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

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Context Standards for treating patients with asymptomatic carotid artery stenosis have been difficult to establish because of the lack of evidence for factors influencing these patients' prognoses. However, preliminary evidence suggests that an alteration in cerebral hemodynamic function may play a relevant role in the occurrence of stroke in patients with carotid artery disease.

Objective To investigate the relationship between cerebrovascular reactivity to hypercapnia and cerebrovascular events in patients with severe unilateral asymptomatic carotid artery stenosis.

Design and Setting Prospective, blinded longitudinal study conducted in an outpatient neurovascular department in Italy between June 1996 and April 1998, with a median follow-up of 28.5 months.

Patients Ninety-four patients with asymptomatic carotid artery stenosis of at least 70% (74 men; mean age, 71 years).

Main Outcome Measures Subsequent occurrence of cerebral ischemic events (transient ischemic attack or stroke) or death, analyzed by cerebrovascular reactivity to hypercapnia (measured by transcranial Doppler ultrasonography and calculated by the breath-holding index values in the middle cerebral arteries).

Results The overall annual rate for all ischemic events was 7.9%. Seventeen patients (18%) had ischemic events, all but 1 of which were ipsilateral to the carotid artery stenosis. Among factors considered, only lower breath-holding index values in the middle cerebral artery ipsilateral to carotid artery stenosis were significantly associated with the risk of an event (hazard ratio, 0.09; 95% confidence interval, 0.02-0.38; $P=.001$, by multivariate analysis). Based on data from previously studied healthy subjects, the cutoff of the breath-holding index for distinguishing between impaired and normal cerebrovascular reactivity was determined to be 0.69. Using this cutoff, the annual ipsilateral ischemic event risk was 4.1% in patients with normal and 13.9% in those with impaired breath-holding index values.

Conclusions These results suggest a link between impaired cerebrovascular reactivity and the risk of ischemic events ipsilateral to severe asymptomatic carotid 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)[1] 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.[2] 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,[3(pp1506-1507)] but to date, there is no evidence of any factor that may influence the prognosis of patients with asymptomatic carotid stenosis.[4]

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 ca-

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rotid occlusion depends on collateral flow.[5] Some studies demonstrated that symptomatic patients differ from asymptomatic patients because of the presence of a more impaired cerebrovascular reserve.[6,7] Preliminary studies also suggested that reduced cerebrovascular reactivity may be a marker of increased risk of stroke in carotid stenosis.[8,9] 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,[1,10,11] 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[12]; diabetes was a concentration of fasting plasma glucose of 6.7 mmol/L (120 mg/dL) or more[13]; 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.[14] 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.[15,16] The vertebrobasilar system was evaluated as described by Bartels.[17] 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 thrombus, 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.[18] 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).[19] 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] multipled 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,[20,21] we defined normative ranges for BHI values and recoded 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 hyperlipidemia when total cholesterol concentration was 6.2 mmol/L (240 mg/dL) or more or low-density lipoprotein cholesterol concentration was 4.1 mmol/L (160 mg/dL) or less.[14] Hypertensive patients were given 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 TIAs 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-year 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 Università 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).

Table 1. Patient Characteristics Considered With Respect to Ipsilateral Ischemic Event Occurrence*

	Ipsilateral Ischemic Events		
	Present (n = 16)	Absent (n = 78)	Total (n = 94)
Sex			
Men	12 (75)	62 (79)	74
Women	4 (25)	16 (21)	20
Age, y†	72.6 (5.3)	70.8 (5)	71.1 (5)
Breath-holding index ipsilateral†	0.47 (0.37)	0.89 (0.41)	0.82 (0.43)
Breath-holding index contralateral†	0.83 (0.31)	1.09 (0.41)	1.04 (0.41)
Stenosis, %			
70-89	8 (50)	59 (76)	67
90-99	8 (50)	19 (24)	27
Hypertension			
Present	9 (56)	57 (73)	66
Absent	7 (44)	21 (27)	28
Diabetes			
Present	5 (31)	22 (28)	27
Absent	11 (69)	56 (72)	67
Hyperlipidemia			
Present	6 (37)	24 (31)	30
Absent	10 (63)	54 (69)	64
Smoking			
Ever	9 (56)	26 (33)	35
Never	7 (44)	52 (67)	59

*Values are expressed as number (percentage) unless otherwise indicated. Hypertension, diabetes, and hyperlipidemia are defined in the "Methods" section.
†Values are expressed as mean (SD).

