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Correlation of Carotid Artery Disease Severity and Vasomotor Response of Cerebral Blood Vessels

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Abstract

We assessed reactivity of cerebral vessels on hypercapnia in patients with carotid occlusive disease. The effects of vascular risk factors on carotid atherosclerosis and vasomotor reactivity (VMR) of cerebral arterioles were also examined. Patients (n = 50) with carotid stenosis (≥30% in 1 or both sides) were included; 30 patients acted as controls. Hypertension, hyperlipidemia, diabetes, cardiac diseases, inflammation, and smoking were recorded. Vasomotor reactivity was assessed with the apnea test by transcranial Doppler ultrasonography and estimated by flow velocity changes in the middle cerebral artery before and after hypercapnia induction. Vasomotor reactivity was defined by the breath holding index, and values under 0.69 were considered critical for VMR impairment. Vasomotor reactivity reduction was significant ($P = .004$) in patients with severe carotid stenosis (>70%) and with symptomatic carotid disease ($P < .05$). The risk factors did not significantly influence VMR reduction. Severe carotid stenosis impairs VMR and may increase the risk of stroke, especially in symptomatic patients.

Keywords

carotid artery stenosis, vasomotor reactivity, cerebral vessels, hypercapnia, vascular risk factors

Introduction

In physiological conditions, blood flow in the brain is constant due to autoregulatory, compensatory brain mechanisms. In the case of increased metabolic demand, small arteries and arterioles react by vasodilation thus augmenting blood flow.[1] In normotensive adults, cerebral flow is on average 50 mL/100 g of brain tissue/min and this leads to cerebral perfusion pressure (CPP) of 60 to 160 mm Hg.[2] Below and above these values, there is a loss of autoregulation and cerebral flow becomes linearly dependent on middle artery pressure.[3,4] When CPP falls under the low limit of autoregulation, cerebral ischemia occurs. Carbon dioxide (CO_2) has a significant and reversible effect on cerebral blood flow; hypercapnia induces cerebral vasodilatation, while hypocapnia causes constriction and consequent reduction in blood flow.[5,6] Inhalation of 5% CO_2 in humans causes an increase in cerebral blood flow by 50%; 7% CO_2 inhalation can increase this flow by up to 100%.[6]

Carotid occlusive disease is considered to be the cause of 15% to 20% of all ischemic strokes (ISs).[7] Progression of stenosis is similar to the progression of atherosclerosis in another vascular bed, but the correlation between plaque progressions, increased degree of stenosis, and clinical manifestations is significantly more complex. The North American Symptomatic Carotid Endarterectomy Trial (NASCET)[8] showed a clear correlation between the degree of stenosis and the risk of IS, but when it comes to asymptomatic patients, this relationship is less clear. One of the main mechanisms responsible for the maintenance of cerebral autoregulation (CA) is the ability of the brain arterioles to constrict or dilate in response to chemical or other stimuli. This capability is referred to as cerebral ''vasomotor reactivity'' (VMR) and plays an important role in maintaining autoregulatory mechanisms and metabolic control of the brain tissue.[9]

Transcranial Doppler (TCD) is widely used in the assessment of VMR of brain vessels as a reflection of CA and

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collateral circulation. Vasomotor reactivity is defined as the ratio between the values of the cerebral flow before and after administration of a potent vasodilatory stimulus.[10] The main objectives of determining VMR of cerebral vessel are to: (1) evaluate the intracranial hemodynamic status in patients with carotid occlusive disease in an attempt to predict ischemic vascular events, (2) compare intracerebral hemodynamic parameters before and after carotid endarterectomy (CEA), (3) compare autoregulation and collateral circulation in different areas of the Willis circle, and, (4) evaluate diseases of the small brain vessels.[11] In terms of carotid artery disease, the presence and condition of collateral flow and CA are very important; intracranial hemodynamic parameters may have prognostic value for the course of symptomatic carotid stenosis (SCS) or asymptomatic carotid stenosis (ACS) and the risk of recurrent stroke.[12]

The aim of this study was to examine the reactivity of cerebral vessels on hypercapnia exposure in patients with carotid occlusive disease in order to identify who are in a higher risk of stroke.

Materials and Methods

This study analyzed 50 adult patients of both genders (27 males) with known carotid disease defined as stenosis >30% of the internal carotid artery (ICA) on 1 or both sides. All patients were treated at the Special Hospital for Cerebrovascular diseases "Sveti Sava" (as inpatients or outpatients) in the period between January and April 2012. The control group consisted of 30 patients without carotid artery stenosis or with stenosis <30%. The control group consisted of outpatients who were examined for symptoms that were not associated with cerebral circulation disorders or were healthy participants. The control group had all the tests as for the study group patients and was treated according to the present disease or risk factors.

