Early Activation of Intracranial Collateral Vessels Influences the Outcome of Spontaneous Internal Carotid Artery Dissection

Mauro Silvestrini, MD; Claudia Altamura, MD; Raffaella Cerqua, MD; Claudio Pedone, MD; Clotilde Balucani, MD; Simona Luzzi, MD; Marco Bartolini, MD; Leandro Provinciali, MD; Fabrizio Vernieri, MD

Background and Purpose—The effectiveness of different treatments for internal carotid artery (ICA) dissection has not been well defined. Lack of early prognostic indicators may represent a major problem in adequately identifying the most appropriate option for treatment. This study aimed at evaluating the influence of patients’ vascular risk profiles and of early cerebral hemodynamic changes in determining the clinical evolution after ICA dissection.

Methods—Sixty-six stroke patients with ICA occlusion due to spontaneous artery dissection were included. Transcranial Doppler was performed within 24 hours from symptom onset to examine cerebral arteries and the patency of the 3 major intracranial collateral vessels (ophthalmic artery and anterior and posterior communicating arteries). Possible recanalization of the occluded ICA within the first month was evaluated. Stroke severity at onset was assessed with the National Institutes of Health Stroke Scale, whereas outcome was defined according to the modified Rankin Scale score at 90 days after stroke onset.

Results—Forty patients had at least 2 activated intracranial collateral vessels. The remaining 26 patients, with none or only 1 collateral vessel, showed a significant increased risk of poor recovery (modified Rankin Scale score ≥2; adjusted relative risk 14.9; 95% CI, 3.24 to 68.46). Poor recovery was not associated with the occurrence of recanalization, with stroke severity at onset, or with vascular risk profile.

Conclusions—Early assessment of cerebral hemodynamic status and, in particular, the activation of intracranial collateral vessels, may help in predicting the outcome of stroke patients with ICA lumen occlusion as a result of spontaneous dissection. (Stroke. 2011;42:139-143.)

Key Words: carotid dissection ■ transcranial Doppler ■ collateral circulation ■ acute stroke

Spontaneous dissection of the carotid artery has traditionally been considered a rare but probably underestimated cause of ischemic stroke. Nowadays, a correct diagnosis of arterial dissection is more frequent, particularly in young patients with ischemic stroke, owing to the increasing availability of vascular imaging techniques in the very early phase of symptom onset. Nevertheless, the best therapeutic approach to reduce ischemic damage progression and the risk of new ischemic events has not yet been defined. Some studies have compared the efficacy of surgical/endovascular versus medical treatment, whereas others have investigated whether anticoagulation can obtain better results than antiplatelet agents. Results have not yet shown clear advantages resulting from 1 approach compared with another and, at the moment, the “gold standard” of treatment remains unclear and options are largely empirical. This lack of evidence supporting the best single, therapeutic approach could result from the overall good prognosis of patients with stroke caused by carotid dissection. Furthermore, it is possible to hypothesize that stroke patients with carotid dissection are not a homogeneous group and that their clinical evolution can be influenced by different aspects, including severity of carotid lumen narrowing, vessel wall properties, and a potential for spontaneous recanalization. Moreover, similar to atherosclerotic internal carotid occlusive disease conditions, the clinical outcome could be influenced by the capability of the cerebral circulation to compensate for the reduction in carotid lumen diameter. An efficient cerebral hemodynamic compensatory adaptation is associated with a favorable prognosis in subjects with severe internal carotid artery (ICA) steno-occlusive disease. In this respect, adequate activation of collateral intracranial pathways seems to play a pivotal role.
Our aim in the present study was to evaluate whether early development of the intracranial collateral circulation and the evolution of lumen narrowing might influence the clinical outcome of patients with stroke due to spontaneous dissection of the ICA. Moreover, we investigated the possible role of the main vascular risk factors. To reduce the variability of the condition, we included subjects with ICA dissection presenting with complete occlusion of the vessel lumen.

