Correlations between cerebral blood flow variations and clinical parameters in temporal lobe epilepsy: an interictal study

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SUMMARY Regional cerebral blood flow (rCBF) measurements were determined by the intravenous Xenon 133 technique in 80 patients suffering from temporal lobe epilepsy. All the patients had a normal CT scan. Three subgroups were differentiated, according to EEG and all-night polygraphic recordings: temporal lobe epilepsy with left (N = 25) or right (N = 25) EEG epileptic abnormalities and temporal lobe epilepsy with EEG abnormalities in both temporal regions with asynchronous occurrence (n = 30). In comparison with a control group (n = 20), there was (1) a marked reduction of blood flow in the temporal region corresponding to the site of the epileptic focus and (2) a reduction in blood flow in distant brain areas and the contralateral hemisphere. The rCBF decrease was highly correlated ($p < 0.001$) with the disease severity (taking into account the complex partial seizure frequency and the number of secondary generalised seizures). Differences were found in the rCBF decrease between left and right temporal lobe epilepsy.

Interictal investigations in partial epilepsy have demonstrated a reduced blood flow in the epileptogenic region of the brain. Such haemodynamic alterations were detected in patients with temporal lobe epilepsy by using various techniques for determining regional cerebral blood flow (rCBF) including 133 Xenon two dimensional clearance technique,¹⁻³ single photon emission computed tomography (SPECT)⁴ and positron emission tomography (PET).⁵ Focal reductions of metabolism also have been found in temporal lobe epilepsy.⁶⁻¹³ The localisation of both hypoperfusion and hypometabolism corresponded to the epileptogenic focus. Until now, the rCBF and metabolism decrease have been attributed to cerebral hypoactivity, but the exact mechanism remains unclear.

Of physiological interest is the fact that the reduction of flow may extend to areas distant from the EEG focus.¹⁴ Therefore, using the two dimensional Xenon 133 method which permits cortical haemodynamic measurements, the aim of this study was:

(1) to confirm the previous preliminary results concerning functional haemodynamic impairment at distance for the EEG epileptic focus in a larger population of epileptic patients with complex partial seizures (N = 80), (2) to determine, using multivariate analysis if some clinical parameters are related to these decreases of rCBF.

Subjects and methods

Eighty epileptic patients (the temporal lobe epilepsy group) (32 females, 48 males, mean age = 27.18; range 9-59 years) underwent rCBF measurements. All but three of the patients were right-handed. None of them had any abnormality on repeated neurological examination and CT scan. All of them had complex partial seizures in accordance with the international classification.^{15 16} Aetiology was unknown in most of the cases, 15 patients had febrile convulsions during childhood, eight had a perinatal insult. A history of epilepsy was found in the families of three patients. According to the new international classification¹⁷ and the fact that all the CT scans were normal, 57 subjects had idiopathic epilepsy.

Four clinical criteria were considered for each subject: age, age at the onset of epilepsy, duration of the disease and severity of the epilepsy. This last parameter was evaluated by a clinical index ("severity index" (SI)) taking into account the frequency of the complex partial seizures (CPS) and the number of secondary generalised tonic-clonic seizures (SGS) by using the following scoring system: (1) one CPS a year;

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(2) one CPS quarterly; (3) one CPS monthly; (4) one CPS biweekly; (5) one CPS weekly; (6) one CPS daily. The number of secondary generalised tonic-clonic seizures was scored (1) for less than five SGS; (2) for a score between five and 10 SGS; (3) for a score between 10 and 20 SGS; (4) for more than 20 SGS. None of them had CPS or SGS during the 48 hour period prior to rCBF measurements. CPS frequency and SGS number were monitored during 2 weeks hospitalisation before rCBF measurements and by a home seizure book, over a minimum of 6 months (because some of the patients had epilepsy which began only 6 months before). Of 100 selected epileptic patients, 20 were excluded because their SI was indeterminable.

