Abnormalities of Interictal Cerebral Perfusion in Classic but Not Common Migraine

Hans L. Lagrèze, MD, Christian Dettmers, MD, and Alexander Hartmann, MD

Regional cerebral blood flow (rCBF) was measured as gray matter blood flow using the $^{133}$Xe inhalation technique in 50 pain-free headache patients. Eight patients having classic migraine with normal computed tomograms were matched to patients having common migraine and to normal controls. Interictal rCBF was determined at least 6 days after the last migraine attack and more than 24 hours before the next one. There were no between-group differences for age, $P_{CO_2}$, mean hemispheric blood flow, interindividual and intraindividual variabilities, hyperfrontality, or rCBF symmetry. However, when subjects were classified as to overall abnormal perfusion, a significant number ($n=4, p<0.04$) of patients with classic migraine had rCBF abnormalities, whereas only one such patient was seen in the group with common migraine. Patients with classic migraine had abnormal mean hemispheric blood flows or disturbed intrahemispheric rCBF patterns. Oligemic and hyperemic regions topographically corresponded to the clinical symptoms in one patient. We conclude that during migraine attacks and interictally there is an instability of rCBF control in patients with classic but not common migraine. (Stroke 1988;19:1108-1111)

Regional cerebral blood flow (rCBF) undergoes significant alterations during migraine attacks.¹⁻¹¹ When headache-free, migraine sufferers are usually considered to have normal cerebral perfusion.³⁻⁶⁻⁸⁻⁹ Anecdotal reports, however, have demonstrated irregularities of interictal rCBF in patients with classic but not common migraine.¹¹⁻¹³ Recently, a systematic study of this topic showed interictal asymmetries of rCBF in patients with both types of migraine.¹⁴ To clarify these controversial issues we systematically evaluated the pertinent characteristics of cerebral perfusion in patients during the pain-free intervals of common and classic migraine.

Subjects and Methods

Using current diagnostic guidelines,¹⁵ we reviewed data of 50 patients from our headache clinic. Since we desired to achieve highly homogeneous subject groups, the following rigid exclusion criteria were applied: mixed or ambiguous diagnoses, abnormalities on cranial computed tomograms, severe electroencephalographic changes, the last migraine attack <6 days before the rCBF measurement, and the next migraine attack <24 hours after the last rCBF study. We thus identified eight patients with classic migraine and 11 with common migraine; 20 healthy members of our department served as normal controls. All subjects were normotensive and medication-free (except for occasional weak analgesics) for at least 2 weeks.

To compare interindividual variability of rCBF between groups, we needed the same number of subjects for each cohort. Therefore, eight normal controls and eight patients with common migraine were matched to the eight patients with classic migraine by measured $P_{CO_2}$ (Table 1) rather than by age and sex because this obviated the need to correct for $P_{CO_2}$ differences. We preferred this approach because the $P_{CO_2}$ response is unpredictable in a given subject¹⁶ and may be altered not only during migraine attacks¹⁷ but also interictally.¹⁸ rCBF was measured using the atraumatic $^{133}$Xe inhalation method¹⁹,²⁰ with 32 stationary detectors placed bilaterally over homologous brain regions (Cerebrograph, Novo Diagnostic Systems, Copenhagen, Denmark). The details of this technique have been reported.²¹ The computation of rCBF was based on the compartmental rCBF model. We selected $F_I$ as an index of cerebral perfusion as it represents gray matter blood flow and is more sensitive to alterations within the high-flow compartment than Risberg's ISI.²²⁻²⁴

Regions of interest (ROIs) were defined by the detector geometry (Figure 1).²¹ Mean hemispheric blood flow (hCBF) and its interindividual variabil-
TABLE 1. Data for Patients With Classic or Common Migraine and for Normal Controls

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Male</th>
<th>Pco2 (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic migraine</td>
<td>8</td>
<td>26.3±10.0</td>
<td>Female</td>
<td>6</td>
<td>34.2±4.5</td>
</tr>
<tr>
<td>Common migraine</td>
<td>8</td>
<td>36.6±11.4</td>
<td>Male</td>
<td>2</td>
<td>35.5±4.3</td>
</tr>
<tr>
<td>Normal controls</td>
<td>8</td>
<td>32.9±7.8</td>
<td></td>
<td>2</td>
<td>37.0±3.4</td>
</tr>
</tbody>
</table>

Statistics

<table>
<thead>
<tr>
<th></th>
<th>F_{2;5} = 2.30</th>
<th>\chi^2 = 5.49</th>
<th>F_{2;21} = 0.91</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability</td>
<td>p&lt;0.02</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are mean ± standard deviation; NS, not significant; \( x^* \), normal controls vs. all migraine patients as a group.

ity, expressed as the percentage coefficient of variation (CV), were calculated from the 16 detectors over each hemisphere (Table 2). The intraindividual variability of rCBF was estimated as mean CV for each hemisphere (Table 3).

