Impaired Cerebral Vasoreactivity and Risk of Stroke in Patients With Asymptomatic Carotid Artery Stenosis

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The management of patients with asymptomatic carotid artery stenosis is one of the most controversial topics in the cerebrovascular disease literature. The results of the Asymptomatic Carotid Atherosclerosis Study (ACAS) showed a reduction of the risk of stroke in patients undergoing endarterectomy compared with those treated medically. However, the actual benefit of carotid endarterectomy in asymptomatic patients, in terms of prevention of annual disabling stroke vs the risk of angiography and surgery, may not justify its introduction into routine clinical practice. The benefit of surgery could be significantly increased in a subgroup of patients with a high predisposition to develop cerebrovascular events. However, defining a high-risk patient with severe asymptomatic carotid stenosis remains difficult. Selecting patients for surgery based on their age, progression of lesion, morphologic characteristics, and degree of carotid stenosis and concomitant risk factors is apparently acceptable, but to date, there is no evidence of any factor that may influence the prognosis of patients with asymptomatic carotid stenosis.

Based on pathophysiological considerations, the hemodynamic intracerebral effects of a cervical artery stenosis could help to identify high-risk patients. There is evidence that the prognosis of stroke patients with...
rotid occlusion depends on collateral flow. Some studies demonstrated that asymptomatic patients differ from asymptomatic patients because of the presence of a more impaired cerebrovascular reserve. Preliminary studies also suggested that reduced cerebrovascular reactivity may be a marker of increased risk of stroke in carotid stenosis. However, the relationship found in these studies between impaired cerebral hemodynamics and stroke is not linear enough to suggest a univocal therapeutic decision in patients with carotid stenosis, especially asymptomatic carotid stenosis. The aim of the present study was to test the possibility of predicting cerebrovascular events in patients with severe unilateral asymptomatic carotid stenosis by means of a transcranial Doppler ultrasonographic evaluation of cerebrovascular reactivity to hypercapnia.

**METHODS**

During a 22-month period between June 1996 and April 1998, we evaluated 137 patients with asymptomatic carotid stenosis (≥70% by means of ultrasonographic examination performed in our outpatient department). Every patient was offered a consultation with an expert vascular surgeon so that the advantages and disadvantages of medical treatment vs surgical and medical management could be explained in detail. Based on evidence reported in the international literature, all patients were informed of the estimated annual stroke risk ipsilateral to carotid stenosis. The 26 patients who considered carotid endarterectomy were referred to the vascular surgery department of our hospital.

The 111 patients who refused surgery underwent a careful neurological and cardiological examination, electrocardiogram, transthoracic echocardiography, and brain computed tomography. In addition, complete blood work and a clinical history with particular attention to the major vascular risk factors (hypertension, diabetes mellitus, smoking, and hyperlipidemia) were obtained from each patient. Based on the results of our investigation or previous medical records (in the case of patients coming under our observation with specific pharmacological treatment), hypertension was defined as a systolic blood pressure of 140 mm Hg or higher and/or a diastolic blood pressure of 90 mm Hg or higher; diabetes was a concentration of fasting plasma glucose of 6.7 mmol/L (120 mg/dL) or more, and hyperlipidemia was a total cholesterol concentration of 5.2 mmol/L (200 mg/dL) or greater and a low-density lipoprotein cholesterol concentration of 3.4 mmol/L (130 mg/dL) or less. These values were confirmed by repeated determinations before a definitive diagnosis was made.

Carotid artery disease was assessed and defined by continuous wave Doppler and color-flow B-mode Doppler ultrasound examination (SPR 8000, Esaote Biomedica, Florence, Italy) according to validated criteria. The vertebralbasilar system was evaluated as described by Bartels. Patients with stenosis of 30% or more in the carotid artery contralateral to the severe stenosis and with significant alteration of the vertebral arteries were excluded (5 patients). Patients with possible or probable embolizing cardiopathy (atrial fibrillation, mitral valve stenosis, prolapse or calcification, mechanical cardiac valves, recent myocardial infarction, left ventricular thombus, atrial myxoma, endocarditis, dilated cardiomyopathies, and patent foramen ovale) were also excluded (4 patients). These exclusion criteria were chosen with the aim of concentrating our investigation on patients in whom the presence of significant internal carotid stenosis could be considered the most relevant risk factor for developing ipsilateral cerebrovascular ischemic events. Intracranial vessels were examined by means of a Multidop X/transcranial Doppler instrument (DWL Elektronische Systeme GmbH, Sipplingen, Germany). Examination of vessels of the circle of Willis was performed as described by Aaslid et al.