The 80 patients were divided into three subgroups according to the EEG findings of repeated standard day time EEG and all night polygraphic recordings: (a) *left temporal group* (N = 25) with focal interictal epileptiform discharges in the left temporal region, (b) *right temporal group* (N = 25) with focal interictal epileptiform discharges in the right temporal region, (c) *bitemporal group* (N = 30) with unstable focal epileptiform discharges found in both temporal regions either alternately or simultaneously but with an asynchronism or an asymmetry between the right and left sides.

Antiepileptic therapy remained unmodified during the months preceding the study. Treatments were different between patients but not between groups. All the patients were treated by monotherapy (carbamazepine or sodium valproate) or polytherapy with a combination of phenobarbitone and carbamazepine or phenytoin and sodium valproate. Six patients had tritherapy with carbamazepine, phenytoin and phenobarbitone at the time of rCBF measurements. The plasma levels of antiepileptic drugs ranged from 16 to 40 $\mu\text{mol/l}$ for carbamazepine, 350 to 840 $\mu\text{mol/l}$ for sodium valproate, 40 to 80 mol/l for phenytoin and 65 to 170 mol/l for phenobarbitone.

Twenty normal volunteers having no history of neurological disease, showing no signs of CNS impairment and receiving no drugs were examined by IV. 133 xenon clearance technique for the determination of rCBF control values. Mean age of normal subjects was 26.75 (range 21–39 years). Eight were females and 12 males.

The EEG was recorded with conventional scalp electrodes prior to or at the time of rCBF measurements. All the patients were also submitted to two or more all night sleep polygraphic recordings in order to establish the localisation and the fixity of the epileptic focus (production of spikes, spikes and waves or sharp waves). It is considered that such an examination gives indications concerning the lateralisation of the epileptic focus similar to the depth EEG recordings when lateral EEG abnormalities are found during waking, NREM sleep and REM sleep.^{18 19}

Clearance of 133 xenon following intravenous injection was used to perform rCBF measurements (Mecaserto system). The tracer (15 mCi) was injected intravenously in a bolus. At the time of measurements, the patient was isolated in a quiet and darkened room. The subject was required to lie down and to refrain from talking. Arterial blood pressure and CO_2 arterial partial pressure (PaCO_2) were performed during and after rCBF measurements. rCBF was computed by a two compartmental analysis of the clearance curve and with a correction for xenon recirculation based on the end-tidal tracer concentration.^{20 21} The study of rCBF was limited

to F1 derived from the initial slope of the clearance curve and considered as grey-matter flow. Reliability of the CBF values was controlled twice or more in some controls and several patients by repeating the measurements in similar conditions. Thirteen sodium iodide crystal scintillation detectors were placed symmetrically over each hemisphere. Two regions of interest were selected on each hemisphere: the temporal region (T) (four detectors) and the extra-temporal region (extraT) (nine detectors). Average CBF values for extraT region (extraTCBF) and for T region (TCBF) were calculated from individual measurements. In order to eliminate the age factor in rCBF values, especially with regard to young patients (<15 years),^{22–27} an rCBF decrease index (DI) was calculated for each subject as follows:

$$\text{DI} = \frac{\text{epileptic rCBF}}{\text{age-matched normal volunteers rCBF}}$$

where epileptic rCBF represents the CBF in the region of interest r of the epileptic patient, and age-matched normal volunteers CBF represents the theoretical CBF value in the region of interest r of an age-matched control patient.

For the different regions of interest, the theoretical rCBF value of an age-matched controls patient is given by the following equations:

$$\begin{aligned} \text{Right temporal CBF} &= (157.453 \times \text{age} - 0.3074) + 3.8 \\ \text{Left temporal CBF} &= (157.453 \times \text{age} - 0.3074) + 2.8 \\ \text{Right extraT CBF} &= (157.453 \times \text{age} - 0.3074) + 5.3 \\ \text{Left extraT CBF} &= (157.453 \times \text{age} - 0.3074) + 4.3 \end{aligned}$$

These equations were derived from rCBF study performed on 40 control subjects (14 females, 26 males, age = 30.75 – range: 13–61 years). Therefore, the equation (DI) conveys the rCBF decrease of each epileptic patient compared with an age-matched control, thus eliminating the age factor.

