Epilepsia, **47**(9):1550–1557, 2006
Blackwell Publishing, Inc.

Ictal Perfusion Patterns Associated with Single MRI-Visible Focal Dysplastic Lesions: Implications for the Noninvasive Delineation of the Epileptogenic Zone

*Patrick Dupont, †Wim Van Paesschen, †‡Andre Palmini, *Rudo Ambayi, §Johannes Van Loon, §Jan Goffin, †Sarah Weckhuysen, ¶Stefan Sunaert, ¶Bejoy Thomas, ¶Philippe Demaerel, ‖Raf Sciot, **Albert J. Becker, ††Hubert Vanbilloen, *Luc Mortelmans, and *Koen Van Laere

*Departments of *Nuclear Medicine, †Neurology, §Neurosurgery, ¶Neuroradiology, ‖Pathology, and ††Radiopharmacy, University Hospital Gasthuisberg, Katholieke Universiteit Leuven, Leuven, Belgium; **Department of Neuropathology, University of Bonn Medical Center, Bonn, Germany; and ‡Division of Neurology and Porte Alegre Epilepsy Surgery Program, Faculty of Medicine and Hospital São Lucas, Pontificia Universidade Catolica do Rio Grande do Sul, Porte Alegre, Brazil*

Summary: *Background:* Invasive electroencephalogram (EEG) studies are often considered necessary to localize the epileptogenic zone in partial epilepsies associated with focal dysplastic lesions (FDL). Our aim was to evaluate the relationships between subtraction ictal SPECT coregistered with magnetic resonance imaging (MRI) (SISCOM) hyperperfusion clusters and MRI-visible FDL, and to establish a preliminary algorithm for a noninvasive presurgical evaluation protocol for MRI-visible FDLs in patients with refractory epilepsy.

Methods: Fifteen consecutive patients with refractory partial epilepsy and a single MRI-visible FDL underwent a noninvasive presurgical evaluation including SISCOM. Each hyperperfusion cluster was visually analyzed, automatically quantitated, and its distance form the lesion as outlined on the MRI was measured. In patients who underwent surgery, the volumes of resected brain tissue containing the FDL, the SISCOM hyperperfusion cluster, and surrounding regions were assessed on postoperative MRI and correlated with surgical outcome.

Results: Fourteen of the 15 patients (93%) showed SISCOM hyperperfusion overlapping with the FDL. The FDL was detected only after reevaluation of the MRI guided by the ictal SPECT in 7 of the 15 patients (47%). Four distinct hyperperfusion patterns were observed, representing different degrees of seizure propagation. Nine patients have been operated on. Five have been seizure-free since surgery and one since a reoperation. The degree of resection of the MRI-visible FDL was the major determinant of surgical outcome. Full resection of the SISCOM hyperperfusion cluster was not required to render a patient seizure-free.

Conclusion: Detailed analysis of SISCOM hyperperfusion patterns is a promising tool to detect subtle FDL on MRI and to establish the epileptic nature of these lesions noninvasively. Overlap between the SISCOM hyperperfusion cluster and MRI-visible FDL in a noninvasive presurgical evaluation with concordant data may suffice to proceed to epilepsy surgery aimed at removing the MRI-visible FDL and the part of the hyperperfusion cluster within and immediately surrounding the FDL. **Key Words:** Refractory epilepsy—Focal dysplastic lesions—Focal cortical dysplasia—Ictal SPECT—SISCOM—Epileptogenic zone—Epilepsy surgery—Surgical outcome.

A key point in the surgical planning of patients with focal dysplastic lesions (FDL) and refractory seizures is the localization of the portion of the epileptogenic zone extending beyond the visible lesion that needs to be resected (1–6). These surrounding regions may harbor microscopic pathology or be immediately engaged in the seizure following rapid propagation, thus needing to be resected (4,7–9).

Accepted March 22, 2006.
Address correspondence and reprint requests to Wim Van Paesschen at Department of Neurology, UZ Gasthuisberg, 49 Herestraat, 3000 Leuven, Belgium. E-mail: Wim.vanpaesschen@uz.kuleuven.ac.be
doi: 10.1111/j.1528-1167.2006.00628.x

Some data suggest that subtraction ictal SPECT coregistered with magnetic resonance imaging (MRI) (SISCOM) (10) can indicate the region of seizure onset. The potential of SISCOM hyperperfusion, however, to represent a true surrogate of the ictal onset zone—eventually substituting for the information provided by intracranial electrodes—has yet to be explored. Doubt remains on whether areas of hyperperfusion represent the primary focus or ictal propagation (8,11). Also, the relevance of areas with lesser—but still significant—degrees of hyperperfusion for seizure generation has not been explored.

We evaluated 15 patients with a single MRI-visible FDL in whom early ictal radioligand injections were obtained, and report the spatial relationships between the regions

of ictal hyperperfusion with the FDL and the surrounding tissue. We also provide preliminary data on the possible role of early SISCOM hyperperfusion as a surrogate of the ictal onset zone in FDL, by reporting the surgical follow-up of patients operated without invasive EEG monitoring.

