Cerebral vasomotor reactivity of bilateral severe carotid stenosis: is stroke unavoidable?

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We evaluated the cerebral hemodynamic features of severe bilateral carotid stenosis by assessing and comparing cerebral vasomotor reactivity (VMR) in the middle cerebral (MCA) and vertebral arteries (VA) by transcranial Doppler and the Diamox (1 g acetazolamide i.v.) test. VMR was evaluated by recording the percentage differences in peak systolic blood flow velocity in each MCA and VA at baseline and by the Diamox test. Twenty-eight symptomatic (SCAS) and 31 asymptomatic (ACAS) patients with bilateral severe (> 70%) internal carotid artery stenosis were studied. The mean MCA VMR% was 29 ± 26.9% in SCAS and 43.2 ± 26.8% in ACAS patients (P < 0.01). Their respective mean VA VMR% was 30.2 ± 36.5% and 39.6 ± 24.4% (P = NS). VMR% of the symptomatic MCA side in SCAS patients was significantly lower than the opposite side (20.5 ± 31.1% and 39.2 ± 37.9% respectively; P < 0.03). In contrast, the VA VMR% of both sides in SCAS patients remained similar (28.1 ± 39.3% and 34.6 ± 47.9% respectively; P = NS). VMR% of the MCA and VA in ACAS patients was also similar for both sides of bilateral carotid stenosis. The cerebral hemodynamic features differ between SCAS and ACAS patients with bilateral carotid occlusive disease in the anterior part of the circle of Willis. An independent cerebral vascular reserve capacity of the posterior circulation is proposed.

Introduction

The occurrence and outcome of cerebral ischemic events in patients with carotid occlusive disease are largely dependent upon the state of competent hemodynamics, cerebral autoregulation and collateralization [1]. Bilateral severe internal carotid artery (ICA) stenosis accounts for approximately 10% of carotid occlusive disease [2,3]. This group represents a high-risk population for ischemic stroke as well as for any perioperative vascular complications after heart, carotid and general surgery [4,5]. The importance of intracranial hemodynamics is heightened significantly in subjects with bilateral high-grade ICA stenosis. The intracranial hemodynamic status can be determined by assessing cerebral vasomotor reactivity (VMR), which provides information on both cerebral autoregulation and collateral circulation [6]. VMR can be assessed by using transcranial Doppler (TCD) and the Diamox test for measuring blood flow velocities (BFVs) before and after the administration of acetazolamide (Diamox) as a vasodilator agent [7]. Indeed, the Diamox test is widely used for the evaluation of VMR in patients with carotid occlusive disease [8,9]. The hemodynamic effects of ICA stenosis on the middle cerebral artery (MCA) with significantly reduced VMRs of the MCA having been demonstrated in patients with high-grade stenosis or occlusion of the ICA [10–13]. The data on the hemodynamic features of bilateral severe carotid stenosis, however, are still scanty [14].

The aim of the present study was to assess and compare the VMR in the MCAs and vertebral arteries (VAs) in symptomatic and asymptomatic patients with severe bilateral ICA stenosis in order to evaluate the intracranial hemodynamic features of bilateral carotid occlusive disease.

Patients and methods

The study cohort consisted of 59 consecutive patients (mean age ± SD 71.9 ± 7.8 years, 41 men) with high-grade (70–99%) bilateral ICA stenosis as measured by Doppler ultrasonography. Twenty-eight of these patients (mean age ± SD 71.3 ± 7.8 years, 21 men) had symptomatic carotid artery stenosis (SCAS) as a result of a prior non-disabling ischemic stroke (23 patients) or transient ischemic attack (five patients) in the at least one of the two hemispheres. The remaining 31 patients (mean age ± SD 72.4 ± 7.8,
20 men) were defined as having asymptomatic carotid artery stenosis (ACAS) by virtue of their having no history or clinical evidence of any prior cerebrovascular event. The ACAS and SCAS patients were comparable with respect to demographic features (age, gender) and common vascular risk factors. The mean extent of the left and right ICA stenosis in the SCAS and ACAS groups was 91.7 ± 8% and 90.8 ± 8.8% and 90.5 ± 7.7% and 91 ± 7% respectively (NS). The cerebrovascular events in all the SCAS patients had occurred not <3 months before their being included into the study. All patients underwent computerized tomography (CT) brain scans. In the 28 SCAS patients it showed seven territorial and 14 single lacunar infarcts in the symptomatic MCA territory, five bilateral lacunar infarcts in the anterior circulation, and two normal scans. In the 31 ACAS patients, it showed six single and two bilateral lacunar infarcts in the anterior circulation and 23 normal scans.

