Reactivity of Cerebral Blood Flow to Carbon Dioxide in Various Types of Ischemic Cerebrovascular Disease: Evaluation by the Transcranial Doppler Method

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Background and Purpose: The response of cerebral blood flow to changes in the arterial carbon dioxide partial pressure (i.e., carbon dioxide reactivity) has been evaluated as a parameter of cerebral perfusion reserve in patients with cerebrovascular disease. In this study, variations in this reactivity in various ischemic cerebrovascular diseases were evaluated by a newly established method, a transcranial Doppler technique.

Methods: Thirty-three patients with symptomatic cerebrovascular disease, 13 patients with asymptomatic cerebral infarction, and 25 age-matched normal control subjects were investigated. The symptomatic patients were divided into three groups; those with unilateral carotid artery obstruction, those with cortical infarction, and those with lacunar infarction. The carbon dioxide reactivity of each subject was determined by simultaneously measuring the mean spatial Doppler frequency in the middle cerebral artery and the end-tidal carbon dioxide partial pressure under normocapnic, hypocapnic, and hypercapnic conditions.

Results: In the patients with carotid obstruction, the carbon dioxide reactivity of the hemisphere ipsilateral to the obstruction was more impaired than the reactivity of the symptomatic hemispheres in any other group, and was significantly less than in the contralateral asymptomatic hemisphere (p < 0.01). In patients with cortical infarction, the carbon dioxide reactivity of the symptomatic hemisphere was significantly less than in normal control subjects (p < 0.05) and was also less than that of the contralateral asymptomatic hemisphere (p < 0.05). In patients with lacunar infarction, the carbon dioxide reactivity of both hemispheres was significantly less than that in normal controls (p < 0.01), although there was no difference between the symptomatic and asymptomatic hemispheres. In patients with asymptomatic infarction, the carbon dioxide reactivity was also less than that in normal controls (p < 0.01).

Conclusions: The carbon dioxide reactivity of cerebral blood flow measured by this transcranial Doppler technique may be useful for characterizing the hemodynamic changes that occur in various types of ischemic cerebrovascular disease. (Stroke 1993;24:670–675)

Key Words • carbon dioxide • cerebral blood flow • cerebrovascular disorders • ultrasonics

Carbon dioxide is a potent cerebral vasomotor agent that plays a significant role in the dynamic regulation of blood flow in accordance with changes in regional metabolic demands that occur with variations in neuronal activity. Thus, the cerebral vasomotor response to changes in the arterial CO₂ partial pressure (PaCO₂) usually reflects the cerebral perfusion capacity under physiological conditions and can be affected by several pathological processes related to the control of cerebral blood flow and metabolism, such as arteriosclerosis and stroke. Cerebrovascular CO₂ reactivity has been measured in stroke patients by various means, mainly involving inert gas or radioisotope techniques.¹⁻³ However, such methods are too complicated and too expensive for routine use in assessing cerebrovascular reactivity in stroke patients or patients at risk of suffering a stroke.

In recent years, transcranial Doppler velocimetry, a noninvasive and reproducible technique,⁴⁻⁵ has become available for the evaluation of changes in cerebral hemodynamics. Critical hemodynamic changes in patients with occlusive carotid lesions have been investigated by assessing the cerebral vascular response to CO₂ using transcranial Doppler sonography.⁶⁻⁷ In our previous study,⁸ we established a transcranial Doppler method for evaluating the cerebrovascular CO₂ responsiveness by the simultaneous measurement of end-tidal CO₂ partial pressure (PETCO₂) and blood flow velocity in the major basal cerebral arteries.
In the current study, using this transcranial Doppler method, we attempted to evaluate and characterize cerebrovascular CO₂ responsiveness in both the affected and nonaffected hemispheres of patients with various types of symptomatic ischemic cerebrovascular disease, including those with unilateral carotid occlusion. Further, this noninvasive method allowed us to evaluate cerebrovascular CO₂ responsiveness in an equivalent number of age-matched control subjects with and without asymptomatic cerebral infarction.

Subjects and Methods

We recruited from among inpatients and outpatients at our department (First Department of Internal Medicine, Osaka University Medical School Hospital) 33 patients with ischemic cerebrovascular accidents (CVA) and 38 age-matched subjects without CVA in whom blood flow signals from the middle cerebral artery (MCA) were detected bilaterally by transcranial Doppler and who had no chronic obstructive pulmonary disease or serious heart disease (including arrhythmias). The 38 non-CVA subjects had no history of CVA, no neurological signs, and no evidence of extracranial or intracranial stenosis of the major supra-aortic vessels as determined by duplex scanning and transcranial Doppler sonography. They were divided into 13 patients with asymptomatic infarction (confirmed by 0.1-T magnetic resonance imaging [MRI] [Siemens-Asahi Meditec Co., Tokyo]) and 25 control subjects without asymptomatic infarction.