Eight patients were excluded because of technical problems caused by poor insonation of the temporal bone window. None of the patients had significant stenosis or occlusion of large intracranial arteries.

Cerebrovascular reactivity to hypercapnia was evaluated by means of the breath-holding index (BHI). 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 mean flow velocity in the middle cerebral arteries. Depth of insonation ranged from 48 to 52 mm. The BHI is obtained by dividing the percentage increase in mean flow velocity occurring during breath holding by the length of time (seconds) subjects hold their breath after a normal inspiration (mean flow velocity at the end of breath holding minus mean flow velocity at rest divided by mean flow velocity at rest) multiplied by 100 divided by seconds of breath holding.

The study was performed at 8 AM in a quiet room, with patients lying in a comfortable supine position without any visual or auditory stimulation. During this time, mean blood pressure and heart rate were continuously monitored with a blood pressure monitor (2300 Finapress, Ohmeda, Louisville, Colo). After a breath-holding period, mean flow velocity, mean blood pressure, and heart rate were recorded over a 4-second interval. Mean flow velocity at rest was obtained by the continuous recording of a 1-minute period of normal breathing. Subjects were asked to hold their breath for 30 seconds. All subjects were normocapnic and able to hold their breath for the required period. The exact length of apnea was checked by means of a respiratory activity monitor (Oxy-cap, Datex, Milan, Italy) and ranged from 29.6 to 30.4 seconds. Before proceeding to the definitive recording, subjects were trained to perform the procedure correctly. Changes after the apnea period were slight: 2% to 4% for heart rate and 3% to 4% for mean blood pressure.

On the basis of our previous results obtained with healthy subjects, we defined normative ranges for BHI values and recorded cerebral hemody-
namic parameters as either impaired (BHI < 0.69) or normal (BHI ≥ 0.69). By using this kind of approach, we obtained a sensitive parameter that was able to discriminate between symptomatic and asymptomatic patients with carotid occlusion in both prospective and retrospective studies.20,21

All subjects abstained from alcohol, beverages containing caffeine, and smoking for at least 24 hours prior to the study. Evaluation of cerebrovascular reactivity was performed in the early morning by the same 2 operators who were not told about the degree of carotid stenosis for each patient.

In addition to antiplatelet therapy with 325 mg of aspirin daily, the best medical management of vascular risk factors was provided for all patients. In particular, in addition to dietary recommendations, patients with diabetes were treated with insulin or oral antidiabetic treatments; statins were prescribed to patients with insulin or oral antidiabetic treatments, patients with diabetes were treated with insulin or oral antidiabetic treatments; statins were prescribed to patients with diabetes or insulinomas; and angiotensin-converting enzyme inhibitors, β-blockers, or diuretics.

Patients were followed up by telephone every 3 months and reevaluated clinically every 6 months by 1 designated investigator, who was blind to the transcranial Doppler ultrasonographic data as well as to the degree and side of carotid stenosis; end points were defined as ipsilateral transient ischemic attack (TIA), stroke, or death. In the case of events not directly observed in our hospital, clinical records were acquired for an exact description. In particular, special attention was given to transient neurological deficits that were accepted as TIsAs on the basis of a history, which was reported in clinical records and recounted by patients themselves, of a focal neurological deficit of abrupt onset lasting at least 30 seconds with maximal clinical expression at onset and resolving completely within 24 hours, without progression of symptoms, loss of consciousness, and convulsions. Moreover, we verified that a rigorous evaluation had been performed during the first hours or days after the onset of symptoms, including the exclusion of other possible causes of transient neurological deficits, such as migraine with aura attacks, acute hypoglycemia, and small hemorrhagic or tumoral lesions, on the basis of clinical history, laboratory investigations, and neuroradiological examinations (contrast-enhanced brain computed tomography or magnetic resonance imaging, or both). The annual rate of end points was calculated by the person-years method. The Kaplan-Meier procedure was used to plot and compare cumulative hazards of the groups considered and Cox regression analysis permitted identification of which factors could be considered independent predictors of ipsilateral ischemic events. Hazard ratios and 95% confidence intervals were reported to indicate the size of the effect. Spearman ρ coefficient was applied to verify correlations between examined variables.

