Vasomotion in Multiple Spontaneous Cervical Artery Dissections

Claudio Baracchini, MD; Simone Tonello, MD; Roberta Vitaliani, MD; Bruno Giometto, MD; Giorgio Meneghetti, MD; Enzo Ballotta, MD

Background and Purpose—The etiology of spontaneous cervical artery dissection (sCAD) is still unknown, even though an underlying arteriopathy impairing vasomotion has often been suspected. This study was undertaken to investigate: (1) spontaneous, (2) endothelial-dependent, and (3) endothelial-independent vasodilation in patients with multiple sCAD.

Methods—In 19 consecutive patients with multiple carotid or vertebral artery dissections high-resolution ultrasound was used to assess spontaneous and endothelial-independent dilations (isosorbide dinitrate-mediated) in the common carotid, vertebral and brachial arteries, and endothelial-dependent dilation (flow-mediated arterial dilation) in the brachial arteries alone. The same parameters were measured in 19 healthy subjects matched for age, sex, and height (controls). Ultrasound studies were performed by one investigator, and off-line analysis by another investigator who was blinded to the clinical data and study status (patient or control).

Results—Spontaneous and endothelial-independent dilations were significantly impaired in the carotid (P=0.0006 and P<0.0001, respectively) and vertebral arteries (P=0.0121 and P=0.0047, respectively) of patients as compared with controls, whereas no statistically significant differences were found in the brachial arteries; conversely, endothelial-dependent dilation of the brachial arteries was significantly lower in patients as compared with controls (P<0.0001).

Conclusions—Patients with multiple sCADs have a significantly impaired vasomotion, which may predispose to dissection. (Stroke. 2008;39:000-000.)

Key Words: carotid artery ■ vertebral artery ■ ultrasonography ■ dissection ■ stroke

Cervical artery dissection (CAD) accounts for 2% of all ischemic strokes, but it is the second most common cause of stroke (10% to 20%) in young adults.1-3 In some cases, a cervical trauma, however mild, can trigger CAD.4 In most cases of CAD, the etiology remains unknown, hence the term of “spontaneous CAD” (sCAD).5 In such cases, an intrinsic nonatheromatous alteration of the vessel wall is thought to be the main predisposing factor—a supposition based merely on indirect evidence, such as associations with fibromuscular dysplasia and hereditary connective tissue disorders,6-8 the presence of intracranial aneurysms,9 concomitant dissections of cervical and renal arteries,10 aortic root dilation,11 and ultrastructural abnormalities of collagen and elastic fibers.12 These findings suggest the presence of an underlying general arteriopathy,13 which might impair vasomotion and predispose to spontaneous dissection. This hypothesis is reinforced by the occurrence of multiple spontaneous carotid or vertebral dissections in some of these patients. The incidence of such events is reportedly less than 15%, but many cases may go undetected because of their asymptomatic or oligosymptomatic presentation and frequently spontaneous recanalization.14

Cervical cerebral arteries are large elastic vessels; their hemodynamic properties derive mainly by the extracellular matrix components of the arterial wall15 and can be evaluated noninvasively by ultrasonography. The aim of this study was to investigate spontaneous, endothelial-dependent, and endothelial-independent vasodilation in patients with multiple sCAD.

