Cerebral Blood Flow in Frontal Lesions of Aneurysms of the Anterior Communicating Artery

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Background and Purpose  The aim of this study was to investigate local and remote cerebral blood flow in patients with prefrontal lesions resulting from rupture (and operation) of aneurysms of the anterior communicating artery.

Methods  The localization and severity of the lesions were evaluated by magnetic resonance imaging on T2 sequences. Blood flow measurements were performed in 21 patients at least 3 weeks after surgery using single-photon emission computed tomography. Flow values were calculated in 10 regions of interest in each cerebral hemisphere and compared with those of 21 control subjects matched for age.

Results  A drop in regional cerebral blood flow (rCBF) values progressively dropped during the first 2 weeks after subarachnoid hemorrhage and that this change was less severe in patients with better outcomes. However, the specific consequences of the site of the vascular malformation were not analyzed.

The aim of the present study was (1) to investigate, at the secondary stage, the local and remote rCBF consequences of prefrontal lesions occurring after rupture and operation of an anterior communicating artery aneurysm (ACAA), with the expectation that a drop of rCBF would be observed in the thalamus and striatum because of the narrow anatomic associations and (2) to evaluate possible correlations between the severity of lesions observed on magnetic resonance imaging (MRI) and flow values in the posterior areas of the brain, with the hypothesis that a remote flow reduction could be related to the severity of prefrontal brain damage.

Subjects and Methods

We evaluated all the patients admitted at the Neurological Rehabilitation unit between 1989 and 1992 after rupture of an ACAA. Inclusion criteria were surgical intervention at least 3 weeks before and the presence of unilateral or bilateral lesions on computed tomographic scan and MRI in the frontal lobe and/or in the territory of the anterior cerebral artery (including the anterior cingulate gyrus and septal area). Exclusion criteria were age older than 70 years, alcoholism, previous neurological or psychiatric disorders, motor or sensory deficit of the upper limb, neuroleptic or antiepileptic treatment, infarct (or lesion) in the territories of the middle cerebral artery and/or of the posterior cerebral artery, and hydrocephalus.

Of 34 patients that were hospitalized after an ACAA operation, 13 did not fulfill the admission criteria, and 21 were included: 13 men and 8 women aged between 18 and 70 years (mean, 47.9±12.8 years). The average time after hemorrhage was 82.8±77.3 days. All subjects had a Barthel Index score between 80 and 100 (of 100), except for one patient who had a motor deficit of the inferior limbs and another who had frontal ataxia. Each patient underwent a complete neuropsychological evaluation (attention, short-term memory, learning verbal and visual information, executive functions, and general intellectual performances).

The severity of the arterial spasm of the medial cerebral artery had been evaluated in 18 patients by means of transcranial Doppler (Transpect TCD, Medisomics) in the first few days after stroke. Comparison with values obtained in control subjects revealed a significant (P=.01) increase of flow velocity in 13 patients (right sided, 5; left sided, 0; bilateral, 8). This phenomenon had always disappeared at the time of blood flow measurement.
The CBF was assessed by means of single-photon emission computed tomography (SPECT), during continuous inhalation of xenon-133, with a Tomomatic 64 system (Medimatic, Copenhagen, Denmark) in 12 cases and a Tomomatic 564 system in 9 cases. The only difference between the two systems was the number of slices (5 versus 3) and their thickness (2 versus 1.5 cm). Colimators, algorithms, and partition and attenuation coefficients were the same.

Examination was conducted under standard conditions after a 15-minute adaptation period in dim light and silence and lasted 4.5 minutes. $PACO_2$ was recorded with a Beckman LB2 capnograph.

With the Tomomatic 64, measurements were obtained in three 2-cm-thick axial transverse slices of brain tissue situated at 1, 5, and 9 cm above the orbitomeatal (OM) plane (ie, OM+1+5+9 cm). The Tomomatic 564 enabled us to define five 1.5-cm-thick slices (ie, OM+1+3+5+7+9 cm). The full-width, half-maximum was 12 mm and the pixel 25 mm$^2$. The reproducibility of the method has been previously described.