To control the α error (as indicated for ad interim analysis) at the end of recruitment (April 1998), we analyzed the collected data at approximate 6-month intervals by using a significance level (.005) lower than the threshold stated for the final analysis (.05). We found a strong significant effect of BHI at the second evaluation period; this study refers to the analysis performed in May 1999.

The study protocol was approved by the ethics committee of the Universita’ di Roma “Tor Vergata,” Rome, Italy, and written informed consent was obtained from each patient. Analyses were performed using statistical software (SPSS Version 7.0, SPSS Inc, Chicago, Ill).

**RESULTS**

Of the 94 patients enrolled, 74 were men and 20 were women (mean [SD] age, 71.1 [5.0] years). They were divided into 2 groups. Group 1 included 67 patients with carotid stenosis of 70%
to 89% and group 2 included 27 patients with carotid stenosis of 90% to 99%. The median follow-up of the 94 patients was 28.5 months, with a minimum of 6 months and a maximum of 35 months. During the study period, no patient underwent surgery and there were no dropouts. Sixteen patients (17.0%) had an ischemic event ipsilateral to carotid stenosis, of which 4 presented with TIA (4.3%) and 12 had strokes (12.7%). A stroke contralateral to carotid stenosis occurred in only 1 patient. One patient had a myocardial infarction. Table 1 shows patient characteristics according to the occurrence of cerebrovascular diseases. The global annual risk of ipsilateral ischemic events was 7.9% (TIA, 2.0%; stroke, 5.9%).

To identify which variable (baseline characteristics, risk factors, degree of carotid stenosis, and cerebral hemodynamic parameters) could predict an ischemic event ipsilateral to the stenotic artery, the Cox proportional hazard regression was applied. Univariate procedures were used to ascertain the role of variables alone and are reported in Table 2. Ipsilateral and contralateral BHI reached the stated significance level (.05) in the univariate analysis. In the multivariate analysis, BHI ipsilateral to carotid artery stenosis entered the model at the first step, but no other variables could be added to improve the model. Therefore, BHI emerged as the most important predictor of ischemic events. Regarding pharmacological treatment of vascular risk factors, no significant difference in the use of insulin, oral antidiabetic treatments, statins, or different classes of antihypertensive drugs was found between patients who remained asymptomatic and patients who developed ischemic cerebrovascular events.

By replacing a continuous variable BHI with a dichotomous factor BHI, impaired was defined as less than 0.69 (40 patients) and 0.69 or more (54 patients) was normal, and the result of the Cox regression was consistent, suggesting that the BHI cutoff may be considered a useful predictive factor. In fact, 11 of the 16 patients who developed symptoms ipsilateral to the carotid stenosis had a BHI value below 0.69. Figure 1 shows the scatter plot of BHI values in patients who had an ipsilateral ischemic event (TIA or stroke) and those who had no event. While the annual ipsilateral ischemic event risk in patients with normal BHI was 4.1%, 0.8% for TIA and 3.3% for stroke, the group with impaired BHI had an annual ipsilateral ischemic event risk equal to 13.9%, 3.8% for TIA and 10.1% for strokes. The only contralateral stroke, as well as the only myocardial infarction, occurred in the group with pathological BHI.

When considering only stroke events ipsilateral to carotid stenosis, the significance of prognostic factors remained unchanged and only the BHI ipsilateral to the carotid stenosis reached the significance level in the multivariate analysis (hazard ratio, 0.09 [95% confidence interval, 0.02-0.38]; \( P = .001 \)). The Kaplan-Meier representation of follow-up in patients with and without pathological BHI values is shown in Figure 2.

**COMMENT**

Our findings show that patients with severe asymptomatic carotid artery stenosis may have different cerebral hemodynamic status. We studied the cerebrovascular reactivity to apnea that expresses the residual capacity of adaptation of intracranial vessels. Under normal physiological conditions hypercapnia induces vasodilatation at the arteriolo-capillary level, resulting in an increase of flow velocity in the large in-

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**Table 2.** Univariate Analysis of Ipsilateral Ischemic Events Estimated by Cox Regression Analysis for Each Factor Considered

