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# Dynamic Susceptibility Contrast (DSC) MRI and Interictal Epileptiform Activity in Cryptogenic Partial Epilepsy

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**Summary:** *Purpose:* To study the possible correlation between interictal EEG patterns and neuroradiologic data obtained by dynamic susceptibility contrast (DSC) magnetic resonance imaging (MRI) in patients with partial epilepsy.

*Methods:* Seventeen subjects with cryptogenic partial epilepsy underwent long-term video-EEG monitoring and DSC-MRI in the same session. Ten patients had temporal lobe epilepsy (TLE) and seven, epilepsy of extratemporal origin (ExTE). MRI data were compared with EEG findings, and the accuracy of DSC-MRI was analyzed considering spiking rate (number of interictal epileptiform abnormalities, IEA/min) and type of epilepsy.

*Results:* DSC-MRI showed a relevant asymmetry in the frontal, temporal, and occipital regions in eight (47%) of 17 patients, consisting of a relative regional cerebral blood volume (rCBV) increase in these areas. Because this region corresponded to the interictal EEG focus (IEF) or to the hemisphere involved in the genesis of epileptic discharges in most patients showing a higher spiking rate, patients were classified in two groups: patients with high spiking rate (HSR, n = 9) and with low spiking rate (LSR, n = 8); the cutoff corresponded to the median value of IEA/min. The rCBV increase corresponded to the IEF or to the hemisphere involved in the genesis of epileptic discharges in seven (77.7%) of nine HSR patients. No patients with LSR showed significant asymmetries in rCBV pattern. In five of six patients with TLE-HSR (83.3%), DSC-MRI showed a relative rCBV increase concordant with IEF or hemisphere involved in the genesis of epileptic discharges; in patients with ExTE-HSR, the concordance was 66%.

*Conclusions:* DSC-MRI is a noninvasive procedure that may provide useful additional information to lateralize and/or localize the IEF when interictal epileptiform activity is sufficiently elevated. **Key Words:** EEG—DSC-MRI—Partial epilepsy—Interictal epileptiform abnormalities (IEA).

It has been shown that neuroimaging techniques are useful in the clinical evaluation of refractory epilepsy the better to localize the epileptogenic zone for possible surgical treatment.

The hallmark of an epileptogenic focus studied interictally is an area of reduced glucose metabolism and reduced cerebral blood flow (CBF); however, the ictal epileptogenic area appears as a hyperperfusion region with increased glucose metabolism. These alterations in CBF and metabolism can be detected by single-photon emission computed tomography (SPECT) and by positron emission tomography (PET), respectively (1–4). Ictal SPECT and interictal PET have been shown to have high specificity and sensitivity in the correct localization of the epileptogenic focus. Interictal SPECT can be useful in the detection of the epileptogenic zone, but it is less accurate than ictal SPECT (5). Theoretically, ictal PET may have superior spatial resolution to that of ictal SPECT and interictal PET studies (6). However, all of these techniques have some limitations, including high cost and the use of radioactive substances. Ictal SPECT studies are often difficult to obtain routinely because of the low in vitro stability of radioligands. Ictal PET is hardly feasible in the large majority of cases because of the short half-lives of the radiotracers. Interictal SPECT, although easier to obtain, has lower sensitivity (ranging from 30 to 80%) and specificity (from 36 to 95%) for the localization of the epileptogenic zone (5,7–10).

Recent advances in magnetic resonance imaging (MRI) have significantly enhanced the diagnosis and management of epilepsy. The introduction of MRI with functional and perfusion techniques has provided new insights into the study of focal epilepsy. These techniques can detect ictal hemodynamic changes analogously to PET, but with improved temporal resolution

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(11–14). Proton $^1$H-MR spectroscopy and volumetric MRI have been shown to lateralize temporal lobe epilepsy (TLE) accurately (15). Moreover, it has been demonstrated that functional MRI (fMRI) is able to visualize the brain areas involved in generating interictal epileptiform discharges by using a blood oxygen level–dependent (BOLD) signal (16). Finally, it also has been demonstrated that regional cerebral blood volume (rCBV) measurement, currently used as a marker of cerebral perfusion, has significant diagnostic value in temporal lobe epilepsy (TLE) (17,18).

