Evaluation of Vasomotor Reactivity by Transcranial Doppler Sonography in Patients With Acute Stroke Who Have Symptomatic Intracranial and Extracranial Stenosis

Ilkay Uzunca, MD, Talip Asil, MD, Kemal Balci, MD, Ufuk Utku, MD

Objective. In patients with large artery disease, determining the cerebral hemodynamic state and following its alterations may be a good marker for predicting long-term outcome. The aim of our study was to compare the changes in vasomotor reactivity (VMR) of patients with symptomatic intracranial and extracranial artery stenosis. We also examined whether VMR after stroke influences the long-term prognosis for these patients. Methods. Forty-one patients were included in the study. To determine the cerebral hemodynamic state, transcranial Doppler ultrasound examinations and acetazolamide tests were performed after acute stroke and repeated after 6 months. We compared the VMR on admission and at 6 months, together with changes in VMR, of the patients with symptomatic intracranial and extracranial artery stenosis. By calculating the Barthel index at 6 months, we examined whether VMR had an effect on an improvement in their quality of life. Results. We observed a significantly higher initial VMR of the ipsilateral hemisphere in patients with intracranial stenosis (22.4 ± 9.1 versus 13.4 ± 12.8; \( P = .013 \)). At 6 months, the VMR obtained from the ipsilateral hemisphere was better in patients with extracranial stenosis than in the patients with intracranial stenosis (\( P = .01 \)). The ipsilateral VMR measured on admission showed a positive correlation with the Barthel index at 6 months (\( P = .007; r = 0.434 \)). Conclusions. Our study showed that VMR in patients with acute stroke who have extracranial and intracranial artery stenosis measured by using a transcranial Doppler examination may have value in predicting long-term outcome. Key words: large artery atherothrombosis; transcranial Doppler examination; vasomotor reactivity.

Cerebral insufficiency is associated with the presence of severe stenotic disease of the carotid arteries. The risk of carotid artery stenosis increases with age. It has been reported that of the population older than 75 years, 7% of the women and 9% of the men had internal carotid artery (ICA) stenosis of more than 50%; however, of the population younger than 50 years, only 1% had ICA stenosis of more than 50%. Intracranial stenosis represents approximately 8% to 12% of all ischemic strokes.

Vasomotor reactivity (VMR) is used to evaluate cerebral perfusion reserve. Vasomotor reactivity is the capacity of cerebral circulation to respond to vasomotor stimuli and shows the vasodilator capacity of cerebral arterioles.
The association of reduced VMR with abnormal cerebral hemodynamics has been reported previously, and VMR measurements can be assessed by using positron emission tomography (PET), single-photon emission computed tomography (SPECT), magnetic resonance imaging, and transcranial Doppler (TCD) imaging. Transcranial Doppler imaging provides noninvasive, reproducible measurements and monitoring of VMR without contrast and radiation use, and the predictive value of cerebral hemodynamic testing with TCD has been shown in patients with carotid artery disease.

In this study, the VMR to acetazolamide was measured with TCD imaging in patients with intracranial and extracranial artery stenosis within 10 days after stroke onset and at 6 months, and then the initial values were compared with those obtained at 6 months. In this way, we decided to evaluate the changes in cerebral hemodynamics and the value of VMR to determine the long-term prognosis after acute stroke caused by symptomatic intracranial and extracranial artery stenosis.

### Materials and Methods

From March 2003 to September 2004, 810 patients were hospitalized with first-time ischemic stroke in the Neurology Clinic of Trakya University; 320 of these patients had acute stroke caused by large artery disease. Forty-one of these patients who met the inclusion criteria of our study, described below, were prospectively enrolled. Twenty-three of the patients had extracranial stenosis, and 18 had intracranial stenosis. The localization of atherothrombosis was evaluated with cranial and cervical magnetic resonance angiography and vertebral-carotid artery Doppler sonography. The patients who had stenosis of more than 50% in the siphon of the ICA and the middle cerebral artery (MCA) were included in the intracranial artery stenosis group. The patients who had stenosis of more than 50% in the extracranial arteries were included in the extracranial artery stenosis group. The distribution of patients according to the localization of stenosis is shown in Table 1.

We excluded patients who had the following: hemorrhagic strokes; ischemic strokes caused by something other than intracranial and extracranial stenosis; cardiac and extracardiac embolic strokes; ischemic strokes for which causes had not been determined; and poor insonation of the cranial window. We also excluded patients with intracranial and extracranial artery tandem stenosis and those with bilateral ICA stenosis. The study protocol was approved by the Clinical Research Ethics Committee of Trakya University. Written informed consent was obtained from the patients or their relatives.