**Subjects and Methods**

We enrolled 66 patients with a first-ever ischemic stroke who clinically showed a large-artery infarction and ultrasonographic (Philips IU22 ultrasound system) evidence of ipsilateral ICA occlusion due to arterial dissection detected within 12 hours from symptom onset. All subjects underwent (1) brain and neck magnetic resonance angiography combined with T1-weighted axial cervical magnetic resonance scans with the fat-saturation technique required to confirm the diagnosis of arterial dissection; (2) brain computed tomography; (3) careful neurologic evaluation; (4) cardiologic examination, ECG, and transthoracic echocardiography to rule out cardioembolic sources; and (5) complete blood chemistry analysis, including homocysteine. In addition, a detailed clinical history was obtained for each patient by paying particular attention to the major vascular risk factors (hypertension, diabetes, smoking, and hyperlipidemia). Stroke severity at admission was assessed with the National Institutes of Health Stroke Scale (NIHSS). Most of the subjects received intravenous heparin followed by oral anticoagulants; 10 patients were treated with aspirin owing to contraindication to anticoagulation. In selected cases, computed tomography angiography or digital subtraction angiography of supraortic arteries was performed to confirm the diagnosis of ICA dissection. The study was approved by the local ethics committee.

**Transcranial Doppler Ultrasonography**

Transcranial Doppler ultrasonography (TCD) was performed with a Multidop X/TCD instrument (DWL Elektronische Systeme GmbH, Germany) to assess intracranial vessels, including activation of the 3 major collateral pathways within 24 hours from symptom onset. The patency of major collateral vessels, namely the ophthalmic artery and anterior and posterior communicating arteries, was evaluated. With the ophthalmic approach, the ophthalmic artery was insonated at a depth of 45 to 50 mm to determine blood flow direction, and collateralization through the external carotid artery was assumed when ophthalmic flow was reversed. A patent anterior communicating artery was indicated by reversed blood flow in the A1 segment of the anterior cerebral artery ipsilateral to the ICA occlusion (this usually occurs in conjunction with acceleration of the contralateral anterior cerebral artery) or by a sudden drop in blood velocity in the relevant middle cerebral artery after compression of the nonoccluded contralateral common carotid artery. Patency of the dissected ICA was monitored weekly for the first month after stroke occurrence by duplex scan examination of neck vessels. All patients were followed up for a 3-month period by weekly examinations to evaluate the possible occurrence of new ischemic events and their clinical evolution. At the end of the follow-up period, all patients underwent a neurologic examination, which included the modified Rankin Scale (mRS) assessment. Based on the mRS score, patients were arbitrarily divided into 2 groups: good recovery (mRS score 0 to 1) and poor recovery (mRS score ≥2).

We grouped the participants according to the number of activated intracranial collateral vessels: 0 or 1, or ≥2. This dichotomization was established a priori on the basis of the results of a previous investigation performed in subjects with ICA atherothrombotic occlusion, wherein those with at least 2 activated intracranial collateral vessels showed an efficient cerebral hemodynamic status and a reduced risk of having a stroke ipsilateral to the ICA occlusion.

**Statistical Analysis**

The groups were compared with respect to demographic and clinical characteristics according to descriptive statistics (proportions, or means and standard deviations, as appropriate). The association between the number of collaterals and the presence or absence of disability at 90 days, defined as an mRS score ≥2, was evaluated by calculating the relative risks. To adjust these estimates for potential confounders, we used a multivariable regression model including variables of clinical interest (age, sex, and stroke severity) and those variables whose distribution showed a clinically important difference between the groups. We decided to use this approach instead of selected variables depending on the probability value, because in a relatively small group of patients such as this, the use of statistically based entry criteria may lead to the exclusion of important confounders. As a first approach to the multivariable analysis, we used a log-binomial model, but owing to the sparseness of data, this failed to converge. Therefore, we opted for a Poisson regression with robust variance estimator according to the SAS GENMOD procedure.

**Results**

We studied 66 patients (male:female = 30:36) with a mean ± SD age of 43.2 years (range, 18 to 78). Forty patients (61%) had 2 or more patent collaterals. Mean time (interval) from stroke onset to TCD evaluation was 12.6 ± 1.1 hours; regarding this aspect, there was no difference between the 2 groups (group with 0 or 1 collateral, 11.7 ± 6 hours vs group with 2 or 3 collaterals, 12.2 ± 5.8 hours). Compared with participants with none or only 1 collateral, patients with ≥2 collaterals were slightly younger (mean age, 41.4 vs 45.9 years, \(P=0.275\)), were more frequently men (57.7% vs 37.5%, \(P=0.133\)), and had a significantly lower stroke severity (mean NIHSS score at entry, 13.1 vs 15.4, \(P=0.015\)). Table 1 shows participants’ clinical characteristics. The differences between the 2 groups did not reach significant levels, including the occurrence of ICA recanalization within 30 days from stroke occurrence. The time course of recanalization was extremely variable among subjects, as was the time of investigation of carotid arteries, which was strongly influenced by the delay in arrival at our hospital. For this reason, we were unable to perform further analysis about the possible

