Cerebral Blood Flow in Migraine Accompaniments and Vertebrobasilar Ischemia

Nabih M. Ramadan, MD; Steven R. Levine, MD; K.M.A. Welch, MD

Background and Purpose Transient neurological symptoms of brain stem or occipital lobe origin may be caused by transient ischemic attack in the vertebrobasilar territory (VB-TIA) or late-onset (or late-life) migraine accompaniment (LOMA). It is often clinically difficult to distinguish between VB-TIA and LOMA.

Methods Cerebral blood flow of 23 patients with VB-TIA, 24 with LOMA, and 28 age-matched control subjects was measured using the $^{133}$Xe inhalation regional cerebral blood flow (rCBF) technique.

Results After adjusting for differences in baseline variables such as blood pressure, hematocrit, and Pco2, patients with VB-TIA had (1) lower mean rCBF than control subjects (P<.003) as measured by the initial slope index method; (2) more frequent anterior rCBF asymmetries than control subjects and patients with LOMA (P<.03 for both comparisons); and (3) higher mean interhemispheric rCBF differences compared with patients with LOMA (P=.08) and control subjects (P<.02).

Conclusions Regional CBF patterns in patients with VB-TIA and LOMA differ, with lower rCBF and more asymmetry of the anterior blood flows in patients with VB-TIA, probably reflecting the effects of stroke risk factors on the cerebral circulation. Patients with LOMA have rCBF patterns more closely resembling those of age-matched healthy subjects. rCBF measurements may assist in the clinical diagnosis of VB-TIA and late-onset migrainous events. (Stroke. 1994;25:1219-1222.)

Key Words • cerebral blood flow • cerebral ischemia, transient • migraine

cerebral blood flow (rCBF) is safe and noninvasive8 and can detect areas of cerebral oligemia or ischemia.9 Because VB-TIA is related to cerebral ischemia, whereas LOMA is presumably induced by neuronal dysfunction unrelated to cerebral ischemia, $^{133}$Xe rCBF may be useful in differentiating between the two conditions when the clinical distinction is difficult. We therefore evaluated whether $^{133}$Xe rCBF patterns differ between LOMA and VB-TIA.

Subjects and Methods

Patient Population

Twenty-three of a total of 91 patients who were diagnosed with VB-TIA and had undergone an rCBF study were randomly chosen from the Henry Ford Hospital Stroke Data Bank. We also selected from our CBF data bank all 24 consecutive patients with LOMA. Twenty-eight healthy volunteers served as control subjects. VB-TIA was clinically diagnosed according to the criteria published in a special report from the National Institute of Neurological Disorders and Stroke.10 The diagnosis of LOMA was made according to the criteria of the International Headache Society (IHS)11 (migraine aura without headache, IHS 1.2.5). In addition, patients with LOMA had to be older than 45 years and without clinical or neuroradiological (cranial computed tomography or magnetic resonance imaging) evidence of cerebral infarction in the territory of the posterior cerebral circulation.

Regional Cerebral Blood Flow Measurements

Regional CBF was measured by the $^{133}$Xe inhalation technique,8 using sixteen 3/4 x 3/4-in. NaI scintillating detectors with 1 x 3/4-in. collimation. The detectors were placed against the subject's head in a hemispheric array of contralaterally symmetrical pairs. Six probe pairs were located anteriorly, and two were posterior. After 1 minute of inhalation of a mixture of air and a trace amount of radioactive $^{133}$Xe, the cerebral washout curves were followed for approximately 14 minutes. Ten-minute portions of the washout curves were used as a
response function, with the end-tidal trace of radioisotope in expired air as the input function. The flow values of a two-compartment cerebral clearance curve (start-fit time when air function reached 20% of peak value) were estimated by a maximum likelihood procedure. Estimates produced by this procedure are within a few percent of the more commonly used unweighted least-squares procedures. A partition coefficient of approximately .83 was used and adjusted for hematocrit. Flow values obtained with this model correspond to values obtained using the $^{133}$Xe intracarotid injection technique.

The initial slope index (ISI) method of Risberg et al. related to the fast clearance rate of the indicator from gray matter corrected for recirculation, was used for rCBF measurements. Regional interhemispheric flow difference (rIFD) was calculated as

\[ rIFD = \frac{|ISI_1 - ISI_2|}{(ISI_1 + ISI_2)/2} \times 100 \]

where ISI$^1$ indicates right ISI and ISI$^2$, left ISI. In 20 young control subjects, the mean $\pm 2$ SDs of rIFD was less than 7%, as previously reported. Therefore, we considered an rIFD greater than 7% asymmetrical; if the value exceeded 10%, we considered it a major asymmetry. Mean interhemispheric flow difference (mIFD) was calculated as

\[ mIFD = \frac{|\Sigma ISI_1 - \Sigma ISI_2|}{(\Sigma ISI_1 + \Sigma ISI_2)/2} \times 100 \]

All rCBF studies were performed in a semidark and quiet room with the subjects in the supine position. Studies were performed at least 48 hours after an iucus, migraine, or transient cerebral ischemia. All medications were withheld for at least 12 hours before the rCBF study. Blood pressure (BP) and hematocrit were also measured in all patients and control subjects. End-tidal P$_{CO_2}$ was measured, but arterial P$_{CO_2}$ was not.

