Outcome of Carotid Artery Occlusion Is Predicted by Cerebrovascular Reactivity

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Background and Purpose—The purpose of this study was to investigate the possibility of obtaining prognostic indications in patients with internal carotid occlusion on the basis of intracranial hemodynamic status, presence of previous symptoms of cerebrovascular failure, and baseline characteristics.

Methods—Cerebral hemodynamics were studied with transcranial Doppler ultrasonography. Cerebrovascular reactivity to apnea was calculated by means of the breath-holding index (BHI) in the middle cerebral arteries. Sixty-five patients with internal carotid artery occlusion were followed-up prospectively (median, 24 months), 23 patients were asymptomatic and 42 symptomatic (20 with transient ischemic attack and 22 with stroke).

Results—During the follow-up period, 11 symptomatic patients and 1 asymptomatic patient had another ischemic event ipsilateral to carotid occlusion. Among factors considered, only lower BHI values in the middle cerebral arteries ipsilateral to carotid occlusion and older age were significantly associated with the risk of developing symptoms (P=0.002 and P=0.003, respectively; Cox regression multivariate analysis). Based on our data, a cut point of the BHI value for distinguishing between pathological and normal cerebrovascular reactivity was determined to be 0.69. All patients except one, who developed TIA or stroke during the follow-up period, had BHI values ipsilateral to carotid occlusion of <0.69.

Conclusions—These data suggest that impaired cerebrovascular reactivity is predictive for cerebral ischemic events in patients with carotid occlusion. (Stroke. 1999;30:593-598.)

Key Words: carotid occlusion ■ cerebrovascular circulation ■ stroke ■ ultrasonography, Doppler, transcranial

The outcome of internal carotid artery (ICA) occlusion is highly variable. Klijn et al1 reviewed 20 observational studies published between 1960 and 1995 that investigated the risk of stroke in patients with occlusion of the ICA. The annual stroke rate varied between 0% and 20%. In these studies, measurements of the cerebral blood flow (CBF) were not performed. Several follow-up studies have attempted to show a correlation between an increased risk of stroke ipsilateral to an occluded internal carotid artery and a compromised CBF; assessments were made with the use of various methods.2–8 The results have not been unequivocal. Moreover, other studies have demonstrated a lower annual stroke risk in asymptomatic patients with ICA occlusion than in symptomatic patients.9,10 Recently, Derdeyn et al11 demonstrated that compromised CBF in patients with ICA occlusion is associated with the presence of previous ischemic symptoms and with no other risk factors; consequently, they remarked on the importance of distinguishing between symptomatic and asymptomatic patients in further investigations of the relationship between hemodynamic compromise and stroke risk.

Transcranial Doppler (TCD) ultrasonography is a noninvasive and nonradioactive technique for evaluation of the blood flow velocity in large cerebral vessels.12–14 Compared with other available methods of CBF investigation such as positron emission tomography (PET) and single-photon emission CT, TCD ultrasonography is much less expensive, simpler, and faster. TCD ultrasonography has been used to measure cerebral perfusion or cerebrovascular reactivity (CVR) because normal cerebral artery blood flow velocity increases in response to a vasodilatory stimulus such as hypercapnia, which is usually induced by CO2 inhalation or acetazolamide administration.15,16 A decreased CVR indicates the presence of preexisting vasodilatation, which reflects a reduced reserve capacity of cerebral autoregulation.

The purpose of this study was to evaluate the possibility of obtaining prognostic indications by means of a simple and noninvasive method of induction of hypercapnia. For this purpose, we used a fixed period of apnea and calculated CVR by means of the breath-holding index (BHI) and evaluated its predictivity for cerebral ischemic events in patients with symptomatic and asymptomatic carotid artery occlusion.
possible role of baseline clinical and epidemiological characteristics in influencing the prognosis of such patients was also considered.