<table>
<thead>
<tr>
<th>Factor Comparison</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
<th>( P ) Value</th>
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<tbody>
<tr>
<td>Men vs women</td>
<td>1.26 (0.40-3.89)</td>
<td>.69</td>
</tr>
<tr>
<td>Age, 1 y</td>
<td>1.08 (0.97-1.20)</td>
<td>.14</td>
</tr>
<tr>
<td>Stenosis of 90%-99% vs 70%-89%</td>
<td>2.36 (0.88-6.30)</td>
<td>.09</td>
</tr>
<tr>
<td>Breath-holding index ipsilateral*</td>
<td>0.09 (0.02-0.38)</td>
<td>.001</td>
</tr>
<tr>
<td>Breath-holding index contralateral</td>
<td>0.19 (0.05-0.82)</td>
<td>.03</td>
</tr>
<tr>
<td>Hypertension†</td>
<td>0.52 (0.19-1.40)</td>
<td>.20</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.17 (0.41-3.37)</td>
<td>.77</td>
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<tr>
<td>Hyperlipidemia‡</td>
<td>1.34 (0.49-3.69)</td>
<td>.57</td>
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<tr>
<td>Ever vs never-smoker</td>
<td>2.53 (0.94-6.85)</td>
<td>.07</td>
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*Multivariate analysis was also performed with a hazard ratio of 0.09 (95% confidence interval, 0.02-0.38) and \( P = .001 \).†Comparison made was between presence and absence of factor.

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**Figure 1.** Scatterplot of Breath-Holding Index Values in Patients With and Without Ipsilateral Ischemic Event

The breath-holding index (BHI) for a group of healthy subjects had a threshold value of 0.69 as normal and is represented by the gray line. Each circle represents a patient with a given BHI value.

**Figure 2.** Kaplan-Meier Curves for Event-Free Survival of Patients

Triangles indicate censored observations.

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tracranial vessels correlating with changes in cerebral blood flow. An already existing intracranial vasodila-
tion to compensate a carotid stenosis will interfere with the ability of the cere-
rebral vessels to dilate further in re-
response to hypercapnia induced by ap-
nea. Accordingly, a reduced BHI reflects a critical hemodynamic condition dis-
tal to carotid stenosis that is reversible after carotid endarterectomy.

Our data suggest that altered cere-
brovascular reactivity influences the prognosis of patients with severe asymptomatic carotid artery stenosis. We found that a reduction of the BHI values ipsilateral to a carotid stenosis strongly increases the probability of oc-
currence of a cerebrovascular ischemic event.

In this study, we used a voluntary ap-
nea period to investigate cerebrovas-
cular reactivity. This method proved to be effective and reproducible in the study of cerebral hemodynamics with transcranial Doppler ultrasonography in both normal and pathological con-
ditions. It has the advantage of be-
ing more rapid and better tolerated than carbon dioxide inhalation and acetazol-
amide injection. In addition, with both carbon dioxide inhalation and acetazol-
amide injection, cardiovascular and ce-
rebrovascular adverse effects were reported. Despite the potential ad-
vantages of our approach, there is not sufficient evidence in the literature for it to be considered reliable and repro-
ducible enough for studying cerebro-
vascular reactivity. A recent study showed that the reproducibility of the hemodynamic effect of breath holding was lower than that of carbon dioxide inhalation. Our approach, consisting of a fixed period of apnea of about 30 sec-
onds, precisely determined by a respira-
atory monitor, is different from that usually used based on a period of maxi-
mal apnea. Regardless of whether the breath-holding period following a nor-
mal inspiration can be considered suf-
fficient to avoid a Valsalva effect, we monitored heart rate and mean blood pressure to identify possible factors able to induce hemodynamic changes.

Various studies have provided contro-
versial information about the impor-
tance of stenosis severity in the probability of ipsilateral stroke in asymptomatic patients. In this study, we were not able to make a relevant contribution to the issue of the rela-
tionships among exact degree of se-
vere carotid stenosis, cerebrovascular reactivity, and risk of stroke. In fact, the diagnosis of severe (70%-99%) caro-
rotid stenosis was made with ultra-
sonographic methods, which are not uni-
versally accepted for a more detailed classification of the degree of stenosis. This problem could not be solved since the performance of angiography, which remains the criterion standard of quan-
tifying stenotic lesions, did not seem to be appropriate in patients not sched-
uled for surgery. However, we tried to obtain at least some indications about this important aspect by considering 2 groups of patients with degrees of ste-
nosis of 90% or more and less than 90%. Our data suggest that impaired cere-
brovascular reactivity is a more strik-
ing predictor of stroke than severity of stenosis. This finding is in accordance with the concept that cerebral perfu-
sion is highly variable from patient to patient with carotid occlusive disease and seems to depend more on the ade-
quacy of collateral circulatory path-
ways than on the degree of stenosis.

However, these concepts should be explored in future studies. The use of a different noninvasive approach, such as magnetic resonance angiography in addi-
tion or as an alternative to ultrasonic methods, could be helpful.

