly between the ictal and interictal scans. On the other hand, areas of the brain associated with seizure focus should vary strongly between interictal and ictal states but usually occupy a comparatively small percentage of the total brain volume. For that reason, we normalized the total counts in all brain slices of the ictal scan to the total counts in all slices in the interictal scan.

Figure 1 shows the result of our registration and image processing technique for a patient. The top row, labeled ictal, shows selected equally spaced transverse slices of the patient's SPECT perfusion scan acquired after injecting HMPAO during seizure. The next row labeled interictal shows the corresponding SPECT slices acquired in the same patient at a later time after no seizures

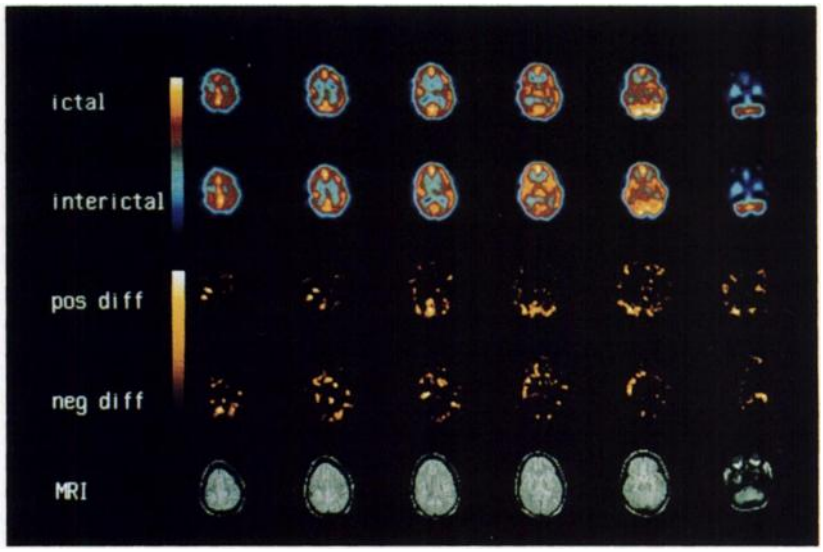

FIGURE 1. Transverse slices showing the SPECT images acquired during seizure (ictal) and between seizures (interictal). After normalization and subtraction, images demonstrating areas of increased perfusion (pos diff) and decreased perfusion (neg diff) are calculated and displayed using a yellow color table. The same patient's MRI scans are registered to the interictal images and shown in the bottom of the figure using gray levels.

had occurred for 24 hr. These two slice sequences were registered to each other using the coregistration techniques described. The third row of data labeled "pos diff" are a series of slices which correspond to the perfusion slices but whose intensity values are a measure of the percent increase of perfusion in the brain during ictus when compared to the interictal state. The third row of images labeled "neg diff" are registered images whose intensities correspond to perfusion decreases during seizure. Perfusion differences are seen outside of the region of the brain and correspond to the subcutaneous regions outside the cranium. The final row of gray level images in Figure 1 show the MRI scans of the same patient. All five sets of images in the figure are registered to each other and contain insightful information concerning perfusion changes and their anatomical location. All patients analyzed in our preliminary study group were processed and viewed in a manner described in this example.

Once the transverse slices have been resliced and normalized for proper registration, two separate difference images are computed. On a pixel-per-pixel basis, the difference in pixel values is divided by the pixel value from the interictal scan and then is multiplied by 100. This new value is written into one of two functional image matrices. Positive values are written into a positive difference image, and negative values are written into a separate negative difference image. In this way increases and decreases of blood perfusion can be viewed separately on a slice per slice basis. These difference images can be superimposed on MRI scans for localization onto anatomy (Figs. 2, 3). Since the values stored in the difference images numerically correspond to the percent change in perfusion, regions of interest can be drawn on the difference images in order to quantify the perfusion changes.

Independent determination of each patient's seizure focus was diagnosed by intracranial EEG or scalp EEG with concordant structural imaging using MRI. When available, successful surgical outcome (cessation of seizure occurrence after removal of the diagnosed seizure site) serves as a final localization of the seizure site.