The patients’ baseline information included age, sex, neurologic examination results, detailed medical history, family history of stroke, systolic and diastolic blood pressure, blood glucose values, and stroke risk factors. Routine blood biochemistry and blood count tests were performed. Cardioembolic stroke was excluded for all patients by means of a 12-lead electrocardiogram, a cardiologic examination, and a transthoracic echocardiogram. On admission to the clinic, results of the Glasgow Coma Scale and the Scandinavian Stroke Scale were recorded; at 6 months, the Barthel index (BI) was recorded for all patients.

### Transcranial Doppler Examination

The TCD imaging study was performed with the patient lying supine after a 10 minute rest. A Multidop X4/TCD8 transcranial Doppler machine (DWL Elektronische Systeme GmbH, Sipplingen, Germany) was used for recording. The TCD examinations were performed with 2-MHz pulsed Doppler transducers with fixed probes on the bilateral temporal bones. Bilateral MCAs were insonated (power, 100 sample; volume, 13; gain, 8). Systolic blood flow velocity (SBFV), diastolic blood flow velocity (DBFV), mean blood flow velocity (MBFV), and pulsatility indices were recorded from bilateral MCAs. The pulsatility index was calculated by using the formulation of Gosling et al.

<table>
<thead>
<tr>
<th>Table 1. Distribution of Patients According to the Localization of Stenosis</th>
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</thead>
<tbody>
<tr>
<td>Extracranial ICA stenosis                  23</td>
</tr>
<tr>
<td>Intracranial ICA stenosis                   3</td>
</tr>
<tr>
<td>Intracranial MCA stenosis                   15</td>
</tr>
<tr>
<td>Total                                        41</td>
</tr>
</tbody>
</table>

Stenosis of all patients was between 50% and 99%. There was no contralateral stenosis or tandem stenosis.
Blood pressure and pulse rates were recorded during the TCD procedure. The SBFV, DBFV, MBFV, and pulsatility indexes of bilateral MCAs were recorded 20 minutes after the patients received intravenous administration of 500 mg of acetazolamide, and heart rate and arterial blood pressure values were measured again.

Vasomotor reactivity was calculated as the percentage change of MBFV by means of the formula described in previous studies \[ \frac{100 \times (MBFV_2 - MBFV_1)}{MBFV_1} \]11–13, where MBFV1 was MBFV obtained from MCA during rest, and MBFV2 was MBFV obtained from MCA 20 minutes after acetazolamide infusion. As described in previous studies, an increase of more than 30% in VMR was accepted as normal; less than 30% was considered abnormal.13

A TCD evaluation was performed within 10 days after stroke onset. The VMR of 41 patients was calculated from ipsilateral and contralateral hemispheres, and the patients were divided into 2 groups according to normal and abnormal VMR results. Compression tests were performed on the patients to determine whether the circle of Willis was complete or incomplete. The VMR values of the contralateral and ipsilateral hemispheres were recalculated at 6 months, the BI results were obtained, and then the initial VMR values were compared with the values obtained at 6 months.14

Statistical Analysis
An independent \( t \) test was used to compare the VMR obtained from the ipsilateral and contralateral hemispheres to stenosis and to compare the VMR obtained from the patients with intracranial and extracranial stenosis. To show the improvement or deterioration of VMR obtained from the ipsilateral and contralateral hemispheres to stenosis, the Pearson correlation test was used to compare the initial VMR, the VMR measured at 6 months, and the BI obtained at 6 months. \( P < .05 \) was accepted as statistically significant.

Results
The mean age \pm SD of the 41 patients (32 men and 9 women) who met the inclusion criteria of the study was 61.5 \pm 12.3 years. Eighteen of the patients (12 men and 6 women) had symptomatic intracranial artery stenosis, and 23 (20 men and 3 women) had symptomatic extracranial artery stenosis. The demographic factors and clinical findings of patients on admission are shown in Tables 2 and 3.

The initial VMR results of 7 patients (4 with intracranial stenosis and 3 with extracranial stenosis) were normal. Three patients died, and 1 patient moved during the 6-month follow-up period. The 3 patients who died had intracranial artery stenosis and low initial VMR of the ipsilateral hemisphere. At 6 months, the BI of 37 patients and the VMR of 32 patients (20 patients with extracranial stenosis and 12 patients with intracranial stenosis) were obtained. The VMR of 5 patients could not be measured at 6 months because they refused the TCD test at that time.