<table>
<thead>
<tr>
<th>Table 1. Clinical Characteristics of Participants</th>
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<tr>
<td>Side of occlusion (left)</td>
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<tr>
<td>Smoking</td>
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<td>Hypertension</td>
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<td>Hypercholesterolemia</td>
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<td>Diabetes mellitus</td>
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<td>High serum homocysteine levels</td>
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<td>Use of anticoagulants</td>
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<tr>
<td>Use of antiaggregants</td>
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<tr>
<td>Internal carotid recanalization</td>
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Values are reported as percentages.
relevance of early (within the first 6 hours) versus late recanalization.

The median mRS score at 90 days was 1. The Figure shows the distribution of the number of patent collaterals according to mRS score. The number of patients with an mRS score $\leq 1$ was significantly higher in the group with 2 or 3 collaterals compared with the group with 0 or 1 collateral ($P<0.001$, Fisher’s exact test). Only 2 patients among those with $>1$ activated collateral had an mRS score $\geq 1$. In relative terms, only 5% of patients with 2 or more activated collaterals had an mRS score $>1$ at 90 days (probability of having an mRS score $\leq 1$ at 90 days was 95%) compared with 76.9% among those with 0 or 1 patent collateral. The resulting relative risk was 15.4 (95% CI, 3.9 to 60.4). After correction for potential confounders (Table 2), the estimate was substantially unchanged (relative risk=14.9; 95% CI, 3.24 to 68.46). In fact, the multiple logistic regression indicated that the number of collaterals was the sole significant predictor of outcome.

**Discussion**

The main finding of our investigation is that efficient intracranial collateral pathways are significantly associated with a favorable clinical evolution in ischemic stroke patients with spontaneous dissection of the ICA. In particular, early detection of 2 or 3 activated collateral vessels that are able to compensate for flow reduction distally to the ICA occlusion can predict a good functional outcome, independently of other traditional prognostic factors like age and NIHSS score at onset. The efficiency of intracranial collateral pathways has already been established as a factor able to predict a reduced risk of ipsilateral stroke in subjects with atherothrombotic ICA occlusion. In the present study, we also demonstrated a role for collateral pathways in limiting ischemic damage. The short follow-up period did not allow us to investigate the risk of stroke relapse.

At present, the prognosis for stroke patients with ICA spontaneous dissection is not well defined, even though there is a general assumption of a good functional outcome. The finding of high mortality or very poor outcome rates in some studies raised the suspicion that ICA dissection may be underestimated owing to the lack of or delay in the diagnosis during the acute phase, especially in patients with severe clinical presentations. In this respect, the extent of cerebral ischemia and the presence of arterial occlusion represent the 2 main factors unfavorably influencing prognosis and reducing the rate of correct diagnoses. Taking into account these considerations, in our study we included subjects with clinical and neuroradiologic findings of cerebral ischemia ipsilateral to an ICA occlusion due to spontaneous arterial dissection. In this subgroup of patients, whose functional outcome is expected to be less favorable, the definition of reliable prognostic indicators could be relevant to identify subjects requiring more aggressive surveillance and treatment. In our study population, $\approx 30\%$ of patients had functional, relevant sequelae 3 months after stroke onset, and this unfavorable outcome could be predicted early in most cases by an inadequate pattern of cerebral vessel compensatory pathways. In fact, 20 of 22 patients who remained significantly disabled at 3 months after stroke had none or only 1 collateral vessel, whereas most subjects (38 of 44) with no significant functional consequences had 2 or 3 early activated collaterals.

A previous study in a smaller sample of patients reported that good collaterals could positively influence functional independence in patient with carotid or vertebral occlusion secondary to arterial dissection. However, the presence of intra- and extracranial collaterals was determined by conventional angiography. Compared with angiography, TCD is a noninvasive, less expensive, and less time-consuming technique and is widely available. The evaluation of collateral pathway efficiency by TCD can be rapidly performed, even in the Emergency Department, to select those patients who are eligible for endovascular recanalization procedures. In fact, although no evidence is available so far, one could speculate that the earlier endovascular treatment is performed, the better would be the clinical outcome.

