Cerebral Oxygen Extraction, Oxygen Consumption, and Regional Cerebral Blood Flow During the Aura Phase of Migraine

Lars Friberg, MD; Jes Olesen, MD, PhD; Niels A. Lassen, MD, PhD; Tom Skyhøj Olsen, MD, PhD; Agnete Karle, MD

**Background and Purpose** The aura phase of migraine is associated with focal blood flow changes, but it has been largely unknown whether these changes are correlated to changes in the cerebral metabolism.

**Methods** Eight patients required carotid angiography for evaluation of transient neurological attacks. Cerebral blood flow (CBF) results, angiography, and clinical observations subsequently suggested the diagnosis: migraine with aura and occasional aura attacks without headache. In the same setting the cerebral angiography was followed by four to six repeated recordings of regional CBF using the intra-arterial $^{133}$Xe injection method. Blood samples were drawn from the carotid artery and the internal jugular vein to measure oxygen extraction fraction and cerebral metabolic rate for oxygen.

**Results** The intracarotid regional CBF technique provoked aura symptoms and typical, migraine-related, posterior focal hypoperfusion in four patients, followed by typical unilateral headache in three patients. The remaining four patients had no symptoms or regional CBF changes during the examination. There was a significant increase (mean, 13%) of global oxygen extraction fraction in the four patients during aura symptoms, whereas no significant changes of oxygen extraction fraction were found in the nonsymptomatic group. The increase in global oxygen extraction fraction in the symptomatic group coincided with a drop in hemispheric $\text{Paco}_2$ (mean, 3%). Cerebral metabolic oxygen rate remained essentially unchanged, as did $\text{Paco}_2$.

**Conclusions** The data presented suggest that the focal flow reduction during the migraine-aura phase is not a secondary phenomenon of reduced cerebral metabolism. However, arteriolar vasodilatation might offer a possible explanation for the regional CBF changes observed during the migraine aura. 

(Stroke. 1994;25:974-979.)

**Key Words** • metabolism • migraine • oxygen • cerebral blood flow

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During migraine attacks with aura, a focal reduction of regional cerebral blood flow (rCBF) has been reported, usually in the posterior aspect of one hemisphere. It is still debated whether this flow reduction is secondary to reduced cortical neuronal activity or it reflects a primary vasoconstriction. Such vasoconstriction would have to be on the level of the resistance vessels (mainly arterioles), as angiographically significant hemodynamic spasms of the large arteries have been seen only in exceptional cases during migraine attacks. Positron emission tomography would be the examination method of choice to study metabolic changes, but to our knowledge only one study of regional oxygen metabolism during migraine attacks in three patients has been performed. Of these patients, only one was studied during the aura phase. In this patient there was increased oxygen extraction in the posterior aspect of the brain where rCBF was also reduced. A primary reduction in neuronal activity lowers the metabolic demand and CBF proportionally, and oxygen extraction remains largely unaltered. In this study we measured the arteriovenous oxygen differences over the brain during migraine attacks with aura simultaneously with serial recordings of rCBF.

**Materials and Methods**

This investigation comprised eight patients, five women and three men (mean age, 40.4 years; range, 30 to 53 years) (Table 1). The patients suffered from attacks that could be classified as migraine with typical aura (classification code 1.2.1) or aura attacks without headache (classification code 1.2.5).

Before this investigation they all had experienced both types of attacks. They were submitted for cerebral angiography and rCBF examination because their neurological symptoms could not rule out that the cause of their attacks could be transient ischemic cerebral episodes. Excluded were patients in whom the angiography revealed signs of intracranial or extracranial arteriosclerosis. The protocol was approved by the Ethical Committee for Copenhagen and Frederiksberg Counties. All patients consented to participate in the scientific part of the investigation (jugular vein catheterization and collection of blood samples) after having received written and oral information. In conjunction with blood samples drawn for measurement of oxygen metabolism, we obtained blood samples analyzed for vasoactive neuropeptides from the same patient group. Results from that part of the investigation will be reported elsewhere. Information about patients is given in Table 1.