The initial VMR measured from the ipsilateral hemisphere to stenosis was higher in the patients with intracranial stenosis than in those with extracranial stenosis \( (P = .013) \); however, no significant difference was found for initial VMR measured from the contralateral hemisphere between the 2 groups \( (18.81 \pm 12.00 \text{ for the patients with intracranial stenosis and } 15.96 \pm 10.49 \text{ for the patients with extracranial stenosis}) \) \( (P > .05) \) (Table 4).

For both groups, the comparisons of the initial VMR and the VMR measured at 6 months are shown in Table 4 \( (P > .05) \). In patients with extracranial stenosis, a statistically significant difference was found between the initial VMR and the VMR measured at 6 months from the ipsilateral hemispheres \( (P = .013) \); however, there was no significant difference between the initial and

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n = 41)</th>
<th>Intracranial Stenosis (n = 18)</th>
<th>Extracranial Stenosis (n = 23)</th>
<th>( P^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female</td>
<td>9/32</td>
<td>6/12</td>
<td>3/20</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>11 (26)</td>
<td>6 (33)</td>
<td>5 (22)</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>21 (51)</td>
<td>12 (67)</td>
<td>9 (39)</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Ischemic heart disease, n (%)</td>
<td>5 (12)</td>
<td>1 (6)</td>
<td>4 (17)</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>15 (37)</td>
<td>8 (44)</td>
<td>7 (30)</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>17 (41)</td>
<td>6 (33)</td>
<td>11 (48)</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Family history, n (%)</td>
<td>14 (34)</td>
<td>4 (22)</td>
<td>10 (43)</td>
<td>&gt;.05</td>
</tr>
<tr>
<td>Age, mean \pm SD</td>
<td>61.51 \pm 12.28</td>
<td>60.83 \pm 15.87</td>
<td>62.04 \pm 8.94</td>
<td>&gt;.05</td>
</tr>
</tbody>
</table>

*Mann-Whitney \( U \) test, \( \chi^2 \) test.
VMR and the VMR measured at 6 months from the contralateral hemispheres (P > .05).

The VMR at 6 months improved better in patients with extracranial artery stenosis than in those with intracranial artery stenosis (P = .01). Although VMR was worse in the patients with intracranial artery stenosis, it was improved in the patients with extracranial artery stenosis at 6 months, but no significant difference was found for the changes in VMR between the 2 groups at 6 months (P > .05).

A positive correlation was found between the initial VMR measured from the ipsilateral hemisphere and the BI at 6 months (P = .007; r = 0.434) (Figure 1); however, no significant difference was found between the initial VMR measured from the contralateral hemisphere and the BI measured at 6 months. There was also no association between the BI measured at 6 months and ipsilateral and contralateral VMR measured at 6 months. There was a statistically significant difference in the mean BI between the patients with an initial VMR of the ipsilateral hemisphere of more than 30% and those with an initial VMR of less than 30% (100 ± 0.00 versus 75.3 ± 27.9) (P = .001).

Discussion

Hemodynamic investigations may increase our understanding of the pathophysiology of ischemic stroke, and the results of these investigations may have value in guiding treatment algorithms.15 The predictive value of cerebral hemodynamic testing has been shown in patients with intracranial and extracranial artery stenosis.11

Cerebral autoregulation maintains constant cerebral perfusion pressure without a considerable change in cerebral blood flow (CBF). This autoregulation is maintained primarily by the changes in precapillary resistance. In this way, CBF is in a normal range when the mean blood pressure is between 50 and 60 and 150 and 160 mm Hg.15 Vasomotor reactivity is known as the compensatory dilatory capacity of cerebral circulation to the vasodilator stimuli.4,11 Reduced cerebral VMR indicates an inadequate response capacity of the cerebral arteries to a change in cerebral perfusion. It has been reported that cerebral VMR improves within 3 months after occlusion because of the development of intracranial collateral pathways.6 Primary collateral circulation suddenly provides blood supply to the ischemic regions through the collateral anastomosis, and then secondary collateral circulation provides blood supply as the leptomeningeal anastomosis improves over time.16,17 Collateral circulation is the determinant of cerebral perfusion in acute focal cerebral ischemia.16

Some authors have reported that cerebral hemodynamics improve over time, and others have concluded that they deteriorate.18–20 In our study, at 6 months, the cerebral hemodynamics improved in patients with extracranial artery stenosis but deteriorated in patients with extracranial artery stenosis.
intracranial artery stenosis. Although, to our knowledge, a TCD study that compared the changes in VMR between patients with acute stroke who have intracranial artery stenosis and those who have extracranial artery stenosis has not been reported previously, our results were in accordance with the results of Okazawa et al. They found that VMR changed back to normal in 18.9% of the patients with ICA occlusion after 24 months, but they found no improvement in VMR in patients with MCA occlusion. The duration of abnormality in VMR was longer in patients with MCA occlusion, and this may be due to the development of collateral pathways in the circle of Willis over time in patients with ICA occlusion. In patients with MCA occlusion, however, only pial collateral circulation and meningeal collateral circulation develop, and insufficient collateral circulation distal to the occlusion of the MCA is reported to cause long-duration hemodynamic failure.