Different factors may be involved in the development of a different pattern of collaterals in subjects with ischemic stroke ipsilateral to a severe ICA steno-occlusive disease. The timing of ICA lumen narrowing and individual anatomic predisposition may be valid explanations for a different hemodynamic supply and for the consequent ability to pre-

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**Table 2. Multivariable Analysis of the Probability of Being Physically Impaired at 90 Days**

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<thead>
<tr>
<th></th>
<th>Adjusted Relative Risk</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Age</td>
<td>1.01</td>
<td>0.97–1.07</td>
</tr>
<tr>
<td>Sex (men)</td>
<td>0.83</td>
<td>0.52–1.32</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.74</td>
<td>0.31–1.74</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>1.03</td>
<td>0.87–1.22</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.00</td>
<td>0.91–1.09</td>
</tr>
<tr>
<td>High serum homocysteine levels</td>
<td>0.80</td>
<td>0.55–1.19</td>
</tr>
<tr>
<td>Internal carotid recanalization</td>
<td>0.94</td>
<td>0.88–1.00</td>
</tr>
<tr>
<td>0/1 activated collaterals</td>
<td>14.9</td>
<td>2.10–68.46</td>
</tr>
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**Figure.** Distribution of the number of patent collateral vessels by mRS score.
vent a potentially devastating vascular event. Compared with patients with ICA atherothrombotic occlusion, in patients with ICA occlusion due to artery dissection, collateral pathways need to be very rapidly established. In this respect, collateral flow would be able to ameliorate the ischemic damage but not prevent its onset. The extreme variability of the evolution of carotid occlusion among subjects prevented us from investigating in detail whether very early recanalization could influence prognosis. However, this aspect may be very relevant and deserves careful evaluation in a future study performed in patients very early after stroke onset.

The fact that these subjects had a lower clinical severity at stroke presentation suggests that hemodynamic changes may be relevant from the very early phases of the disease. It is worth noting that the number of activated collaterals was a better predictor of clinical outcome than neurologic status at onset. This result suggests that an efficient collateral circulation could hinder progressive ischemic damage, inducing prompt reperfusion of the ischemic penumbra and possibly facilitating cerebral plastic reorganization subtending clinical recovery. The younger age and the prevalence of men in the group with a better hemodynamic response could be explained by the fact that the adaptability of cerebral vessels may be influenced by different factors. In this respect, previous studies have demonstrated age and sex differences in the modulation of cerebral circulation and in the risk of stroke. The differences in smoking, diabetes mellitus, and hyperhomocysteinemia were not statistically significant. Despite this, considering that these vascular risk factors are not trivial from a clinical point of view and because there are plausible biological explanation for some effects on cerebral hemodynamic changes, we also considered their possible influence on the outcome and found no significant interference with the role of an early development of collateral pathways. The fact that the differential characteristics between the groups with 2 or 3 and 0 or 1 collateral vessels did not show a direct effect on outcome may have different explanations. It is possible that their influence was not sufficiently relevant to impact clinical evolution. On the other hand, their action could influence cerebral hemodynamic mechanisms so as to justify only an indirect action on clinical outcome. Obviously, we cannot exclude that the relatively low number of subjects included in our study may have influenced the finding.

Although our results do not offer therapeutic indications, our findings suggest that early evaluation of the efficiency of intracranial collateral pathways, compensating for the ICA lumen reduction, may provide reliable information to predict functional outcome. The different prognoses in patients with ICA dissections with comparable carotid narrowing might also contribute to explaining the lack of evidence about the superiority of 1 treatment over another. In fact, studies investigating the effect of pharmacologic or interventional procedures in stroke patients with ICA dissection have not considered cerebral hemodynamic status as a possible determinant of prognosis. On the other hand, in ICA occlusion secondary to dissection, hyperperfusion has been suggested to play a significant role in the pathogenesis of ischemic damage, and as such, an unfavorable hemodynamic status could be counteracted by endovascular revascularization. Based on these findings, further studies are needed to investigate whether early assessment of cerebral collateral efficiency can help in better defining the aggressiveness of treatment in subjects with stroke due to spontaneous ICA dissection. In particular, the possibility of selecting those patients at highest risk of an unfavorable outcome could contribute to identifying those who might benefit most from endovascular recanalization procedures. Further studies are also necessary to confirm the possible role of hyperhomocysteinemia and other vascular risk factors in hindering the activation of collateral pathways and in indirectly influencing the clinical evolution in patients with stroke due to arterial dissection.

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Disclosures
None.

References


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