Subjects and Methods
The participants in the study were recruited from consecutive patients with occlusion of the extracranial segment of the internal carotid artery admitted to our stroke unit from April 1993 to May 1997 for a transient ischemic attack or an intracerebral vascular territory of middle cerebral artery (MCA) or for a functionally independent or minor stroke (Rankin Scale score of 1 to 2) in the same district. Patients with major stroke were not considered because of the difficulty of obtaining their full cooperation and of evaluating the occurrence of any further ischemic event. Exclusion criteria were poor insonation of the temporal bone window, possible or probable emboli, cardiopathy (atrial fibrillation, mitral valve stenosis, prolapse or calcification, mechanical cardiac valves, recent myocardial infarction, left ventricular thrombus, atrial myxoma, endocarditis, dilated cardiomyopathies, and patent foramen ovale), stenosis ≥30% in the carotid artery contralateral to the occluded one, and significant alteration of the vertebral arteries. Of the 47 recruited patients, 5 were excluded (3 for poor insonation of the temporal bone window, and 2 for the presence of cardiopathies). Among the 42 included patients, 20 had TIA and 22 had minor stroke. Twenty-three patients with asymptomatic carotid occlusion were also enrolled during the same period. These patients were selected from 25 consecutive subjects who underwent ultrasonographic examination in the outpatient department and who were referred by their general practitioner for suspected carotid stenosis. Two patients were excluded for a poor insonation of the temporal bone window. All patients underwent a careful neurological and cardiological examination, ECG, transthoracic or transesophageal echocardiography, and brain CT scan 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. Patients were reinvestigated clinically every 6 months; end points were defined as ipsilateral TIA, stroke, or death. The severity of stroke that occurred during the follow-up period was assessed by means of the Rankin Scale (score 0 to 2: minor stroke; 3 to 5: major stroke). This evaluation was performed at least 2 months after stroke. During the study period, no patient underwent surgical intervention and no dropout occurred.

Carotid artery disease was assessed and defined by color flow B-mode Doppler ultrasound (SPR 8000 Esaote Biomedica, Italy) according to the standardized criteria.17,18 The vertebobasilar system was evaluated as described by Bartels.20 Additional conventional angiography was performed in the 42 symptomatic patients and in 3 asymptomatic patients. In these patients, the degree of carotid stenosis contralateral to the occlusion was quantified according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria.21 Intracranial vessels were examined by means of a Multi-Dop X/TCD transcranial Doppler instrument (DWL Elektronische Systeme GmbH). CVR to hypercapnia was evaluated by means of the BHI at the beginning of the observation period. The index is obtained by dividing the percent increase in mean flow velocity (MFV) occurring during breath-holding by the length of time (seconds) that subjects hold their breath after a normal inspiration ([MFV at the end of breath-holding – rest MFV]/rest MFV)×100/second of breath-holding. End-tidal expiratory CO2 was measured by means of a capnometer (Oxy-cap Datex). All subjects were normocapnic. The study was performed in a quiet room, with the subject lying in a comfortable supine position without visual or auditory stimulation. Evaluation of CVR was performed in the early morning by the same 2 operators, who were unaware of the patient’s clinical status (except when signs of stroke were evident) and the results of the extracranial carotid studies. Two dual 2-MHZ transducers fitted on a headband and placed on the temporal bone windows were used to obtain a bilateral continuous measurement of MFV in the MCAs. MFV and end-tidal CO2 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 and heart rate were continuously monitored by means of a blood pressure monitor (2300 Finapress, Ohmeda). After a breath-holding period, MFV, mean blood pressure, and heart rate over a 4-second interval were recorded. Subjects were asked to hold their breath for 30 seconds after a normal inspiration. The exact length of apnea was checked by means of the respiratory activity monitor. All the study subjects were able to hold their breath for the required period. End-tidal CO2 during the first exhalation after apnea was evaluated. Before proceeding to the definitive recording, patients were trained to perform the procedure correctly. BHI was calculated when the rise in end-tidal CO2, from baseline to the first expiration after breath-holding was >8 mm Hg. This method of induction of hypercapnia proved to be effective and reproducible in the study of cerebral hemodynamics in both normal and pathological conditions.21,22

Breath-holding indices were also measured in 30 subjects (17 men, 13 women; mean age, 62±5.5) recruited from consecutive patients with vascular risk factors who underwent ultrasonic examination, which excluded any vascular stenosis. This group allowed us to define normative ranges for BHI values and thus to recode cerebral hemodynamic parameters in our patients as either compromised or normal.