The purpose of our study was to investigate the relation between EEG interictal patterns and neuroradiologic data obtained by dynamic susceptibility contrast (DSC) MRI in patients with cryptogenic partial epilepsy to evaluate the diagnostic value of this technique for the spatial definition of the epileptogenic zone.

## METHODS

Seventeen subjects (seven male and 10 female patients; age range, 11–78 years; mean age, 39.4 ± 18 years) with partial seizures were studied after giving their informed consent, which in minors was obtained from parents. The Ethics Committee of the University of Rome Tor Vergata approved the study protocol. Exclusion criteria were organic or psychiatric disorders and the use of drugs, other than the antiepileptic therapy, interfering with the central nervous system. Furthermore, based on MRI examinations, we excluded patients with cerebral lesions or focal atrophy. On the basis of previous clinical, neuroradiologic, and ictal–interictal EEG characteristics, all patients were diagnosed as having partial cryptogenic epilepsy according to criteria of the International League Against Epilepsy (ILAE) (19). In particular, 10 patients had TLE, and seven patients, epilepsy of extratemporal origin (ExTE). Clinical features of patients are summarized in Table 1.

**TABLE 1.** *Clinical features of patients*

| Patient age (yr) sex | Epilepsy onset (yr) | Seizure frequency | Type of seizure | AEDS at entry |
|---|---|---|---|---|
| 17M | 12 | Weekly | SPS → SG | CBZ, TPM |
| 37M | 32 | Daily | CPS → SG | TPM, PB |
| 60F | 57 | Monthly | CPS | CBZ |
| 78M | 78 | 2–3/yr | SPS → SG | PB |
| 18F | 18 | Monthly | SPS + CPS | CBZ |
| 59F | 22 | Monthly | CPS | CBZ |
| 48F | 37 | Monthly | CPS → SG | PB, TPM |
| 43F | 21 | Monthly | SPS + CPS | CBZ |
| 34F | 20 | Weekly | CPS | CBZ |
| 20F | 20 | Daily | SPS → SG | CBZ |
| 48F | 16 | Daily | CPS → SG | CBZ, PRM |
| 22M | 5 | Monthly | SPS → SG | CBZ, PHT |
| 11M | 11 | Monthly | CPS | CBZ |
| 52F | 12 | 2–3/yr | SPS + CPS | LTG, CBZ |
| 33F | 26 | Monthly | SPS → SG | CBZ |
| 45M | 44 | 1/yr | SPS → SG | CBZ |
| 46M | 14 | Monthly | CPS → SG | CBZ |

SPS, simple partial seizures; CPS, complex partial seizures; SG, secondary generalization; AEDs, antiepileptic drugs; CBZ, carbamazepine; TPM, topiramate; PB, phenobarbital; LTG, lamotrigine; PRM, primidone; PHT, phenytoin.

The EEG recordings were performed through a 32-channel video-telemetry system (4,000 BMSI). The EEG signal was transmitted from the patient's room to the laboratory, where it was collected and simultaneously stored on hard disk and on magnetic tape. Recordings were obtained by scalp EEG electrodes placed according to the 10-20 International System, by using a common average reference and a time constant of 0.1 s. Specifically, EEG montage consisted of 24 referential EEG channels, with the possibility of different bipolar reconstructions. Interictal epileptiform abnormalities (IEAs) were continuously analyzed and calculated by means of specific computer programs (Stellate Systems) for automatic detection of events like spikes and seizures. The automatic recognition of spikes and/or sharp waves allowed the quantification of such events, providing data on temporal and spatial distribution for the entire duration of the monitoring. All detected paroxysmal events were visually evaluated and edited for false detections. The total number of IEAs occurring in 1 min (IEA/min) was considered in each patient. Patients with clinical seizures within the 24 h preceding and/or during the last video-EEG recording were excluded from the study.

DSC-MRI was performed on all patients immediately after the video-EEG monitoring. MRI with $T_2$-weighted echo-planar sequence (TR = 620 ms; TE = 30 ms; slice thickness, 7 mm; nine slices, FA = 40°; matrix = 128 × 64; 40 dynamic scans; no. average 1; time of acquisition, 1 min 22 s) was used to obtain DSC Images along the anteroposterior commissural (AP-CP) plane. A triple dose of 0.3 mmol/kg of gadolinium-DTPA (Magnivist; Schering) was injected via an antecubital vein, by using a power injector (spectris MP injector; Medrad) at the rate of 5 ml/s. The bolus perfusion data were processed and converted into parameter maps for rCBV.