PATIENTS AND METHODS

Included were 15 consecutive patients (11 women) with medically refractory seizures who underwent a presurgical evaluation between 1998 and 2004, and in whom MRI showed a lesion compatible with a FDL. The imaging protocol included T_1-, T_2-weighted fluid attenuated inversion recovery (FLAIR) images, and a magnetization prepared rapid gradient echo (MPRAGE) sequence acquired on a Siemens 1.5 T Vision or Symphony (Erlangen, Germany) scanner in all patients and a Philips 3.0 T Intera (Eindhoven, The Netherlands) scanner from 2003 in nine patients. A FDL was considered to be present if one or more of the following criteria were met: localized increased thickness of the cortical ribbon; blurring of the cortico-subcortical transition; increased signal in the lesion or in the immediately adjacent subcortical region; or a path of increased signal extending from the lesion to the lateral ventricle (transmantle sign). The descriptive terminology FDL was used because a histopathological diagnosis was not obtained in all patients. All images were independently reviewed by two neuroradiologists and two epileptologists experienced with FDL. For the purpose of localization of eloquent cortex, functional MRI (FMRI) studies were also performed (12,13).

Thirty-two channel video-EEG monitoring allowed determination of the distribution of interictal epileptiform abnormalities and the correlation of seizure semiology with ictal EEG. The setup for ictal SPECT injection in our hospital was described in detail elsewhere (14). ^{99m}Tc-ECD (600–1,000 MBq) was injected during at least one seizure of each patient. Post hoc video-EEG analysis permitted determination of the delay of injection from clinical and EEG onset.

Acquisition of SPECT imaging started within 1 h of tracer injection. Images were acquired in step and shoot mode using a triple-head gamma-camera (Triad XLT 20, Trionix Research Laboratory, Twinsburg, OH, U.S.A.) equipped with low energy ultra-high-resolution parallel collimators. The step angle was 3 degrees and 120 views per detector head were acquired for 15 s. Images were reconstructed using a filtered back projection algorithm with a Butterworth filter (0.6 cycles/cm, power 10). Attenuation correction was performed according to the Chang method, using an attenuation coefficient of 0.12/cm. Images were reconstructed in 64 transaxial sections with an isotropic voxel size of 2.54 mm. Injection of the tracer for the interictal SPECT was performed under surface EEG monitoring.

Interictal and ictal SPECT scans were coregistered using an automatic registration algorithm based on mutual information (15) and the interictal image was subtracted from the ictal after normalization for global brain counts. The difference image was smoothed using a 3D-Gaussian smoothing kernel (full width at half maximum = 12 mm) and transformed into a z-score using the mean and the standard deviation of the differences in all brain voxels. Furthermore, the mean image of the ictal and interictal coregistered images was used for coregistration with the MR images. The same transformation was then applied to the z-map. These images were covisualized with T_1-weighted and FLAIR images, using the MRIcro software (http://www.psychology.nottingham.ac.uk/staff/cr1/mricro.html) (16). For this overlay, a fixed threshold of $z = 2$ was used (17).

In the assessment of the individual patients, we used the methodology illustrated in Fig. 1. The FDL was manually outlined on consecutive sections of the MPRAGE images using the region of interest (ROI) tool in MRIcro. If the FDL had an increased FLAIR signal, which was usually easily visible, the outlining was guided by coregistered FLAIR images in addition to the cortical changes that were visible on MPRAGE. If no increased FLAIR signal was present, the outlining was guided by the cortical changes that were visible on MPRAGE. Lesion volume was thus calculated (Fig. 1 A–C). The maximum z score and the size (cm^3) of each subtracted SPECT cluster were determined, as well as all voxels showing local maximal z scores within the cluster (Fig. 1D). We then (i) determined whether there was an overlap between the manual outline of the FDL and any of the SPECT clusters; (ii) calculated the degree of overlap between the FDL and the hyperperfusion cluster as absolute overlapping volume (cm^3); (iii) calculated the distance between the voxel with the highest z score in the cluster that overlapped with the FDL and the FDL (Fig. 1E); and (iv) looked at all other SPECT clusters that did not overlap with the FDL, and retained only those clusters that were bigger, had a higher maximum z score, or both, compared with the SPECT cluster overlapping with the FDL. The different cutoff values for the z score on the overall SPECT hyperperfusion cluster configuration were also evaluated.

Nine patients were operated on the basis of spatial congruence of the noninvasive data. We regarded the overlapping between FDL and SISCOM hyperperfusion as an indication of the epileptic nature of the FDL and an essential element to proceed to surgery without invasive monitoring. The extent of resection was determined preoperatively on the 3D brain images in all patients, and the operative strategy was to remove the MRI-visible FDL and SISCOM hyperperfusion cluster overlapping with the FDL. Intraoperative electrocorticography (ECoG) and electrical stimulation were not part of our initial protocol, and were performed in five by A.P. since his arrival as