RESULTS

We performed preliminary patient studies assessing the feasibility and utility of calculating ictal, interictal blood flow difference images for localizing putative seizure foci in 12 complex partial seizure patients. This technique was compared with conventional visual assessments of ictal and interictal perfusion scans.

For temporal lobe focus patients, six patients had localization to medial temporal lobe using all available data exclusive of SPECT scans. Visual analysis of ictal images was concordant with final localization in only two of the six temporal seizure patients. The area with greatest increase

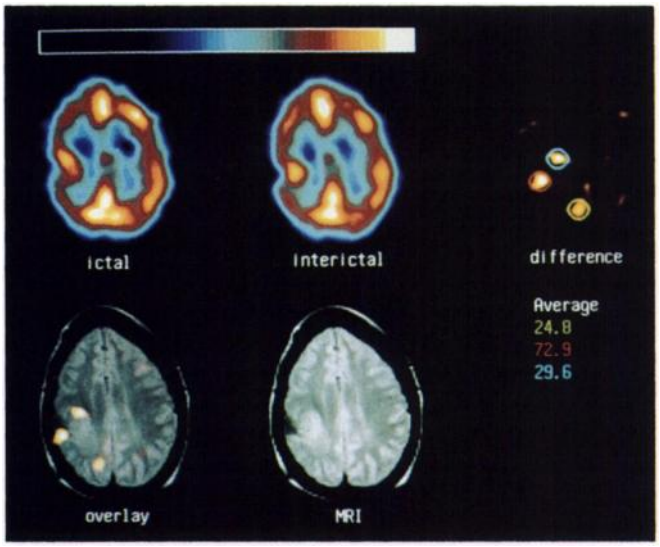

FIGURE 2. Selected slice of a patient showing ictal and interictal registered SPECT transverse slices (two top left images). The yellow color scale is used to highlight areas of increased perfusion during seizure in the positive difference image (top right). These foci circumscribe the heterotopic tissue responsible for initiating the seizures. ROIs are drawn on the three brightest difference foci. ROI analysis (average counts per pixel) gives a measure of the average percent change in perfusion within these regions. The results are listed under the title "Average" and are coded to their respective regions by color. The difference image is shown superimposed onto the corresponding MRI image (bottom left). The original MRI reference slice is shown in the bottom right.

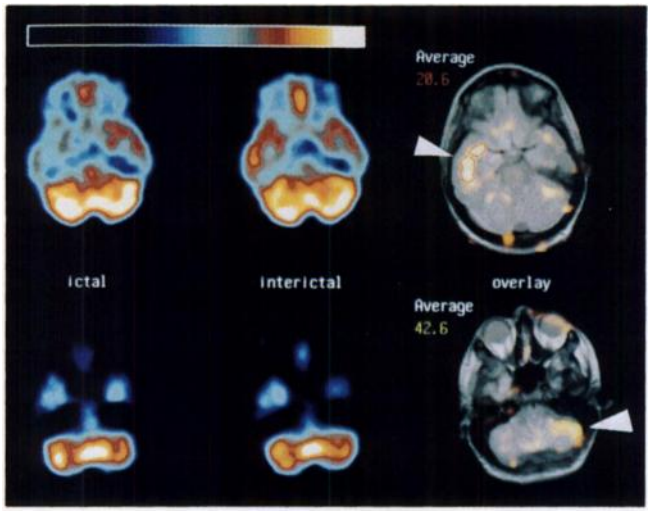

FIGURE 3. Selected slices of the same patient in Figure 2 show the ictal and interictal SPECT transverse slices and highlighted perfusion decreases (white arrows) shown as yellow overlaid highlights on the corresponding MRI images. ROI analysis gives quantitative measure of percent perfusion decreases. Noteworthy is the area of temporal lobe (top arrow), which corresponds to an area of hypoperfusion adjacent to the heterotopia during ictus. Contralateral hypoperfusion is also noted in the cerebellum (bottom arrow).

on SPECT difference images were concordant with the final localization in five of these patients and inconclusive in the remaining patient. Extratemporal seizure patients had localized foci in frontal (two patients) and parietal (two patients) cortices using all available clinical data, exclusive of SPECT scans. Visual analysis of ictal and interictal images was concordant with final localization in two patients, discordant in one patient and inconclusive in one patient. Difference images were concordant with final localization in all four patients. Additionally, the difference images provided more precise information regarding the location of the seizure focus (Table 1).