**Statistical Analysis**

ANOVA was used for the comparison of mean ISI values and mIFD between the three study populations. The Wilcoxon two-sample $t$ test was used to compare the groups for regional asymmetries. Fisher's exact test was performed to evaluate sex differences between groups. Because rCBF may vary with age, sex, P$_{CO_2}$, hematocrit, and BP, ANCOVA was used to adjust for group differences with respect to baseline parameters.

**Results**

The demographic and baseline variables for the three study populations are shown in Table 1. The mean age of the three groups was not significantly different. However, there were more women in the LOMA group than in the other two groups. Patients with VB-TIA had lower systolic BP values than the BP of control subjects ($P<.09$, sex-adjusted $P<.07$) and that of patients with LOMA ($P<.004$, sex-adjusted $P<.06$). The mean hematocrit was significantly lower (sex-adjusted $P<.007$) in the LOMA group (40±2%) than in control subjects (44±3%). End-tidal P$_{CO_2}$ values (Table 1) in patients with VB-TIA were lower than those of control subjects ($P<.05$, sex-adjusted $P<.04$) but similar to the mean P$_{CO_2}$ of patients with LOMA.

Regional CBF profiles of the three groups are shown in Table 2. The mean ISI of the VB-TIA group was lower than the mean ISI of patients with LOMA ($P<.02$; $P<.90$, adjusting for differences in BP, P$_{CO_2}$, sex, and hematocrit) and that of control subjects ($P<.0003$; adjusted $P<.003$). Seventy-nine percent of patients with LOMA, 78% of the VB-TIA group, and 75% of control subjects had at least one regional probe-pair asymmetry ($rIFD >7\%$). However, 22% of patients with VB-TIA had four or more probe pairs with rIFDs greater than 7%, compared with none of the patients with LOMA ($P<.03$). No difference was found between the three groups when the total number of asymmetrical probe pairs was less than 4. When the three groups were compared with respect to any major ($rIFD >10\%$) interhemispheric flow differences, 53% of patients with VB-TIA, 38% of those with LOMA, and 25% of control subjects had at least one probe pair with major asymmetry. The difference was not significant between LOMA and VB-TIA groups and was of borderline significance ($P<.08$) between VB-TIA and control subjects. On evaluation of the distribution and the total number of probe pairs showing major asymmetry in each group, patients with VB-TIA had a larger number of probe pairs with major asymmetry compared with control subjects ($P<.03$) and patients with LOMA ($P<.08$). In addition, patients with VB-TIA had more major asymmetry of the anterior probes (1 through 6, 9 through 16) compared with patients with LOMA ($P<.03$) and control subjects ($P<.03$); 52% of the VB-TIA group, 25% of the patients with LOMA, and 25% of control subjects had at least one major asymmetry of the anterior probe pairs. Both control subjects and patients with LOMA had either no or only one anterior probe pair with rIFD exceeding 10%. In contrast, 21% of patients with VB-TIA had two or more anterior probe pairs with rIFD values exceeding 10%. The frequency of posterior probe-pair asymmetries was not different between groups.

The mean mIFD (Table 2) of patients with VB-TIA was higher (5.39±0.51) than that of patients with LOMA (3.75±0.21) and that of the control group (3.90±0.28).

**Table 1. Demographics and Baseline Variables**

<table>
<thead>
<tr>
<th>Group</th>
<th>LOMA</th>
<th>VB-TIA</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>24</td>
<td>23</td>
<td>28</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>65 (9)</td>
<td>65 (8)</td>
<td>65 (7)</td>
</tr>
<tr>
<td>% Female</td>
<td>87</td>
<td>35</td>
<td>57</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>40 (2)</td>
<td>41 (9)</td>
<td>44 (3)</td>
</tr>
<tr>
<td>P$_{CO_2}$, mm Hg</td>
<td>32 (5)</td>
<td>32 (3)</td>
<td>34 (4)</td>
</tr>
<tr>
<td>BP, mm Hg</td>
<td>82 (7)</td>
<td>84 (10)</td>
<td>83 (10)</td>
</tr>
</tbody>
</table>

LOMA indicates late-onset migraine accompaniment; VB-TIA, transient ischemic attack in the vertebrobasilar territory; and BP, blood pressure. Numbers in parentheses are SD.