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 TIAs (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 TIAs and 10.1% for strokes. The only contralateral stroke, as well as the only myocardial infarction, occurred in the group with pathological BHI.

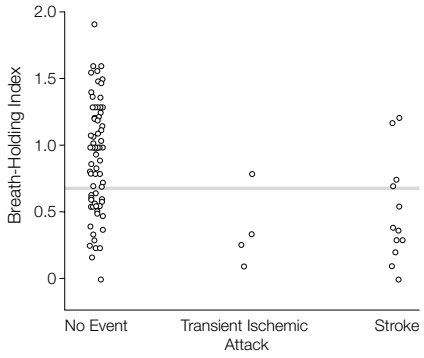
When considering only stroke events ipsilateral to carotid stenosis, the significance of prognostic factors remained unchanged and only the BHI ipsilateral to the carotid stenosis reached the significance level in the multivariate analysis (hazard ratio, 0.09 [95% confidence interval, 0.02-0.38]; P=.001).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

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

Factor Comparison	Hazard Ratio (95% Confidence Interval)	*P* Value
Men vs women	1.26 (0.40-3.89)	.69
Age, 1 y	1.08 (0.97-1.20)	.14
Stenosis of 90%-99% vs 70%-89%	2.36 (0.88-6.30)	.09
Breath-holding index ipsilateral*	0.09 (0.02-0.38)	.001
Breath-holding index contralateral	0.19 (0.05-0.82)	.03
Hypertension†	0.52 (0.19-1.40)	.20
Diabetes†	1.17 (0.41-3.37)	.77
Hyperlipidemia†	1.34 (0.49-3.69)	.57
Ever vs never-smoker	2.53 (0.94-6.85)	.07

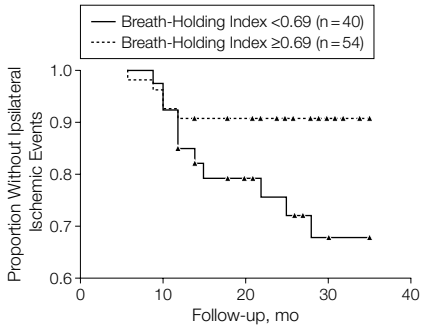
*Multivarate analysis was also performed with a hazard ratio of 0.09 (95% confidence interval, 0.02-0.38) and P = .001.
†Comparison made was between presence and absence of factor.

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.

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-

tracranial vessels correlating with changes in cerebral blood flow.[22] An already existing intracranial vasodilatation to compensate a carotid stenosis will interfere with the ability of the cerebral vessels to dilate further in response to hypercapnia induced by apnea. Accordingly, a reduced BHI reflects a critical hemodynamic condition distal to carotid stenosis that is reversible after carotid endarterectomy.[19,23]

Our data suggest that altered cerebrovascular 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 occurrence of a cerebrovascular ischemic event.

In this study, we used a voluntary apnea period to investigate cerebrovascular reactivity. This method proved to be effective and reproducible in the study of cerebral hemodynamics with transcranial Doppler ultrasonography in both normal and pathological conditions.[23,24] It has the advantage of being more rapid and better tolerated than carbon dioxide inhalation and acetazolamide injection. In addition, with both carbon dioxide inhalation and acetazolamide injection, cardiovascular and cerebrovascular adverse effects were reported.[25,26] Despite the potential advantages of our approach, there is not sufficient evidence in the literature for it to be considered reliable and reproducible enough for studying cerebrovascular reactivity. A recent study[27] 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 seconds, precisely determined by a respiratory monitor, is different from that usually used based on a period of maximal apnea. Regardless of whether the breath-holding period following a normal inspiration can be considered sufficient to avoid a Valsalva effect,[19] we monitored heart rate and mean blood pressure to identify possible factors able to induce hemodynamic changes.