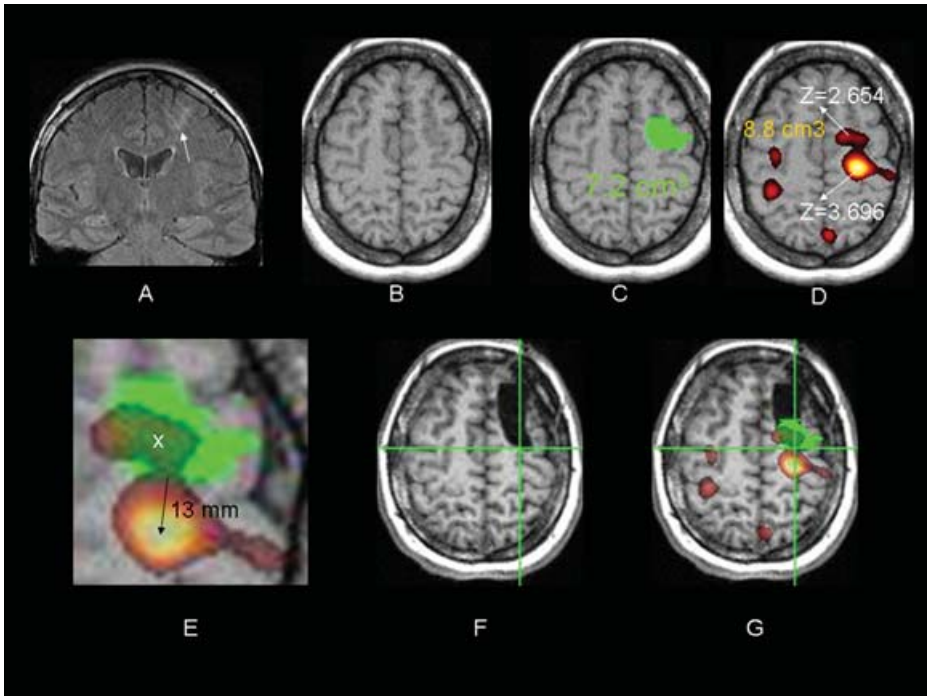

FIG. 1 . Methodology (Patient 6). **A** FLAIR image showed an increased signal in the left superior and middle frontal gyrus (A, white arrow), and on a T_1-weighted image **(B)**, there was an increased cortical thickness and blurring of the gray–white matter transition, consistent with a FDL. The FDL was manually outlined in green **(C)**, and its volume was 7.2. cm^3. On a SISCOM **(D)**, thresholded at $z = 2$, the cluster with the largest size had the configuration of an hourglass, and measured 8.8 cm^3. This cluster also contained the highest z score of the study ($z = 3.696$), and a lower local maximal z score ($z = 2.654$). Coregistration of the manual outline of the FDL and SISCOM **(E)** showed that the voxel with the lower local maximal z score fell within the FDL (white x in E), and that the highest z score was at a distance of 13 mm from the FDL, measured from the margin of the manual outline of the FDL (E, black arrow). Twenty-four percent of the FDL showed an overlap with the SPECT cluster, while 20% of the SPECT cluster overlapped with the FDL. The surgical resection site **(F)** was outlined in blue (not shown). The surgical resection removed 85% of the FDL (green) and 19% of the SISCOM hyperperfusion cluster (red) **(G)**. This patient, who had around 1–2 frontal lobe complex partial seizures daily, has remained seizure-free since surgery for nearly 4 years and has discontinued antiepileptic drugs. Removal of the part with the lower local maximal z score of the "hourglass" cluster overlapping with the FDL and extending up to the narrowing of the "hourglass" together with the MRI-visible FDL was sufficient to render the patient seizure-free.

a visiting professor in our program in 2003. In these five patients, the total extent of the resection could be slightly modified intraoperatively, based upon the spatial distribution of ictal-like or continuous epileptogenic discharges and also of frequent discontinuous spikes on the acute ECoG, limited by the boundaries of eloquent cortex as dictated by electrical stimulation. One patient, however, was studied with chronically implanted subdural grids and strips to determine the location of the epileptogenic zone with respect to the primary motor cortex (Fig. 2). A postoperative MPRAGE was obtained (Fig. 1F) and the surgical resection site was outlined using the ROI tool in MRIcro. We then coregistered the pre- and postoperative MPRAGE using mutual information (15), and visually assessed the goodness of fit of pre- and postoperative MPRAGE. A good fit was obtained for seven of the nine patients. The extent of resection was assessed for both the structural and hyperperfusion abnormalities (Fig. 1G) and correlated with surgical outcome. Postoperative seizure outcome was rated as completely seizure-free or not seizure-free since surgery.

We used the Mann–Whitney *U* test to compare the extent of resection of the FDL and SISCOM hyperperfusion cluster between the group of patients who were rendered seizure-free and the group of patients who were not rendered seizure-free after surgery.

RESULTS

Fifteen patients (11 women) with refractory partial epilepsy were included. Median age was 43 years (range: 21–53). Median age at onset was 10 years (range: 0–32). Median frequency of seizures was 20 per month (range: 1–600). Seven patients had lobar and eight had multilobar interictal epileptic discharges, predominating in extratemporal regions. Similar findings were observed for the ictal EEG localization.

Nine patients (60%) had a FDL in the frontal lobe, four (27%) in the temporal neocortex, and two (13%) in the parieto-occipital lobes (Table 1). The median volume of the lesion was 3.9 cm^3 (range: 0.6–17.4). In seven patients (47%), the lesion bordered or involved