Regional flow values were quantified (1) in the cerebellum on the lower slice (OM+1); (2) in nine areas (size, 650 to 800 mm$^2$, ie, 25 pixels or more) on the intermediate slice (OM+5) passing through the basal ganglia (Fig 1), including frontal anterointernal, frontal anteroxternal, frontal posteroxternal, temporal anterior, temporal posterior, temporo-occipital, occipital, lenticular, and thalamic; and (3) in the paramedian frontal area on the upper slice (OM+9). Each area was traced manually (Tomomatic 64) or automatically defined by the analyzing system (Tomomatic 564) and later adjusted manually.

The rCBF values of patients (Fig 2) were compared with those of 21 control subjects, 13 men and 9 women ranging in age from 21 to 73 years (mean age, 37.1±15.3 years). To ensure correct matching for age, we adjusted the individual rCBF values of the control subjects, using the regression coefficient and slope index of rCBF versus age for each area. Since $PACO_2$ was not statistically different in patients (mean, 5.5%) and control subjects (5.2%) and there was no significant correlation between $PACO_2$ and rCBF values, we did not correct rCBF values for this factor.

The severity of the cerebral injury was evaluated on MRI (Fig 3), performed approximately at the same time as the CBF measurements (mean interval after stroke, 70 days). An MR-max machine (General Electric) with super-conducting magnet operating at 0.5 T was used. T2-weighted spin-echo sequences were used (repetition time, 2000 milliseconds; echo time, 100 milliseconds) in axial slices (bicommissural plane). The surface of the hyperecho was measured in the same scanner slice (passing through basal ganglia and thalamus) and in the same frontal areas as those selected for rCBF measurements. Lesions were estimated by two independent observers as follows: 0, absent; 1, hyperintensity area (HA) <25% of total area; 2, 25%<HA<50%; 3, 50%<HA<75%; 4, 75%<HA<100%.

For statistical comparison of the rCBF values of patients and control subjects, we used repeated-measures ANOVA with an $\alpha$ risk of $P<.05$ and Bonferroni adjustment for multiple comparison (SAS package; SAS Institute, Cary, NC). We also looked for simple correlations (Pearson test) between (1) rCBF values and (2) time after stroke, age, presence of treatment with calcium antagonist (nimodipine, 4 cases; nifedipine, 1 case; nicardipine, 5 cases), type of apparatus (Tomomatic 64 versus Tomomatic 564), and lesion severity (on MRI) in frontal areas.

Results

The lesions (hyerecho on T2-weighted sequences) were more severe on the right side (Table 1) and in the frontal anteroexternal area. This was thought to be related to the side of the surgical operation. In most cases (15 of 21), those lesions were bilateral but asymmetric. Patients operated on the right side had predominant right-sided lesions in 15 of 18 cases, and those operated on the left side always had predominant left-sided lesions (3 of 3).

