Effect of Collateral Blood Flow and Cerebral Vasomotor Reactivity on the Outcome of Carotid Artery Occlusion

Fabrizio Vernieri, MD; Patrizio Pasqualetti, PhD; Maria Matteis, PhD; Francesco Passarelli, MD; Elio Troisi, MD; Paolo M. Rossini, MD; Carlo Caltagirone, MD; Mauro Silvestrini, MD

Background and Purpose—Evidence suggests that an alteration in cerebral hemodynamics plays a relevant role in the occurrence of stroke in patients with carotid occlusion. The purpose of the present study was to evaluate the relationships among baseline characteristics, type and number of collateral pathways, cerebral vasomotor reactivity (VMR), and outcome of patients with carotid occlusion.

Methods—One hundred four patients with symptomatic or asymptomatic internal carotid artery occlusion were followed up prospectively for a median period of 24 months. Cerebral VMR to apnea was calculated with transcranial Doppler ultrasonography by means of the breath-holding index (BHI) in the middle cerebral arteries. The patency of the 3 major intracranial collateral vessels was also evaluated.

Results—During the follow-up period, 18 patients experienced an ischemic stroke ipsilateral to internal carotid artery occlusion. Among factors considered, only older age, number of collateral pathways, and BHI values in the middle cerebral artery ipsilateral to the occluded side were significantly associated with the risk of ipsilateral stroke (P<0.001, P=0.008, and P<0.001, respectively; multiple Cox regression analysis). A normal VMR and favorable prognosis characterized patients with full collateral development; in this group, no patient experienced an ischemic event. On the other hand, an impaired VMR and increased probability of experiencing a stroke were found in patients without collateral pathways; the annual risk of ipsilateral stroke in this group was 32.7%. Patients with 1 or 2 collateral pathways showed a different VMR ranging from normal to strongly reduced BHI values. The ipsilateral stroke event risk was 17.5% in patients with 1 collateral vessel and 2.7% in patients with 2 collateral pathways. In this case, the risk of cerebrovascular events occurring during the follow-up period was significantly related to VMR.

Conclusions—These data suggest that cerebral hemodynamic status in patients with carotid occlusive disease is influenced by both individual anatomic and functional characteristics. The planning of strategies to define the risk profile and any attempt to influence patients’ outcome should be based on the evaluation of the intracranial hemodynamic adaptive status, with particular attention to the number of collateral vessels and the related VMR. (Stroke. 2001;32:1552-1558.)

Key Words: carotid artery occlusion ■ collateral circulation ■ ischemic ■ stroke ■ ultrasonography, Doppler, transcranial ■ vasomotor reactivity

Patients with complete carotid artery occlusion may show no evidence of intracranial hemodynamic compromise, because collateral circulation compensates for the decrease in cerebral blood flow (CBF).1-3 Anterior and posterior communicating arteries are considered the primary collateral pathways; the ophthalmic artery (OA) and blood flow via leptomeningeal vessels are considered the secondary pathways. When these collateral pathways are not adequate to maintain normal blood flow, vasodilatation of arterioles occurs and reduces cerebrovascular resistance for sustaining normal cerebral perfusion. This phenomenon is known as cerebrovascular autoregulation.4 Decreased cerebral vasomotor reactivity (VMR) indicates the presence of preexisting vasodilation, which reflects a reduced capacity of cerebral resistance vessels to adapt their caliber in response to changes in cerebral perfusion.

Compromised CBF plays an important role in causing ipsilateral ischemic events in patients with occlusion of the internal carotid artery (ICA).5,6 In fact, there is evidence that cerebral hemodynamic status can predict the outcome of ICA occlusion.7-12

Controversial results were reported in previous studies that used different techniques to investigate the effect of the type and number of collateral pathways on cerebral hemodynamic status.13-19

Transcranial Doppler (TCD) ultrasonography provides a simple and noninvasive technique to evaluate blood flow
velocity in larger cerebral vessels\(^\text{20-22}\) and to measure cerebral VMR.\(^\text{23,24}\) TCD also is a reliable tool for evaluating the collateral supply in patients with ICA occlusions.\(^\text{25,26}\)

The aim of the present study was to evaluate prospectively the influence of the type and number of collateral pathways and the related VMR on the outcome of patients with carotid artery occlusion.

