Cerebral vasomotor reactivity of patients with acute ischemic stroke: Cortical versus subcortical infarcts: An Israeli–Turkish collaborative study

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Abstract

Background: Cerebral hemodynamic features of patients with different types of acute ischemic stroke are still obscure. We compared cerebral vasomotor reactivity (VMR) in acute cortical (CI) and subcortical (SI) brain infarcts.

Methods: Acute stroke patients (within 72 h of stroke onset) underwent transcranial Doppler and the Diamox test (1 g acetazolamide IV). The percent difference between blood flow velocities in the middle cerebral arteries before and after acetazolamide was defined as VMR%. CI and SI infarcts were confirmed by computerized tomography and/or magnetic resonance imaging. Clinical status and disability were assessed by means of the National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS) respectively. VMR% values and stroke severity and disability parameters were compared between CI and SI groups using ANOVA and Pearson’s correlation (r) coefficients.

Results: VMR% values of the ipsilateral side to the brain infarct in the CI group were significantly lower as compared with SI group (12.2±15.9% and 25.6±24.4% respectively, P=0.03). VMR% values in both groups were not correlated with stroke severity and disability (P>0.2).

Conclusions: Our results suggest greater vulnerability of resistance arterioles in the setting of cortical gray matter infarcts. Although gray matter VMR is physiologically higher than white matter VMR, patients with acute CI have impaired cerebral vascular reserve.

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1. Introduction

Hemodynamic factors may play a key role in the acute phase of ischemic stroke, predict stroke severity, progression and outcome. Different methods have been developed for the evaluation of cerebral hemodynamics. One of the ways of determining cerebral hemodynamic status is by assessing cerebral vasomotor reactivity (VMR) which provides information on cerebral autoregulation and the collateral circulation [1,2]. VMR is defined as a shift between cerebral blood flow (CBF) or cerebral blood flow velocity (BFV) before and after administration of a potent vasodilatory stimulus test. VMR of the middle cerebral artery (MCA) was frequently assessed in patients with extracranial carotid occlusive disease, and several studies showed that high-grade stenosis or occlusion of the internal carotid artery (ICA) can significantly reduce VMR of the ipsilateral MCA [3–6]. Furthermore, the predictive value of impaired VMR for ischemic stroke occurrence was convincingly confirmed in subjects with carotid occlusive disease [7–11]. Data on the features of VMR in patients with acute ischemic stroke who do not have carotid occlusive disease, however, are very scanty [12,13].

VMR can be assessed by using transcranial Doppler (TCD) and the Diamox test, measuring BFV before and after administration of 1 g acetazolamide IV.
the administration of acetazolamide (Diamox) as a vasodilator agent [14]. TCD with the Diamox test is easy to perform and does not need the patient’s cooperation. These advantages might be crucial for evaluations conducted during the acute phase of ischemic stroke.

The aim of the present study was to assess VMR in patients with acute ischemic stroke without carotid occlusive disease in order to identify and compare the cerebral hemodynamic features unique to cortical and subcortical brain infarcts.

2. Patients and methods

Forty-seven patients with first-ever acute ischemic stroke were prospectively studied within 72 h of stroke onset in this Israeli–Turkish collaborative study. Twenty-two of them were examined in the Tel Aviv Sourasky Medical Center (TASMC) and 25 in the Department of Neurology, Osmangazi University, Eskisehir, Turkey. All the study participants were recruited according to the following criteria: 1. first-ever ischemic stroke in the anterior circulation (i.e., the MCA territory); 2. no evidence of significant carotid occlusive disease (<50% internal carotid artery [ICA] stenosis) as measured by Doppler and stenotic changes of vertebral arteries as measured by Doppler or TCD; 3. evidence of acute cortical or subcortical brain infarcts on computerized tomographic (CT) scan or magnetic resonance imaging (MRI); 4. moderate or severe neurological deficit as demonstrated by a National Institutes of Health Stroke Scale (NIHSS) score > 6 [15,16]; 5. no evidence of significant handicap or disability of any reason before stroke with a pre-stroke modified Rankin Scale (mRS) score ≤ 1 [17]; 6. presence of a bilateral temporal acoustic window for optimal TCD evaluation; 7. no evidence of allergy to sulfa group or any contraindications for acetazolamide administration.

2.1. Clinical assessment

The patients’ clinical status and disability were assessed before TCD and the Diamox test by means of the NIHSS and mRS, which were administered by senior neurologists who were certified for their application (AG, DG, NÜ) by NIHSS. The vascular risk factors were defined as follows: 1. use of antihypertensive agents or systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg for hypertension; 2. use of oral hypoglycemic agents, insulin, or glycosylated hemoglobin > 7.0% for diabetes mellitus; 3. use of antihyperlipidemic agents or a serum cholesterol level > 220 mg/dL for hypercholesterolemia; 4. any cigarette usage for current smoking.