*P<.001 LOMA vs VB-TIA, P<.04 LOMA vs control subjects, P>.16 VB-TIA vs control subjects.
$P>.07$ VB-TIA vs control subjects.
$P>.14$ VB-TIA vs control subjects.
$P>.51$ LOMA vs VB-TIA, P>.23 LOMA vs control subjects, P>.05 VB-TIA vs control subjects.
$P>.04$ LOMA vs VB-TIA, P>.81 LOMA vs control subjects, P>.09 VB-TIA vs control subjects.
Table 2. Cerebral Blood Flow Profiles

<table>
<thead>
<tr>
<th>Group</th>
<th>LOMA</th>
<th>VB-TIA</th>
<th>C</th>
<th>LOMA vs VB-TIA</th>
<th>LOMA vs C</th>
<th>VB-TIA vs C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ISI</td>
<td>44.99</td>
<td>39.88</td>
<td>47.71</td>
<td>&lt;.02/NS*</td>
<td>NS/&lt;.03*</td>
<td>&lt;.0003/-.003*</td>
</tr>
<tr>
<td></td>
<td>(1.48)</td>
<td>(1.38)</td>
<td>(1.31)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rIFD &gt;7%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;0 pp, %</td>
<td>79</td>
<td>78</td>
<td>75</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>&gt;3 pp, %</td>
<td>0</td>
<td>22</td>
<td>7</td>
<td>&lt;.03</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>rIFD &gt;10%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;0 pp, %</td>
<td>38</td>
<td>53</td>
<td>25</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>1 pp, %</td>
<td>0</td>
<td>30</td>
<td>7</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Mean mIFD</td>
<td>3.75</td>
<td>5.39</td>
<td>3.90</td>
<td>&lt;.07/&gt; .07*</td>
<td>NS</td>
<td>&lt;.02/-.02*</td>
</tr>
<tr>
<td></td>
<td>(0.21)</td>
<td>(0.51)</td>
<td>(0.28)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LOMA indicates late-onset migraine accompaniment; VB-TIA, transient ischemic attack in the vertebrobasilar territory; C, control; ISI, initial slope index; rIFD, regional interhemispheric flow difference; pp, probe pair; and mIFD, mean interhemispheric flow difference. Numbers in parentheses are SEM.

*P adjusted for group differences in sex, blood pressure, Pco2, and hematocrit; NS = P > .1.

Discussion

Our data suggest that patients with VB-TIA have (1) reduced rCBF and (2) asymmetrical CBF, both interhemispheric and in the anterior carotid circulation, compared with patients with LOMA. These rCBF profiles support the hypothesis that patients with VB-TIA have rCBF patterns that differ from those of patients with LOMA.

The reduction of CBF in VB-TIA is diffuse and occurs in both anterior and posterior cerebral circulations. This is probably because VB-TIA is symptomatic of multifocal cerebrovascular disease, most likely atherosclerotic, which involves the carotid as well as the vertebrobasilar circulation. This cerebral hypoperfusion is likely a reflection of (1) decreased metabolic demand as a result of reduced cerebral tissue mass from silent and/or symptomatic infarction and (2) decreased arterial supply secondary to diffuse cerebral vessel (large and/or small) occlusive disease.

Young patients with migraine studied interictally have reduced rCBF. Posterior rCBF asymmetries and elevated mean asymmetry scores are also observed. In contrast, our results have shown that CBF studies of patients with LOMA do not demonstrate either hemispheric or regional asymmetries. Although CBF decreases with age, the rate of CBF decrease is slower in migraineurs than in age-matched control subjects, and the rCBF asymmetries that are observed in the young migraine population tend to disappear with age.

Our study has several limitations. First, patients with LOMA entered into the study were not randomly selected for rCBF evaluation, unlike the patients with VB-TIA. This difference in selection could introduce a systematic bias in the comparison of the two groups. To randomly select patients with LOMA for rCBF evaluation, a large number of patients with this condition need to be studied, an impractical consideration because of the relative rarity of LOMA compared with VB-TIA. Second, only one patient with LOMA underwent cerebral angiography (no atherosclerotic or occlusive disease was found in the posterior circulation), and therefore we could have diagnosed LOMA in patients with atherosclerotic disease of the vertebrobasilar system. We have relied on the clinical situation, a normal neurological examination, and a normal neuroimaging study to diagnose LOMA. Thus, those patients with coexisting vertebrobasilar disease and LOMA were more likely included in the VB-TIA group. Despite our inclusion bias, which skews against finding an rCBF difference between groups, we observed distinctly different rCBF profiles in patients with LOMA and VB-TIA. Third, with the intent of using noninvasive procedures, we measured end-tidal, not arterial, Pco2 during the rCBF testing and found no statistically significant differences between the three groups. Although arterial Pco2 is known to affect CBF, the error in measuring end-tidal Pco2 would be consistent in all three groups, and therefore it is unlikely that the results would have been changed by arterial Pco2 measurements.

This preliminary report suggests that the 133Xe rCBF patterns may be different for LOMA and VB-TIA. These differences could be helpful when the clinical features of LOMA and VB-TIA are similar or difficult to distinguish for a given patient. Furthermore, distinguishing between these two conditions has significant prognostic implications, since the natural history of the former is more benign. A prospective study of the predictive value of 133Xe rCBF profiles in differentiating between VB-TIA and LOMA will be necessary to establish the clinical utility of 133Xe rCBF in these conditions.

Acknowledgments

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References


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