Regions of interest (ROIs) were drawn on rCBV maps of all the acquired slices. The cortex was treated as a ring, and the circular ROIs (5 pixels) were manually positioned in four different brain regions (frontal, temporal, parietal, and occipital) taking care to exclude areas supposed to include blood vessels (Fig. 1). ROIs obtained in cortical regions were averaged for each region. (Fig. 1). DSC-MRI also was performed in a control group of 13 healthy subjects matched for age (seven male, six female subjects; age range, 20–65 years; mean age, 42.4 ± 23 years). Conventional MRI sequences including coronal fluid-attenuated inversion recovery (FLAIR) imaging (TR, 6000; TE, 100; IR, 2,000; matrix, 256 × 512; 2 mm thickness without gap; three averages acquisition; time, 5.42 min) on the hippocampus were performed as well.

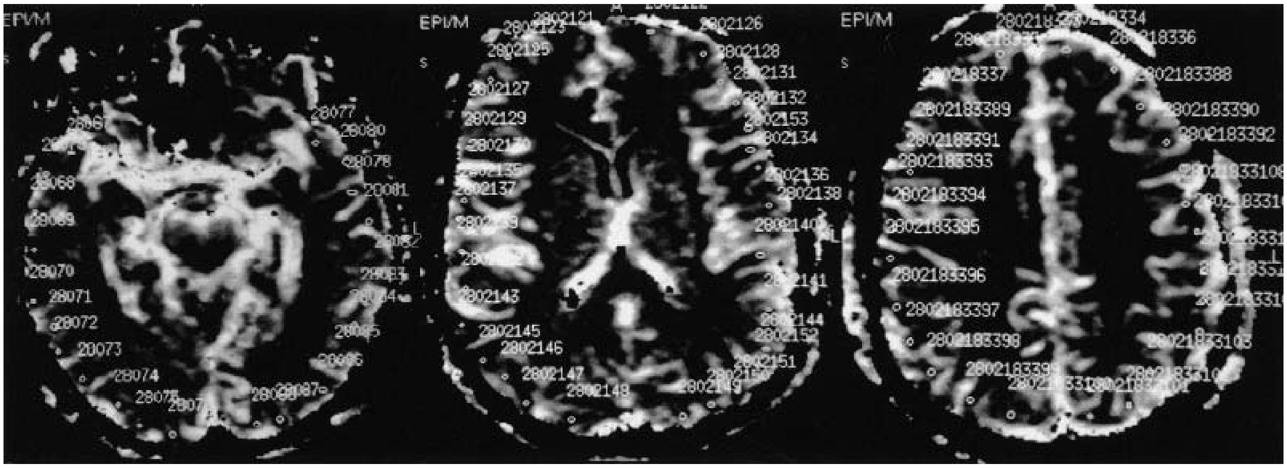

**FIG. 1.** Regions of interest (ROIs) manually positioned on regional cerebral blood volume maps at three different levels.

The asymmetry index (AI) was calculated as the ratio between the rCBV difference of two homologous regions and the rCBV mean of the same regions: [(right – left)/0.5 × (right + left)] for the control subjects and [(ipsilateral – contralateral)/0.5 × (ipsilateral + contralateral)] for the patients with respect to the "epileptic" hemisphere.

AI and rCBV values were compared between patients and controls by means of analysis of variance (ANOVA) with group (i.e., patients and controls) as "between" factor and cortical area (i.e., frontal, temporal, parietal, and occipital) as "within" factor. Findings were considered significant when $p < 0.05$. Significant results were further analyzed with the post hoc Sheffé test for multiple comparisons.

The experiment was single-blinded; that is, neuroradiologists were kept blind about the identity of the recorded subject and localization of interictal EEG focus (IEF).

Finally, DSC-MRI data were compared and correlated with EEG findings.

## RESULTS

### DSC-MRI data: asymmetry indexes

The mean value of AI of each cortical region was significantly higher in patients than in control subjects (Fig. 2). No significant rCBV asymmetry was detected by DSC-MRI in the control group.