### Subjects and Methods

Between January 1995 and December 1998, 123 consecutive symptomatic or asymptomatic subjects with occlusion of the extracranial segment of the ICA underwent ultrasonicographic examination. Carotid artery disease was assessed and defined by color flow B-mode Doppler ultrasound (SPR 8000; Esaote Biomedica) according to standardized criteria.\(^\text{27,28}\) The vertebralbasilar system was evaluated as described by Bartels.\(^\text{29}\) All patients underwent a careful neurological and cardiological examination, ECG, transesophageal echocardiography, and brain CT or MRI. Moreover, complete blood chemistries and a clinical history with particular attention to the major vascular risk factors (hypertension, diabetes, smoking, and hyperlipidemia) were obtained from each patient. Exclusion criteria included poor insonation of the temporal bone window, possible or probable embolizing cardiopathy (atrial fibrillation, mitral valve stenosis, prolapse or calcification, mechanical cardiac valves, recent myocardial infarction, left ventricular thrombus, atrial tachycardia, or dilated cardiomyopathies, and patent foramen ovale). Patients with stenosis contralateral to ICA occlusion of \(>70\%\) and patients with significant alteration of the vertebral arteries were also excluded from further evaluation to avoid interference with the hemodynamic effects of the carotid occlusion.

Nineteen of the 123 patients were excluded: 9 due to poor insonation of the temporal bone window, 5 due to the presence of a cardiopathy (atrial fibrillation in 3 patients and myocardial infarction and successive cardiac failure in 2 patients), and 5 due to severe carotid stenosis contralateral to the occlusion. Of 104 eligible patients, 71 were symptomatic in the vascular territory of the middle cerebral artery (MCA) ipsilateral to the carotid artery occlusion. Of these, 35 had a TIA and 36 were investigated for a functionally independent or minor stroke (Rankin Scale score 1 or 2). Patients with major stroke were not included because of the difficulty of obtaining their full cooperation and in evaluating the occurrence of any further ischemic event. In the same period, 33 patients with asymptomatic carotid occlusion were also enrolled. These subjects undergoing ultrasonographic examination in the outpatient department who were referred by their general practitioner for suspected carotid stenosis.

Two dual 2-MHz transducers fitted onto a headband and placed on the temporal bone windows were used to obtain a bilateral continuous measurement of MFV in the MCAs. Mean flow velocity and end-tidal CO\(_2\) at rest were obtained by the continuous recording of a 2-minute period of normal room air breathing. During the same period, mean blood pressure (MBP) and heart rate (HR) were continuously monitored by means of a blood pressure monitor (2300 Finapress; Ohmeda). After a breath-holding period, MFV, MBP, and HR were recorded during a 4-second interval. Subjects were asked to hold their breath for 30 seconds after a normal inspiration; all subjects were able to hold their breath for the required period. Before proceeding to the definitive recording, patients were trained to perform the procedure correctly. The exact length of apnea was checked by means of a respiratory activity monitor (Oxy-cap Datex) and ranged from 29.6 to 30.4. Changes in HR and MBP after the apnea period were slight: 2% to 4% for HR and 3% to 5% for MBP. This method of induction of hypercapnia proved to be effective and reproducible in the study of cerebral hemodynamics under both normal and pathological conditions.\(^\text{20,21}\)

In symptomatic patients, all TCD evaluations were performed \(\geq 3\) months after stroke (range 96 to 115 days), because it has been demonstrated that cerebral VMR usually improves 2 to 3 months after the occlusion has occurred, probably due to full development of the intracranial collateral pathways.\(^\text{32,33}\)

Examination of vessels of the circle of Willis was performed as described by Aaslid et al.\(^\text{34}\) The patency of major collateral vessels, namely OA, anterior (ACoA), and posterior (PCoA) communicating arteries, was evaluated. A patent ACoA was indicated by reversed blood flow in the A1 segment of the anterior cerebral artery (ACA) ipsilateral to the ICA occlusion (this usually occurs in conjunction with acceleration of the contralateral ACA) or by a sudden drop in blood velocity in the relevant MCA after compression of the nonoccluded contralateral common carotid artery (CCA). A patent PCoA was indicated by a marked increase of blood flow velocity in the basilar artery (>70 cm/s) or in the P1 segment of the posterior cerebral artery ipsilateral to the relevant MCA after compression of the nonoccluded contralateral CCA. With the ophthalmic approach, the OA was insonated at a depth of 45 to 50 mm to determine blood flow direction, and collateralization through the external carotid artery (OA) was assumed if ophthalmic flow was reversed. All 3 possible collateral sources were assessed.\(^\text{15,26}\)