A first repeated-measures ANOVA analyzed variations of the rCBF values in the cerebral hemispheres, with one between-subjects factor (group, patients versus control subjects) and two within-subjects factors: side (right versus left) and area (10 areas). We observed a significant main effect for the side ($F=11.74, df=1, P=.001$), with flow values lower on the right side, as well as for the area ($F=37.94, df=9, P=.0001$). The following interactions were also significant: group×side ($F=10.51, df=1, P=.002$), with lower rCBF values observed on the right side in patients; group×area ($F=8.86, df=9, P=.0001$), with flow values lower in the frontal areas and more elevated in the posterior areas in patients; side×area ($F=4.66, df=9, P=.0001$), with lower rCBF values in the right side compared with the left side in the frontal areas; and group×side×area ($F=3.13, df=9, P=.0012$), as this phenomenon was observed in patients. Because the group×area interaction was significant, we further evaluated the differences between flow values of patients and control subjects for each of the 10 areas using Bonferroni adjustment. rCBF values were significantly inferior in patients (Table 1) for the frontal anterointernal, anteroxternal, and posteroxternal areas on the right side. Flow values in patients were superior in the posterior cortical areas on both sides, and differences with control subjects were significant in the temporo-occipital and occipital areas on the right side and in the temporal posterior, temporo-occipital, and occipital areas on the left side. No difference was observed in the lenticular nucleus and the thalamus.
A second ANOVA investigated the rCBF values in the cerebellum with one between-subjects factor (group, patients versus controls) and one within-subjects factor (side, right versus left). We found a significant main effect of the factor group ($F=4.78$, $df=1$, $P=0.009$), with rCBF values superior in patients, and a significant group $\times$ side interaction ($F=4.78$, $df=1$, $P=0.035$), with the difference between patients and control subjects more important on the left side.

We analyzed the correlations between (1) the rCBF values of the frontal areas and of the lenticular and thalamic areas and (2) the rCBF values of the frontal areas and of the temporo-occipital and occipital areas. Significant correlations (Table 2) were observed between flow values of the frontal areas and of the lenticular and thalamic areas. Correlations between rCBF values of the frontal and posterior areas were often negative (even if not significant), principally on the right side, as lower anterior flow values were associated with higher posterior values.

We investigated correlations between the severity of brain lesions and rCBF values of the posterior cerebral and cerebellar areas. Significantly positive correlations were observed between the importance of the hyper-echo on MRI in the right frontal areas and the temporal posterior, temporo-occipital, and occipital rCBF values on the same side and on the contralateral side (Table 3) but not between left-sided frontal hyperecho and posterior flow values.

We found no significant correlation between rCBF values and age of patients, presence of calcium channel inhibitor therapy, and hematocrit, nor were rCBF values correlated with type of apparatus, except in the cerebellum (right, $r=0.468$, $P=0.032$; left, $r=0.55$, $P=0.009$). Time after stroke was negatively correlated with frontal
TABLE 1. Severity of Patients' Lesions and Regional Cerebral Blood Flow Values in Each Area of Interest for Patients and Control Subjects