Computed tomography (CT) and contrast angiography of the brain were performed in all CVA patients who had gone over 1 month after their first ictus. None of these patients had an exceptionally rapid onset of the CVA, occlusive lesions in the trunk of either MCA, or ulcerated plaques in the major supra-aortic vessels. MRI was also performed when no cerebral infarction was found by CT. Based on the neurological signs and the above-mentioned examinations,8–11 these patients were divided into the following three groups: those with occlusion or severe stenosis (>90% of the luminal diameter) in the unilateral common or internal carotid artery and no occlusive lesions on the contralateral side (five patients), those with symptomatic cortical infarction in the territory of the cortical branches of the MCA without major vessel obstruction (eight patients), and those with symptomatic lacunar infarction in the territory of the perforating arteries arising from the MCA without major vessel obstruction (20 patients).

The cerebrovascular response to CO₂ was measured by transcranial Doppler sonography essentially according to the procedures described by Markwalder et al12 and Ogawa et al.8 Each subject was placed in a half-sitting position, and P_{ET}CO₂ was continuously monitored with an infrared gas analyzer (model 1H26B, NEC San-ei, Tokyo). The blood flow signal from the trunk of the MCA was obtained using a transcranial Doppler velocimeter with a 2-MHz transducer (model TC2-64, Eden Medizinische Elektronik, Überlingen, FRG). The signal was analyzed with a fast-Fourier transformation wave-analysis system (Echospec, Diagnostic Electronics Corporation, Lexington, Mass.), and the mean spatial Doppler frequency was calculated. The subjects were instructed to breathe normally under normocapnic and hypercapnic (21% oxygen, 74% nitrogen, and 5% CO₂) conditions and to hyperventilate under hypocapnic conditions. In each ventilatory state, both the mean spatial Doppler frequencies and P_{ET}CO₂ were measured several times after conditions had stabilized, and normal breathing of room air was used to achieve normocapnia after hypercapnia or hypocapnia to obtain feedback about position artifacts of the probe and other factors that might affect the results (Figure 1). The mean spatial Doppler frequencies of the MCA were plotted against P_{ET}CO₂ in each steady state, and the relation between them was expressed by the following exponential equation: (mean spatial Doppler frequency)=A exp (k P_{ET}CO₂), where k was a parameter that reflected the individual CO₂ reactivity of each vessel. Figure 2 shows examples of this relation for a patient with carotid obstruction and a normal subject without cerebrovascular disease. In a separate preliminary study, we repeated the measurement of CO₂ reactivity twice in 1 day for 15 young, healthy volunteers and obtained a coefficient of variation of 9.7% for consecutive k value measurements, thus confirming that the reproducibility of this method was satisfactory.
The χ² test was used for analysis of overall differences in the incidence of each risk factor for cerebral atherosclerosis. One-way analysis of variance (ANOVA) was used for analysis of overall differences in k values among the asymptomatic hemispheres in the CVA patients and the values obtained in the non-CVA patients. When significant differences were found by ANOVA, Scheffé's test was applied to confirm the significant differences in the k values among each group. ANOVA and Scheffé's test were similarly applied to compare the symptomatic hemispheres of the CVA patients and the data of the non-CVA patients. A paired t test was employed for comparison of k values between symptomatic and asymptomatic hemispheres in patients with symptomatic cerebral infarctions. Differences were considered statistically significant when the level of confidence exceeded 95%.

Results

As shown in Table 1, there were no significant differences in age or in the incidence of several established risk factors for cerebral atherosclerosis (i.e., male sex, hypertension, diabetes mellitus, and hyperlipidemia) among each group of subjects.

Table 2 summarizes the infarcts detected by CT in the CVA patients. Of the five patients with carotid obstruction (two with ICA occlusion, two with severe internal carotid artery stenosis, and one with common carotid artery occlusion), one had no infarction and four had watershed infarcts (<5 cm in diameter) in the symptomatic hemisphere; asymptomatic deep subcortical infarcts (<1.5 cm in diameter) were also detected in two patients. The patients with cortical infarction all had small-to-moderate infarcts (<3 cm in diameter) in the symptomatic hemisphere, and three patients had additional asymptomatic deep subcortical infarcts (<1.5 cm in diameter) in the symptomatic or contralateral hemisphere. In the patients with lacunar infarction, additional deep subcortical infarcts (<1.5 cm in diameter) were often observed in both the symptomatic and contralateral hemispheres (in 11 and nine of the 20 patients, respectively). In the five CVA patients with no infarction shown by CT, MRI demonstrated small infarcts responsible for their CVA symptoms in the symptomatic hemisphere, and additional infarcts were also detected by MRI in the contralateral hemisphere of two CVA patients with lacunar infarction.