Conventional angiography was performed in 48 of the 71 symptomatic patients during hospitalization to optimize treatment and to exclude significant contralateral carotid or ipsilateral external carotid stenosis, as well as severe intracranial atherosclerotic disease. The remaining 23 symptomatic patients underwent a magnetic resonance angiography (MRA) examination. MRA was also performed in 24 of the 33 asymptomatic patients. The results of these evaluations were always in accordance with ultrasonographic findings. In the remaining 9 patients with asymptomatic carotid occlusion, diagnosis of the ICA occlusion and the type and number of collateral pathways were performed only by means of ultrasonography.

All patients included in our study were receiving antiplatelet therapy with 325 mg/d aspirin or 500 mg/d ticlopidine. Furthermore, all patients had the best medical treatment for any treatable vascular risk factor.\(^\text{34-36}\) In particular, careful attention was paid to the treatment of hypertension, with the aim of obtaining values of systolic and diastolic pressure in the range of 130 to 145 and 80 to 85 mm Hg, respectively. More aggressive treatment was avoided, as suggested by Widder et al.\(^\text{37}\)

Our patients were followed-up by telephone every 3 months and reevaluated clinically every 6 months by 1 designated investigator, who was unaware of the TCD data. End points were defined as stroke ipsilateral or contralateral to the carotid occlusion and death. In the case of stroke occurrence, a CT and/or MR was performed. For the events not directly observed in our hospital, clinical records were acquired for an exact description.

The study was approved by the local ethics committee. Each subject gave informed written consent.

### Statistical Analysis

The annual rate of adverse events was calculated by means of the person-year method. Between-group comparisons with and without
events were made by $\chi^2$ and t test, as appropriate. Logistic and Cox regression analyses allowed us to determine which factors could be considered as independent predictors of ipsilateral ischemic events. The likelihood-ratios (LR) forward stepwise method was chosen to select variables. Hazard ratios and 95% CIs were reported to indicate the size effect. The goodness-of-fit of the final model was tested by Hosmer and Lemeshow’s index. Pearson’s $r$ coefficient was applied to verify the correlation between the examined variables. The analyses were performed with the use of SPSS 8.0 software (SPSS Inc). The significance level was set at 0.05 throughout the statistical analysis.

**Results**

The median follow-up for the 104 patients was 24 months (minimum 8 months, maximum 60 months). Twenty-seven were women (26%) and 77 were men (74%). Mean age was 68.7 years (SD 7.4 years). During the follow-up period, 18 patients had a stroke ipsilateral to ICA occlusion; only 2 strokes occurred contralateral to the occluded side. All strokes were of ischemic origin as confirmed by CT or MR examination.

All of the patients’ baseline characteristics are reported in Table 1, including the main risk factors (hypertension, diabetes, smoking, and hyperlipidemia) and hemodynamic parameters.

Of all parameters considered, we found significant differences between patients who had a ipsilateral ischemic stroke during the follow-up period and those who did not with respect to the following variables: clinical status at the first evaluation, number of collateral pathways, age, and ipsilateral and contralateral BHI. Regarding clinical status, different percentages of events were observed in the 3 groups considered ($P=0.01$), indicating an annual risk of stroke equal to 1.3% in asymptomatic patients, 7.7% in the TIA group, and 16.7% in minor stroke patients. Concerning the number of collateral pathways, the significance of the $\chi^2$ statistic is