<table>
<thead>
<tr>
<th>Area</th>
<th>Side</th>
<th>Patients' Lesions</th>
<th>Controls</th>
<th>rCBF, mL · 100 g⁻¹ · min⁻¹</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal anterointernal</td>
<td>R</td>
<td>1.43 (1.26)</td>
<td>51.29 (17.47)</td>
<td>63.29 (9.44)</td>
<td>.009</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>1.33 (0.99)</td>
<td>58.52 (14.54)</td>
<td>65.19 (12.65)</td>
<td>.121</td>
</tr>
<tr>
<td>Frontal anteroexternal</td>
<td>R</td>
<td>1.71 (1.48)</td>
<td>41.86 (14.39)</td>
<td>52.52 (7.62)</td>
<td>.005</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>0.38 (0.57)</td>
<td>54.19 (10.77)</td>
<td>53.05 (8.22)</td>
<td>.701</td>
</tr>
<tr>
<td>Frontal posteroexternal</td>
<td>R</td>
<td>0.52 (0.85)</td>
<td>49.76 (11.57)</td>
<td>58.81 (8.11)</td>
<td>.006</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>0.05 (0.21)</td>
<td>56.57 (10.80)</td>
<td>58.71 (9.68)</td>
<td>.502</td>
</tr>
<tr>
<td>Temporal anterior</td>
<td>R</td>
<td>0.00 (0.00)</td>
<td>64.81 (13.05)</td>
<td>60.81 (10.18)</td>
<td>.275</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>0.00 (0.00)</td>
<td>67.67 (14.54)</td>
<td>60.86 (11.39)</td>
<td>.099</td>
</tr>
<tr>
<td>Temporal posterior</td>
<td>R</td>
<td>0.00 (0.00)</td>
<td>60.00 (9.12)</td>
<td>56.52 (8.88)</td>
<td>.218</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>0.00 (0.00)</td>
<td>64.52 (11.43)</td>
<td>55.19 (8.43)</td>
<td>.005</td>
</tr>
<tr>
<td>Temporo-occipital</td>
<td>R</td>
<td>0.00 (0.00)</td>
<td>50.57 (10.31)</td>
<td>44.62 (5.77)</td>
<td>.028</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>0.00 (0.00)</td>
<td>51.57 (8.27)</td>
<td>45.71 (6.17)</td>
<td>.015</td>
</tr>
<tr>
<td>Internal occipital</td>
<td>R</td>
<td>0.00 (0.00)</td>
<td>67.19 (12.61)</td>
<td>58.86 (8.45)</td>
<td>.017</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>0.00 (0.00)</td>
<td>67.57 (10.51)</td>
<td>59.00 (9.14)</td>
<td>.009</td>
</tr>
<tr>
<td>Striatal</td>
<td>R</td>
<td>0.14 (0.35)</td>
<td>68.90 (13.06)</td>
<td>64.62 (14.57)</td>
<td>.446</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>0.19 (0.39)</td>
<td>71.90 (15.25)</td>
<td>67.67 (14.16)</td>
<td>.356</td>
</tr>
<tr>
<td>Thalamic</td>
<td>R</td>
<td>0.00 (0.00)</td>
<td>65.33 (12.96)</td>
<td>64.81 (15.06)</td>
<td>.904</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>0.00 (0.00)</td>
<td>67.24 (12.89)</td>
<td>62.24 (12.50)</td>
<td>.209</td>
</tr>
<tr>
<td>Frontal superior</td>
<td>R</td>
<td>0.33 (0.78)</td>
<td>58.52 (15.00)</td>
<td>62.19 (13.63)</td>
<td>.412</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>0.38 (0.78)</td>
<td>60.33 (16.73)</td>
<td>60.62 (13.58)</td>
<td>.952</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>R</td>
<td>0.00 (0.00)</td>
<td>66.28 (13.17)</td>
<td>58.14 (10.79)</td>
<td>.034</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>0.00 (0.00)</td>
<td>68.19 (11.98)</td>
<td>57.43 (9.12)</td>
<td>.002</td>
</tr>
</tbody>
</table>

Values are mean, with SD in parentheses. Patients' lesions were scored from 0 to 4. rCBF indicates regional cerebral blood flow.

rCBF on the right side, probably because rCBF analyses with inhalation of ¹³³Xe were realized after a longer delay in patients with more severe frontal lesions.

Discussion

The rCBF drop in frontal lobes clearly predominated on the right hemisphere and extended into the postero-external frontal area. This was correlated with the T2 hyperecho areas observed by MRI, at a time when the arterial spasm of the initial stage had subsided.49 Three observations suggest that lesions and rCBF drop were for a large part associated with cerebral insult during operation: in most cases lesions predominated on the side of the anteroexternal flap, they were more severe in

TABLE 2. Correlations (r) Between Regional Cerebral Blood Flow Values of the Right and Left Hemispheres

<table>
<thead>
<tr>
<th>Area</th>
<th>Right side</th>
<th>Left side</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fai</td>
<td>Fae</td>
</tr>
<tr>
<td>Lnu</td>
<td>.477*</td>
<td>.477*</td>
</tr>
<tr>
<td>Tha</td>
<td>.330</td>
<td>.386</td>
</tr>
<tr>
<td>T-o</td>
<td>−.121</td>
<td>−.099</td>
</tr>
<tr>
<td>Occ</td>
<td>−.207</td>
<td>−.106</td>
</tr>
<tr>
<td>Lnu</td>
<td>.685‡</td>
<td>.665‡</td>
</tr>
<tr>
<td>Tha</td>
<td>.513*</td>
<td>.770‡</td>
</tr>
<tr>
<td>T-o</td>
<td>−.057</td>
<td>.442*</td>
</tr>
<tr>
<td>Occ</td>
<td>.029</td>
<td>.523</td>
</tr>
</tbody>
</table>

Fai indicates frontal anterointernal; Fae, frontal anteroexternal; Fpe, frontal posteroexternal; Fsu, frontal superointernal; Lnu, lenticular nucleus; Tha, thalamus; T-o, temporo-occipital; and Occ, occipital.