Puncture of the relevant common carotid artery was done using local anesthesia, and angiography of the carotid system and cerebral vessels was performed by administering the contrast medium through the cannula. The angiograms were...
Table 1. Patient Data and Clinical Observations

<table>
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<th>Variable</th>
<th>Patient No.</th>
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<tr>
<td>Sex</td>
<td>M</td>
</tr>
<tr>
<td>Age, y</td>
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</tr>
<tr>
<td>No. of AV samples</td>
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<tr>
<td>No. of rCBFs</td>
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<tr>
<td>Injected carotid</td>
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<td>Symptoms developed during examination</td>
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</tr>
<tr>
<td>rCBF</td>
<td>Posterior hypoperfusion</td>
</tr>
<tr>
<td>Comments</td>
<td>ICA</td>
</tr>
</tbody>
</table>

AV indicates arteriovenous; rCBF, regional cerebral blood flow; M, male; F, female; R, right; L, left; ICA, internal carotid artery; CCA, common carotid artery; and CT, computed tomography.

inspected immediately. Using the Seldinger technique, we introduced a small, soft polyethylene catheter into the internal carotid artery after the angiography. In three patients (Nos. 3, 4, and 5), it was not technically possible to introduce the catheter into the internal carotid artery; therefore, the tip of the catheter was placed in the common carotid artery 1 to 2 cm below the bifurcation. These three patients did not develop aura symptoms or migraine headache in connection with the examination (Table 1). From the angiograms it was decided which of the two internal jugular veins had the largest diameter and therefore drained the largest portion of blood from the brain. Generally, one jugular vein was considerably larger than the other. After a direct puncture using local anesthesia, the largest vein was catheterized by Seldinger technique, and the catheter was advanced proximally placing the tip of the catheter a few centimeters from the bulbus. Thus, the intracarotid and jugular vein catheters were not necessarily placed on the same side of the neck. Five to six sets of blood samples were taken simultaneously from the two catheters. The arterial sample was obtained by mounting a low-friction glass syringe on the catheter, allowing the syringe to be filled by the arterial blood pressure only. The venous samples were taken at the same rate at which the arterial syringes were filled. This procedure was carried out to ensure that there was no contamination from retrograde drawn blood.

Immediately after the cerebral angiography, we measured rCBF with the intracarotid 133Xe injection technique.11,12 133Xe was inserted into the internal carotid artery after the angiography. The first set of blood obtained for each patient (time, 0 seconds) was analyzed twice, and the mean value was used for further calculations. Hemoglobin concentrations were analyzed on the routine analyzer in the Department of Clinical Chemistry. Oxygen extraction fraction (OEF) was calculated in percent as OEF equals arterial oxygen content minus venous oxygen content. Cerebral metabolic rate for oxygen (CMRO2) was calculated as

\[
CMRO2 = Hb \cdot \text{wHb} \cdot O_2/Hb \cdot \text{rCBF} (\text{mL O}_2/100 \text{ g/min})
\]

where Hb is the hemoglobin concentration (mmol/mL), wHb is the relative weight of hemoglobin (16.125 g/mmol), O2/Hb is the relative oxygen content at 100% saturation (1.34 mL O2/g), and rCBF is the cortical mean flow (mL/100 g/min).

We chose to perform statistical analysis on calculated percent-change data after plotting both absolute-change and percent-change data versus baseline values and ensuring that the percent changes were independent of the baseline values.13 The first set of blood obtained for each patient (time, 0 minutes) was used as a baseline value. The statistical analysis was carried out on serial measurements from each patient.14,15 We analyzed the data for significant changes in the area under the curve (AUC) and maximum values on data from each series of samples (the percent changes in OEF, CMRO2, and global CBF).
patients did not develop neurological symptoms or where is the number of point measurements of oxygen
values (two unpaired samples). 18

Because the number of rCBF examinations and therefore the examination time were different from
case to case, the AUC was calculated per minute.

Statistical analysis was done by calculating 95% confidence intervals for the means and differences of AUC and maximum
values (two unpaired samples). 18

Results

Angiography did not reveal stenosis or signs of vaso-
spasm in any of the examined patients. During the rCBF
investigation four patients (Nos. 1, 6, 7, and 8) developed aura symptoms (Figure). In three of these patients
(Nos. 1, 6, and 8), aura was followed by migraine headache developing toward the end of the examination.