Materials and Methods

Patients and Controls

Between April 2001 and July 2006, among 76 consecutive patients with sCAD admitted to our department, 24 (15 men and 9 women; mean age, 45.2±9.4) presented with multiple sCAD and were enrolled for the study. The diagnosis of sCAD suggested by ultrasound was confirmed by MR angiography or conventional angiography (string sign, pseudoaneurysm, intimal flap) and cervical MRI using T1 fat suppression technique (wall hematoma).16 There
were 31 dissections in the internal carotid artery (ICA; 16 right and 15 left) and 22 in the vertebral artery (VA; 11 right and 11 left). Signs and symptoms consisted of cerebral ischemia (n=13); retinal ischemia (n=2); Horner’s syndrome (n=9); head or neck pain (n=8); cranial nerve palsy (n=2); and tinnitus (n=1), in various combinations. An inclusion criterion for the present study was that multiple sCAD had occurred more than 6 months before their evaluation for the purposes of the study to avoid any effects of stroke on vessel function, or any morphological and hemodynamic change attributable to the healing process within the dissected vessels. Exclusion criteria included a history of other neurological disease, coronary artery disease, peripheral artery disease, connective tissue disorder, trivial or obvious cervical trauma, smoking, arterial hypertension, diabetes mellitus, hypercholesterolemia, hyperhomocysteinemia, cerebrovascular atherosclerosis at the transcranial Doppler ultrasound study, occlusion or residual ICA/VA stenosis ≥50%, pregnancy, breastfeeding, contraindication to the use of nitrates, and caffeine or alcohol intake ≤12 hours before the study baseline. Of the 24 enrolled patients, 5 were excluded for the following reasons: 1 died of a vertebral-basilar ischemic stroke attributable to a left VA dissection extending to the basilar artery and occluding the vessel, and ultrasound follow-up at 6-month diagnosed an occlusion of the ICA in 2 patients, an occlusion of the right VA and a severe stenosis of the ipsilateral ICA in 1 patient, and a severe stenosis of the left ICA in another patient. The remaining 19 patients (12 men and 7 women; mean age, 47.4±9.5 years) met the inclusion criteria: ultrasound follow-up at 6-month showed complete recanalization in 14 of them (58.5%), whereas 5 (20.8%) had residual stenosis <50%. Nineteen healthy volunteers (12 men and 7 women; mean age, 46.6±13) matched for age, sex, and height were also enrolled as a control group. The study was approved from the local ethics committee, and written informed consent was obtained from all patients or controls who consented to participate. None of the patients or controls were on statin therapy during the study period. All patients were on aspirin 100 mg/d.

**Ultrasound Investigation of the Cerebral Arteries and Vasodilation**

Patients and controls underwent a complete extracranial and intracranial ultrasound assessment with a color-coding duplex sonography scanner (Hitachi Logos Hi Vision CV) using a 2- to 9-MHz linear probe for the cervical arteries and a 1- to 5-MHz phased-array probe for the intracranial arteries. The examination was performed by an experienced neurosonographer (B.C.) and was always done in the same room, in a quiet atmosphere, with the subjects lying in a supine position. All measurements were taken using “Hi Quantification” software (Hitachi) and offline analysis by a second operator (T.S.) who was blinded to the clinical data and study status (patient or control). Complete recanalization of a dissected ICA was diagnosed when the peak systolic velocity was ≤50 cm/s in women or ≤80 cm/s in men; complete recanalization of a dissected VA was diagnosed when the peak systolic velocity was ≤60 cm/s.18-20

Spontaneous vasodilation, defined as a change in vessel diameter from end-diastole to peak-systole during a normal cardiac cycle, was studied in a longitudinal section of the common carotid artery (CCA) far from the carotid bifurcation (2 cm), in a straight portion of the intertransverse V2 segment of the VA and in a longitudinal section of the brachial artery (BA) about 5 to 15 cm above the elbow. CCA and VA were studied, whenever possible, on the side opposite the dissection, whereas BA was always measured on the side of the nonparietal arm. In the case of a bilateral carotid or vertebral dissection, measurements were taken on both sides and the mean value was recorded. In controls, the vessels were investigated on the same body side as in the study patients. The diameter of each vessel was measured at end-diastole and peak-systole, as indicated by an ECG running under the B-mode image. The measurements were taken from the near wall to the far wall, on the border between the media and the adventitia. Each measurement was repeated 3 times, and the mean value was recorded. Then a relative diameter change was calculated for each vessel as follows: [(systolic diameter–diastolic diameter)/diastolic diameter]×100.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients (n=19)</th>
<th>Controls (n=19)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years (SD)</td>
<td>47.4 (9.5)</td>
<td>46.6 (13)</td>
<td>0.83</td>
</tr>
<tr>
<td>Sex, men/women</td>
<td>12/7</td>
<td>12/7</td>
<td>...</td>
</tr>
<tr>
<td>Height, mean cm (SD)</td>
<td>173.4 (8.6)</td>
<td>171.9 (8.1)</td>
<td>0.58</td>
</tr>
<tr>
<td>BMI, mean Kg/m² (SD)</td>
<td>22.8 (3.1)</td>
<td>23.2 (2.8)</td>
<td>0.68</td>
</tr>
<tr>
<td>SBP, mean mm Hg (SD)</td>
<td>133.4 (10.5)</td>
<td>129.4 (9.4)</td>
<td>0.22</td>
</tr>
<tr>
<td>DBP, mean mm Hg (SD)</td>
<td>80.6 (9.9)</td>
<td>78.9 (8.3)</td>
<td>0.57</td>
</tr>
<tr>
<td>HR, mean (SD)</td>
<td>71.6 (6.1)</td>
<td>69.9 (6.5)</td>
<td>0.56</td>
</tr>
<tr>
<td>CCA diameter, mean (SD)</td>
<td>6.15 (0.62)</td>
<td>5.82 (0.54)</td>
<td>0.09</td>
</tr>
<tr>
<td>ICA diameter, mean (SD)</td>
<td>4.65 (0.48)</td>
<td>4.43 (0.57)</td>
<td>0.21</td>
</tr>
<tr>
<td>VA diameter, mean (SD)</td>
<td>3.54 (0.52)</td>
<td>3.72 (0.59)</td>
<td>0.33</td>
</tr>
<tr>
<td>BA diameter, mean (SD)</td>
<td>3.85 (0.82)</td>
<td>3.89 (0.92)</td>
<td>0.89</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; CCA, common carotid artery; ICA, internal carotid artery; VA, vertebral artery; BA, brachial artery.

