Cerebrovascular CO₂ reactivity in migraine: assessment by transcranial Doppler ultrasound

C. Hater¹,² and R. von Kummer²

¹Department of Neurosonology, The Bowman Gray School of Medicine, Winston-Salem, North Carolina, USA
²Department of Neurology, University of Heidelberg, Heidelberg, Federal Republic of Germany

Received January 22, 1990 / Received in revised form June 15, 1990 / Accepted September 17, 1990

Summary. Cerebrovascular reactivity to CO₂ inhalation was studied by transcranial Doppler sonography in 30 patients with classic or common migraine and 39 healthy controls without clinical or ultrasonic signs of arteriosclerosis. Systolic and diastolic Doppler frequencies of the middle cerebral artery were plotted against end-tidal CO₂ partial pressure; the reactivity index (I × R) was defined as relative frequency change during a PCO₂ increase of 5 mmHg. In the normal subjects, I × R was 20.0 ± 6.3 for systolic velocities, and 26.0 ± 8.2 for diastolic values. Migraineurs during their headache-free interval had significantly higher I × R values on the affected side (mean: 41.6 systolic, 61.2 diastolic), compared with either controls (P < 0.01) or the contralateral side (mean: 28.3 systolic, 30.8 diastolic; P < 0.01). During the headache attack, CO₂ reactivity was significantly lower than normal only for systolic velocities (mean: 8.3; P < 0.05). Increased CO₂ reactivity is thought to be one phenomenon of migraine. Transcranial Doppler CO₂ testing of cerebrovascular reactivity is a reliable method that may be of interest for the diagnostic evaluation and management of migraine patients.

Key words: Migraine - Transcranial Doppler ultrasound - Cerebrovascular reactivity - Carbon dioxide

Introduction and literature review

Because of the largely unknown pathophysiology of migraine, the array of therapeutic approaches proposed for its prophylactic interval treatment is more remarkable for diversity than for results. Drugs that are used include ergot derivatives, β₂-receptor blockers, platelet antagonists, Ca channel blockers, and monoamine oxidase inhibitors. The response to these various treatments is highly individualized, and the effect of the drugs is difficult to assess.

Transcranial ultrasonic (TCD) CO₂ testing of cerebrovascular reactivity, first described by Markwalder et al. [8], is a simple, completely non-invasive method for determination of the capacity of the cerebral resistance vessels to react to changes of arterial CO₂ partial pressure (P₉CO₂) with dilatation or constriction, giving a measure of their residual autoregulatory capacity. In the literature, there are two concepts for assessing cerebrovascular reactivity by TCD: Ringelstein et al. [9] determined the whole extent of CO₂ regulation, whereas Widder et al. [13] scored a "normalized autoregulatory response", defined as relative increase of mean flow velocity during a moderate hypercapnia from 40 to 46.5 mmHg.

According to the vascular concept of migraine, the attack itself is associated with changes in the intra- or extracranial arteries. Lauritzen [5, 6] and Lauritzen et al. [7] stated that reactivity to changes of P₉CO₂ and to mental activation is reduced, whereas blood pressure regulation is normal. During the attack-free interval, an increased CO₂ reactivity has been reported by Sakai and Meyer [10], who presented regional cerebral blood flow (rCBF) measurements in 79 patients, and by Thomas and Harpold (poster presentation at the 1987 meeting of the American Neurological Association, San Francisco) who reported ultrasonic CO₂ testing in 10 patients. Thie et al. [11] detected vasospasms during and after the migraine attack in three patients by TCD, without, however, correlating angiographic findings, and with normal response to hyperventilation.

The purpose of this study was to determine whether changes in CO₂ reactivity can be consistently recognized in affected patients by means of transcranial Doppler ultrasound.

Materials and methods

Since a modification of the method suggested by Widder et al. [13] revealed normally distributed reactivity index values in a healthy
Table 1. Systolic and diastolic reactivity index values (I × R) of the middle cerebral arteries ipsi- and contralateral to the headaches of migraine patients and age- and sex-matched controls

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>I × R-systolic</th>
<th>I × R-diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Standard deviation</td>
<td>Median</td>
</tr>
<tr>
<td><strong>Between attacks</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>32</td>
<td>41.6</td>
<td>14.5</td>
</tr>
<tr>
<td>Contralateral</td>
<td>18</td>
<td>28.3</td>
<td>8.4</td>
</tr>
<tr>
<td>Controls</td>
<td>32</td>
<td>20.6</td>
<td>6.5</td>
</tr>
<tr>
<td><strong>During attacks</strong></td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>7</td>
<td>8.3</td>
<td>4.8</td>
</tr>
<tr>
<td>Contralateral</td>
<td>3</td>
<td>14.3</td>
<td>2.4</td>
</tr>
<tr>
<td>Controls</td>
<td>7</td>
<td>17.1</td>
<td>4.8</td>
</tr>
</tbody>
</table>

Population [14], the index of reactivity (I × R) was determined in the following way:

1. Continuous insonation of the middle cerebral artery (MCA) at a depth of 50–55 mm through the temporal squama (transcranial ultrasound device TC 2-64, EME, Uberlingen, FRG).