In symptomatic patients, all TCD ultrasonography evaluations were performed at least 3 months after stroke (range 92 to 105 days) because it has been demonstrated that cerebral hemodynamics may be disturbed during the first days after stroke.23 Moreover, it has been shown that CVR usually improves, probably because of the full development of intracranial collaterals, 2 to 3 months after the occlusion has occurred.24,25 Examination of vessels of the circle of Willis was performed as described by Aaslid et al.13 The patency of major collateral vessels, namely ophthalmic, anterior, and posterior communicating arteries, was evaluated by means of compression tests. Blood flow through these major collateral vessels was determined as a residual flow in MCA after each compression.26,27 Moreover, collateralization was assumed through the anterior part of the circle of Willis when anterior cerebral artery flow ipsilateral to the carotid occlusion was reversed (this usually occurred in conjunction with acceleration of the contralateral anterior cerebral artery); through the external carotid artery when ophthalmic flow was reversed; and through the basilar artery when the ratio of ipsilateral to contralateral velocity in the posterior cerebral artery was >50%. All 3 possible collateral sources were assessed.28

The annual rate of adverse events was calculated by means of person/year method. The Kaplan-Meier procedure was used to plot and compare cumulative hazard of the considered groups, and Cox regression analysis allowed us to determine the factors that could be considered as independent predictors of ipsilateral ischemic events. Relative risks (RRs) and 95% CIs were reported to indicate the effect size. Spearman’s ρ coefficient was applied to verify correlation between the examined variables. Normative ranges for BHI (mean±2 SD) were calculated after logarithmic transformation of raw data to better fit a normal distribution (Shapiro-Wilks statistic was used to test normality). The analyses were performed with the use of SPSS 7.0 software (SPSS Inc). The significance level was set at 0.05 throughout the statistical analysis.

The study was approved by the local ethics committee, and each subject gave informed consent.

Results
The median follow-up of the 65 patients was 24 months (minimum=8; maximum=61). Fifteen were women (23.1%), and 50 were men (76.9%). Mean±(SD) age was 67.8 years±5.5. Mean BHI value of symptomatic patients was significantly lower than that of asymptomatic ones (P<0.001). Only 1 of the 23 asymptomatic patients (4%) had an ipsilateral minor stroke after 33 months from the enrollment in this study, which resulted in an annual stroke rate of
Four of 20 patients with TIA (20%) experienced an ipsilateral vascular event: 2 had a stroke (1 minor and 1 major stroke) and the remaining developed a TIA (annual ipsilateral ischemic event rate = 9.0%; annual stroke rate = 4.5%). In the group of 22 patients with nondisabling stroke, 7 patients experienced a vascular event (32%): 6 had a stroke (2 minor and 4 major strokes) and 1 had a TIA. This resulted in an annual ipsilateral ischemic event rate of 14.6% and an annual stroke rate of 12.5%. All ischemic events in the 2 symptomatic groups occurred between 8 and 25 months from the beginning of the study, with a global annual ipsilateral ischemic event rate of 11.9% (Figure 1). During the follow-up period, only 3 cerebrovascular ischemic events occurred contralateral to carotid occlusion (1 in the TIA group, and 2 in the stroke group). In all cases, the strokes were minor.

Patient characteristics are reported in Table 1. To determine the variables (baseline risk factors, symptomaticity, and cerebral hemodynamic parameters) that could predict an ischemic event ipsilateral to the occluded artery, the Cox proportional hazard regression model was applied; patients were considered censored if no event or contralateral ischemic event occurred. Both univariate and multivariate procedures were used: the former to ascertain the role of variables as alone; the latter to determine the factors that remain in the final model as independent predictive factors. All results are reported in Table 2. Only BHI, age, and the number of collateral circles reached the stated significance level ($P < 0.05$) in the univariate analysis. In the multivariate analysis, at the first step, BHI entered the model, followed by age (second step), and no other variables could be added to improve the model. In fact, the effect of the number of collateral circles is reduced with respect to the univariate approach, probably because of the significant correlation with BHI (Spearman’s $r = 0.36$; $P = 0.003$). Nevertheless, its RR is near significance, as shown in Table 2.

Because an inverse correlation is expected between BHI values and risk of ischemic event occurrence (the lower the BHI, the higher the risk), we preferred to change the sign of the BHI and to multiply the original value by 10, to simplify the interpretation of the RR. In this manner, by looking at the statistics reported in Table 2, we can observe that a BHI decrement of 0.10 induces an RR equal to 1.30, which indicates that the risk of a stroke during the entire follow-up is increased by 30%. In addition, the effect of age resulted in a RR of 1.23, meaning that for each year the risk tends to increase by 23%.