*P<.05, †P<.01, ‡P<.001.
the anterointernal area (classic territory of the anterior cerebral artery), and on transcranial Doppler the arterial spasm, when present, was most often bilateral. Most of those lesions could have been created by the pressure exerted by the surgical retractor and not by classic arterial spasm. The CBF study probably overestimated the severity of brain dysfunction because the severe flow reduction in the right posteroexternal frontal area was associated with discrete lesions on MRI.

We failed to demonstrate any reduction of rCBF values in the striatal and thalamic areas. Such a phenomenon would have been analogous to the rCBF reductions in frontal areas that have been observed in the case of anterior thalamic lesions.13 This could be explained by limitations of the SPECT technique (pixel size, slice thickness). However, significant correlations were observed between striatothalamic and frontal flow values, which could be explained by the narrow and reciprocal anatomic links between prefrontal areas and the dorsomedial nucleus of the thalamus14,15 or the striatum.

We observed an elevation of the rCBF values in the posterior cortex and cerebellum. This did not correspond to our initial hypothesis. The possibility of a methodological bias giving rise to this result may be considered but seems unlikely. Patients and control subjects were matched in a strict manner, and in a previous work16 using the same technique and the same group of control subjects, the rCBF values of patients were clearly lower than those of control subjects. Patients with cerebral lesions could also have been impaired in their ability to place themselves in a “mental rest” state compared with normal subjects; however, prefrontal involvement most often gives rise to indifference without anxiety. Another possible mechanism is an increase of rCBF values related to calcium antagonist therapy: nimodipine was shown to increase CBF of normal subjects from 3% to 12%.17 However, flow values were lower in the posterior cortical areas in patients receiving such treatment. Elevated flow values secondary to arterial spasm might also be considered, but the average poststroke delay was relatively long so that spasm had disappeared at that time. A bias due to the use of two different Tomomatic systems cannot be ruled out for the cerebellum because we observed a significant correlation between rCBF values and the type of apparatus; however, this observation could also be related to a “series effect” or to chance. Furthermore, the two systems are identical in most features, and an influence of the scanner slice thickness seems unlikely.

Another hypothesis that we would propose is that frontal structures have a physiological inhibitory influence on the activity of the posterior cortex, which could become released as a result of lesions. The frontal cortex would exert an inhibitory control on relatively automatized operations18–20 and an inhibitory-modulatory control for more complex, sequential operations.21 Luria22 considered that the frontal cortex exerts a control on the posterior systems, enabling the perception, analysis, and storage of information. Our results are also supported by the observation that a paradoxical increase of the amplitude of the primary cortical auditory and somesthetic evoked potentials has been observed in patients with prefrontal lesions.23

If the posterior and cerebellar hyperactivity is confirmed by other studies, one could consider that a remote rCBF increase could be the consequence of a localized lesion. We have previously observed a similar phenomenon at the thalamic level in a patient with a cerebellar hematoma,16 and this was also described by Sönmezoglu et al.24 Those observations suggest that the “diaschisis” concept, created and defined by Von Monakow,25 has to be reexamined. A lesion would not systematically induce remote hypoactivity (as in classic diaschisis26) but could also be the source of hyperactivity, as has been shown in humans16,24,27 and animals.28 This hyperactivity could by itself be the origin of pathological effects affecting the relation between patients and their close environment.

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