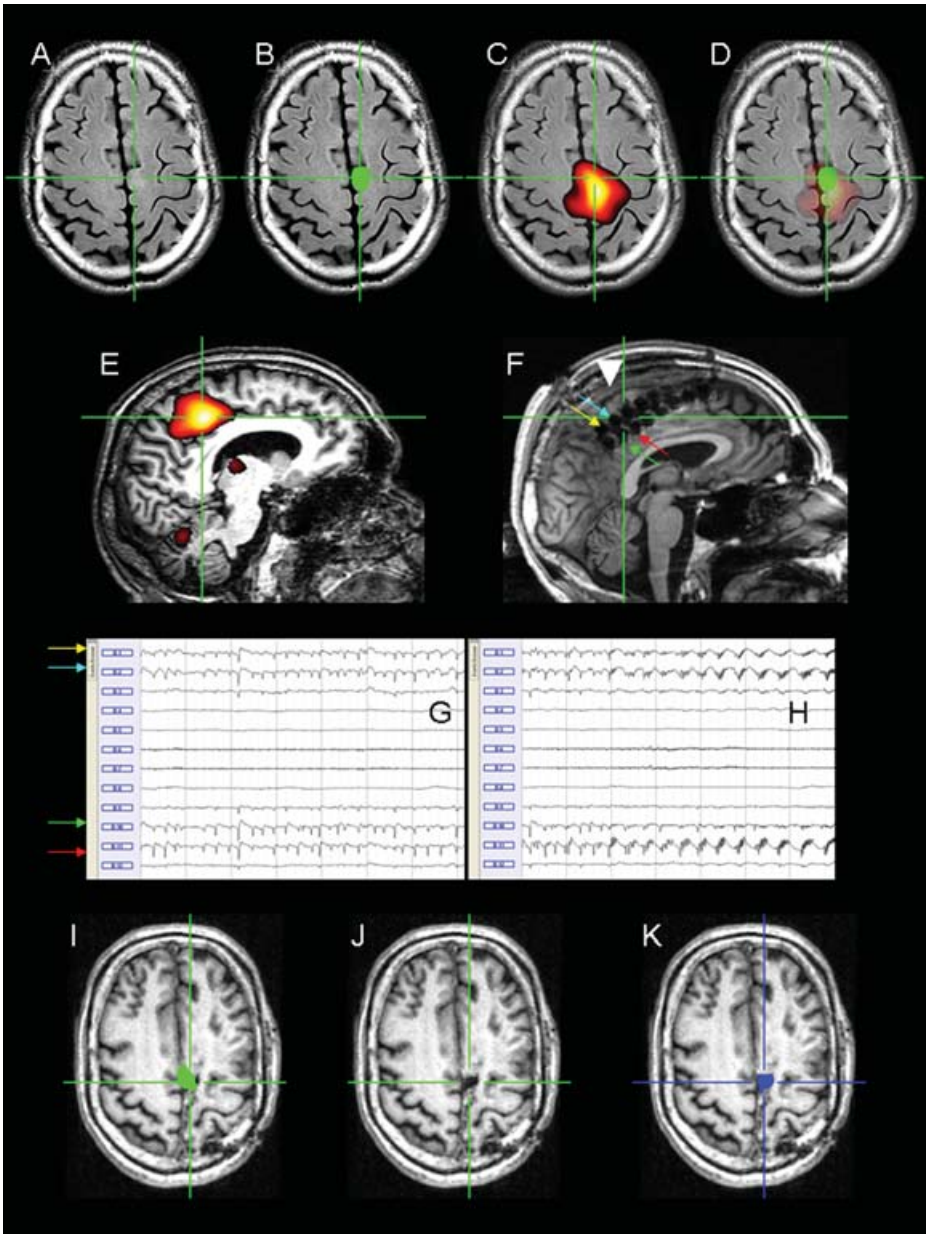

FIG. 2 . (Patient 2). FLAIR showed a small region with a faintly increased signal (**A**, green cross), which was manually outlined in green **(B)** and overlapped with a region of SISCOM hyperperfusion **(C and D)**. A sagittal SISCOM image **(E)** was coregistered with a T_1-weighted MRI section showing the position of an 8 × 2 subdural grid placed along the medial wall of the left frontal lobe **(F)**. Note that the oblique antero-posterior trajectory of the grid did not provide coverage of the upper half of the anatomically inferred paracentral lobule (**F**, white arrowhead). The upper row consisted of electrode contacts 1–8 and the lower row of contacts 9–16 (1 and 9 were most posterior). Bilateral dystonic posturing of the legs and ipsilateral posturing of the (left) arm were elicited with bipolar electrical stimulation of contacts 1–2, 2–3, and 3–4 at 2–5 mA, implying that these contacts were covering the portion of the SMA underneath the medial primary motor cortex. The interictal subdural EEG (**G**) showed continuous, strikingly rhythmic spiking recorded from contacts 1 (yellow arrow, **F and G**), 2 (blue arrow, F and **G**), 10 (green arrow, F and), and 11 (red arrow, **F and G**), consistent with the classical pattern of ictal/continuous epileptiform discharges described in FDLs (5). An ictal subdural EEG recording **(H)** showed focal ictal onset involving the same electrode contacts 1, 2, 10, and 11, confirming that the FDL (**A and B**) and SISCOM hyperperfusion (**C**, **D**, **and E**) represented the ictal onset zone. Coregistration of the preoperative FDL manual outline **(I)** with postoperative MPRAGE **(J)** showed that the surgical resection (blue manual outline in **K**) removed 58% of the FDL and 14% of the SISCOM hyperperfusion cluster. This patient, who had around three frontal lobe complex partial seizures daily, has remained seizure-free since surgery for more than 15 months.

eloquent cortex, i.e., primary motor cortex (n = 4), Wernicke's area (n = 2), and Broca's area (n = 1). The FDL was not detected on the initial reading of the MRI, but only after reassessment of the MRI, guided by the ictal SPECT findings in seven of the 15 patients (47%). In three, the lesion was seen only on the 3T MRI and SISCOM guided the detection of these small lesions.