DSC-MRI, as demonstrated in Table 2, showed a relevant asymmetry in the frontal, temporal, and occipital regions in eight (47%) of 17 patients, consisting of the presence of a relative rCBV increase compared with the contralateral area. In particular, in five patients, this relative rCBV increase corresponded with the IEF; in two, it was concordant with the hemisphere involved in the generation of epileptiform discharges; in one, it was contralateral to the IEF. In the remaining nine (53%) patients, no significant asymmetries were detected with DSC-MRI.

The following results emerged from the study of the relation between MRI data and type of epilepsy: in six of 10 patients with TLE, DSC-MRI showed a relative rCBV increase; in four patients, it corresponded to the IEF; in one, it was concordant only with the hemisphere involved in the generation of epileptiform discharges; and in one, it was contralateral. In the remaining four TLE patients, DSC-MRI was not informative.

In five of seven patients with ExTE, DSC-MRI did not demonstrate any asymmetry; in the remaining two, a

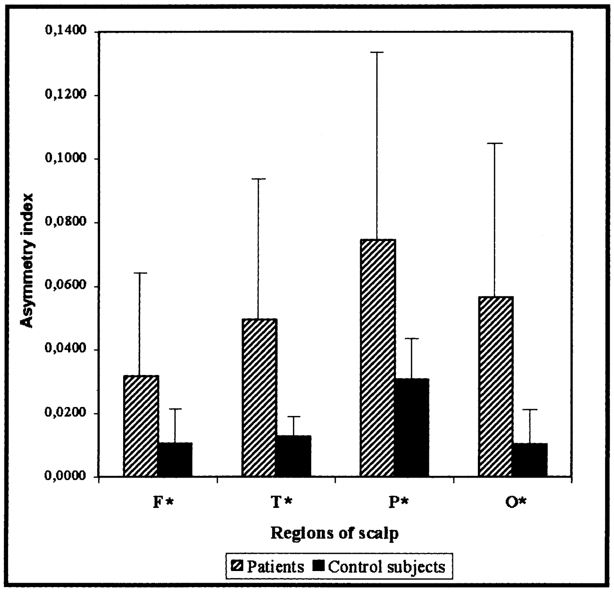

**FIG. 2.** Mean values of the asymmetry index (AI) calculated in the frontal (F), temporal (T), parietal (P), and occipital (O) regions: comparison between patients and control subjects. *$p < 0.05$ (two-way analysis of variance).

**TABLE 2.** *Correlation between interictal spiking rate and DCS-MRI data*

| Patients | IEA/10 min | | Interictal EEG | Type of epilepsy | DSC-MRI |
|---|---|---|---|---|---|
| 1 | 4.56 | HSR | Left frontal | ExTE | Hyper left frontal |
| 2 | 4.65 | HSR | Right anterior–temporal | TLE | Hyper right temporal |
| 3 | 5.25 | HSR | Right central–temporal | TLE | Hyper right temporal |
| 4 | 4.33 | HSR | Left midtemporal | TLE | Hyper left temporal |
| 5 | 4.03 | HSR | Right anterior–temporal | TLE | Hyper right occipital |
| 6 | 3.67 | HSR | Bilateral frontal with right predominance | ExTE | Hyper right occipital |
| 7 | 2.51 | HSR | Left posterior–temporal | TLE | Hyper left temporooccipital |
| 8 | 3.27 | HSR | Right anterior–temporal | TLE | Hyper left frontotemporal |
| 9 | 4.61 | HSR | Left central–parietal | ExTE | No asymmetry |
| 10 | 0.97 | LSR | Left frontal | ExTE | No asymmetry |
| 11 | 0.56 | LSR | Left anterior–temporal | TLE | No asymmetry |
| 12 | 0.32 | LSR | Left frontal | ExTE | No asymmetry |
| 13 | 0.16 | LSR | Right midtemporal | TLE | No asymmetry |
| 14 | 0.41 | LSR | Bilateral posterior–temporal with left predominance | TLE | No asymmetry |
| 15 | 0.61 | LSR | Left frontal | ExTE | No asymmetry |
| 16 | 0.41 | LSR | Bilateral frontal | ExTE | No asymmetry |
| 17 | 0.34 | LSR | Bilateral anterior–temporal | TLE | No asymmetry |

HSR, High spiking rate; LSR, low spiking rate; TLE, temporal lobe epilepsy; ExTE, extra–temporal lobe epilepsy; DSC, dynamic susceptibility contrast; MRI, magnetic resonance imaging; IEA, interictal epileptiform activity.

relative rCBV increase was evident, corresponding in one to the IEF, and in the other, to the hemisphere.