The populations were normally distributed (χ^2 test) and their variance values were comparable (Fischer test, $p < 0.01$). The different groups were compared by the Student *t* test. Differences were not considered significant if the level of confidence did not exceed 95%. Because it was not possible to examine the hierarchy between the clinical parameters contributing to the rCBF decrease on the basis of a single-factor analysis, multivariate analysis, which shows the reciprocal relationships between factors, was used. We tried to explain some of the quantitative variables (rCBF variations) for each epileptic localisation by other quantitative variables (clinical data) by showing a hierarchy in the occurrence of these variables. For this purpose, we used a stepwise method which associated a forward selection and a backward elimination. The test used to hierarchically select the variables was the Fisher Snedecor test (the multiple correlation coefficient was supplied) (In all these studies : = 1% for Ho elimination and: 5% for Ho acceptance).

Results

rCBF decrease pattern of temporal lobe epilepsy (n = 80)

For the 20 normal volunteers, the mean right and left extra TCBF values were respectively $63.88 \pm 9.6 \text{ ml/100 g/min}$ and $62.94 \pm 9.3 \text{ ml/100 g/min}$. The mean right TCBF was $62.54 \pm 8.4 \text{ ml/100 g/min}$ and

Fig 1 Reproducibility of rCBF determination in six normal subjects. Black = first measurement; grey = second measurement; RT = right temporal region; LT = left temporal region; R extra T = right extratemporal region; L extra T = left extratemporal region.

mean left TCBF was 61.14 ± 8.3 ml/100 g/min. There was no difference between homo- and contralateral rCBF values. Figure 1 shows the reproducibility in the right and left TCBF and extraTCBF values for investigations repeated under the same conditions. The rCBF decrease index (DI) was 1.01 ± 0.13 for each region of interest (table 1). This result proves the validity of the DI.

The overall results of patients with temporal lobe epilepsy showed a rCBF decrease for the TCBF ($p < 0.001$) and extra TCBF ($p < 0.01$) (table 1). rCBF in the temporal group with left EEG epileptic focus was

Valmier, Touchon, Daures, Zanca, Baldy-Moulinier characterised by a global decrease (-14%), which was greater in the left temporal region (-20%) (table 1). rCBF in the temporal group with right EEG epileptic focus showed a reduction of blood flow only in the right temporal region (-10%) as compared with the control group (table 1). rCBF in the temporal group with bilateral and asynchronous or unilateral and alternative EEG epileptic focus had a rCBF decrease with the extraT DI ($p < 0.05$) and the TDI ($p < 0.01$) (table 1).

The decrease index values (DI) for the temporal epileptic regions ($p < 0.02$), the ipsilateral extra-temporal regions ($p < 0.02$), the contralateral epileptic regions ($p < 0.05$) and the contralateral extra-temporal regions ($p < 0.05$) were significantly different between right and left temporal lobe epilepsy groups.

Correlation between rCBF decrease and clinical parameters

For the temporal group ($n = 80$, mean age = 27.18 , range 9–59 years), with no consideration of the site of the epileptic focus, the age at the onset of the disease was 16.62 ± 10.59 years, the duration of the disease 10.57 ± 9.06 years, and the severity index 5.44 ± 2.4 . The correlations between the four clinical parameters and the four regional DIs are shown in table 2. The severity index was negatively correlated with the rCBF values ($p < 0.001$). The age of the patient, the age at the onset of the epilepsy and the duration of the disease showed no significant correlations. To improve the validity of the severity index (SI) vari-