The attacks corresponded to the spontaneous attacks experienced by the patients. The remaining four
patients did not develop neurological symptoms or headache.

The measured and calculated values are given in
Tables 2 and 3. The relative change in global OEF, CMRO 2, PacO 2, and CBF are shown in the Figure. In
the four patients with aura symptoms, this coincided
with development of the typical focal hypoperfusion
that has been described extensively in previous publica-
tions from our group using the same rCBF method as in
this study, 2,3,6,19 rCBF in the hypoperfused region
dropped between 20% and 30%. The hypoperfused
region included most of the occipital lobe and the
posterior aspect of the parietal and temporal lobes of
the affected hemisphere. In the remaining part of the
affected hemisphere, rCBF was essentially unaffected
throughout the examination. There were no systematic
changes in PacO 2; specifically, the PacO 2 changes could
not account for the changes in global CBF. (See Table
1 for corresponding values of PacO 2 and global CBF.)

When rCBF was measured at the time the patients
were experiencing symptoms, the number of detectors
recording rCBF values ≤20% below mean hemispheric
CBF was a minimum of 32 to 43, increasing to a
maximum of 68 to 94 detectors during subsequent rCBF
recordings. Each detector covered 0.9 cm×0.9 cm=0.81
cm 2 of the outer brain surface. This corresponded to
a minimum of 26 to 35 cm 2 (13% to 17%) and a maximum
of 55 to 76 cm 2 (27% to 37%) of the outer surface of the
hemisphere.

In the four nonsymptomatic patients the rCBF distrib-
ution was normal and unchanged throughout the ex-
amination. A computed tomographic scan of patient
No. 3 revealed an infarct in the left occipital lobe; correspondingly, the patient had right-sided homony-
mous hemianopsia, which had developed in connection
with a migrainelike attack a few weeks before our
examination. This patient did not develop symptoms
during the present examination, and the rCBF pattern
was normal. The infarct was localized in the posterior
cerebral artery domain, which explains why it was not
visualized by the rCBF recording during which the flow
tracer was administered only to the anterior and middle
cerebral artery supply territories of the examined hemispheric.

As shown in the Figure, there was a significant,
systematic increase in oxygen extraction in the patients
who developed a migraine attack compared with those
who had no symptoms, while the OEF changes in the
nonsymptomatic patients were less marked and not
significant (Table 4). The mean value of maximum OEF increase was 8.3% higher (P<.0001) in the attack group than in the
nonsymptomatic group (Table 4). CMRO 2 was essen-
tially unchanged. It could be ruled out that the system-
atic global CBF decreases were caused by correspond-
ing decreases in PacO 2. We have given the measured
PacO 2 values in Tables 2 and 3. However, in this study
we have not corrected the individual CBF values for
changes in PacO 2 because the cerebrovascular CO 2
response most likely is abnormal in the region affected
by hypoperfusion during migraine aura. 3,20,21

Discussion

The present study contains important information
about changes in oxygen metabolism in the human brain
during the onset phase of migraine aura. Taking into
consideration the typical blood flow results, the normal
angiography, other laboratory investigations, and
the cerebral imaging and the subsequent course of
the patients, we can conclude that these patients in fact had
migraine with aura. The investigation provided a unique

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AUC was calculated according to Matthews et al 16 as

\[
AUC = \frac{1}{2} \sum_{i=0}^{n+1} (t_i - t_{i+1})(y_i + y_{i+1})
\]

where \( n+1 \) is the number of point measurements of oxygen
extraction, CBF, and CMRO 2, and \( y \) is the value (percent change) at the time \( t \). Because the number of rCBF examina-
tions and therefore the examination time were different from
case to case, the AUC was calculated per minute.