### Table 1. Patient Characteristics Relative to Ipsilateral Ischemic Event Occurrence

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>Statistical Test, Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical status at T0, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>33 (31)</td>
<td>1 (3)</td>
<td>32 (97) $\chi^2, P=0.010$</td>
</tr>
<tr>
<td>TIA</td>
<td>35 (34)</td>
<td>6 (17)</td>
<td>29 (83)</td>
</tr>
<tr>
<td>Minor stroke</td>
<td>36 (35)</td>
<td>11 (31)</td>
<td>25 (69)</td>
</tr>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>77 (74)</td>
<td>14 (18)</td>
<td>63 (82) $\chi^2, P=0.691$</td>
</tr>
<tr>
<td>F</td>
<td>27 (26)</td>
<td>4 (15)</td>
<td>23 (85)</td>
</tr>
<tr>
<td><strong>Hypertension, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>68 (65)</td>
<td>13 (19)</td>
<td>55 (81) $\chi^2, P=0.503$</td>
</tr>
<tr>
<td>No</td>
<td>36 (35)</td>
<td>5 (14)</td>
<td>31 (86)</td>
</tr>
<tr>
<td><strong>Diabetes, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>34 (33)</td>
<td>7 (21)</td>
<td>27 (79) $\chi^2, P=0.538$</td>
</tr>
<tr>
<td>No</td>
<td>70 (67)</td>
<td>11 (16)</td>
<td>59 (84)</td>
</tr>
<tr>
<td><strong>Smoking, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>45 (43)</td>
<td>7 (16)</td>
<td>38 (84) $\chi^2, P=0.680$</td>
</tr>
<tr>
<td>No</td>
<td>59 (57)</td>
<td>11 (19)</td>
<td>48 (81)</td>
</tr>
<tr>
<td><strong>Hyperlipidemia, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>30 (29)</td>
<td>3 (10)</td>
<td>27 (90) $\chi^2, P=0.210$</td>
</tr>
<tr>
<td>No</td>
<td>74 (71)</td>
<td>15 (20)</td>
<td>59 (80)</td>
</tr>
<tr>
<td><strong>Contralateral stenosis, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0%</td>
<td>37 (36)</td>
<td>5 (14)</td>
<td>32 (86) $\chi^2, P=0.443$</td>
</tr>
<tr>
<td>&lt;40%</td>
<td>39 (37)</td>
<td>6 (15)</td>
<td>33 (85) Test for linear association,</td>
</tr>
<tr>
<td>40–69%</td>
<td>28 (27)</td>
<td>7 (25)</td>
<td>21 (75) $P=0.243$</td>
</tr>
<tr>
<td><strong>Collateral vessels, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>5 (5)</td>
<td>3 (60)</td>
<td>2 (40) $\chi^2, P&lt;0.001$</td>
</tr>
<tr>
<td>1</td>
<td>38 (37)</td>
<td>12 (32)</td>
<td>26 (68) Test for linear association,</td>
</tr>
<tr>
<td>2</td>
<td>49 (47)</td>
<td>3 (6)</td>
<td>46 (94) $P&lt;0.001$</td>
</tr>
<tr>
<td>3</td>
<td>12 (11)</td>
<td>0 (0)</td>
<td>12 (100)</td>
</tr>
<tr>
<td><strong>Age, y, mean±SD</strong></td>
<td>68.7±7.4</td>
<td>73.4±5.6</td>
<td>67.7±7.4 t test, $P=0.003$</td>
</tr>
<tr>
<td><strong>BHI ipsilateral, mean±SD</strong></td>
<td>0.72±0.42</td>
<td>0.37±0.27</td>
<td>0.79±0.41 t test, $P&lt;0.001$</td>
</tr>
<tr>
<td><strong>BHI contralateral, mean±SD</strong></td>
<td>1.00±0.35</td>
<td>0.86±0.30</td>
<td>1.03±0.35 t test, $P&lt;0.001$</td>
</tr>
</tbody>
</table>
strengthened by the high significance of its linear component (test for linear association, \(P < 0.001\)), confirming the highest risk of stroke in patients with absent collateral blood flow. In particular, we found an annual risk of 32.7% in patients with no collateral pathways, 17.5% in patients with 1 collateral pathway, and 2.7% in patients with 2 collateral pathways. However, no patient with 3 compensatory circles had an ischemic event; the estimated risk was 0%. Figure 1 shows the percentages of stroke according to the type of collateral pathway. Considering patients with only 1 activated collateral pathway, ipsilateral stroke occurred in 36% of patients with OA, in 38% of patients with PCoA, and in 26% of patients with ACoA (\(P = 0.783\), NS). Similarly, no difference was observed in the percentages of stroke in the 3 groups of patients with 2 collateral pathways (PCoA + OA 13%, ACoA + OA 7%, ACoA + PCoA 0%, \(P = 0.522\), NS), although no event was observed in the latter group. Figure 2 shows the Kaplan-Meier survival plot about the occurrences of ipsilateral ischemic events in the groups with 0, 1, 2, and 3 collateral pathways.