The intraindividual rCBF patterns were further studied in three additional ways (Table 3). First, the anterior-posterior blood flow distribution was estimated by a hyperfrontality index (HFI) calculated as the mean of the five pairs of frontal ROIs (Fl-5) divided by the mean of the five pairs of parieto-occipital ROIs (P2-4, 01, and 02) (Figure 1). Second, we calculated symmetry ratios for each detector pair by dividing the smaller rCBF value by the larger one. Within each subject, we then counted the number of asymmetric probe pairs, defined as those with symmetry ratios outside the 99% confidence intervals for normal controls (deviation, >19.2%). The third parameter was the number of abnormal ROIs, defined as those outside the 99% confidence interval for the symmetry ratios while being outside the 99% confidence interval for the normal intrahemispheric variation (deviation of rCBF from hCBF, >21.3%).

Finally, we classified the subjects as having overall abnormal interictal perfusion when at least one of two requirements was met: hCBF outside the 95% confidence interval for normal controls (54.9-95.3 ml/100 g/min) or at least two abnormal ROIs as defined above. Two abnormal ROIs per subject were needed because three of eight normal controls had one abnormal ROI. This number is close to that expected by chance (2.56) and indicates that the normal controls were truly normal.

Confidence intervals were calculated as proposed by Matthews and Farewell.25 We preferred 99% confidence intervals when 95% intervals produced false-positive results by chance. We applied one-way analysis of variance (ANOVA) and \( F \) statistics to continuous data to test the null hypothesis that there were no between-group differences for means. We used ANOVA on the interindividual variation of hCBF expressed by the differences between group hCBF and individual hCBF. We analyzed categorical variables using contingency tables and \( \chi^2 \) statistics. The overall level of significance was \( p<0.05 \).

Results

The subjects' characteristics are listed in Table 1. Groups did not differ in age and \( \text{Pco}_2 \), but the sex distribution was different when we compared nor-

TABLE 2. Intercital Mean Hemispheric Blood Flow in Patients With Classic or Common Migraine and in Normal Controls

<table>
<thead>
<tr>
<th></th>
<th>Right mean±SD (ml/100 g/min)</th>
<th>CV (%)</th>
<th>Left mean±SD (ml/100 g/min)</th>
<th>CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic migraine</td>
<td>73.2±15.0</td>
<td>20.5</td>
<td>72.2±15.6</td>
<td>21.6</td>
</tr>
<tr>
<td>Common migraine</td>
<td>66.7±15.5</td>
<td>23.2</td>
<td>66.9±15.2</td>
<td>22.7</td>
</tr>
<tr>
<td>Normal controls</td>
<td>74.7+9.9</td>
<td>13.3</td>
<td>75.2±11.2</td>
<td>14.9</td>
</tr>
<tr>
<td>Statistics</td>
<td>( F_{2;5} = 0.78 )</td>
<td></td>
<td>( F_{2;21} = 0.71 )</td>
<td></td>
</tr>
<tr>
<td>Probability</td>
<td>NS</td>
<td></td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

SD, standard deviation; CV, coefficient of variation; NS, not significant.
normal controls with all migraine patients as a cohort ($p<0.02$). However, the sex distribution was identical in both patient groups and thus cannot explain the differences between them.

Mean hCBF was not significantly different in any group. Compared with normal controls, there was a nonsignificant trend toward higher interindividual variability of hCBF in both patient groups (Table 2). Parameters of the intrahemispheric blood flow distribution, such as intrahemispheric CV and HFI, also did not differ significantly. There were no significant differences in the number of subjects with more than one asymmetric probe pair or more than one abnormal ROI (Table 3).

When subjects were classified by overall abnormality criteria (Table 4), cerebral perfusion was abnormal in four of eight patients with classic migraine, in one of eight patients with common migraine, and in no normal controls; this difference was significant ($p<0.04$). One patient with classic migraine had elevated, another one reduced hCBF on both sides. In two patients with classic migraine the physiologic rCBF pattern was disrupted; the first had two hyperemic ROIs and one oligemic ROI within the left hemisphere (this patient suffered from right-sided hemiparesthesias at migraine onset), and in the second patient two oligemic ROIs were found over the parietotemporal regions of either side (she had transient paresthesias on the left). The patient with common migraine had slightly reduced global hCBF.