*Student's t test.

Endothelial-independent vasodilation is the physiological ability of the endothelial vasculature to relax; it can be assessed by administrating a nitric oxide (NO) donor that has a direct relaxing effect on the vascular smooth muscle cells. We evaluated endothelial-independent dilation in CCA, VA, and BA, both at rest and after the sublingual administration of isosorbide dinitrate (5 mg). Because the drug begins to take effect within 2 to 3 minutes and its effects remain stable for 60 minutes, we measured the diameter change in the vessels after 5 minutes. Endothelial-independent vasodilation was calculated as follows: [(diameter after nitrate administration–diameter at rest)/diameter at rest]×100.

Endothelial-dependent vasodilation was assessed by measuring the flow-mediated dilation (FMD), which is the response of the vessel to an increase in shear stress. One of the principal mediators of FMD is endothelial-derived NO. We evaluated the endothelial-dependent dilation by measuring the diameter of the BA in the nonparietal arm at rest and after postischemic hyperemia. At rest, the probe was placed longitudinally above the elbow and the end-diastolic BA diameter (near to far wall) was measured, which coinciding with the R wave on the ECG; distal ischemia was induced by inflating a pneumatic cuff placed around the forearm to about 40 mm Hg above the systolic pressure for 2 minutes. The artery was scanned before inflation to measure the diameter at rest, and again 2 minutes after deflation, to measure the maximal diameter during hyperemia. A FMD index was calculated as follows: [(diameter after hyperemia–diameter at rest)/diameter at rest]×100.21-23

**Statistical Analysis**

Both groups were compared as regard general characteristics and ultrasound variables using the unpaired t test. After assessing the normality of distribution with the Kolmogorov-Smirnov test, the data regarding the mean relative diameter change in the vessels in both groups were compared using the unpaired t test for all methods. Significance was inferred at P<0.05.

**Results**

The baseline characteristics of the patients and controls are shown in Table 1: the 2 groups were comparable for age, sex, height, body mass index, blood pressure values, heart rate, and CCA, ICA, VA, and BA diameters.

There were 25 dissections in the ICA (13 right and 12 left) and 17 in the VA (8 right and 9 left), distributed as follows: ICA and VA (n=8; 42%), bilateral ICA (n=6; 32%), bilateral VA (n=2; 11%), bilateral ICA and bilateral VA (n=1; 5%), bilateral ICA and VA (n=1; 5%), ICA and bilateral VA

**Table 1. Baseline Characteristics of Patients and Controls**
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et al,22 who found an impaired endothelial-dependent dilation of the BA, however. On this occasion, differences between patients and controls as regards spontaneous and endothelial-independent dilation of the BA could be involved in both carotid and vertebral dissections, showing that the same arterial wall dysfunction, occlusion, or significant residual stenosis) capable of influencing the dynamic properties of the vessels. The endothelial-dependent dilation of the cervical vessels was not measured because it requires an invasive procedure that would have been unethical in this setting.

To our knowledge, this is the first functional study on patients with multiple sCAD. The main findings are that spontaneous and endothelial-independent dilations were significantly impaired in the cervical vessels of our study patients by comparison with our healthy controls, whereas no such differences were observed in the BAs (P = 0.7811). Likewise, endothelial-dependent dilation values were significantly lower in the CCA (P < 0.0001) and VA (P = 0.0047) of patients as compared with controls, but no such differences emerged in the BAs (P = 0.8918). The endothelial-dependent dilation values for the BAs were significantly lower in patients as compared with controls (P < 0.0001).