Figures 2–3 illustrate detailed findings of a sample seizure focus in a 23-yr-old female patient with a history of intractable seizures in the context of right parietal heterotopia. The patient had persistent seizures despite limited surgical resection of the right parietal cortex. Both ictal and interictal ^{99m}Tc-HMPAO brain SPECT blood flow scans revealed a small photopenic defect at the resection site with an annular zone of increased flow consistent with prior surgery. On the positive difference images (Fig. 2), there are more discrete regions of increased flow, limited to a smaller margin of the resection site, anterior and lateral to the heterotopia, suggesting residual hyperexcitable tissue. Regions of interest (ROI) drawn on the difference images reveal that the three suspected foci exhibit perfusion alterations of approximately 73%, 30% and 25%. The negative difference images (Fig. 3) show an area of decreased perfusion contralateral to the right parietal lesion and an ipsilateral region of decreased ictal blood flow in the right temporal cortex consistent with a zone of surrounding hypoperfusion. The two separate areas of decreased perfusion were analyzed by applying ROIs and are shown to correspond to values of 21% and 43%, respectively.

These images are representative of the quantitative ROI analysis applied to all 12 patients studied. The two areas exhibiting the highest percent increased perfusion were determined and entered in the column "pos-diff." The same was done for quantitative perfusion decreases in the column "neg-diff."

To appreciate the significance of these levels of perfusion changes measured by ROI analysis, we placed ROIs positioned away from foci which highlight large percent differences. The average pixel value in these nonaffected areas of the brain measure approximately 5%. We consider

TABLE 1
Seizure Site Localization Data

Patient no.	Age at onset (yr)	Scalp EEG	Depth EEG	MRI	Surgery Location	Surgery Outcome	Visual Analysis	pos-diff (%)	neg-diff (%)
1	9	Unlocalized	LFT	bi F heterotopia	—	—	L hem	RF= 51, LF=40	RPM=36, LM=30
2	12	Unlocalized	not done	Earlier RT resection	—	—	RF	RF= 51, LF=47	LP=53, RMF=26
3	13	RT	RT and LT	bi HC atr	LT	E	RC	RT=126, LT=95	F=33, RP=31
4	16	Bilateral-T	LMT	LHC and T2	LT	E	Normal	LO= 62, LP=32	LP=31, RT=30
5	18	RT	not done	RHC atr and T2	RT	E	LT	RT=295, LT=234	RP=45, LP=27
6	28	RT	not done	nrl	—	—	RC	C= 53, C=45	LT=48, F=35
7	1	Multifocal	not done	LHC atr and T2	LT	E	LC	LF= 42, LP=28	LT=47, F=35
8	38	LT, O	LMT	R C atr	—	—	LT	LT= 57, RP=45	C=29, FM=29
9	16	LT	LMT	LHC atr	LT	G	RT	RP= 56, LO=33	LP=57, LP/LO=25
10	1	LT	not done	RHC atr and T2	—	—	RC	RF=342, LF=153	RP=35, LP=27
11	6	R hem	RMF	nrl	RMF	E	RF	RMF= 90, LO=90	RF=49, LF=48
12	8	L post T	LT, O	LO lesion	LO	SR	Normal	RSP= 46, RF=30	LP=55, LC=25

R = right; L = left; S = superior; atr = atrophy; bi = bilateral; E = excellent—no seizures; G = good—less than three seizures after surgery; SR = >75% seizure reduction; HC = hippocampus; F = frontal; T = temporal; P = parietal; O = occipital; M = medial; C = central/midbrain; hem = hemisphere.

this 5% to be a typical error in renormalizing, registering and ROI placement of our analysis technique and corresponds to a measure of no change in perfusion between the interictal and ictal states.