### Correlation between interictal spiking rate, AI, and type of epilepsy

We observed that the relative rCBV increase, detected by DSC-MRI, corresponded either by area or by side to the IEF only in patients with a high spiking rate, as shown in Table 2. Therefore, on the basis of IEA level, patients were classified in two groups: with high spiking rate (HSR, n = 9) and with low spiking rate (LSR, n = 8); the cutoff corresponded to the median value of IEA/min (2.39).

The AI mean values of each region observed in HSR patients was significantly higher than that in the LSR patients, who showed values similar to those of control subjects (Fig. 3).

In the subgroup of TLE-HSR patients, the post hoc analysis (Sheffé test) showed that the AI calculated in the different cortical regions was significantly higher in the temporal area than in other regions (frontal region, 0.029; temporal region, 0.09; parietal region, 0.071; occipital region, 0.078; $p < 0.05$).

In addition, we found a significant correlation between interictal spiking rate (IEA/min) and AI, calculated at the level of the regional IEF and its homologous contralateral region (R = 0.32; Fig. 4).

In the HSR group, the relative rCBV increase detected by DSC-MRI was homolateral or concordant with the IEF in seven (77.7%) of nine patients, contralateral to the IEF in one (11.1%), and in the remaining patient (11.1%), DSC-MRI did not show any asymmetry in the hemodynamic pattern. Conversely, DSC-MRI was never able to detect relevant rCBV asymmetries in any patients with LSR.

We also considered the relation between spiking rate level and type of epilepsy. In the HSR group, six patients had TLE, and three, ExTE. In all six TLE patients, DSC-MRI showed a relative rCBV increase, which in four subjects (66.6%; patients 2, 3, 4, and 7) corresponded with IEF, in one (16.7%; patient 5) was concordant with the side, and in one (16.7%; patient 8) was contralateral to the epileptogenic discharge.

DSC-MRI showed a relative rCBV increase in two (patients 1 and 6) of three patients with ExTE HSR. It

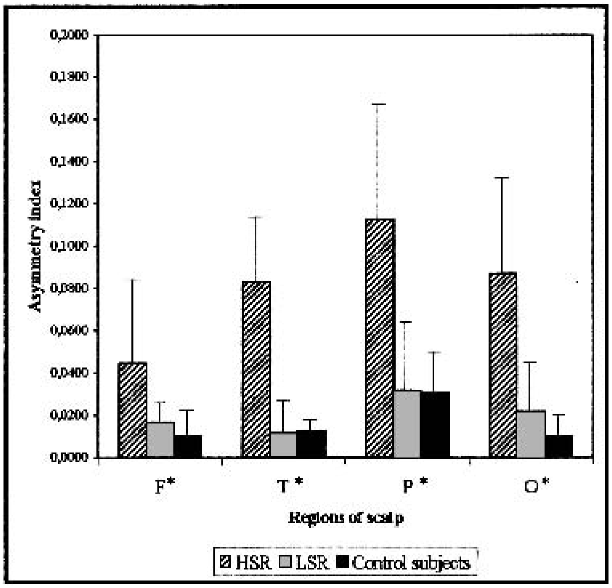

**FIG. 3.** Mean values of the asymmetry index (AI) calculated in the frontal (F), temporal (T), parietal (P), and occipital (O) regions: comparison between patients with high spiking rate (HSR), with low spiking rate (LSR), and control subjects. *p < 0.05 (two-way analysis of variance).