On the basis of data collected in control subjects, we tried to obtain a cut point for the BHI value in which a subject should be considered as having a pathological CVR. For this purpose, a logarithmic transformation was applied to data to achieve a better fit to the normal distribution (Shapiro-Wilks statistic = 0.95; df = 30; $P = 0.21$ [not significant]). Because >95% of cases would fall within the interval (mean = 2 SD with the assumption of normality), the value mean - 2 SD was chosen as threshold. This procedure provided a cut point of 0.69 as the normative threshold value for BHI. All 30 control subjects, 20 asymptomatic patients, and 9 symptomatic patients (8 TIA and 1 stroke) had BHI values above the normative threshold; 3 asymptomatic patients and 33 symptomatic patients (12 TIA and 21 stroke) were below the defined cut point. By the replacement of the BHI as conti-
uous variable with the BHI as dichotomous factor (pathological: <0.69; normal ≥0.69), the results of Cox regression were perfectly consistent, which suggested only BHI and age as potential predictive factors. In fact, 11 of 12 patients who developed symptoms ipsilateral to the occlusion had BHI values <0.69. All of them had experienced previous symptoms. The only asymptomatic patient who had a stroke during follow-up also had a BHI above the threshold value. The Kaplan-Meier representation of follow-up in patients with and without pathological BHI values is plotted in Figure 2.

Finally, predicted probability of ipsilateral ischemic events was plotted against age and the 2 BHI groups (Figure 3). The effect of age emerges as more important in patients with pathological BHI values and allows us to identify a subgroup of patients at major risk of an adverse event.

### Discussion

The results of our study show that an impairment of CVR to hypercapnia is significantly associated with an increased risk of ischemic events ipsilateral to carotid occlusion. In fact, in our study population, 11 of 12 patients who developed an ischemic event during the follow-up period had a BHI value <0.69. Four of these 11 patients were in the TIA group; the remaining 7 subjects had experienced a previous minor stroke. In all cases, neurological events occurred in the first 25 months of follow-up. On the other hand, only 1 of the 29 subjects with a BHI value ≥0.69 developed symptoms 33

### Table 2. RR of Ipsilateral Ischemic Events Estimated by Means of Cox Regression Analysis For Each Factor Considered

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M vs F)</td>
<td>0.64</td>
<td>0.64</td>
</tr>
<tr>
<td>Age (1-y increase)</td>
<td>1.15</td>
<td>1.23</td>
</tr>
<tr>
<td>Symptomatocity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIA vs asymptomatic</td>
<td>5.12</td>
<td>5.12</td>
</tr>
<tr>
<td>Stroke vs asymptomatic</td>
<td>7.83</td>
<td>7.83</td>
</tr>
<tr>
<td>BHI (0.10 decrease)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>1.28</td>
<td>1.30</td>
</tr>
<tr>
<td>Contralateral</td>
<td>1.10</td>
<td>1.10</td>
</tr>
<tr>
<td>Hypertension (Y vs N)</td>
<td>2.28</td>
<td>2.28</td>
</tr>
<tr>
<td>Diabetes (Y vs N)</td>
<td>1.04</td>
<td>1.04</td>
</tr>
<tr>
<td>Hyperlipidemia (Y vs N)</td>
<td>0.38</td>
<td>0.38</td>
</tr>
<tr>
<td>Smoking (Y vs N)</td>
<td>0.51</td>
<td>0.51</td>
</tr>
<tr>
<td>Collateral circles (n)</td>
<td>0.38</td>
<td>0.38</td>
</tr>
</tbody>
</table>

**Figure 2.** Kaplan-Meier hazard plot of ipsilateral ischemic events. Patients are divided on the basis of BHI cut point value of 0.69: ●, BHI<0.69; ○, ≥0.69; and +, censored.

**Figure 3.** Graphical representation of the final model in which the predicted probability of ipsilateral ischemic events is shown as a function of age and BHI values. According to this finding, we can speculate that, in case of normal BHI value, the risk of ipsilateral ischemic event is near to 0 in patients up to 70 years old and increases to about 15% in 80-year-old patients. On the other hand, in conditions with a pathological BHI value >0.69, it increases significantly with age. It increases from about 10% in 60-year-old patients to 35% in 70-year-old patients and, finally, close to 75% in 80-year-old patients: ●=BHI<0.69, ○=≥0.69.
months after entering the study. Moreover, this subject was the only asymptomatic patient who had a stroke during the follow-up period. On the basis of these data, low values of BHI can be considered the most important factor for predicting further cerebrovascular ischemic events in patients with ICA occlusion. Among the other factors considered, only age approached significant association with symptomatity. As shown in Figure 3, a clear interaction between BHI and age was found, which suggested that the effect of age becomes important when combined with an impaired CVR. On the other hand, the risk of a further cerebral ischemic event, in normal cerebral hemodynamics, does not appear to be strongly associated to age. The RR of a lower number of collateral vessels was near significance, and it could be interesting to develop this finding in an additional investigation. The apparent contradiction of the lack of correlation between low number of collaterals and reduced CVR could be explained by postulating that BHI is a more accurate hemodynamic measure than the evaluation of the number of collaterals whose efficiency cannot be quantified by the simple determination of their presence.