Carotid artery narrowing was determined by ultrasound, and the degree of stenosis was determined according to the criteria of a consensus statement.[13] Each patient completed a questionnaire containing medical history data on symptoms, previous states and medical conditions, results of blood laboratory tests, and results of diagnostic procedures (extracranial ultrasound findings, TCD, and heart ultrasound in patients with cardiac disease). We defined hypertension as blood pressure above 140/90 mm Hg, diabetes as blood glucose level >6.1 mmol/L or preexisting known condition, and hyperlipidemia as serum total cholesterol >5.7 mmol/L or low-density lipoprotein cholesterol >3.88 mmol/L or previously treated disease. Cardiac diseases in our patients were hypertensive cardiomyopathy, angina pectoris, and mild valvular disease. The patients with atrial fibrillation, presence of thrombotic masses in the heart, severe valvular defects, and other potential cardioembolic risk were excluded from study. For all patients, TCD and a VMR test were performed after carotid ultrasound examination. The apnea test was used involving cessation of breathing for 30 seconds. Mean flow velocity (MFV) of the middle cerebral artery at a depth of 55 mm on both sides before and after the 30 seconds period of apnea and VMR value is shown as breath holding index (BHI) according to the following formula: BHI = MFV after apnea − MFV basal/basal MFV × 100/30. A BHI value of ≥0.69 indicates preserved VMR, while values <0.69 characterize impaired VMR.[14]

Laboratory analyses were performed including serum glucose, lipid profile, urea, creatinine, and inflammatory factors (ie, C-reactive protein and fibrinogen). Patients were divided into those with mild carotid stenosis (ie, 30%-50%), moderate stenosis (ie, 50%-70%), and severe stenosis (ie, >70%) which we regarded as hemodynamically significant. According to the symptoms, patients were divided into those with SCS (ie, those who had a transient ischemic attack, IS, or amaurosis fugax) and those with ACS. In a number of patients, there were nonspecific symptoms (headache as an isolated symptom, dizziness, and tinnitus) and all of them were regarded as asymptomatic. All patients were treated according to clinical, laboratory, and ultrasound findings.

Statistical Analysis

Data analysis was performed using the statistical program PASW Statistics 18. Values of continuous variables are presented as mean ± standard deviation, and the value of the interrupt variables as frequencies (n, %). The differences in the mean of continuous variables between groups were tested by Student *t* test, Mann-Whitney *U* test, and the Kruskal-Wallis test. Comparison of discontinuous variables was assessed by the chi-square (χ^2) test. The relationship between variables was tested using Spearman rank correlation. As a measure of the effect, we used the odds ratio (OR) and 95% confidence interval (CI) that was obtained by the logistic regression method. Independent risk factors for carotid artery stenosis and disturbed vasomotor activity were assessed by multivariate logistic regression. A 2-tailed $P < .05$ was considered significant.

Results

Mean age was 64.4 ± 7.3 years for the control group and 67.0 ± 9.8 years for patients with ICA stenosis ($P > .05$; Table 1). With regard to the biochemical parameters, only serum glucose levels were significantly higher in patients with ICA stenosis than those in controls ($P = .02$; Table 2).

All risk factors in univariate logistic regression analysis that showed statistical significance were assessed in multivariate analysis. Hyperlipidemia and hypertension ($P < .01$ and $P < .05$, respectively) were found to be independent risk factors for carotid disease. Specifically, in patients with hyperlipidemia, the risk of carotid disease was almost 5 times higher than in patients without hyperlipidemia (OR = 4.95; 95% CI, 1.73-14.15), whereas the risk was approximately 4 times higher in patients with hypertension than in normotensive individuals (OR = 4.11; 95% CI, 1:19-14:16; Table 3).

Furthermore, we tested the association between the degree of carotid stenosis and the BHI value ispilateral to ICA stenosis degree. With increasing degree of carotid stenosis, BHI was reduced (Figure 1). This association was significant only for

Table 1. Biochemical Parameters in Patients With and Without Stenosis of the ICA.[a]

	Control Group (n = 30)	Patients With ICA Stenosis (n = 50)	P
Blood glucose, mmol/L	5.7 ± 1.2	6.8 ± 2.4	**.020**[b*]
Urea, mmol/L	5.6 ± 1.7	6.1 ± 1.6	.238[c]
Creatinine, μmol/L	82 ± 15	90 ± 25	.111[c]
Cholesterol, mmol/L			
Total	5.3 ± 1.0	5.7 ± 1.4	.275[c]
HDL	1.9 ± 0.3	2.0 ± 0.4	.612[c]
LDL	3.3 ± 0.7	3.5 ± 0.7	.276[c]
CRP, mg/L	2.2 ± 1.9	6.3 ± 2.6	.662[b]
Fibrinogen, g/L	4.1 ± 1.1	4.6 ± 1.5	.119[c]

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; CRP, C-reactive protein; ICA, internal carotid artery.
[a] Data are presented as mean ± standard deviation.
[b] Mann-Whitney *U* test.
[c] Student *t* test.
*p<0.05.