DISCUSSION

Experience with depth electrode recordings shows that the lateralization of ictal and interictal changes on scalp EEG can sometimes be completely misleading and localization, or even lateralization, of frontal lobe foci on ictal scalp EEG is particularly unreliable (*27*). In addition, interobserver variability may be significant. In a study with 54 patients with localized, multifocal or unlocalized depth EEGs, blind analysis of 144 ictal scalp EEGs by three independent observers revealed an average of only 67% (50% when corrected for chance) agreement between observers for hemisphere of seizure onset and only 59% (40% when corrected for change) agreement between observers for lobe of seizure onset (*28*). In the same study, ictal scalp EEG and depth EEG studies agreed on hemisphere of seizure onset in 48% (27% when corrected for chance) and lobe of seizure onset in 29% (3% when corrected for chance). When grouped by lobe of seizure onset, ictal scalp EEG and depth EEG studies agreed on lateralization in 58% (38% when corrected for chance) of studies from patients with temporal seizure onset (n = 56) and in 18% (0% when corrected for chance) of studies from patients with frontal seizure onset (n = 24). Structural lesions are better characterized by x-ray computed tomography (CT) and MRI than by scalp EEG. Although scalp EEG is often abnormal in such cases, it is seldom as specific or sensitive as the imaging techniques (*27,28*).

Although depth and subdural EEG can detect and localize deeper foci than scalp EEG, they can sample only limited areas of the brain. These procedures are also invasive and are associated with surgical risk. The risk of major complications, including infection and intracranial hemorrhage, is 1%–4%, with seven cases of permanent neurological deficits and two fatalities reported in the literature (*29*). A noninvasive procedure which would help to direct or streamline the initial procedure for implanting depth electrodes (or ideally would obviate its need) is highly desirable. Additionally, a screening technique which could be conducted outside of the few existing epilepsy specialist centers would improve patient care and deliver earlier diagnosis.

Structural neuroimaging is more accurate at defining the seizure onset zone than scalp EEG (*30*); the location of space-occupying lesions is highly correlated with seizure onset, as judged by very high rates of seizure cessation when the structural lesion is resected (*31,32*). Recently, volumetric analysis of hippocampal size on MRI showing atrophy has been found to correlate highly with medial temporal lobe seizure onset recorded with depth electrodes. This imaging technique has thus allowed increasing sensitivity and accuracy in the diagnosis of temporal lobe epilepsy without the necessity for intracranial EEG (in certain patients) as well as in other patients with extratemporal epilepsy when a space-occupying lesion is present. Patients without hippocampal atrophy or space-occupying lesions seen on MRI, often with extratemporal seizure onset, remain a difficult diagnostic challenge.

SPECT perfusion scans are traditionally analyzed by visually comparing each cerebral region with the homologous region of the contralateral hemisphere. This method has the immediate drawback that diffuse, monotonic, bilateral changes or focal, symmetric, monotonic, bilateral changes in perfusion cannot be appreciated. Hence, perfusion scans performed in some patients with partial seizures do not demonstrate localizing or lateralizing features when analyzed in this manner. In some cases, areas of hypo- and hyperperfusion are found in areas remote from the site of an EEG abnormality (*14*). The potential difficulties that arise when ictal, or postictal, and interictal perfusion scans are compared in the conventional manner include: (a) the lack of normalization of the two studies, arising from differing quantities of injected radiopharmaceutical in the two studies or differences in the amount of time that has elapsed between injection of the radiopharmaceutical and acquisition of the scan; (b) the inability to accurately compare slices slice by slice, arising from differences in patient positioning during the two studies; (c) the lack of a quantitative assessment of the difference between the two sets of images; and (d) the limited ability of perfusion scans to demonstrate anatomy.

Interictal SPECT often shows hypoperfusion and an ictal study is expected to reflect increased blood flow to the area of seizure onset. These changes might be inaccessible to visual scrutiny because of their degree or distribution, or because comparison of unnormalized scans is not appropriate. We reasoned that a method to demonstrate the functional change in perfusion from the interictal to ictal state should result in increased sensitivity of diagnosis.