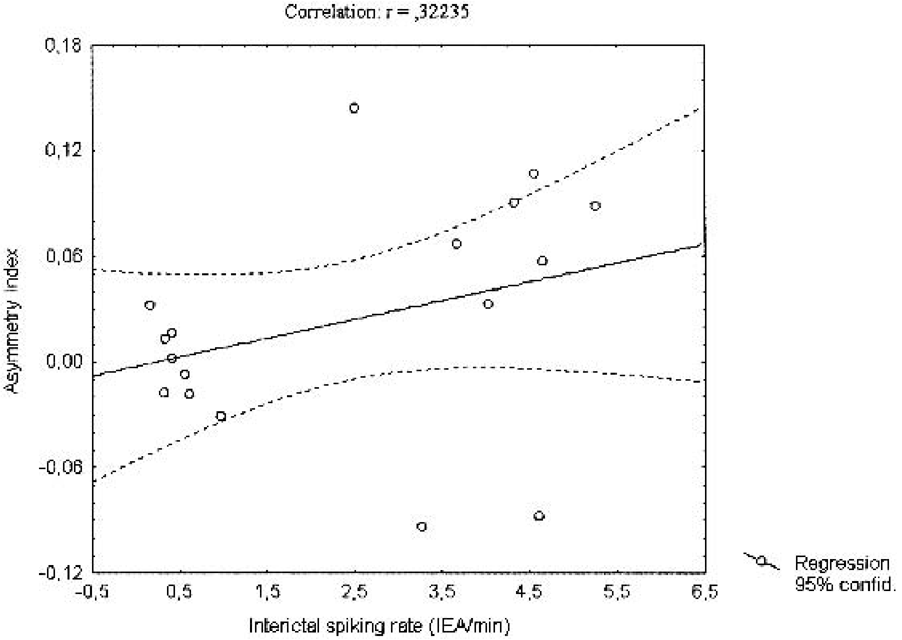

**FIG. 4.** Correlation between interictal spiking rate and the asymmetry index (AI) calculated at the level of the interictal EEG focus (IEF) and its homologous contralateral region. The negative values indicate the lack of concordance between relative regional cerebral blood volume increase and IEF.

was concordant with the IEF in one patient and with the side in the other patient. No asymmetry was detected by DSC-MRI in the third patient (patient 9).

### rCBV values

The hemispheric rCBV values calculated in healthy subjects were significantly lower than those in epilepsy patients: in particular, when considering the correlation with spiking rate, the HSR patients showed rCBV values significantly increased, particularly in the hemisphere involved in the genesis of epileptic discharges; on the contrary, LSR patients showed hemispheric rCBV values similar to those observed in healthy subjects in both sides (Table 3A).

In TLE patients, similar findings were observed: TLE-HSR patients showed rCBV values significantly higher in both the temporal regions more evident in the side of seizure origin; TLE-LSR patients showed temporal rCBV values analogous to those observed in healthy controls in both sides (Table 3B).

**TABLE 3A.** *Hemispheric rCBV and AI values in patients and control subjects*

| Patients | "Epileptic" hemisphere | Contralateral hemisphere | AI | p value |
|---|---|---|---|---|
| All patients (no = 17) | 136.7 ± 41 | 132.1 ± 38 | 0.034 | <0.05 |
| HSR patients (no = 9) | 152.2 ± 48 | 144.2 ± 45 | 0.054 | <0.01 |
| LSR patients (no = 8) | 119.2 ± 24 | 118.4 ± 24 | 0.007 | NS |
| | Right hemisphere | Left hemisphere | | |
| Control subjects (no = 13) | 118.4 ± 23 | 119.1 ± 25 | 0.006 | NS |

AI, asymmetry index; NS, not significant.

## DISCUSSION

Good agreement between relative regional CBF maps obtained with SPECT and DSC-MRI was recently demonstrated in normal volunteers (20).

The most interesting finding of our study is the presence of a relative rCBV increase in the area or, at least, in the hemisphere involved in the genesis of IEA in most patients showing a high spiking rate; in addition, the level of this rCBV asymmetry was significantly related to the interictal spiking rate.