Table 2. Presence of Risk Factors in the Control Group and the Group of Patients With Stenosis of the ICA.[a]

	Control Group (n = 30)	Patients With ICA Stenosis (n = 50)	P
Age, mean ± SD, years	64.4 ± 7.3	67.0 ± 9.8	.226[b]
Gender (m), n (%)	13 (43)	27 (54)	.356[c]
Hypertension, n (%)	19 (63)	44 (88)	**.009**[c**]
Diabetes type 2, n (%)	9 (30)	16 (32)	.852[c]
HLP, n (%)	12 (40)	38 (76)	**.001**[c**]
Cardiac diseases, n (%)	8 (27)	12 (24)	.750[c]
Cigarette smoking, n (%)	11 (37)	18 (36)	.952[c]

Abbreviations: HLP, hyperlipidemia; ICA, internal carotid artery; χ^2, chi-square; LDL-C, low-density lipoprotein cholesterol; m, male.
[a] HLP, serum total cholesterol >5.7 mmol/L, or LDL-C >3.88 mmol/L or previously treated disease.
[b] Student *t* test.
[c] χ^2 test.
**p<0.01.

the left carotid artery (Table 4). Breath holding index value decreased with increasing age, but this was not significant on both sides.

Only severe ICA stenosis was significantly associated with VMR impairment, even after adjustment for other risk factors. Specifically, the risk of VMR impairment was about 11 times higher in patients with hemodynamically significant stenosis of ICA than in patients without hemodynamically significant ICA stenosis (OR = 10.90; 95% CI, 1.63-73.05, $P = .014$; Tables 5 and 6).

With regard to the preservation of VMR, no difference was observed between patients with unilateral and those with bilateral hemodynamically significant stenosis. Patients with severe unilateral or bilateral ICA stenosis often had significantly more VMR impairment than those with mild–moderate stenosis ($P = .004$; Table 7).

Table 3. Independent Risk Factors for Carotid Artery Stenosis.

	OR (95% CI)	P
HLP	4.95 (1.73-14.15)	.003*
Hypertension	4.11 (1.19-14.16)	.025**

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval; HLP, hyperlipidemia.
*p<0.05. **p<0.01.

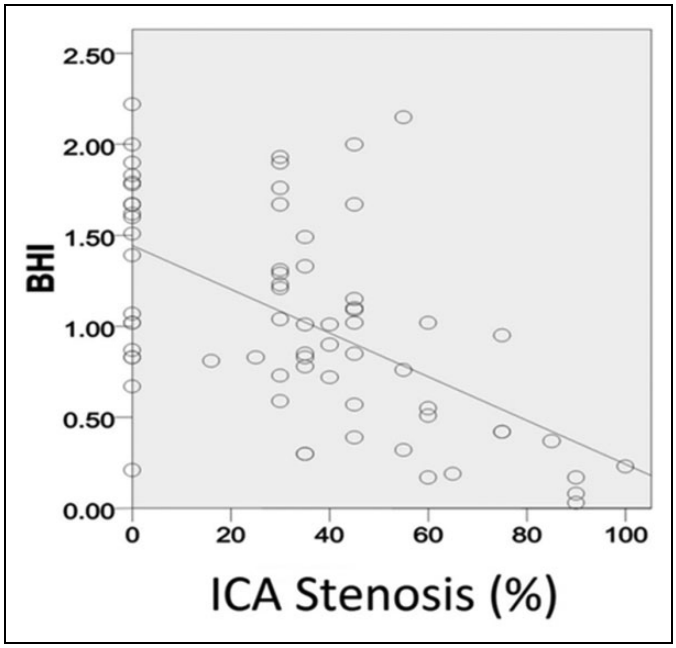

Figure 1. Correlation of ICA stenosis and BHI value. BHI indicates breath holding index; ICA, internal carotid artery.

Figure 2 shows the distribution of VMR impairment in patients with SCS compared with those with ACS. The frequency of impaired VMR was significantly greater in the SCS group than in the ACS group (57.1% vs 13.3%, respectively; $P < .05$). Furthermore, we compared the frequency of SCS in patients with impaired VMR in relation to whether the impairment was unilaterally or globally; patients with symptoms were significantly more frequent in the global VMR impairment group than in the unilateral VMR impairment group but this difference was not significant (91.7% vs 60.0%, respectively; $P = .078$).