TABLE 1 . *Ictal SPECT and MRI data*

Patient	Perfusion pattern	Injection time (s)	Duration of injected seizure (s)	Size of SISCOM hyperperfusion cluster overlapping with FDL (cm^3)	Lobe of FDL	FDL size (cm^3)
1	1	2	91	13.8	P	5.3
2	1	2	33	31.2	F	0.6
3	1	34	92	23.3	T	3.9
4	1	1	42	40.7	PO	7.6
5	2	9	81	12.1	T	3.9
6	2	15	19	8.8	F	7.2
7	2	18	70	20.6	F	2.5
8	2	15	57	35.8	T	9.4
9	3	3	18	14.5	F	17.4
10	3	30	53	3.4	T	7.5
11	3	3	18	6.6	F	3.5
12	3	10	46	2.5	F	3.0
13	3	3	17	4.9	F	2.6
14	3	32	65	14.9	F	1.5
15	4	11	56	–	F	8.9

P, parietal lobe; F, frontal lobe; T, temporal lobe; PO, parietooccipital lobe.

Ictal SPECT data are given in Table 1. The injection for ictal SPECT was given a median of 10 s (range: 1–34) after seizure onset and the median duration of the injected seizures was 53 s (range: 17–92). The injected seizure was a partial seizure in 13 patients (87%) and a secondarily generalized seizure in two patients (13%). In one of the latter (patient 1), the injection was given 2 s after seizure onset, and 35 s before generalization. In the other (patient 15), the seizure immediately generalized, and the injection was given 11 s after onset.

The SISCOM hyperperfusion cluster overlapped with the FDL in 14 of 15 patients (93%). The median size of this cluster was 14.15 cm^3 (range: 2.5–40.7). On average 16.5% (range: 2–67) of the SISCOM hyperperfusion cluster overlapped with the FDL. On the other hand, 46% (range: 17–100) of the FDL showed overlap with the SISCOM hyperperfusion cluster.

Four perfusion patterns were recognized (Table 1). In perfusion pattern 1 (n = 4), the highest z score and largest SISCOM cluster fell within or near the FDL (Fig. 2). Three of these patients had injections within 2 s of seizure onset during a seizure that lasted >30 s.

In perfusion pattern 2 (n = 4), the SISCOM hyperperfusion cluster had a bilobulated, "hourglass" appearance, i.e., the two lobules were connected by a trail of hyperperfusion (Fig. 1). The voxel with the maximum z score was at a median distance of 20 mm (range: 13–28) from the FDL, while the "lobule" with a lower z score fell within (n = 3) or at a distance of 3 mm (n = 1) from the FDL. The ictal SPECT injection was given at a median of 15 s (range: 9–18 s) from seizure onset. Postoperative image analysis (Fig. 1) and SISCOM-clinical correlations suggested that the lobule with the lower z score represented the ictal onset zone and the lobule with maximum z score propagated ictal activity.

Perfusion pattern 3 (n = 6) was similar to pattern 2, except that the cluster with the maximum z score was a separate cluster at a median distance of 54 mm (range: 10–58) from the FDL (Fig. 3). However, when the SISCOM was thresholded at z = 1 instead of 2, the two clusters were connected in a multilobulated structure by narrow trails of hyperperfusion. Injection was relatively late, or the injected seizure was rather short.

Finally, in perfusion pattern 4 (n = 1), there was no hyperperfusion within or near the FDL, in the only patient with injection during a generalized tonic–clonic seizure.

Nine patients underwent surgery. On average 11.8 cm^3 of brain tissue was resected (range: 4.3–34.7) during surgery. Five patients have remained seizure-free since the first operation with a median follow-up of 28 months (14–92), and three of these have discontinued antiepileptic drugs. One patient became seizure-free after a second operation. Pre- and postoperative imaging of patients 6, 2, and 13 are given in Figs. 1–3, respectively. The extent of resection of the FDL in the seizure-free group was on average 85%, and was significantly larger than in the nonseizure-free group, in whom it was on average 49% (Table 2). The extent of resection of the SISCOM hyperperfusion cluster was on average 27% (range: 3–52%), and did not differ significantly between the seizure-free and nonseizure-free group. Seventy-three percent of the resected brain tissue (range: 27–86) did not overlap with FDL or SISCOM hyperperfusion cluster.

In five patients, intraoperative acute ECoG was performed. In one patient, no spikes were detected. In four patients, spikes were spatially coincident with the lesion and the overlapping region of SISCOM hyperperfusion (Fig. 2). In two patients who were rendered seizure-free, postoperative ECoG did not show spikes. In two patients who were not rendered seizure-free because of incomplete