Figure 3 shows the k values of each group of subjects. The mean±SD k value of the non-CVA patients with asymptomatic infarction (0.027±0.005) was significantly lower than that of the control subjects without infarction (0.033±0.005). The k values for the symptomatic hemispheres of CVA patients were all significantly lower than those of the control subjects, and the mean k value for the symptomatic hemisphere of CVA patients with carotid obstruction (0.017±0.004) was significantly lower than that of CVA patients without carotid obstruction (0.027±0.004) in CVA patients with

Table 1. Risk Factors for Atherosclerosis in All Subjects

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>n</th>
<th>Age (years, ±SD)</th>
<th>Male (%)</th>
<th>HT (%)</th>
<th>DM (%)</th>
<th>HL (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without symptomatic infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>25</td>
<td>57.3±6.5</td>
<td>68</td>
<td>60</td>
<td>24</td>
<td>48</td>
</tr>
<tr>
<td>Asymptomatic infarction</td>
<td>13</td>
<td>59.2±8.4</td>
<td>77</td>
<td>69</td>
<td>38</td>
<td>54</td>
</tr>
<tr>
<td>With symptomatic infarction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carotid obstruction</td>
<td>5</td>
<td>60.4±6.3</td>
<td>100</td>
<td>80</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Cortical infarction</td>
<td>8</td>
<td>53.5±9.5</td>
<td>88</td>
<td>63</td>
<td>38</td>
<td>75</td>
</tr>
<tr>
<td>Lacunar infarction</td>
<td>20</td>
<td>59.6±6.8</td>
<td>95</td>
<td>60</td>
<td>45</td>
<td>55</td>
</tr>
</tbody>
</table>

n, Number of subjects. Male, HT, DM, HL: incidence of male sex, hypertension, diabetes mellitus, and hypercholesterolemia, respectively. Except for male sex, there were no significant differences among the subjects with regard to any of these factors.
TABLE 2. Detection of Infarcts by Computed Tomographic Scanning

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>None*</th>
<th>Single</th>
<th>Multiple†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Symptomatic hemisphere only</td>
<td>Bilateral hemispheres</td>
<td></td>
</tr>
<tr>
<td>Carotid obstruction</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Cortical infarction</td>
<td>8</td>
<td>0</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Lacunar infarction</td>
<td>20</td>
<td>4</td>
<td>5</td>
<td>9</td>
</tr>
</tbody>
</table>

n, Number of patients.

*MRI demonstrated small infarcts responsible for the cerebrovascular accident (CVA) symptoms in the symptomatic hemispheres.

†Infarcts other than those responsible for the CVA symptoms were all small and were found in the deep subcortical area.

both cortical and lacunar infarctions), which was not significantly different from the value in non-CVA patients with asymptomatic infarction. When the mean k value of the symptomatic hemisphere in all CVA patients without carotid obstruction was compared with that of the 38 non-CVA subjects, a significant difference was again found (0.027±0.004 and 0.031±0.006, respectively).

On the other hand, with regard to the mean k values of the asymptomatic hemispheres of the CVA patients, only the patients with lacunar infarction (0.028±0.004) had a significantly lower mean value than that of the control subjects, even though it was not significantly different from that of the non-CVA patients with asymptomatic infarction. The mean k values in the patients with carotid obstruction and in those with cortical infarction (0.028±0.009 and 0.031±0.008, respectively) were not significantly different from the value in the control sub-

jects. In addition, when the mean k value of the asymptomatic hemispheres of all CVA patients without carotid obstruction (0.029±0.006) was compared with that of the 38 non-CVA subjects, no significant difference was found.

Regarding k values for the symptomatic and asymptomatic hemispheres of the CVA patients, there were significant differences in both patients with carotid obstruction and in those with cortical infarction, whereas there was no significant difference in the patients with lacunar infarction.