In our study, we considered TIA oc-
currence as an end point. The fact that a TIA does not permanently affect a pa-
tient may cause diagnostic errors and consequently may bias the interpreta-

The ACAS demonstrated a 5.9% ab-
solute reduction in the 5-year risk of ip-
silateral ischemic stroke in patients who underwent endarterectomy of severe ca-
rotid stenosis compared with those medically treated. After the publica-
tion of these results, many clinicians changed their approach to the manage-
ment of these patients. This led to a dra-
matic increase in surgical treatment for severe asymptomatic carotid stenosis.

However, despite the initial enthusi-
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gest that, even when considering the average 2% risk of ipsilateral stroke per year, 85 asymptomatic patients would have to be operated on to prevent 1 stroke per year, and this number would have to be increased to 170 when con-
sidering only disabling stroke. These considerations suggest the need to concentrate the surgical procedure on a selected subgroup of patients, in which the risk of stroke is expected to be higher than about 2% per year. The association between impaired cerebral hemo-
dynamics and the risk of stroke has been suggested by different studies in which increased risk of ischemic events has been described in patients with symp-
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of stroke in patients with carotid dis-
ease who are undergoing surgical revas-
cularization. Accordingly, while the
present study suggests that the BHI can
identify a subset of patients with asympto-
tomatic carotid disease who have in-
creased risk of stroke, additional stud-
ies will be required to determine whether
derendarterectomy in these patients will
substantially reduce this risk.

In this study, we found an annual rate of
stroke ipsilateral to carotid stenosis of
5.9%; this is higher than the rate previ-
ously reported. In particular, the most
recent trials, ACAS and Veterans Af-
fairs trial, comparing the efficacy of ca-
rotid endarterectomy combined with op-
timal medical management vs optimal
medical management alone in the pre-
vention of cerebrovascular ischemic
events showed a 2% to 2.5% annual ip-
silateral stroke risk in medically treated
patients. The apparent contradiction be-
tween these data and our findings is
probably caused by the different char-
acteristics of the study populations. The
other clinical trials enrolled highly se-
lected patients on the basis of low sur-
gical risk. Moreover, the mean age of the
medically treated patients in the ACAS
and in the Veterans Affairs trial was lower
than that of patients included in our
study. Our patients probably belonged
to a different risk category since the mean
degree of stenosis seems to be higher than
that considered in the ACAS and Veter-
ans Affairs trials. A large prospective
study by Norris et al., in which pa-
tients with asymptomatic carotid occlu-
sive disease were followed up for a mean
period of 41 months, showed that the an-
nual rate for ipsilateral cerebral isch-
ic events was about 8% for patients
with carotid stenosis of more than 75%.
In this case, the incidence of ischemic
events was similar to that observed in our
study when considering TIA and stroke
together. On the other hand, the an-
nual rate of ipsilateral stroke was 3.3%.
Even in this case, the characteristics of
patients included could account for the
differences in the results. These are hy-
potheses that need a definitive demon-
stration.

At this time it is not possible to ex-
tend our finding of a significant link be-
tween impaired cerebral hemodynam-
ics and risk of cerebrovascular events
to all patients with a severe asympto-
tomatic carotid stenosis. The need exists
for other larger studies to provide defini-
tive information about whether re-
duced cerebrovascular reactivity can be
considered useful in selecting patients
with severe asymptomatic carotid ste-
nosis, in which a new trial of carotid
endarterectomy could be warranted in
the attempt to improve the expected
benefits of surgery.