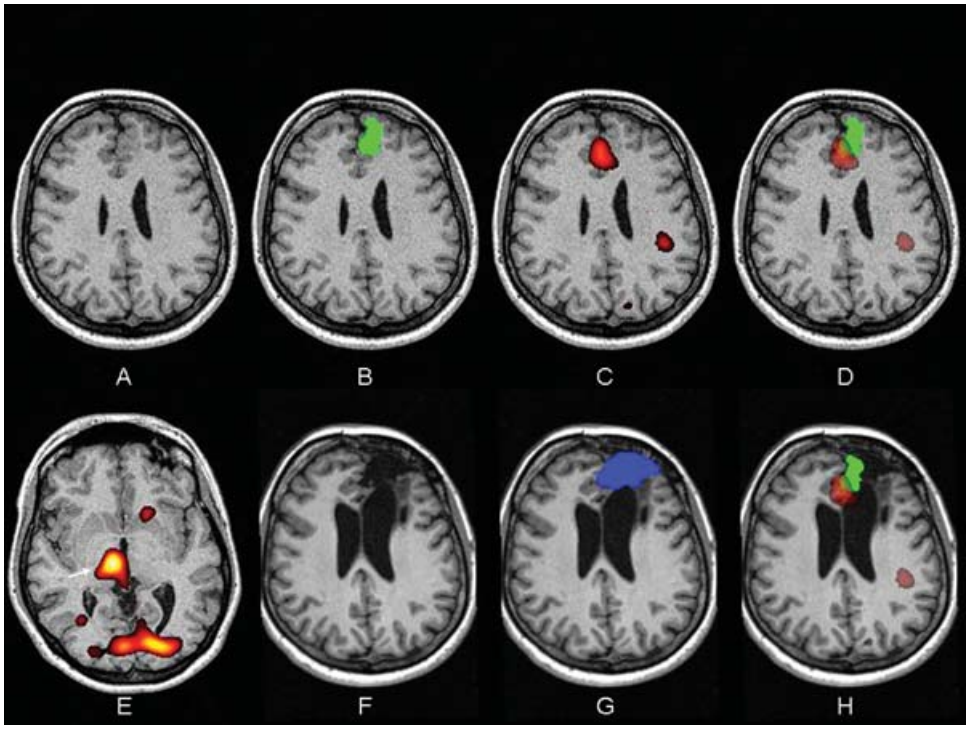

FIG. 3 . Perfusion pattern 3 (Patient 13). MPRAGE showed a region of thickened cortex with blurring of gray–white matter transition in the left superior frontal gyrus **(A)**, which was manually outlined in green **(B)**. SISCOM hyperperfusion **(C)** was present in the same area and partially overlapped with the FDL **(D)**. The hyperperfusion cluster with the highest z score, however, was present as a separate cluster in the right thalamus at a distance of 55 mm from the FDL (**E**, white arrow). SISCOM images at a lower threshold ($z = 1$, not shown) showed that these two cluster were part of a large cluster with complex configuration, which we interpreted as propagated seizure activity from the FDL. The surgical resection **(F)** was outlined in blue **(G)**, and removed 88% of the FDL and 22% of the SISCOM hyperperfusion cluster (red and green in **H**, respectively). These figures should, however, be interpreted with caution in view of the postsurgical changes, which are obvious when one compares ventricular size on the coregistered pre- and postoperative MPRAGES (**A and F**). This patient, who had around 10 frontal lobe complex partial seizures daily, has remained seizure-free since surgery for more than 9 years and discontinued all antiepileptic drugs. Pathology showed focal cortical dysplasia.

removal of the FDL, postoperative ECoG showed spikes in one. Intraoperative electrical cortical stimulation determined the limits of resection of lesions bordering eloquent cortex in four patients.

Pathology showed Taylor-type FCD in four patients. In the other five, the available brain tissue was not sufficient to allow a pathological diagnosis.

DISCUSSION

We studied patients with refractory partial epilepsy and imaging-defined FDL with ictal SPECT and SISCOM, and found four ictal perfusion patterns. Patterns 1–3 were found in all patients injected during a partial seizure. Characteristic for these was hyperperfusion within and immediately surrounding the MRI-visible FDL, consistent with intrinsic epileptogenicity of FDL (5,18) and confirming previous reports (11,19–21). These patterns followed a gradient of hyperperfusion in which the region with the maximum z score was either (i) at the lesion or its immediate surroundings (pattern 1), (ii) about 2 cm away from the lesion but connected to a second lobe of the hyperperfusion cluster at the lesion or its immediate surroundings through a propagation trail (pattern 2), or (iii) about 5 cm away from the lesion but connected to another hyperperfusion cluster at the lesion or its immediate surroundings through a propagation trail (pattern 3). The hyperperfusion SISCOM clusters had the appearance of an hourglass, and we propose that this spatial configuration is the signature of ictal propagation. The favorable surgical control of the seizures in patients displaying patterns 2 and 3 also suggested that the associated regions of maximal hyperperfusion away from the lesion represented propagation. The exclusion of these latter regions from the resection did not preclude a favorable outcome. In perfusion pattern 1, only

TABLE 2 . *Extent of resection of FDL and SISCOM hyperperfusion cluster and epilepsy surgery outcome*

	Seizure-free (n = 6)	Nonseizure-free (n = 4)	Mann–Whitney *U* test
%FDL removed	85 (50–90)	49 (15–53)	$p = 0.038$
% SISCOM hyperperfusion cluster removed	21 (11–36)	5 (3–52)	$p > 0.25$

Note that patient 1 was operated twice. The results of the first operation are in the nonseizure-free group, and the second is in the seizure-free group.

25% of seizures were of frontal lobe origin, in pattern two 50%, and in pattern three 83%, which could be explained by faster propagation of frontal lobe seizures, compared with seizures originating from other brain regions. Postictal changes could also explain perfusion pattern 3. Taking a transit time of the ligand from injection site in a brachial vein to the brain of around 30 s into account, the SPECT could be considered early postictal in four of the six patients with this pattern. In perfusion pattern 4, there was no hyperperfusion within or immediately surrounding the lesions but at a distance from the FDL. This discordance between FDL and ictal SPECT hyperperfusion could be due to fast propagation of ictal activity during a seizure that generalized immediately after onset.