Discussion

Many methods have been used to measure the vaso-
motor response of cerebral vessels to Pco2 changes (i.e., the cerebrovascular CO2 reactivity) in patients with cerebral infarction and potential impairment of the structure or function of smaller vessels that could cause a reduction in CO2 reactivity. In the present study, we used transcranial Doppler and exponential regression analysis to evaluate the cerebrovascular CO2 responsiveness of the MCA region of the brain in patients with or without CVA affecting this region. Determination of CO2 reactivity by exponential regression analysis has been performed before by conventional methods\(^ {13}\) and has been used for clinical evaluation.\(^ {14}\) Transcranial Doppler has been also used previously to measure CO2 responsiveness, but not for clinical evaluation\(^ {8,12}\) or in association with exponential regression analysis.\(^ {6,7}\)

In this study, a quantitative evaluation of CO2 reactivity by exponential regression analysis was attempted for individual patients in the clinical setting. This method has been previously proved to correlate well with conventional methods,\(^ {15,16}\) and in our experience it provides a good reproducibility when compared with that of cerebral blood flow measurements by other conventional methods.\(^ {17–19}\)
In the current study, cardioembolic infarction would be unlikely since none of the CVA patients had an exceptionally rapid onset of the ictus, ulcerated carotid plaques, or severe heart disease (including arrhythmias). Therefore, the subjects had atherothrombotic or lacunar infarction (other than cardioembolic infarction), according to the clinical classification of cerebral infarction by the National Institute of Neurological Disorders and Stroke.\textsuperscript{11}

As reported previously,\textsuperscript{2} the patients with unilateral carotid obstruction showed severely impaired CO\textsubscript{2} reactivity of the hemisphere ipsilateral to the obstruction. Transcranial Doppler assessment of the CO\textsubscript{2} responsiveness has been reported to be useful for detecting hemodynamically critical carotid stenosis and occlusion,\textsuperscript{5,7} and quantitative assessment of CO\textsubscript{2} reactivity by exponential regression analysis should also be useful for investigating hemodynamically critical carotid stenosis.

In the symptomatic CVA patients without obstruction of the carotid or basal cerebral arteries, the difference in k values between hemispheres was significant for the subjects with cortical infarction and not for those with lacunar infarction. In these two types of cerebral infarction, the cerebrovascular bed might show different patterns of impairment (i.e., local in patients with cortical infarction and diffuse in patients with lacunar infarction). Infarcts other than those responsible for the symptoms were detected by CT more often in the patients with lacunar infarction than in those with cortical infarction.

It has been reported by Yamamoto et al\textsuperscript{20} that cerebral vasomotor responsiveness to hypercarbia was reduced to a greater extent in the ischemic hemisphere than in the contralateral hemisphere, although both were impaired when compared with the response in normal healthy volunteers. Our results were largely in agreement with those of Yamamoto et al except that we could not detect impaired CO\textsubscript{2} reactivity in the asymptomatic hemisphere when compared with control subjects. This might have occurred because our control subjects had risk factors for cerebral atherosclerosis, which had impaired CO\textsubscript{2} reactivity to some extent. Nevertheless, our study newly suggested that the cerebrovascular bed was differentially impaired according to the type of cerebral infarction and that CO\textsubscript{2} reactivity determined by the transcranial Doppler method could delineate this impairment.

The patients with asymptomatic infarction were only diagnosed as having lesions by MRI and could otherwise have been regarded as normal control subjects. Despite this, their mean k value was significantly lower than that of age-matched normal control subjects. Asymptomatic infarction is more often seen in hypertensive than in normotensive individuals, and the appearance of such lesions could be associated with hypertensive damage to the cerebrovascular bed.\textsuperscript{21} The clinical significance is also uncertain; e.g., it is not clear whether these changes can be correlated with nonspecific symptoms like dizziness and headache, and it is not clear whether patients with such infarcts are likely to later develop overt CVA or dementia. Therefore, we wished to evaluate the effects of asymptomatic infarction on the cerebral circulation and so avoided selecting subjects as normal controls merely because of the absence of clinical CVA.

Various risk factors for cerebral atherosclerosis have been reported to be involved in causing impairment of the cerebrovascular bed and thus reducing CO\textsubscript{2} reactivity.\textsuperscript{20} Normal aging has been reported by some authors\textsuperscript{20,22} to have a similar effect, but it has also been reported to have no such effect.\textsuperscript{23} In this study, there was no significant difference among the subjects with regard to age or the incidence of risk factors. We were thus able to evaluate the effect of cerebrovascular disease on CO\textsubscript{2} reactivity without any influence from other factors.

In conclusion, measuring the CO\textsubscript{2} vasoreactivity by noninvasive transcranial Doppler ultrasound could document the characteristic changes in vascular reactivity in the different types of ischemic cerebrovascular disease (i.e., carotid obstruction, cortical or lacunar infarction, and asymptomatic infarction). Although patients with cardioembolic infarction and moderate or bilateral carotid stenosis were not evaluated in this study, the CO\textsubscript{2} reactivity determined by this method probably should also enable assessment of impairment of the cerebrovascular bed in such cases.

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