HSR patients showed rCBV values statistically increased, particularly in the hemisphere involved in the genesis of epileptic discharges; on the contrary, LSR patients showed hemispheric rCBV values similar to those observed in healthy subjects in both sides. For this reason, we can reasonably argue that the asymmetric rCBV pattern reflects a real "hyperperfusion" homolateral to the putative side of seizure origin. This result apparently contrasts with findings of previous studies. Interictal SPECT and PET showed hypoperfusion and hypometabolism in the epileptogenic region (1,2), whereas ictal SPECT and PET demonstrated hyperperfusion and hypermetabolism in the seizure focus, respectively (1,3,4,6,10,21). Recent investigations reported temporal lobe hypoperfusion on MRI perfusion studies in TLE (17,18). However, in the article by Wu et al. (17), most of patients showed temporal lobe hypoperfusion to correlate with ipsilateral temporal lobe atrophy. This suggests that neuronal loss in the hippocampus would coincide with the lower blood volume, and it may be responsible for hemodynamic impairments extending beyond the lesion detectable by MRI. It is possible that no

**TABLE 3B.** *rCBV and AI values in temporal regions of epilepsy patients and control subjects*

| Patients | "Epileptic" side | Contralateral side | AI | p value |
|---|---|---|---|---|
| TLE patients (no = 10) | 158.9 ± 55 | 148.8 ± 48 | 0.065 | <0.001 |
| TLE-HSR patients (no = 6) | 176.5 ± 64 | 161.3 ± 57 | 0.090 | <0.0001 |
| TLE-LSR patients (no = 4) | 132.4 ± 28 | 129.9 ± 27 | 0.019 | NS |
| | Right side | Left side | | |
| Control subjects (no = 13) | 127.6 ± 30 | 129.7 ± 24 | 0.016 | NS |

AI, asymmetry index; NS, not significant; rCBV, regional cerebral blood volume; HSR, high spiking rate; LSR, low spiking rate; TLE, temporal lobe epilepsy.

rCBV decrease was observed in our patients because we excluded patients with atrophy and/or focal lesions.

Because the large majority of HSR patients showed an rCBV increase detected by DSC-MRI homolateral to or concordant with the IEF, we suggest that the IEDs of these patients were so frequent that they resembled an EEG ictal pattern. Previous studies using fMRI techniques, possibly associated with EEG monitoring, demonstrated focal hemodynamic changes correlated with both clinical and subclinical epileptic discharges (11,12, 14,16). Very recently, it was reported that 34.9% of individual focal interictal epileptiform spikes were associated with significant focal hemodynamic activations detectable with BOLD fMRI (22).

Our findings indicate that the localizing and lateralizing power of this technique is evident when patients showing an active epileptogenic focus are considered. However, in two HSR patients, DSC-MRI failed to provide information about the epileptogenic zone. In one case, DSC-MRI showed a relative rCBV increase contralateral to the IEF; this mislateralizing result, although difficult to explain, could be due to transient metabolic changes occurring distant from the discharging epileptic focus, as observed in both experimental and clinical epilepsies (23). In the second case, DSC-MRI was not informative. The lack of MRI hemodynamic asymmetry can probably be explained by the high tendency of EEG epileptiform discharges to spread bilaterally.

Conversely, in LSR patients, DSC-MRI has not been able to provide useful information about the area of the brain or hemisphere involved in the generation of IEAs. This finding may be explained by different factors: (a) the lack of IEAs during the acquisition of MRI; or (b) an IEA level that was too low to induce relevant CBV changes for detection by DSC-MRI.

Another intriguing result of our study is represented by the bilateral hemodynamic activation observed in HSR patients more accentuated in the hemisphere involved in the genesis of epileptic abnormalities: we suggest that frequent epileptiform discharges spreading to the contralateral homologous region may be responsible for this bilateral asymmetric "hyperperfusion."

Finally, both the lateralizing and localizing values of DSC-MRI in patients with HSR were higher in TLE than in ExTE patients (83.3 vs. 66%). This lower sensitivity observed in the latter group is consistent with previous SPECT and PET studies (1), although our limited sample size narrows the relevance of this finding.

These data appear to be particularly interesting considering that no patient in our population was affected by mesial sclerosis or other structural brain lesions.

DSC-MRI is a noninvasive procedure that may provide useful additional information to lateralize and/or localize the epileptogenic area when interictal epileptiform activity is sufficiently elevated in patients with cryptogenic epilepsy. Because patients with drug-resistant epilepsy, candidates for surgical treatment, are likely to have frequent interictal discharges, mainly during the withdrawal monitoring, this technical procedure may be indicated as an ancillary test in the presurgical evaluation of these selected patients.

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