A current debate centers on how much of the epileptogenic zone in patients with FDL, particularly FCD, is contained within the visible lesion and what is the contribution of the perilesional tissue. Data from different centers suggest that resection of both the MRI-visible lesion and the ictal onset zone defined electrophysiologically (usually through intracranial electrodes) is necessary to control the seizures (1,4,9,22). Although both tended to colocalize, successful resections almost always involved some extent of perilesional tissue. Several neurophysiological ways to attempt at localizing the epileptogenic zone in its entirety have been explored in patients with FDL. The less invasive methodology is intraoperative ECoG, seeking for ictal-like or continuous epileptogenic discharges (5,23,24). Disadvantages are that the resection is performed without a precise localization of the ictal onset zone, and that ictal-like or continuous epileptogenic discharges are not seen in all patients with FDL (5,25,26). More invasive methods to localize the epileptogenic zone rely on chronic recording with either subdural grids or depth electrodes (1–4,8,9,22). These techniques may localize the actual zone of ictal onset and its relation to the structural lesion. Surgical strategy in patients thus evaluated consists of resection of the lesion and of the ictal onset zone—which may or may not be entirely colocalized with the visible structural abnormality. Disadvantages are the discomfort, the morbidity and rarely mortality associated with invasive recordings (27), a limited sampling area that may not cover the epileptogenic zone (8), and the cost of the procedures (28). In comparison with invasive EEG techniques, ictal SPECT is noninvasive and covers the whole brain. Further advantages are the ability to coregister SISCOM with fMRI to assess involvement of eloquent cortex noninvasively (29), the detection of subtle FDL at the site of ictal SPECT hyperperfusion in patients whose MRI was initially read as negative (30,31), which was the case in seven patients in the present study, and the ability to carefully plan the operation on 3D images, and to bring the imaging data into a neuronavigation system.

From our data, we believe that a better understanding of the spatial relationships between the structural lesions and the patterns of hyperperfusion may be sufficient to determine the epileptogenic zone, and may eventually obviate the need for chronic invasive recordings in patients with MRI-visible small FDLs. A careful consideration of the dynamic relationships between the delay of injection of the radioligand with respect to seizure onset, seizure duration, the seizure type at the moment of injection, and the a priori MRI-based knowledge of the presence of a FDL may allow a noninvasive determination of the ictal onset zone and the ictal propagation zones. In this regard, we propose the terminology "hourglass-type" of seizure propagation to describe the spatial distribution of the ictal SPECT hyperperfusion clusters. This propagated activity could be related to the phenomenon of intraictal secondary activation described by Jayakar and colleagues (7) in patients studied with subdural electrodes. These authors showed that ictal activity could be recorded focally, from nonadjacent electrodes in a subdural grid, after a latency of a few seconds from the actual electrographic seizure onset. This phenomenon suggests ictal propagation through a "trail pathway" instead of through contiguous intracortical neuronal bodies.

From the analysis of our postsurgical results, we draw the following preliminary conclusions. First, removal of the entire or a large proportion of the MRI-visible FDL is probably required to render the patient seizure-free, confirming previous reports (3,4,6,11,22,32,33). Second, a full "SISCOM excision" (34) was not required to render a patient seizure-free. Resection of the ictal SPECT cluster overlapping with the FDL in pattern 1, and the part with the lower local maximal z score of the "hourglass" cluster overlapping with the FDL and extending up to the narrowing of the "hourglass" (that is, to the point where the SISCOM hyperperfusion trail begins, most likely indicating ictal propagation) in patterns 2 and 3 may be sufficient to render the patients seizure-free (see Fig. 1). Of note, these regions were highly colocalized with those displaying ictal-like or continuous epileptogenic discharges on acute ECoG. Third, our results indicate that further optimization of image-guided neurosurgical techniques will be required, which can be done using a combination of neuronavigation techniques to open the skull, and peroperative recognition of predefined anatomical landmarks, such as sulci, gyri, and blood vessels.

Potential limitations of our study include the relatively small number of patients and the fact that only four of the nine who were operated had histopathological confirmation of a dysplastic lesion. We believe this series, albeit small, is representative of an ever increasing number of patients referred to epilepsy surgery centers with refractory seizures associated with high-resolution MRI-identified small FDL. The imaging characteristics, the analysis of two experienced neurologists, and the ECoG patterns (Fig. 2) in the operated patients in whom pathology was

not available leave little doubt about the dysplastic nature of these small lesions.

Further studies using our methodology will enable to optimize the noninvasive surgical strategies of patients with refractory partial epilepsy due to small FDLs. At this point, we believe that these results provide a further step in supporting a noninvasive approach in patients with FDLs, with resections based on high-resolution MRI, SISCOM, and ECoG.

Acknowledgment: This work was funded by grant Research Fund Katholieke Universiteit Leuven Interdisciplinair Onderzoeksprogramma (IDO)/99/5 and IDO/03/010. We thank K. Baete, D. Vandermeulen, S. Srivastava, and J. Vervisch for their help.