In addition, as shown in Table 1, patients who developed an ipsilateral stroke were significantly older (73.4 versus 67.7 years) and had more impaired ipsilateral (0.37 versus 0.79) and contralateral (0.86 versus 1.03) BHI. No other variable considered was significantly related to the occurrence of the adverse event.

All parameters reported in Table 1 were entered in the Cox regression procedure to determine which variables could predict an ischemic event ipsilateral to the occluded artery. The final regression model is reported in Table 2. Age was forced in the first block of the stepwise procedure to remove its effect on the parameters addressed in the present study. On the basis of the forward LR method applied to the second block, the first variable to be considered in the model was the number of collateral pathways, followed by ipsilateral BHI. No other variable could be added to improve the model. The nonsignificant value of Hosmer and Lemeshow’s goodness-of-fit test (\(P = 0.464\)) confirmed the nice data fitting of the final model. The risk was 17% greater for each additional year of age. However, for each additional collateral vessel, the risk of stroke decreased by \(\approx 64\%\). Finally, when BHI increased by 0.10, the hazard ratio equaled 0.72, indicating that the risk of stroke decreased by \(\approx 28\%\). It is worth noting that these predictive parameters are independent of each other, because each effect is adjusted to the effect of the other significant factors. Table 1 (univariate analysis) and Table 2 (multivariate analysis) present the results in detail. The contralateral BHI (strongly significant in Table 1) did not enter the final model, because its effect is fully absorbed by the strong and consistent effect of ipsilateral BHI. On the other hand, both the number of collateral vessels and the ipsilateral BHI entered the final model (after age adjustment) and should be considered as independent predictors. Actually, these 2 factors are significantly correlated but not enough to exclude 1 of them as the prognostic factor. In particular, only 22% of the BHI variance is accounted for by the number of collateral pathways (Pearson’s \(r = 0.47\), \(P < 0.001\)), suggesting that BHI may also depend on other factors. With regard to Figure 3 (in which the obvious effect of age was removed), it should be noted that there is no overlapping of BHI values in patients without collateral pathways (global estimated risk >60%, BHI range 0.10 to 0.48) and with 3 collateral pathways (global estimated risk < 0.5%, BHI range 0.63 to 1.65). Actually, considering only these 2 opposite groups, the Cox analysis did not select BHI as a predictive factor (\(P > 0.05\)), because the risk of stroke depends only on the number of collateral vessels, which are able to explain both

### Table 2. Multiple Cox Regression for Ipsilateral Ischemic Events: Parameters of the Final Model

<table>
<thead>
<tr>
<th>Independent Prognostic Factor</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of collateral vessels</td>
<td>0.35</td>
<td>0.16–0.76</td>
<td>0.008</td>
</tr>
<tr>
<td>Age, y</td>
<td>1.17</td>
<td>1.07–1.27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BHI ipsilateral*</td>
<td>0.72</td>
<td>0.60–0.87</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*BHI raw values were multiply by 10 for a simpler interpretation of the result.
The results of the present study further emphasize the importance of cerebral hemodynamics in determining the prognosis of patients with ICA occlusion. In fact, in addition to age, which is the most important and obvious risk factor for stroke, the prognosis of patients with carotid artery occlusion was significantly influenced by the number of collateral pathways and by cerebral VMR. It is worth noting that we did not find in any of our patients a direct relationship between the anatomic configuration of collateral blood flow and the capacity of the intracranial vessels to adapt their caliber after a vasodilating stimulus. This finding is in accordance with the results of a recent study that demonstrated the lack of a vasodilating stimulus. This finding is in accordance with the results of a recent study that demonstrated the lack of a vasodilating stimulus.