There is much evidence to suggest that, in addition to embolism, compromised cerebral blood flow may play an important role in causing ipsilateral ischemic events in patients with occlusion of the ICA; in these cases, ischemia would occur by the failure of the collateral blood flow through the circle of Willis, the ophthalmic artery, or the leptomeningeval collaterals.1

To date, 7 follow-up studies have compared prognosis in medically treated patients with and without compromised cerebral blood flow, evaluated by different methods (PET, single-photon emission CT, xenon CT, and TCD). In 3 of the 7 studies,2–4 no clear association between a compromised CBF and an increased risk of stroke during follow-up could be demonstrated. On the contrary, in each of the other 4 studies,5–8 patients with compromised CBF were shown to have a worse prognosis than similar patients with normal CBF measurements. In particular, in 1 of these studies, Kleiser and Widder5 investigated CVR by means of a transcranial Doppler CO₂ test in 85 patients with ICA occlusion. They distinguished between 3 categories of sufficient, diminished, and exhausted cerebrovascular capacity. A significant correlation between ipsilateral ischemic events and a diminished or exhausted CO₂ reactivity was found. In cases with exhausted CVR, neurological events occurred more often during the first months.8 Note that in the study reported, the authors had not distinguished between symptomatic and asymptomatic patients, and the data were not analyzed separately for these 2 groups.

Recently, Derdeyn et al11 investigated the relationship between misery perfusion (increased oxygen extraction fraction, [OEF]) and risk factors in patients with carotid occlusion by PET. The data showed that the presence of increased OEF is associated with prior ischemic symptoms and not with the other considered risk factors for stroke. This finding is consistent with an association between prior ipsilateral symptoms and absent CO₂ reactivity assessed by TCD.24 The fact that asymptomatic patients had lower frequency of hemodynamic abnormalities (increased OEF) must be taken into consideration when investigating the relationship between hemodynamic factors and stroke risk. This assumption is in accordance with our results. In fact, we found that asymptomatic patients had significantly lower BHI values than symptomatic ones. However, our results also suggest that the reduction of CVR to apnea is associated with an increased risk of further ischemic events and not only with a previous TIA or stroke.

The importance of hemodynamic factors in influencing the prognosis of patients with carotid occlusion is also suggested by the evidence that ICA occlusion is one of the main causes of border-zone infarction, and this association is more evident in the presence of compromised cerebral hemodynamics.10 In our study, we did not find a particularly high prevalence of watershed infarction. In fact, in the 9 strokes ipsilateral to carotid occlusion that occurred during follow-up period, CT or MRI examination showed watershed infarction in only 3 cases. This finding, however, does not play down the possible implications of hemodynamic factors in the pathogenesis of stroke associated with carotid occlusion. In fact, it has been demonstrated that the possibility of tissue damage due to a cerebral embolic event, which is still considered the main pathogenic mechanism of a cerebral ischemic event, is higher in the presence of an impaired capability of cerebral vessels to adapt their caliber after vasodilatatory stimulus.31

On the basis of these considerations, it has been suggested that the therapeutic approach selected for patients with carotid artery occlusion could be differentiated on the basis of cerebral hemodynamic status.1 The actual therapeutic options in patients with ICA occlusion seem to be limited after the failure of the extracranial/intracranial (EC/IC) bypass surgery.32 However, in the EC/IC bypass trials, selection of patients based on the CVR had not been performed in spite of the fact that this surgical approach has been associated with an improvement of cerebral hemodynamics.33 In this study, we have demonstrated that intracerebral hemodynamic consequences of carotid occlusion can be very different. Exhausted or diminished CVR and an established BHI value, determined in our data to be <0.69, could constitute the basis for reconsidering the possibility of testing the efficacy of the classic or a new type of surgical EC/IC bypass approach in a subgroup of patients considered to be at highest risk of developing stroke and with the most favorable odds of benefiting from surgical intervention. In this study, we considered patients with strictly unilateral internal carotid occlusion. The possible application of our results to other conditions such as bilateral carotid occlusion or carotid occlusion associated with contralateral hemodynamically significant stenosis should be validated by additional studies.

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References
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