2. Continuous measurement of end-tidal CO2 partial pressure (PETCO2) by infrared analysis (capnometer LB 2 of Sensor Medics, Essen, FRG).

3. Reading of the “normal” PETCO2 (PECO2N) of the individual patient, and reading of systolic and end-diastolic TCD frequencies (F).

4. Induction of moderate hypercapnia by application of Carbogene gas (5% CO2, 95% O2); reading of varied PETCO2 (PErCO2w, R) and varied TCD frequencies (FVAR) after a steady state over five heart and breathing cycles was reached.

5. Control of TCD frequencies and blood pressure in a second normocapnie steady state.

6. Calculation of reactivity index for both systolic and diastolic frequencies. I × R = percent increase of TCD frequencies during a PETCO2 increase of 5 mmHg:

\[
I \times R = \frac{(F_{VAR} - F_{S})}{F_{S}} \times \frac{500 \times (PCO2_{VAR} - PCO2_{N})}{(PCO2_{VAR} - PCO2_{N})}
\]

We did not measure TCD frequencies during hypocapnia because we found that readings during voluntary hyperventilation are less reliable than those during CO2 breathing [2].

We studied 30 non-treated patients clinically diagnosed as having classic or common migraine. Twenty-five patients (8 males, 17 females; aged 19–56 years, mean 38.8 years) were examined during a headache-free interval (subgroup 1); the other 5 patients (1 male, 4 females); aged 23–54 years, mean 38.8 years) underwent TCD CO2 testing during an acute headache attack (subgroup 2). Extracranial Doppler studies were performed in all patients in order to exclude cerebrovascular obstructive disease.

In 18 patients of subgroup 1, who had consistently unilateral headaches, we compared the reactivity of the MCA ipsilateral to the headaches with that of the contralateral, presumably normal MCA.

In both subgroups, 32 (group 1) and 7 (group 2) affected vessels were compared with the MCA of 39 age- and sex-matched healthy controls.

Data were statistically analysed by the Wilcoxon signed-rank test.

Results

In the two control subgroups, CO2 reactivity values were 20.0, SD 6.3 (range: 6.8–32.2) for systolic values, and 26.0, SD 8.2 (range: 14.7–44.2) for diastolic values.

During the attack-free interval (Table 1, Fig. 1), the CO2 reactivity of the ipsilateral MCA was 41.6, SD 14.5 (range: 18.3–78.4), and 61.2, SD 27.4 (20.4–120.5), for systolic and diastolic calculations, respectively. The contralateral MCA had a reactivity of 28.3, SD 8.4 (systolic frequencies) and 30.8, SD 6.8 (diastolic values). Analysis by the Wilcoxon test revealed for both systolic and diastolic reactivity index values significant differences between patients and controls (P<0.01), and also between the ipsi- and contralateral MCA of the same patients (P<0.01).

During the headache attack (Table 1, Fig. 2), index values ranged from 2.7 to 17.7 (mean: 8.3) for systolic readings, and from 9.1 to 50.6 (mean: 17.8) for diastolic readings. A significant difference between patients and controls was only seen for index values based on systolic TCD readings (P<0.05). Because of the small number of patients with unilateral headaches in this group we were not able to compare the ipsi- and the contralateral MCA.

The underlying absolute Doppler frequencies and the “normal” PETCO2 values were similar in all patients and controls (PCO2: 32.5–43.8 mmHg; mean: 39.6; systolic diastolic: 1.1/0.5–3.4/1.5 kHz, mean 2.6/1.0). After variation of the CO2 concentration of the breathing gas PETCO2 and TCD values reached a new steady state after 1.5–3.5 min in both patients and controls.

Discussion

Only the relative CO2 reactivity is constant in various regions of the central nervous system, whereas the absolute responses are greater in better perfused areas and vice versa [3]. To avoid confusion, the CO2 reactivity should be determined in relation to a definite CBF or velocity value [1, 3]. In a former study, however, measuring and calculating with frequencies at identical PETCO2 levels, i.e. 40 and 45 mmHg in all patients, revealed only a poor correlation with a standard normal distribution [14]. In this report, CO2 reactivity was determined by relating the hypercapnic MCA Doppler frequencies to those at the “normal” PETCO2 of the individual patient, which provides a normal distribution in a control population.