In our study, as shown in Figure 3, the absence of any collateral pathways or the presence of all 3 collateral pathways was linked to a strongly impaired or normal cerebral angiography, and increased oxygen extraction fraction, measured by PET in patients with ICA occlusion.37

There are controversial findings in the literature regarding the role of collateral pathways in vasomotor reactivity. Norving et al1 first demonstrated that patients with collateral flow via the primary pathways have better CO2 reactivity than do patients who depend on the OA. In addition, it was shown that patients with collateral flow through both ACoA and PCoA have better cerebral hemodynamics than do patients with only 1 functioning primary pathway.13 Moreover, a TCD study14 found that OA is recruited only if both communicating arteries of the circle of Willis are unavailable or insufficient. Ringelstein et al15 described a hierarchy of collateral pathways to the brain, indicating a key role of the ACoA in compensating for ICA occlusion. The PCoA emerged as a second-ranked, somewhat less effective pathway. More recently, it was remarked that collateral flow through PCoA alone is a sign of deteriorated cerebral perfusion.16 On the other hand, it has been reported that only a small or absent PCoA can be considered as a significant risk factor for watershed infarctions.17 Finally, a recent study suggested that patients with ICA occlusion who had a decreased CO2 reactivity more often showed absent willisian collateral flow and less often showed collateral flow via both primary pathways compared with patients who had a normal CO2 reactivity.40

A study with MRA and TCD48 demonstrated that in symptomatic patients with ICA occlusions, different collateral flow patterns via the ACoA, PCoA, or OA have no effect on hemodynamic and metabolic parameters as long as 1 of these pathways is present. The absence of collateral flow via VMR, respectively. These conditions were correlated with a high or low probability of a stroke, respectively. On the other hand, the presence of 1 or 2 collateral pathways was correlated with a different risk of stroke in relation to the intracranial vascular reserve capacity. In other words, in many patients, namely those with 1 or 2 intracranial collateral pathways, the functional aspect of cerebral hemodynamics appeared to be more important than the simple anatomic configuration in influencing their outcome. According to our final model (represented in Figure 3), in the presence of BHI values of $\geq 1$, indicating good VMR,12 patients with 1 or 2 collateral vessels presented a similar estimated risk of stroke. On the other hand, in the group with only 1 collateral pathway, a patient with a BHI value of $> 0.8$ has an estimated risk of stroke near 10%, whereas a patient with a BHI value of 0.3 has a risk level of 40%. Although less, this strong dependence on the hemodynamic parameter of the probability of a stroke is also clear in the group with 2 collateral pathways.

In our patient group, we found that 72 patients (69%) had collateral blood flow via ACoA, and in 39 subjects (37%), PCoA was present as a collateral pathway. Our TCD data agree with angiographic findings. In fact, in several studies that investigated patients with severe unilateral ICA stenosis or occlusion, collateral flow was found in 47% to 72% of the patent anterior collateral pathways and in 36% to 59% of the patent ipsilateral PCoAs.26,38,39 Moreover, in a recent MRA study, collateral flow was found in 69% of the patent anterior collateral pathways and in 32% of the patent ipsilateral PCoAs.18

Discussion

The results of the present study further emphasize the importance of cerebral hemodynamics in determining the prognosis of patients with ICA occlusion. In fact, in addition to age, which is the most important and obvious risk factor for stroke, the prognosis of patients with carotid artery occlusion was significantly influenced by the number of collateral pathways and by cerebral VMR. It is worth noting that we did not find in any of our patients a direct relationship between the anatomic configuration of collateral blood flow and the capacity of the intracranial vessels to adapt their caliber after a vasodilating stimulus. This finding is in accordance with the results of a recent study that demonstrated the lack of correlation between pattern of collateralization, studied by cerebral angiography, and increased oxygen extraction fraction, measured by PET in patients with ICA occlusion.37

In our study, as shown in Figure 3, the absence of any collateral pathways or the presence of all 3 collateral pathways was linked to a strongly impaired or normal cerebral angiography, and increased oxygen extraction fraction, measured by PET in patients with ICA occlusion.37

Figure 3. Predicted probabilities of ipsilateral ischemic events as calculated by Cox multivariate regression. The risks are plotted against BHI values and number of collateral vessels.
ACoA, ipsilateral PCoA, and ipsilateral OA can result in severely deteriorated hemodynamic and metabolic status, presumably increasing the risk of stroke. Moreover, Hedera et al.\(^6\) analyzed the relationship between number of collateral vessels and outcome of the ICA occlusion. They found that the presence of >1 major collateral pathway (ACoA, PCoA, and OA) supplying the hemisphere on the side of the occlusion was positively associated with better outcome in the patients.