Table 1 Decrease index values of the right (RTDI) and left (LTDI) T regions, of the right (R extraTDI) and left (L extra TDI) extraT regions for the five groups: control group (CG), temporal lobe epilepsy group (TLE) with left (LTLE), right (RTLE) and bitemporal (BiTTLE) EEG focus

	RTDI	LTDI	RextraTDI	LextraTDI
CG	1.01 ± 0.14	1.01 ± 0.12	1.01 ± 0.13	1.01 ± 0.12
TLEG	$0.91 \pm 0.14\ddagger$	$0.89 \pm 0.14\ddagger$	$0.94 \pm 0.15\ddagger$	$0.94 \pm 0.14\ddagger$
LTLEG	$0.88 \pm 0.15\ddagger$	$0.82 \pm 0.13\ddagger$	$0.90 \pm 0.15\ddagger$	$0.89 \pm 0.16\ddagger$
RTLEG	$0.91 \pm 0.15^*$	0.97 ± 0.14	0.96 ± 0.14	1.00 ± 0.14
BiTLEG	$0.91 \pm 0.14\ddagger$	$0.88 \pm 0.14\ddagger$	$0.93 \pm 0.16^*$	$0.93 \pm 0.13^*$

* $p < 0.05$; $\ddagger p < 0.01$; $\ddagger\ddagger p < 0.001$.

Table 2 Correlation between the four clinical parameters and decrease index of the right (R TEMPORAL) and left (L TEMPORAL) temporal regions and of the right (R extraT) and left (L extraT) extraT regions in the temporal lobe epilepsy group ($n = 80$)

	N	Sex			Onset of the disease (years)	Duration of the disease (years)	Severity index
		M	F	Age (years)			
LTLEG	25	14	11	30.48 ± 11.32	17.65 ± 14.27	12.87 ± 9.95	$*6.26 \pm 1.98$
RTLEG	25	13	12	28.48 ± 10.8	18.68 ± 9.05	9.8 ± 0.08	4.72 ± 2.65
BiTLEG	30	21	9	23.48 ± 7.92	14.03 ± 7.9	9.41 ± 8.24	5.41 ± 2.36

* $p < 0.05$ between RTLEG and LTLEG.

Fig 2 Comparison of severity index in matched left and right temporal epileptic groups. LTG = left temporal group ($n = 13$). RTG = right temporal group ($N = 9$). The CBF decrease index values (DI) are significantly different in the contralateral temporal (CEF) and contralateral extratemporal (CH) regions and not in the temporal epileptic (EF) and the ipsilateral extratemporal (EH) regions.

able, SI monotonic transformations (square roots, logarithm) were performed. The results were unchanged.

Influence of the EEG focus lateralisation on the rCBF decrease

The intensity and the spatial extent of the hypoperfusion were found to be different between the three subgroups (table 1). Furthermore, their SI ($p < 0.05$) (table 2) and the localisation of their EEG epileptic focus were also different. In order to understand the respective influence of the lateralisation of the EEG epileptic focus and of the severity of the illness upon the rCBF decrease pattern, two populations were selected and compared, one with a stable right EEG epileptic focus and the other with a stable left epileptic focus, both presenting a matched severity index. Whereas the rCBF determinations in the T and extraT regions corresponding to the EEG epileptic focus showed equivalent values, the contralateral hemispheric CBF to the epileptic focus was significantly decreased ($p < 0.05$) in the SI matched left temporal group as compared with the SI matched right temporal group (fig 2).

It is known that anticonvulsant drugs may decrease cerebral metabolism¹³ and perhaps CBF. Therefore it was required that the two groups (with a matched severity index) receive equivalent drug therapy. Two sets of parameters were analysed and compared; the duration of the treatment (years) and the taking of polytherapy, using the following score: (1) monotherapy (2) bithrapy (3) trithrapy. No difference was found between these two groups.