### Discussion

To our knowledge, this is the first functional study on patients with multiple sCAD. The main findings are that spontaneous and endothelial-independent dilations were significantly impaired in the cervical vessels of our study patients by comparison with our healthy controls, whereas no such differences were found in the BAs. Moreover, endothelial-dependent dilation of the BAs was significantly lower in patients than in controls.

Baumgartner et al24 recently reported similar findings in a group of 27 patients with single sCAD when they studied spontaneous and endothelial-independent dilation of the CCA, ICA, and BA. Our study differs in that we also included VA dissections, showing that the same arterial wall dysfunction could be involved in both carotid and vertebral dissections. The above-mentioned authors did not investigate endothelial-dependent dilation of the BA, however. On this issue, our results correlate well with those reported by Lucas et al,22 who found an impaired endothelial-dependent dilation of the BA in ischemic stroke patients with spontaneous carotid or vertebral dissection, whereas they found no difference between patients and controls as regards spontaneous and endothelial-independent dilation of the BA. Here again, the study suffers from the drawback that only changes in BA diameter were measured.

In contrast with both Baumgartner et al’s24 and our own results, Guillon et al17 surprisingly found a higher spontaneous relative change in CCA diameter among patients with single sCAD than in controls, but these authors included smokers and hypertensive patients in their study group and this might well explain the discrepancy in the results because smoking and hypertension have been associated with abnormal vasorelaxation.25,26 We took great care to adopt a reliable method for studying arterial wall function, excluding patients and control subjects with any vascular risk factors that have been shown to modify the functional features of the arterial wall.25–28 Our results in terms of spontaneous vasodilation changes are further reinforced by our findings after sublingual isosorbide dinitrate administration, whereas Guillon et al17 investigated neither spontaneous BA nor nitroglycerin-induced dilation.

Vessel distensibility is generally determined by the components of the vessel wall, ie, elastin, collagen, and smooth muscle cells. Cervical cerebral arteries are elastic vessels, and their distensibility is determined mainly by the relative amounts of elastin and collagen and their anatomic relationship.25,26 The relative diameter changes measured by ultrasonography in the CCA and VA represent a measure of distensibility.30 This hemodynamic property is altered in patients with multiple sCAD, the majority of whom reportedly have a stiffer cervical artery wall,31 with ultrastructural elastic and collagen fibers abnormalities resembling the changes seen in Ehlers-Danlos syndrome type II-IV.32,33 Guillon et al34 recently reported higher plasmatic levels of proteases (particularly the matrix metalloproteinase-2) in patients with multiple sCAD, suggesting that an increased proteolysis in the arterial wall may act as a susceptibility factor. These findings all point to an extracellular matrix defect, which could explain the impaired vasodilation observed in our study.

This study has a few limitations, mainly related to the small number of patients involved and the fact that we did not measure endothelial-dependent dilation of the CCAs and VAs. A small sample size can naturally limit the power of the comparison between cases and controls, but we believe that a larger sample would not alter the main findings for the relative changes in CCA, VA, and BA diameter, which were already significant. Our study also attempted a reliable assessment of the functional characteristics of the cervical vessels in patients with multiple sCAD, so strict inclusion criteria were used to avoid factors (eg, smoking, hypertension, occlusion, or significant residual stenosis) capable of influencing the dynamic properties of the vessels. The endothelial-dependent dilation of the cervical vessels was not measured because it requires an invasive procedure that would have been unethical in this setting.

### Table 2. Spontaneous, Endothelium-Independent, and Endothelium-Dependent Dilations of the Common Carotid, Vertebral, and Brachial Arteries in Patients and Controls

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Spontaneous Dilation</th>
<th>Endothelial-Independent Dilation</th>
<th>Endothelial-Dependent Dilation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>Controls</td>
<td>P Value*</td>
</tr>
<tr>
<td>CCA</td>
<td>7.7 (2.4)</td>
<td>10.5 (2.2)</td>
<td>0.0006</td>
</tr>
<tr>
<td>VA</td>
<td>4.9 (1.6)</td>
<td>6.7 (2.5)</td>
<td>0.0121</td>
</tr>
<tr>
<td>BA</td>
<td>4.6 (2.1)</td>
<td>4.8 (2.3)</td>
<td>0.7811</td>
</tr>
</tbody>
</table>

All data are expressed as percentage of dilation of the vessel (mean relative diameter change, ± SD).

*Student t test.
In conclusion, the present study suggests that patients with multiple sCAD have a significantly impaired vasomotion, which may predispose to dissection.

Disclosures

None.

References

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