Statistical analysis was done by calculating 95% confidence intervals for the means and differences of AUC and maximum
values (two unpaired samples). 18

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the patients, we can conclude that these patients in fact had
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TABLE 2. Measured and Calculated Values for Four Patients Having Migraine Attack With Aura

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Symptoms*</th>
<th>CBF Time, min</th>
<th>Global OEF, %</th>
<th>Global CMRO2, mL/100g/min</th>
<th>Pco2, mm Hgt</th>
<th>Global CBF, mL/100 g/min</th>
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</tbody>
</table>

*Symptoms present during regional CBF measurement

CBF indicates cerebral blood flow; OEF, oxygen extraction fraction; CMRO2, cerebral metabolic rate for oxygen; and (Aura), aura in regression.

opportunity to record the changes from the very beginning of the attack, as the attack was triggered by the investigation procedure (most likely the cerebral angiography). The study showed that the global cerebral oxygen extraction increased during the aura phase of a migraine attack simultaneously with the development of focal hypoperfusion. CMRO2 was largely unaffected, and the CBF decrease was of the same magnitude as the OEF increase. Because the CMRO2 in brain tissue was unchanged during the aura phase, it became clear that the CBF reduction was not a phenomenon secondary to reduced oxygen metabolism.

In the one patient studied with positron emission tomography during migraine aura, the findings were focally reduced CBF, focal increased OEF, and normal focal oxygen consumption.9 Our results are in full agreement with this.

The intra-arterial procedure often triggers an attack in patients suffering from migraine with aura. Sometimes the symptoms start during the angiography but more often begin up to 1 hour after.3,6,7,16 In this study three patients had the tip of the arterial catheter placed in the common carotid artery, not in the internal carotid artery as did the remaining five patients. However, the oxygen content in the common carotid artery did not differ from that in the internal carotid artery. It is our clinical experience that attacks are more likely to precipitate when the tip of the catheter is placed in the internal carotid artery. For the purpose of measuring arteriovenous differences of oxygen content over the brain, we do think that the material can be considered homogeneous. The four patients who did not develop attacks served as control subjects.

Because of the two-dimensional nature of the detector system, the 133Xe clearance from both submerged and superficial cortical tissue is recorded as projected to the outer, spherical hemispheric surface. This is two to three times smaller than the actual surface of the folded cortical structure, and this study did not provide information on the exact anatomy of the cortical structures below the spherical surface. Second, we have only an outline of the rCBF distribution for four to six 1-minute glimpses during the whole 30- to 40-minute period over which the rCBF changes evolved. For these reasons the largest area of the cortical surface affected by hypoperfusion can only be estimated to between 20% and 40% of the total hemisphere.

Theoretically, rCBF values recorded by a common carotid artery injection tend to be lower than those after intracarotid injection because they are influenced by the slow washout of isotope distributed to extracranial structures. However, because more than 80% of the common carotid blood flow enters the internal carotid artery, the extracranial contribution to the total measured radioactivity is small. Usually, extracranial blood flow is low and approximates the levels of white matter flow.22 In this study we used the initial slope as an expression for the cortical (gray matter) rCBF; this
value greatly favors detection of high rCBF values (cortical). Therefore, the errors of the calculated rCBF values obtained in the three patients undergoing common carotid 133Xe injections are minor (underestimated less than 5%) and cannot be considered of major importance in relation to the calculations of CMRO₂.

The precise level of reduced tissue perfusion in the affected focus of the brain might not be measured correctly with the intra-arterial 133Xe injection technique. This might be partly due to some influence of scattered radiation, which tends to smooth out differences between rCBF in the hypoperfused region and normal blood flow values in the remaining normally perfused brain regions. Furthermore, there are observations indicating that tissue perfusion is not constant over time in the affected focus and that the obtained rCBF values only represent mean values over the recording time. Actually, rCBF might drop to very low

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**Table 3. Measured and Calculated Values for Four Patients Without Symptoms**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>CBF Time, min</th>
<th>Global OEF, %*</th>
<th>Global CMRO₂, mL/100 g/min†</th>
<th>P&lt;sub&gt;c&lt;/sub&gt;O₂, mm Hg*</th>
<th>Global CBF, mL/100 g/min*</th>
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*CBF Indicates cerebral blood flow; OEF, oxygen extraction fraction; and CMRO₂, cerebral metabolic rate for oxygen.*

*Measured values.*

†Calculated values.