### Discussion

Comparing group means, we found no meaningful differences seemingly supporting previous notions of unaltered rCBF in headache-free migraine sufferers. However, a significant number of patients with classic migraine had abnormal interictal perfusion when classified individually.

The observed irregularities of hCBF could be interpreted as $P_{CO_2}$ effects, but all groups were matched for this factor. Alternatively, higher anxiety of patients than of controls may account for global hCBF differences. If this interpretation were true, we should have seen a significant number of patients with abnormal hCBF in not only the classic but also the common migraine group. As this was not the case, we believe that the observed hCBF differences are truly related to the disease. The salient feature of classic migraine, however, was the disruption of the intrahemispheric regional blood flow pattern. Due to the low spatial resolution of our system we could topographically correlate rCBF abnormalities and neurologic symptoms in only one patient. Since subjects with structural central nervous system changes were excluded, we feel safe concluding that our findings indicate a functional disturbance of interictal cerebral perfusion.

Methodology may explain why we found a significant number of patients with classic migraine who had abnormal perfusion while others have not. Some authors used very small cohorts, and others pooled data from classic and common migraine so that specific alterations might have been obscured. Also, the slight rCBF abnormalities of classic migraine went unnoticed when we compared group means. The large physiologic intersubject variability of rCBF may account for this effect. Lauritzen et al. observed abnormal interictal rCBF in just one of 11 patients with classic migraine. These authors used single-photon emission tomography (SPECT), which, due to its low spatial resolution, is insensitive to rCBF changes within the thin cortical mantle. Böttger et al. found more abnormal interictal SPECT scans in patients with classic migraine when higher photon energy was used for nonquantitative rCBF imaging.

Statistical rigor ensured that there were no false-positive results. Therefore, we believe that our systematic study provides valid evidence to support the anecdotal reports of rCBF abnormalities in patients with classic migraine. As to common migraine, we fully agree with other authors.

### Table 3. Interictal Patterns of Regional Cerebral Blood Flow in Patients With Classic or Common Migraine and in Normal Controls

<table>
<thead>
<tr>
<th>Region of Interest</th>
<th>Classic migraine</th>
<th>Common migraine</th>
<th>Normal controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right CV (%)</td>
<td>$11.0 \pm 1.3$</td>
<td>$11.2 \pm 3.3$</td>
<td>$10.9 \pm 4.0$</td>
</tr>
<tr>
<td>Left CV (%)</td>
<td>$11.1 \pm 4.5$</td>
<td>$9.1 \pm 2.8$</td>
<td>$11.7 \pm 4.1$</td>
</tr>
</tbody>
</table>

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### Table 4. Classification of Patients With Classic or Common Migraine and Normal Controls by Abnormality Criteria

<table>
<thead>
<tr>
<th>Category</th>
<th>Normal</th>
<th>Abnormal*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic migraine</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Common migraine</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Normal controls</td>
<td>8</td>
<td>0</td>
</tr>
</tbody>
</table>

*Abnormal mean hemispheric blood flow or $>1$ abnormal region of interest. $\chi^2_0 = 6.57; p<0.04$. 
that there are no relevant rCBF disturbances during headache-free intervals.

Our data do not contribute to the current controversy on the pathogenesis of migraine.\textsuperscript{27-30} We cannot determine whether the observed rCBF abnormalities are related to the cause or to the effects of classic migraine. In either case, however, we concur with Levine et al\textsuperscript{14} that the abnormalities reflect an instability of rCBF control. This hypothesis is further substantiated by the fact that antivasoconstrictive agents, such as calcium entry blockers,\textsuperscript{31-33} not only seem to normalize interictal rCBF\textsuperscript{12} but also effectively prevent migraine attacks.\textsuperscript{34,35}

During migraine episodes, rCBF changes occur in patients with classic but not common migraine\textsuperscript{8-11}; the same appears to be true for the headache-free interval. It still remains to be established, however, whether the two types of migraine differ on pathophysiologic grounds\textsuperscript{11} or whether they just represent two clinically distinct components of the same disease spectrum.

Acknowledgment

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References

6. Sakai F, Meyer JS: Regional cerebral hemodynamics during chronic and cluster headaches measured by the \textsuperscript{133}Xe inhalation method. \textit{Headache} 1978;18:122–132
27. Olesen J: The ischemic hypothesis of migraine. \textit{Arch Neurol} 1987;44:321–327
29. Hachinski V: The nature of migraine (editorial). \textit{Arch Neurol} 1987;44:327

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