The change observed between ictal and interictal scans of a patient are stored in the difference image whereby each pixel value corresponds to the percent change measured between these two patient conditions. ROI analysis indicates that the brightest areas noted in the difference images exhibit perfusion changes of 50% or larger. In many cases, these areas correspond to primary seizure sites as confirmed by depth electrodes and can be interpreted as areas which exhibit the largest change in perfusion. Five percent changes, which correspond to most areas of the brain, can apparently be interpreted as an area of no change or represent the error in calculating perfusion differences.

It is not clear, however, that normalization based on total counts in the brain is the best method for preprocessing the SPECT data before calculating difference images. This normalization is complicated by the fact that extraction fraction of HMPAO becomes nonlinear to flow rates above 55 ml/min/100 g (*33*). We propose to investigate other normalization schemes which may improve the final analysis. In one proposed normalization scheme, we will

normalize the SPECT data according to the ratio measured in the white matter. The white matter has a concentration level of approximately 25% of that in the grey matter, and it could be argued that white matter uptake levels are not strongly affected by perfusion changes in the grey matter. This normalization scheme may give improved results. A second normalization scheme normalizes the data according to concentration levels found in the cerebellum. Yet a third scheme suggests that the brain stem may be the structure to which radiopharmaceutical uptake can be best normalized.

The preliminary data suggest ictal-interictal subtraction image sets may enhance the utility of brain perfusion SPECT studies for localization of seizure foci. In the temporal lobe group, localization by use of difference images compared favorably with MRI and electrode methods. In extratemporal patients, difference image methods improved the ability to locate seizure foci as well as provided more precise anatomical location than visual comparison of ictal and interictal scans.