Carotid artery disease in all the patients was assessed and defined using color-flow B-mode Doppler ultrasonography (Gateway 2D, VST, C20060; Diasonics Ultrasound, Santa Clara, CA, USA) according to validated criteria [15,16].

The intracranial arteries were evaluated by TCD (Rimed Ltd., Trans-link 9900 TCD, Herzliya, Israel). The TCD examination was carried out with the patient in a supine position. It included transtemporal insonation of the MCA at a depth of 50–55 mm and trans-occipital insonation of the VA at a depth of 60–90 mm using a 2-MHz hand-held probe [17]. The most powerful signal during a 10-s period was used for the measurements of the BFV. Blood pressure and heart rate were monitored simultaneously during the Diamox test: an increase in these parameters of >20% excluded the data from analysis. The results of patients with stenotic changes of their VA based on the carotid Doppler or TCD results were also excluded from the study.

VMR was evaluated by recording the percentage differences in peak systolic blood flow velocity in each MCA and VA at baseline and by the Diamox test. An intravenous (i.v.) injection of 1.0 g acetazolamide was given over 5 min, and BFV_{mca} and BFV_{va} were again measured with the ultrasound sample volume at the same depth 20 min later. The TCD examination after i.v. acetazolamide injection was accomplished within 30 min in order to accommodate the timing of the maximum vasodilating effect of Diamox [18]. There were no significant side effects after acetazolamide administration in any of our patients: 12 patients complained of feelings of dizziness, paresthesias or fever which subsided within 30–60 min.

**Statistical analyses**

The nonparametric Mann–Whitney test was used to compare BFV and VMR in the MCAs and VAs in the SCAS and ACAS patients. Results with \( P < 0.05 \) were considered statistically significant.

**Results**

The mean BFVs in the MCA before the Diamox test in both the SCAS and the ACAS patients were similar (77.2 ± 24.4 cm/s and 79.5 ± 20.7 cm/s respectively; \( P = 0.4, \) NS). There was also no significant difference in the mean BFVs of the VA between both patient groups (59.6 ± 15.2 cm/s and 61.3 ± 18.3 cm/s respectively; \( P = 0.6, \) NS). Following the Diamox test, the mean MCA VMR% values were 29 ± 26.9% in SCAS and 43.2 ± 26.8% in ACAS patients \((P < 0.01)\). The mean VA VMR% values in SCAS and ACAS patients were 30.2 ± 36.5% and 39.6 ± 24.4%, respectively \((P < 0.1, \) NS). The findings according to the side of carotid stenosis for both the SCAS and ACAS patients are shown in Table 1. The VMR% of the symptomatic MCA side in the SCAS patients was 20.5 ± 31.1%, that was significantly lower than the VMR% on the opposite side, i.e. 39.2 ± 37.9% \((P < 0.03)\). In contrast, the VA VMR% of both sides in the SCAS patients remained similar (28.1 ± 39.3% and 34.6 ± 47.9% respectively; \( P = \) NS). There was no significant difference between the VMR% of the right and left MCA or the right and left VA in the ACAS patients (48.4 ± 40.8% and 44.9 ± 52.5%, and 35.1 ± 31.2% and 49.6 ± 47.3% respectively; NS).

<table>
<thead>
<tr>
<th>VMR%</th>
<th>SCAS (n = 28)</th>
<th>ACAS (n = 31)</th>
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<tr>
<td></td>
<td>MCA</td>
<td>VA</td>
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<tr>
<td>Symptomatic side</td>
<td>20.5 ± 31.1</td>
<td>34.6 ± 47.91</td>
</tr>
<tr>
<td>Opposite side</td>
<td>39.2 ± 37.9</td>
<td>28.1 ± 39.3</td>
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<tr>
<td>P-value</td>
<td>&lt; 0.01</td>
<td>&lt; 0.5 (NS)</td>
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Values are given as mean ± SD.