Discussion

rCBF decrease was observed in areas distant from the EEG epileptic focus

This study shows: (1) a marked reduction occurs in

blood flow in the temporal region corresponding to the site of a stable EEG epileptic focus, (2) rCBF decreases in cortical areas at a distance from the epileptic focus.

The cortical hypoperfusion corresponding to the EEG epileptic focus, in the interictal state, has been confirmed by the other rCBF two dimensional methods.^{1 28-30} Tridimensional methods such as PET⁵ and SPECT,⁴ (which provide information concerning cortical and deep rCBF abnormalities) have shown that hypoperfusion often extends to the mesial temporal areas.

The existence of a rCBF decrease at a distance from the epileptic focus confirms preliminary studies.¹⁴ The hypoperfusion in distant brain areas was always less than in the temporal epileptic region.

Clinical parameters were correlated with rCBF decrease

One of the remarkable findings in this study was the demonstration of the existence of a strongly significant negative correlation between the EEG epileptic focus, CBF, and the illness severity parameters, regardless of the epileptic focus localisation. This correlation exists as much for the TCBF reduction ($p < 0.01$) as for the extra TCBF reduction ($p < 0.01$). To our knowledge, this relationship has not been previously reported.

If the rCBF decrease depends upon a microscopic pathological process, often invisible with CT scan, sometimes visible with MRI,³¹ it also implies a functional process. The mechanisms of this must still be specified. The hyperaemia in the region of the EEG epileptic focus characterised by an rCBF decrease during the interictal period,^{7 32-35} is accompanied by normal vascular functional reactivity of the epileptogenic areas to variations of PaCO_2 .³⁶ This underlines the functional aspect of the rCBF decrease in the region of the EEG epileptic focus. Furthermore, surgical removal of focal epileptic lesions may be followed by normalisation of the distant hypoperfused cerebral areas.³⁷

The proof of a rCBF decrease in areas distant from the EEG focus on the one hand and of a negative correlation between this hypoperfusion and clinical parameters on the other hand represents an additional argument for the existence of functional mechanisms in relation to the rCBF pattern of temporal lobe epilepsy.

Does a functional haemodynamic asymmetry exist between right and left temporal epileptic regions?

Other issues raised by the present study are the particular features of the distribution pattern of rCBF in each subgroup. The flow reduction at a distance from the EEG focus is larger and more intense in patients

with a left-sided temporal focus than in those with a right temporal focus. On the one hand the temporal lobe epilepsy group showed a rCBF decrease mostly correlated with the severity of the disease; on the other hand the left temporal lobe epilepsy group had a severity index greater than that of the right temporal lobe epilepsy group. This result raises the question of the respective role of the illness severity on the one hand and of the EEG epileptic focus lateralisation on the other, in determining the rCBF pattern difference between the left and right temporal lobe epilepsy group. In order to answer this question, two matched populations receiving equivalent drug therapy, one with a stable right EEG epileptic focus, and the other one with a stable left EEG epileptic focus were selected and compared. The results suggest that the lateralisation of the epileptic focus plays an important part in the haemodynamic decrease of the contralateral region. The rCBF decrease seemed larger when the EEG epileptic focus was in the left temporal region than in the right temporal region.

In conclusion, the proof of a correlation between the illness severity and the rCBF decrease opens up a new field of haemodynamic investigations in temporal lobe epilepsy. From a physiopathological point of view, it would be interesting to determine if any correlation exists between the rCBF decrease and other clinical, aetiological, pharmacological and psychological data. Furthermore, it would be interesting to investigate with three dimensional methods if such rCBF abnormalities are also present in deep cerebral regions at a distance from the EEG epileptic focus, and whether these correlate with some clinical parameters. Finally, the study of the haemodynamic asymmetries existing as a function of the EEG epileptic focus lateralisation seems to be a good investigative tool for certain mechanisms that underlie the cerebral functional activity and the hemispheric specialisations.

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