REFERENCES

1. Ward AA. Perspectives for surgical therapies of epilepsy. In: Ward AA, Penry JK, Purpura D, eds. *Epilepsy* (ARNMD 61). New York: Raven Press; 1983:371–390.
2. Jensen I. Temporal lobe surgery around the world. Results, complications and mortality. *Acta Neurol Scand* 1975;52:354–373.
3. Engel J Jr. Outcome with respect to epileptic seizures. In: Engel Jr, J, ed. *Surgical treatment of the epilepsies*. New York: Raven Press; 1987:553–571.
4. Penfield W, Von Santha K, Cipriani A. Cerebral blood flow during induced epileptiform seizures in animal and man. I. *Neurophysiol* 1939;2:257–267.
5. Plum F, Posner JB, Troy B. Cerebral metabolic and circulatory responses to induced convulsions in animals. *Arch Neurol* 1968;18:1–13.
6. Broderson P, Paulson OB, Bolwig TG, et al. Cerebral hyperemia in electrically induced epileptic seizures. *Arch Neurol* 1973;28:334–338.
7. Engel J Jr, Brown WJ, Kuhl DE, et al. Pathological findings underlying focal temporal lobe hypometabolism in partial epilepsy. *Ann Neurol* 1982;12:518–528.
8. Bernardi S, Trimble MR, Frackowiak RSJ, et al. An interictal study of partial epilepsy using positron emission tomography and the oxygen-15 inhalation technique. *J Neurol Neurosurg Psychiatry* 1983;46:473–477.
9. Theodore WH, Newmark ME, Sato S, et al. Fluorine-18-fluorodeoxyglucose positron emission tomography in refractory complex partial seizures. *Ann Neurol* 1984;14:429–437.
10. Engel J Jr. Positron emission tomography in frontal lobe epilepsy. *Epilepsia* 1988;29:213.
11. Theodore WH, Fishbein D, Dubinsky R. Patterns of cerebral glucose metabolism in patients with partial seizures. *Neurology* 1988;38:1201–1206.
12. Roger J, Genton P, Bureau M. Progressive myoclonus epilepsies. In: Dam M, Gram L, eds. *Comprehensive epileptology*. New York: Raven Press; 1991:215–232.
13. Lundborg H. *Die progressive Myoclonusepilepsie (Unverricht's Myoklonei)*. Uppsala: Almqvist and Wiskell; 1903:1–207.
14. Devous MD Sr, Leroy RF, Holman RW. Single photon emission computerized tomography in epilepsy. *Semin Nucl Med* 1990;20:325–341.
15. Andersen AR, Lassen NA. Single-photon emission computed tomagraphy in temporal lobe epilepsy. In: Dam M, Gram L, eds. *Comprehensive epileptology*. New York: Raven Press; 1991:375–384.
16. Magistretti P, Uren R, Blume H, Schomer D, Royal H. Delineation of epileptic focus by single photon emission tomography. *Eur J Nucl Med* 1982;7:484–485.
17. Sanabria E, Chauvel P, Askienazy S, et al. Single photon emission computed tomography (SPECT) using I-123-isoprpyliodo-amphetamine (IAMP) in partial epilepsy. In: Baldy Moulinier M, Ingvar D-H, Meldrum BS, eds. *Current problems in epilepsy: cerebral blood flow metabolism and epilepsy*. London: John Libbey; 1983:82–87.
18. Biersack HJ, Reichmann K, Stefan H, et al. Technetium-99m-hexamethylpropylene-amine-oxime photon emission scans in epilepsy. *Lancet* 1985: 1436–1437.
19. Ryding E, Rosen I, Ingvar DH. SPECT measurements with ^{99m}Tc-HMPAO in focal epilepsy. *J Cereb Blood Flow Metab* 1988;8:S95–S100.
20. Rowe CC, Berkovic SF, Sia STB, et al. Localization of epileptic foci with postictal single photon emission computed tomography. *Ann Neurol* 1989; 26:660–668.
21. Rowe CC, Berkovic SF, Austin MC, McKay WJ, Kalnins RM, Bladin PF. Postictal SPECT in epilepsy. *Lancet* 1989;i:389–390.
22. Lee BI, Markand ON, Wellman HN, et al. HIPDM-SPECT in patients with medically intractable partial complex seizures. Ictal study. *Arch Neurol* 1988;45:397–402.
23. Stefan H, Bauer J, Feistel H, et al. Regional cerebral blood flow during focal seizures of temporal and frontocentral onset. *Ann Neurol* 1990;27:162–166.
24. Pellizarri CA, Chen GTY, Spelbring DR, Weichelbaum RR, Chen CT. Accurate three-dimensional registration of CT, PET and/or MRI images of the brain. *J Comp Assist Tomogr* 1989;13:20–26.
25. Zubal IG, Zhang L, Tagare H, Duncan JS. Three-dimensional registration of SPECT and MRI brain images [Abstract]. *J Nucl Med* 1993;34:187.
26. Zubal IG, Tagare H, Zhang L, Duncan J. Three-dimensional registration of intermodality medical images. *Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society* 1991;13:293–294.
27. Spencer SS. Depth electroencephalography in selection of refractory epilepsy for surgery. *Ann Neurol* 1981;9:207–214.
28. Spencer SS, Williamson PD, Bridgers SL, et al. Reliability and accuracy of localization by scalp ictal EEG. *Neurology* 1985;35:1567–1575.
29. Stefan H, Burr W. Absence signs: Long term therapeutic monitoring. In: Schmidt D, Morselli P, eds. *Intractable epilepsy: experimental and clinical aspects*. New York: Raven Press; 1986:187–193.
30. Spencer SS, McCarthy G, Spencer DD. Diagnosis of medial temporal lobe seizure onset: relative specificity and sensitivity of quantitative MRI. *Neurology* 1993;43:2117–2124.
31. Spencer SS. Selection of candidates for invasive monitoring. In: Cascino G, Jack C, eds. *Neuroimaging in epilepsy*. Stoneham, MA: Butterworth-Heinemann; 1995: in press.
32. Spencer SS. Temporal lobectomy: selection of candidates. In: Wyllie E, ed. *The treatment of epilepsy: principles and practices*. Baltimore: Lea F. Febiger; 1993:1062–1074.
33. Andersen AR, Friberg H, Lassen NA, Kristensen K, Neirinckx RD. Serial studies of cerebral blood flow using ^{99m}Tc-HMPAO: a comparison with ^{133}Xe. *Nucl Med Commun* 1987;8:549–557.