Table 1 Vasomotor reactivity (VMR%) of the middle carotid arteries (MCAs) and vertebral arteries (VAs) on the sides of bilateral carotid stenosis in symptomatic (SCAS) and asymptomatic (ACAS) patients.
Discussion

An increased stroke risk as predicted by impaired VMR in patients with severe carotid stenosis or occlusion has been confirmed in several studies [19–23]. These results support the value of TCD with vasodilatory tests for identifying high-risk subgroups of patients with carotid occlusive disease. Bilateral severe carotid stenosis can result in persistent low-flow states in the cerebral vasculature because of the loss of the cerebral autoregulatory mechanism in chronically dilated intracerebral vessels [24,25]. In consideration of the progressive aging of the population worldwide, severe bilateral carotid stenosis has become a more frequent condition and may be a hemodynamically critical state [26]. The data stemming from these studies have suggested a potentially higher risk of ischemic stroke in patients with significant bilateral occlusive disease and impaired cerebral hemodynamics than in persons with preserved cerebrovascular reserve capacity. Therefore, evaluation of the intracranial hemodynamic status, especially in patients with bilateral carotid stenosis, might be useful in selecting patients for surgery, in choosing the side of carotid endarterectomy and in deciding whether or not to use a shunt during the procedure.

We examined the VMR of the anterior and posterior parts of the circle of Willis in asymptomatic and symptomatic patients with bilateral severe carotid stenosis. Our findings showed that the VMR of the MCA in symptomatic patients with bilateral severe carotid stenosis is significantly lower than in asymptomatic patients and, in contrast, that the VMR of the posterior circulation remained similar in patients with either a symptomatic or an asymptomatic course of bilateral carotid stenosis.

Liu et al. [14] investigated cerebral blood flow (CBF) and cerebrovascular reactivity capacity using xenon CBF measurements and the acetazolamide challenge test in patients with bilateral high-grade ICA stenosis. There was no significant change in either the CBF or VMR measurements in the territories of these stenoses. The CBF increased significantly after acetazolamide in only one of the four studied asymptomatic patients with bilateral severe carotid stenosis. Six other patients in this study were diagnosed as having unilateral ICA occlusion with high-grade stenosis in the contralateral side. Based on these limited data, the authors did not recommend performing the acetazolamide test to assess cerebrovascular reactivity. Vernieri et al. 2001 [27] measured cerebral hemodynamics in patients with carotid artery occlusion and contralateral moderate or severe internal carotid artery stenosis. The VMR in the MCA was evaluated by calculating the breath-holding index (BHI), and their data demonstrated that the cerebral hemodynamic status of patients with occlusive ICA disease is influenced by individual anatomical and functional characteristics, with particular emphasis upon collateral pathways. Our results agree with those of Matteis et al. [28] who endorsed the use of TCD and BHI to evaluate patterns of cerebrovascular reactivity in asymptomatic and symptomatic patients with carotid occlusion and severe contralateral stenosis. There was a significant decrease of the VMR on the occluded side of symptomatic patients compared with the asymptomatic ones. The VMR on the stenotic side in the asymptomatic patients was significantly higher than in the symptomatic ones. The pattern of cerebrovascular reactivity in patients with severe bilateral carotid steno-occlusive disease was observed as being strictly dependent on the presence of previous symptoms. Similar results were obtained by Orosz et al. [29] and by Reinhard et al. [26] who assessed VMR as a part of a study designed to analyze dynamic cerebral autoregulation and collateral flow patterns in patients with bilateral severe carotid artery stenosis or occlusion. They noted that clinically symptomatic patients had a significantly lower phase shift as a parameter of cerebral autoregulation, and that they also had lower VMR values.

Our data support the presence of different cerebral hemodynamic features in symptomatic versus asymptomatic patients with bilateral carotid occlusive disease. Based on these data, it may be speculated that patients with carotid stenosis become symptomatic because of their impaired VMR, and that asymptomatic patients remain asymptomatic because of their effective cerebrovascular reserve capacity [30]. In addition, our findings on the VMR of the VA suggest an independent cerebrovascular reserve capacity of posterior circulation in the presence of carotid occlusive disease and a key role for the circle of Willis in intracerebral hemodynamics. Taken together with our previous data on the VMR in the MCA and VA in patients with unilateral carotid stenosis [31], our results demonstrate the necessity of assessing the anterior and posterior parts of the circle of Willis separately in patients with bilateral carotid stenosis. These results also support the importance of detecting by means of TCD the different patterns of collateral circulation – anterior and posterior communicating arteries or ophthalmic artery, although, it was not the scope of our study.

Our data mandate the assessment of intracerebral hemodynamics before making final decisions on carrying out carotid revascularization in asymptomatic patients with bilateral severe carotid stenosis because carotid endarterectomy may not always be justified in this category of carotid occlusive disease – at least not from the hemodynamic point of view.
Acknowledgement

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References