2.2. Computed tomographic (CT) studies

All patients underwent CT brain scans before VMR assessment within 72 h of stroke onset. MRI was performed in six patients in order to confirm the CT scan results. CT/MRI scans were reviewed and interpreted by experienced neuroradiologists in both centers who noted the presence, size, number and location of hypodense lesions of vascular etiology. Acute brain infarcts were defined as either cortical (superficial territory of the MCA without any involvement of the subcortical gray matter) or subcortical (deep territory of the MCA without any involvement of the cerebral cortex). The criteria used in the analysis of CT scans have been previously reported [18]. Patients with infarcts < 2 cm in diameter and involving more than two-thirds of the MCA territory were excluded.

2.3. Carotid Doppler ultrasonography

All the patients underwent color-flow B-mode Doppler ultrasonography (Diaionsics ultrasound, Gateway 2D, VST, C20060, Santa Clara, CA, USA in TASMC and Multidop X4 DWL; Elektronische Systeme GmbH, Sipplingen, Germany in Osmangazi University, Faculty of Medicine, Eskisehir, Turkey) according to validated criteria [19,20].

2.4. VMR assessment

The intracranial arteries were evaluated by TCD (Rimed Trans-link 9900 TCD, Herzliya, Israel in TASMC and Multidop X4 DWL and TCD8 software; Elektronische Systeme GmbH, Sipplingen, Germany in Osmangazi University, Faculty of Medicine, Eskisehir, Turkey). Author DG was trained in the Doppler laboratory of TASMC for TCD measurements and for performing and interpreting the Diamox test. The TCD examination was carried out with the patient in a supine position. It included transtemporal insonation of the MCA at a depth of 45–55 mm with a 2-MHz hand-held probe [21]. The most powerful signal during a 10-second period was used for the measurements of the BFV. Blood pressure and heart rate were monitored simultaneously during the Diamox test: an increase in peak systolic BFV in each MCA at baseline and after Diamox administration. An intravenous (IV) injection of 1.0 g acetazolamide was given over 5 min, and the MCA BFVs were again measured with the ultrasound sample volume at the same depth 20 min later [6].

Table 1

Demographics and risk factor profiles in the cortical (CI) and subcortical (SI) brain infarct groups

<table>
<thead>
<tr>
<th>Demographics and risk factors</th>
<th>CI n=23</th>
<th>SI n=24</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD, years</td>
<td>72±13.67</td>
<td>60.5±13.71</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Gender (males)</td>
<td>15</td>
<td>14</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>18 (72.8%)</td>
<td>20 (83.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>10 (43.4%)</td>
<td>15 (62.5%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>7 (30.4%)</td>
<td>10 (41.6%)</td>
<td>NS</td>
</tr>
<tr>
<td>Cigarette smoking, n (%)</td>
<td>8 (34.7%)</td>
<td>12 (50%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Turkey/Israel</td>
<td>9/14</td>
<td>16/8</td>
<td></td>
</tr>
</tbody>
</table>
2.5. Statistical analyses

Demographic data and vascular risk profiles of patients with cortical and subcortical infarcts were compared by Student’s t-test. BFV and VMR% values of the MCAs ipsilateral and contralateral to the cortical or subcortical brain infarcts were compared by the ANOVA test. Pearson’s correlation coefficients (r) and the ANOVA were applied to verify correlation between VMR% and parameters of stroke severity (NIHSS and mRS). The analyses were performed with the use of SPSS 9 and SPSS 11 softwares (SPSS Inc). A level of P<0.05 was accepted as statistically significant.

3. Results

Forty-seven patients (mean age±SD, 76±12.8 years, 29 men) with acute ischemic stroke in the MCA territory were studied. Based on neuroradiological data, these patients were divided into two groups, one with cortical infarcts (CIs; n=23) and the other with subcortical infarcts (SIs; n=24). The patients’ demographics and risk factor profiles are shown in Table 1. There were no significant differences between the CI and SI groups in terms of gender, hypertension and hypercholesterolemia. The SI group was younger and had more patients with diabetes mellitus and smoking. The two groups were comparable in terms of clinical deficit and disability (mean NIHSS score 12.6 [range 8–18], mean mRS 3.9 [3–5] for the CI group and mean NIHSS score 13.8 [9–20] and mean MRS 3.09 [2–5] for the SI group). The mean BFVs of the MCAs in the side ipsilateral to the infarct in the CI and SI groups before administration of the acetazolamide were 61.57±6.90 cm/s, 61.37±6.90 cm/s, respectively (P=0.2, NS). There were also no significant differences between the mean BFVs of the MCAs in the side contralateral to the infarct in the CI and SI groups before administration of the acetazolamide (59.71±12.70 and 62.71±12.55 cm/s, respectively, P=0.2, NS) (Fig. 1). After the Diamox injection, the VMR% of the ipsilateral side to the brain infarct in the CI group was significantly lower compared with both the SI group (12.2±15.9% and 25.6±24.4%, respectively, P=0.03) and the contralateral side of the CI group (30.6±28.1%, P=0.05). In contrast, there was only a nonsignificant trend of a better VMR% of the side contralateral to the brain infarct in the CI group (30.6±28.1%) versus the SI group (19.1±19.5%, P=0.06, NS) (Fig. 2). The VMR% were not correlated with stroke severity (mean NIHSS) and disability (mean mRS) (Table 2).