Various studies have provided controversial information about the importance of stenosis severity in the probability of ipsilateral stroke in asymptomatic patients.[1,28] In this study, we were not able to make a relevant contribution to the issue of the relationships among exact degree of severe carotid stenosis, cerebrovascular reactivity, and risk of stroke. In fact, the diagnosis of severe (70%-99%) carotid stenosis was made with ultrasonographic methods, which are not universally 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 quantifying stenotic lesions, did not seem to be appropriate in patients not scheduled for surgery. However, we tried to obtain at least some indications about this important aspect by considering 2 groups of patients with degrees of stenosis of 90% or more and less than 90%. Our data suggest that impaired cerebrovascular reactivity is a more striking predictor of stroke than severity of stenosis. This finding is in accordance with the concept that cerebral perfusion is highly variable from patient to patient with carotid occlusive disease and seems to depend more on the adequacy of collateral circulatory pathways than on the degree of stenosis.[29] However, these concepts should be explored in future studies. The use of a different noninvasive approach, such as magnetic resonance angiography in addition or as an alternative to ultrasonic methods, could be helpful.

In our study, we considered TIA occurrence as an end point. The fact that a TIA does not permanently affect a patient may cause diagnostic errors and consequently may bias the interpretation of results. However, we believe the inclusion of TIAs in our evaluation is important. The occurrence of such an event changes the therapeutic approach to patients with severe asymptomatic carotid stenosis, who become strong candidates for carotid endarterectomy. We were careful about accepting a diagnosis of TIA, thus reducing to a minimum all possible causes of diagnostic errors. However, when considering only stroke events, the results of our study remained substantially unchanged and the relationship between impaired cerebrovascular reactivity and the outcome of asymptomatic carotid stenosis was highly significant.

The ACAS demonstrated a 5.9% absolute reduction in the 5-year risk of ipsilateral ischemic stroke in patients who underwent endarterectomy of severe carotid stenosis compared with those medically treated.[1] After the publication of these results, many clinicians changed their approach to the management of these patients. This led to a dramatic increase in surgical treatment for severe asymptomatic carotid stenosis.[4] However, despite the initial enthusiasm based on results of the ACAS, serious concerns impeded the acceptance of the indication of surgical treatment in asymptomatic patients. Practical considerations about the cost-effectiveness of surgery in these patients suggest 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 considering only disabling stroke.[2]

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 hemodynamics and the risk of stroke has been suggested by different studies in which increased risk of ischemic events has been described in patients with symptomatic carotid occlusion or stenosis on the basis of different investigation techniques.[6,8,29-31] A recent review discussed the existing evidence on the association between hemodynamic compromise and the risk of stroke in the presence of carotid disease and suggested that only randomized controlled trials can provide a definitive demonstration of a direct relationship between improvement in cerebrovascular reactivity and reduction of the risk

of stroke in patients with carotid disease who are undergoing surgical revascularization.[32] Accordingly, while the present study suggests that the BHI can identify a subset of patients with asymptomatic carotid disease who have increased risk of stroke, additional studies will be required to determine whether endarterectomy 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 previously reported.[33-35] In particular, the most recent trials, ACAS[1] and Veterans Affairs trial,[11] comparing the efficacy of carotid endarterectomy combined with optimal medical management vs optimal medical management alone in the prevention of cerebrovascular ischemic events showed a 2% to 2.5% annual ipsilateral stroke risk in medically treated patients. The apparent contradiction between these data and our findings is probably caused by the different characteristics of the study populations. The other clinical trials[1,11] enrolled highly selected patients on the basis of low surgical 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 Veterans Affairs trials. A large prospective study by Norris et al,[10] in which patients with asymptomatic carotid occlusive disease were followed up for a mean period of 41 months, showed that the annual rate for ipsilateral cerebral ischemic 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 annual 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 hypotheses that need a definitive demonstration.

At this time it is not possible to extend our finding of a significant link between impaired cerebral hemodynamics and risk of cerebrovascular events to all patients with a severe asymptomatic carotid stenosis. The need exists for other larger studies to provide definitive information about whether reduced cerebrovascular reactivity can be considered useful in selecting patients with severe asymptomatic carotid stenosis, in which a new trial of carotid endarterectomy could be warranted in the attempt to improve the expected benefits of surgery.

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