REFERENCES

1 . Boonyapisit K, Najm I, Klem G, et al. Epileptogenicity of focal malformations due to abnormal cortical development: direct electrocorticographic-histopathologic correlations. *Epilepsia* 2003;44:69–76.
2 . Najm IM, Bingaman WE, Luders HO. The use of subdural grids in the management of focal malformations due to abnormal cortical development. *Neurosurg Clin N Am* 2002;13:87–92.
3 . Tassi L, Colombo N, Garbelli R, et al. Focal cortical dysplasia: neuropathological subtypes, EEG, neuroimaging and surgical outcome. *Brain* 2002;125:1719–32.
4 . Chassoux F, Devaux B, Landre E, et al. Stereoelectroencephalography in focal cortical dysplasia: a 3D approach to delineating the dysplastic cortex. *Brain* 2000;123:1733–51.
5 . Palmini A, Gambardella A, Andermann F, et al. Intrinsic epileptogenicity of human dysplastic cortex as suggested by corticography and surgical results. *Ann Neurol* 1995;37:476–87.
6 . Palmini A, Gambardella A, Andermann F, et al. Operative strategies for patients with cortical dysplastic lesions and intractable epilepsy. *Epilepsia* 1994;35(suppl. 6):S57–71.
7 . Jayakar P, Duchowny M, Resnick TJ. Subdural monitoring in the evaluation of children for epilepsy surgery. *J Child Neurol* 1994;9(suppl. 2):61–6.
8 . Kaminska A, Chiron C, Ville D, et al. Ictal SPECT in children with epilepsy: comparison with intracranial EEG and relation to postsurgical outcome. *Brain* 2003;126:248–60.
9 . Paolicchi JM, Jayakar P, Dean P, et al. Predictors of outcome in pediatric epilepsy surgery. *Neurology* 2000;54:642–7.
10 . O'Brien TJ, So EL, Mullan BP, et al. Subtraction ictal SPECT co-registered to MRI improves clinical usefulness of SPECT in localizing the surgical seizure focus. *Neurology* 1998;50:445–54.
11 . O'Brien TJ, So EL, Cascino GD, et al. Subtraction SPECT coregistered to MRI in focal malformations of cortical development: localization of the epileptogenic zone in epilepsy surgery candidates. *Epilepsia* 2004;45:367–76.
12 . Dymarkowski S, Sunaert S, Van OS, et al. Functional MRI of the brain: localisation of eloquent cortex in focal brain lesion therapy. *Eur Radiol* 1998;8:1573–80.
13 . Sunaert S, Yousry TA. Clinical applications of functional magnetic resonance imaging. *Neuroimaging Clin N Am* 2001;11:221–36.
14 . Vanbilloen H, Dupont P, Mesotten L, et al. Simple design for rapid self-injection ictal SPET during aura. *Eur J Nucl Med* 1999;26:1380–1.
15 . Maes F, Collignon A, Vandermeulen D, et al. Multimodality image registration by maximization of mutual information. *IEEE Trans Med Imaging* 1997;16:187–98.
16 . Rorden C, Brett M. Stereotaxic display of brain lesions. *Behav Neurol* 2000;12:191–200.
17 . O'Brien TJ, O'Connor MK, Mullan BP, et al. Subtraction ictal SPET co-registered to MRI in partial epilepsy: description and technical validation of the method with phantom and patient studies. *Nucl Med Commun* 1998;19:31–45.
18 . Morioka T, Nishio S, Ishibashi H, et al. Intrinsic epileptogenicity of focal cortical dysplasia as revealed by magnetoencephalography and electrocorticography. *Epilepsy Res* 1999;33:177–87.
19 . Kameyama S, Fukuda M, Tomikawa M, et al. Surgical strategy and outcomes for epileptic patients with focal cortical dysplasia or dysembryoplastic neuroepithelial tumor. *Epilepsia* 2001;42(suppl. 6):37–41.
20 . Kuzniecky R, Mountz JM, Wheatley G, et al. Ictal single-photon emission computed tomography demonstrates localized epileptogenesis in cortical dysplasia. *Ann Neurol* 1993;34:627–31.
21 . Matsuda K, Mihara T, Tottori T, et al. Neuroradiologic findings in focal cortical dysplasia: histologic correlation with surgically resected specimens. *Epilepsia* 2001;42(suppl. 6):29–36.
22 . Urbach H, Scheffler B, Heinrichsmeier T, et al. Focal cortical dysplasia of Taylor's balloon cell type: a clinicopathological entity with characteristic neuroimaging and histopathological features, and favorable postsurgical outcome. *Epilepsia* 2002;43:33–40.
23 . Ferrier CH, Alarcon G, Engelsman J, et al. Relevance of residual histologic and electrocorticographic abnormalities for surgical outcome in frontal lobe epilepsy. *Epilepsia* 2001;42:363–71.
24 . Palmini A, Najm I, Avanzini G, et al. Terminology and classification of the cortical dysplasias. *Neurology* 2004;62:S2–8.
25 . Wennberg R, Quesney F, Olivier A, et al. Electrocorticography and outcome in frontal lobe epilepsy. *Electroencephalogr Clin Neurophysiol* 1998;106:357–68.
26 . Wennberg R, Quesney LF, Lozano A, et al. Role of electrocorticography at surgery for lesion-related frontal lobe epilepsy. *Can J Neurol Sci* 1999;26:33–9.
27 . Pilcher WH, Rusyniak WG. Complications of epilepsy surgery. *Neurosurg Clin N Am* 1993;4:311–25.
28 . Spencer SS, So NK, Engel J Jr., et al. Depth electrodes. In: Engel J Jr., ed. *Surgical treatment of the epilepsies*. New York: Raven Press, 1993:359.
29 . Murphy MA, O'Brien TJ, Morris K, et al. Multimodality image-guided surgery for the treatment of medically refractory epilepsy. *J Neurosurg* 2004;100:452–62.
30 . Van Paesschen W. Ictal SPECT. *Epilepsia* 2004;45(suppl. 4):35–40.
31 . Zhang W, Simos PG, Ishibashi H, et al. Multimodality neuroimaging evaluation improves the detection of subtle cortical dysplasia in seizure patients. *Neurol Res* 2003;25:53–7.
32 . Bingaman WE. Surgery for focal cortical dysplasia. *Neurology* 2004;62:S30–4.
33 . Hader WJ, Mackay M, Otsubo H, et al. Cortical dysplastic lesions in children with intractable epilepsy: role of complete resection. *J Neurosurg* 2004;100:110–7.
34 . O'Brien TJ, So EL, Mullan BP, et al. Subtraction peri-ictal SPECT is predictive of extratemporal epilepsy surgery outcome. *Neurology* 2000;55:1668–77.