4. Discussion

The cerebral vasculature has a unique ability to dilate during hypercapnia and to constrict during hypocapnia. The differences between CBF at rest and after the induction of hypercapnia reflect the state of VMR and, hence, cerebrovascular reserve capacity. These effects of carbon dioxide (CO2) on the cerebral circulation are mostly demonstrated in resistance brain arterioles. VMR is defined as the vasodilation capacity of resistance brain arterioles to external stimuli, such as increasing extracellular pCO2 and decreasing extracellular pH [22–24]. In our current study, we found that VMR in the side of acute cortical infaracts was significantly impaired compared with the side of an acute subcortical infarct or the contralateral side of cortical infarcts. Cupini et al. [12] compared VMR in three groups of patients with acute ischemic stroke (cortical, single subcortical and subcortical with multiple silent subcortical infarcts) and controls using the holding index technique. Their main finding was that patients with lower VMR had subcortical infarction with multiple silent subcortical infarctions. Those authors did not observe...
any statistical differences in VMR in the single subcortical infarction group or the cortical infarction group versus the controls. Moreover, the side of the infarct was not found to significantly influence VMR, so the authors used the mean of the right and left VMR for statistical analysis. Those results are not in accordance with our findings. There could be a physiological explanation for our results. It is well known that capillary density is about three-fold higher in cerebral gray matter (1000 mm/mm³) than in white matter in the normal brain [25]. Some studies have shown that while both gray and white matter blood flows increase with hypercapnia, the white matter blood flow increase was less than that of the gray matter [26]. Based on these data, it can be assumed that a cortical infarct with a predominantly gray matter lesion may more significantly damage the resistance arterioles and, therefore, reduce their ability to dilate after a vasodilatory stimulus. Thus, it is reasonable that a more impaired VMR can be observed on the side of cortical than subcortical brain infarcts or than the contralateral asymptomatic hemisphere. Maeda et al. [27] evaluated VMR to a CO2 stimulus in various types of ischemic stroke and in normal controls. VMR of the symptomatic hemisphere was significantly less in patients with cortical infarcts than in normal control subjects and also less than that in the contralateral asymptomatic hemisphere. Although they evaluated VMR in the non-acute phase of stroke, their data support our present findings. There are only two published studies on VMR of the MCA in patients with acute ischemic stroke [12,13]. The aim of Alvarez et al.’s investigation [13] was to determine the predictive role of cerebrovascular reserve capacity within 24 h of stroke onset in early neurological deterioration. Reduced values of cerebrovascular reserve capacity in the symptomatic hemisphere were significantly associated with deteriorating stroke. We did not find any correlation between VMR values in acute ischemic stroke and parameters of stroke severity (NIHSS) or disability (mRS).

Our study has some limitations. MRI, which is a more informative tool for describing acute brain infarcts than CT, was performed in a relatively small number of patients. We tried to recruit only the patients with definitively confirmed (albeit by CT) cortical or subcortical acute brain infarcts in order to obtain the most appropriate data for the study purposes. Another limitation is related to the size of infarcts and existence of asymptomatic lacunar infarcts in the study groups. Silent brain infarcts were recorded in the neuroradiological data, but the small numbers of patients in each group precluded a statistical analysis based on infarct size and number of lacunar infarcts. Nevertheless, the two study groups were quite comparable in respect to infarct size (>2 cm and <2/3 of the MCA territory).

In summary, our data showed differences in VMR in acute cortical and subcortical brain infarcts. An impaired VMR in a patient with a cortical infarct suggests greater vulnerability of resistance arterioles in the setting of cortical gray matter infarcts. VMR values in the acute phase of stroke did not correlate with stroke severity, and future studies with larger numbers of patients are needed to determine the prognostic role of VMR in stroke outcome.

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References