REFERENCES
1. Executive Committee for the Asymptomatic Car-
rotid Atherosclerosis Study. Endarterectomy for asymp-
tomatic carotid stenosis. JAMA. 1995;273:1421-
1428.
2. Warlow C. Surgical treatment of asymptomatic ca-
rotid stenosis. Cerebrovasc Dis. 1996;6(suppl 1):7-
14.
3. Toole JF. Endarterectomy for asymptomatic ca-
Do the facts and figures warrant a 10-fold increase in
the performance of carotid endarterectomy on asymp-
5. Hedera P, Bujakova J, Traubner P. Effect of col-
lar flow patterns on outcome of carotid occlu-
6. Kleiser B, Widder C. Course of carotid artery oc-
duction with impaired cerebrovascular reactivity.
Evidence for misery perfusion and risk of recurrent stroke
in major cerebral arterial occlusive diseases from
8. Yonas H, Smith HA, Durham SR. Increased stroke
risk predicted by compromised cerebral blood flow re-
9. Gur AY, Bova I, Bornstein NM. Is impaired cere-
bral vasomotor reactivity a predictive factor of stroke
in asymptomatic patients? Stroke. 1996;27:2188-
2190.
of carotid endarterectomy for asymptomatic carotid stenosis.
11. The Fifth Report of the Joint National Commit-
tee on Prevention, Detection, Evaluation, and Treat-
ment of High Blood Pressure. Arch Intern Med. 1993;
153:154-183.
12. World Health Organization. Diabetes Mellitus: Re-
port of a WHO Study Group. Geneva, Switzerland:
13. Summary of the second report of the National
Cholesterol Education Program (NCEP) Expert Panel
on Detection, Evaluation, and Treatment of High Blood
14. Gortler M, Niethammer R, Widder B. Differenti-
ating subtotal carotid artery stenoses from occlusion
by colour-coded duplex sonography. J Neurol. 1994;
241:301-305.
15. De Bray JM, Blatt B. Quantification of athero-
matous stenosis in the extracranial internal carotid ar-
16. Bartels E. Vertebral sonography. In: Tegler CH,
Bakken VL, Gomez CR, eds. Neurosonology. St Louis,
17. Audard R, Markwalder TM, Nornes H. Noninva-
sive transcranial doppler ultrasound recording of flow
velocity in the basal cerebral arteries. J Neurol. 1982;
219:769-774.
18. Markus HS, Harrison MJ. Estimation of cerebro-
vascular reactivity using transcranial Doppler, includ-
ing the use of breath-holding index as the vasodila-
19. Vernieri F, Pasqualetti P, Passarella F, Rossini PM,
Silvestrini M. Outcome of carotid artery occlusion is
predicted by cerebrovascular reactivity. Stroke. 1999;
30:593-598.
20. Silvestrini M, Vernieri F, Troisi E, et al. Cerebro-
vascular reactivity in carotid artery occlusion: possi-
ble implication for surgical management of selected
groups of patients. Acta Neurol Scand. 1999;99:187-
191.
parison of transcranial Doppler and cerebral blood flow
studies to assess cerebral vasoreactivity. Stroke. 1992;
23:15-19.
22. Silvestrini M, Troisi E, Mattes M, Cupini LM, Cal-
tagione C. Transcranial Doppler assessment of cere-
brovascular reactivity in symptomatic and asymptom-
atic severe carotid stenosis. Stroke. 1996;27:1970-
23. Silvestrini M, Troisi E, Mattes M, Cupini LM, Ber-
nardi G. Effect of smoking on cerebrovascular reac-
24. Gietelman DR, Prohovnik I, Tatemichi TK. Safety of
hypercapnic challenge: cardiovascular and neuro-
logic considerations. J Cereb Blood Flow Metab. 1991;
11:1036-1040.
25. Kuwabara Y, Ishiya Y, Sasaki M, Yoshida T, Ma-
suda K. Time dependency of the acetazolamide ef-
fect on cerebral hemodynamics in patients with chronic
occlusive cerebral arteries: early steal phenomenon
demonstrated by H2O posimion emission tomogra-
26. Totoro R, Marini C, Baldassarre M, Carolei A. Ce-
brovascular reactivity evaluated by transcranial Dop-
pler: reproducibility of different methods. Cerebro-
vasc Dis. 1999;14:2-145.
27. The European Carotid Surgery Trialists Collaborative
Group. Risk of stroke in the distribution of an asymp-
28. Powers WJ. Cerebral hemodynamics in ischemic
240.
29. Widder B, Kleiser B, Krapf H. Course of cerebro-
vascular reactivity in patients with carotid artery oc-
30. Grubb RL, Derdeyn CP, Fritsch SM, et al. Impor-
tance of hemodynamic factors in the prognosis of
symptomatic carotid occlusion. JAMA. 1998;280:
1095-1060.
31. Derdeyn CP, Grubb RL, Powers WJ. Cerebral he-
modynamics impairment: methods of measurements
and association with stroke risk. Neurology. 1999;53:
251-259.
32. Lamsa DJ, Krycio RJ. Endarterectomy for asym-
tomatic internal carotid artery stenosis. Neurology.
1997;48:1481-1490.
33. Chaturvedi S, Hachinski V. Does the neurologist
add value to the carotid endarterectomy patient? Neu-
lines for carotid endarterectomy: a statement for health-
care professionals from a special writing group of the

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