Derdeyn et al. showed an improvement in cerebral hemodynamics over time with a PET study in patients with ICA occlusion and concluded that the development of the collateral circulation caused this improvement. Yokota et al. reported that the CBF of the ipsilateral hemisphere improved within 40 months after atherothrombotic infarction, and the development of collateral pathways, recanalization, and regression of atheromatous plaque were reported as the related mechanisms.

In our study, acetazolamide was administered for vasodilatation. Acetazolamide has been widely used to assess the cerebral perfusion reserve in patients with stenotic vascular disease. Acetazolamide administration does not alter blood pressure and is easy to perform, and it induces vasodilatation better than carbon dioxide inhalation. Ogasawara et al. evaluated 20 hemispheres of 10 healthy subjects with SPECT after acetazolamide administration and found a blood flow velocity of 41 to 53.8/100 g and a regional VMR of 22.5% to 34%. Okazawa et al. reported a 33.5% change in global CBF with PET after acetazolamide administration. For this reason, we considered a change of VMR to less than 30% after acetazolamide administration to be an abnormal result.

Vorstrup showed that increments of CBF start 2 minutes after acetazolamide injection and attain a maximal effect at 20 minutes; this lasts for 30 minutes after injection of acetazolamide. Okazawa et al. reported that the maximal response was observed 10 minutes after acetazolamide administration, and no significant difference was reported between the CBF results obtained at 10 and 20 minutes. We also measured CBF velocity and VMR on admission and 20 minutes after acetazolamide administration.

Kazumata et al. measured a VMR of 11.3% for the ipsilateral hemisphere and 36.7% for the contralateral hemisphere with SPECT after acetazolamide administration in patients with occlusion of the ICA and the MCA. In our study, the initial VMR was significantly higher in patients with intracranial stenosis than in those with extracranial stenosis. This may be due to the slow deterioration of cerebral hemodynamics within a long period in patients with extracranial stenosis. In patients with chronic MCA stenosis, few microembolic signals were seen; for this reason, the primary mechanism of intracranial stenosis was thought to be hemodynamic insufficiency. Occlusion of small penetrating arteries and artery-to-artery embolism are other causes of stroke.

Marshall et al. showed that cerebral hemodynamics may spontaneously progress or regress over time, and they reported that hemodynamic tests can be used to follow the carotid occlusion. Yamauchi et al. reported an improvement in cerebral hemodynamics with a long follow-up period in patients with ICA occlusion.

Figure 1. Correlation between initial VMR and BI at 6 months.
Evaluation of Vasomotor Reactivity by Transcranial Doppler Sonography

Most of the previous prognostic studies in association with VMR were studies of stroke recurrence.\textsuperscript{18,19,25,26} In some studies, no significant difference was found for stroke recurrence between the patients with normal and abnormal VMR,\textsuperscript{18,25} but other studies found a positive correlation between stroke recurrence and abnormal VMR.\textsuperscript{19,26} The different results of these studies may be due to the methods of the studies, the small sample sizes, and the evaluation of symptomatic and asymptomatic patients together; however, we studied the correlation between the BI at 6 months and the initial VMR to evaluate the quality of life after acute ischemic stroke and found a positive correlation between the initial VMR measured from the ipsilateral hemisphere and the BI at 6 months.\textsuperscript{6,26} Vernieri et al\textsuperscript{6} also reported the importance of the intracranial hemodynamic adaptive status (the number of collateral vessels and related VMR) to estimate the outcome after stroke. Although our study had a relatively short follow-up period, 6 months is a common clinical interval for serial assessment in patients with carotid artery disease.\textsuperscript{19} We had no stroke recurrence within the 6-month follow-up period, and our results may have more value if we continue to follow the patients after stroke recurrence.

In conclusion, our TCD study compared the changes of VMR over time in patients with acute stroke who had intracranial and extracranial artery stenosis, and we found that VMR of the ipsilateral hemisphere to stenosis may have value in determining the long-term prognosis of patients with acute stroke.

References