The results of our investigation are in accordance with the last 2 studies. In fact, the relevant aspect of our study is that the number of collateral pathways was more effective than the type in determining a better intracranial hemodynamic status. Also, the patients’ prognosis was significantly influenced by the number and the efficiency of the intracranial collateral vessels.

Several follow-up studies compared prognosis in medically treated patients with and without compromised CBF.\(^7\)–\(^12\) In these studies, patients with impaired cerebral hemodynamics had a worse prognosis than did similar patients with normal CBF measurements; in particular, our previous study demonstrated that low BHI values can be considered the most important predictive factor for further cerebrovascular ischemic events in patients with ICA occlusion.\(^12\)

In the present study, we did not find a significant link between cerebral infarction characteristics and hemodynamic compromise; in fact, of the 18 strokes that occurred in our population ipsilateral to the occluded carotid artery, only 8 had the neuroradiological distribution of watershed infarctions. It should be emphasized that an impairment in the capacity of intracranial circulation to compensate for a condition of cerebral hyperperfusion can cause not only increased susceptibility to ischemic damage during negative hemodynamic systemic events but also reduced possibility of hindering the effect of an acute embolic event. In fact, it has been demonstrated that the probability of a microembolism becoming symptomatic is increased in the presence of a reduced cerebrovascular reserve.\(^41\) Accordingly, the hypothesis was recently advanced that hyperperfusion and embolism often coexist and that their consequences on regional CBF can be interactive.\(^6\)

The aim of the present investigation was not only to confirm our previous findings but also to support a pathophysiological explanation of the link between vasomotor reactivity and outcome in patients with carotid artery occlusion. In particular, we wanted to determine the role of intracranial collateral pathways. The most important aspect is that the anatomic and functional characteristics of intracranial circulation may be regulated by different factors. Although the first issue can be studied using imaging techniques, the second requires functional measurements with techniques able to investigate metabolic and/or hemodynamic features that are not usually part of the routine investigation of patients with carotid occlusion. This can result in confusion in the practical management of patients. For instance, it must be established when conventional angiography or MRA, showing a particular collateralization pattern, can be considered sufficient to define cerebral hemodynamic status and, consequently, a patient’s prognosis or further investigation is required for a better characterization. Our results demonstrate that patients with carotid occlusion can be separated into 2 groups. In the first group, which includes patients without any collateral pathways and patients with 3 collateral pathways, the anatomic characteristics of intracranial collateralization are associated with the cerebrovascular reserve and they are able per se to define the risk of the development of cerebrovascular ischemic events. Therefore, although in this case the anatomic definition can be considered sufficient, in most patients with 2 and particularly with 1 collateral pathway (group 2), a functional dynamic evaluation is necessary to define the risk profile. In fact, in this category of patients, the study of VMR to define the efficiency of intracranial reserve supports more accurate parameters than the simple evaluation of the number of collateral pathways. From a practical point of view, these findings lead to a reconsideration of the opportunity of graduating the use of sophisticated investigations in patients with carotid occlusion to better define their prognosis and assess the need for more or less aggressive treatment.

**Acknowledgments**

This study was supported by AFAr (Associazione Fatebenefratelli per la Ricerca) and by IRCCS S. Lucia grants. The authors wish to acknowledge Maria M. Filippi, MD, and Francesco Tibuzzi, MD, for their important role in clinical evaluation of the patients during the follow-up period.

**References**


Effect of Collateral Blood Flow and Cerebral Vasomotor Reactivity on the Outcome of Carotid Artery Occlusion

Fabrizio Vernieri, Patrizio Pasqualetti, Maria Matteis, Francesco Passarelli, Elio Troisi, Paolo M. Rossini, Carlo Caltagirone and Mauro Silvestrini

*Stroke*. 2001;32:1552-1558
doi: 10.1161/01.STR.32.7.1552

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/32/7/1552

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org//subscriptions/