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**Table 4. Statistical Analysis of Serial Data**

<table>
<thead>
<tr>
<th></th>
<th>Attack Mean (range), n=4</th>
<th>No Attack Mean (range), n=4</th>
<th>Difference of Means</th>
<th>95% Confidence Intervals*</th>
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<td>Global OEF, AUC/min</td>
<td>4.28 (2.9 to 4.53)</td>
<td>1.85 (0.28 to 4.45)</td>
<td>2.43</td>
<td>−0.18 to 5.04</td>
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<td>Global CMRO₂, AUC/min</td>
<td>−0.70 (−6.73 to −0.68)</td>
<td>2.39 (−0.65 to 4.30)</td>
<td>3.09</td>
<td>−8.92 to 2.74</td>
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<tr>
<td>Global CBF, AUC/min</td>
<td>−4.71 (−8.74 to −0.43)</td>
<td>−0.22 (−4.81 to 3.24)</td>
<td>−4.55</td>
<td>−9.55 to 0.58</td>
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<td>Global OEF, maximum values</td>
<td>13.1 (11.7 to 15.1)</td>
<td>5.3 (3.4 to 6.2)</td>
<td>7.8</td>
<td>5.64 to 9.87†</td>
</tr>
<tr>
<td>Global CMRO₂, maximum values</td>
<td>6.26 (−3.10 to 21.47)</td>
<td>8.68 (5.50 to 13.56)</td>
<td>−2.42</td>
<td>−14.51 to 9.67</td>
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<tr>
<td>Global CBF, maximum values</td>
<td>−0.19 (−4.08 to 0.00)</td>
<td>2.59 (−9.67 to 11.26)</td>
<td>2.78</td>
<td>−13.76 to 8.21</td>
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</tbody>
</table>

*OEF Indicates oxygen extraction fraction; CMRO₂, cerebral metabolic rate for oxygen; AUC, area under the curve; and CBF, cerebral blood flow.*

*Calculated by two unpaired samples.*

†P < .001.
(ischemic) values for short (20- to 30-second) intervals alternating with short intervals with normal rCBF values during the aura phase. 19, 21

In our calculation of global CMRO₂ changes, we have used the very robust values of measured global OEF and hemispheric mean CBF. The importance of whether rCBF is in steady state and whether the focal rCBF values were measured correctly becomes less significant to the main outcome of the current investigations. Because blood flow decrease using the hemispheric mean value and increase in OEF were roughly of equal magnitude, it can be concluded that the global CMRO₂ was normal and unchanged during attack. It must be pointed out, however, that fairly large focal changes in oxygen extraction are necessary if they are clearly reflected as changes in internal jugular venous blood. We cannot rule out small changes in local cerebral oxygen metabolism, which we could not pick up as changes in the internal jugular vein.

The repeated rCBF measurements showed that all patients in the attack group developed posterior hypoperfusion in the examined hemisphere, as reported in many previous publications.3, 5, 6, 9, 24 The moderate decrease of hemispheric CBF was a result of a more pronounced rCBF decrease in the hypoperfused region, whereas rCBF in the remaining parts of the hemisphere was unchanged. Although we did not measure the regional OEF, one interpretation of our results could be that the moderate global OEF increase might result from a more substantial OEF increase within the region affected by hypoperfusion. From the rCBF patterns it is difficult to exactly circumscribe the hypoperfused region for the reasons mentioned in the "Methods" section and because the borders of the hypoperfused zone are "blurred" due to scattered radiation. 9 We observed that between 20% to 40% of the examined hemispheres were affected by hypoperfusion during attack. This suggests that the rCBF reduction affected 10% to 20% of the total brain because the rCBF changes in the majority of aura attacks affect only one hemisphere. 25 A weighted estimate of the actual regional OEF changes within the hypoperfused region would result in a much higher regional OEF than that actually measured as a global value.

The possible conclusions from this study are: (1) Most importantly, hemispheric CMRO₂ is unchanged during the early phase of attacks of migraine with aura. Therefore, local CMRO₂ is either normal or exhibits only moderate changes that could not be picked up with the current method. (2) Marked focal reduction of rCBF during attacks of migraine with aura is due to vasoconstriction and is not secondary to decreased metabolism. (3) One interpretation of the data could be that the global OEF changes observed during attack reflected increased focal OEF in the hypoperfused focus, indicating that true rCBF in this focus approached lower values than were actually measured with the \(^{133}\text{Xe}\) clearance technique.

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