Discussion

The percentage of patients with hypertension and hyperlipidemia was significantly higher in the group with ICA stenosis than in the control group. In contrast, incidence of diabetes was nonsignificantly higher in the ICA stenosis group, whereas smoking rates were similar between the 2 groups (Table 1). With regard to biochemical parameters, only glucose levels were significantly higher in patients with carotid artery stenosis than those in the control group (Table 2). These results are in

Table 4. Average Values of BHI With Different Degrees of ICA Stenosis.

	ICA Stenosis Degree, %				
	<30	30-49	50-69	≥70	*P*
BHI (right)	0.92 ± 0.27	0.93 ± 0.49	0.59 ± 0.25	0.37 ± 0.28	0.192
BHI (left)	1.02 ± 0.00	1.09 ± 0.46	0.72 ± 0.61	0.33 ± 0.29	0.001

Abbreviations: BHI, breath holding index; ICA, internal carotid artery.

Table 5. Presence of Risk Factors Among Patients With Preserved and Impaired VMR.

	Preserved VMR (n = 28)	Impaired VMR (n = 22)	*P*
Age, mean ± SD, years	65.0 ± 10.2	69.4 ± 8.9	.115[a]
Gender (m), n (%)	12 (43)	15 (68)	.075[b]
Hypertension, n (%)	23 (82)	21 (95)	.150[b]
Diabetes type 2, n (%)	8 (29)	8 (36)	.558[b]
HLP (%)	19 (67.9)	19 (86.4)	.128[b]
Cardiac diseases, n (%)	6 (21.4)	9 (40.9)	.136[b]
Cigarette smoking, n (%)	9 (32.1)	9 (40.9)	.522[b]
ICA stenosis ≥70%, n (%)	2 (7.1)	9 (40.9)	**.004**[b**]

Abbreviations: HLP, hyperlipidemia; ICA, internal carotid artery; VMR, vasomotor reactivity; χ^2, chi-square; m, male; SD, standard deviation.
[a] Student *t* test.
[b] χ^2test.
**p<0.01.

Table 6. Biochemical Parameters in Patients With Preserved and Disturbed VMR.[a]

	Preserved VMR (n = 28)	Impaired VMR (n = 22)	*P*
Blood glucose, mmol/L	7.1 ± 2.7	6.6 ± 1.9	.544[b]
Urea, mmol/L	6.0 ± 1.8	6.1 ± 1.5	.736[c]
Creatinine, μmol/L	84 ± 16	97 ± 31	.058[c]
Cholesterol, mmol/L			
Total	5.8 ± 1.3	5.5 ± 1.5	.533[c]
HDL-C	1.9 ± 0.5	2.0 ± 0.3	.489[c]
LDL-C	3.6 ± 0.6	3.4 ± 0.7	.406[c]
CRP, mg/L	6.2 ± 2.6	6.4 ± 2.6	.663[b]
Fibrinogen, g/L	4.5 ± 1.6	4.7 ± 1.5	.693[c]

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CRP, C-reactive protein; VMR, vasomotor reactivity.
[a] Data are presented as mean ± standard deviation.
[b] Mann-Whitney *U* test.
[c] Student *t* test.

agreement with those of others thus emphasizing the significance of hyperlipidemia as a risk factor for carotid atherosclerosis.[15] In our study, there were no significant differences between the study and control groups in lipid variables probably because all patients with hyperlipidemia were treated with statins; 38 patients in the study group and 12 in the control group. Hypertension was also a risk factor for ICA stenosis and it was significantly more frequent in the ICA stenosis group than in the controls; this is consistent with previous results.[16,17] The Framingham Heart Study showed that for every 20 mm Hg elevation in systolic blood pressure, the risk of carotid stenosis progression (from minimal [ie, <25%] to moderate [≥25%]) was doubled in both genders.[18] A meta-analysis of 17 studies that included >50 000 patients concluded that hypertension treatment may prevent 38% of all ISs and 40% of fatal strokes.[17]

Inflammatory factors did not differ significantly between the groups, despite the known role of inflammation in carotid atherosclerosis, probably due to the small sample size. However, we found that the degree of carotid stenosis increased significantly with decreasing BHI values and that a significantly higher proportion of patients with impaired VMR had >70% ICA stenosis. Karnik et al[19] measured VMR before and after surgical treatment of ICA occlusion. They concluded that the reduction in cerebral autoregulatory response of the arterioles to acetazolamide significantly correlated with the increase in the degree of stenosis; in 75% of patients where surgery resolved the ICA occlusion, there was a significant improvement in VMR 3 months after surgery.[19] In our study, some patients with moderate ICA stenosis (51%-70%) had average BHI value below 0.69. This finding suggests that a number of respondents have impaired VMR and no hemodynamically significant stenosis. In addition, due to the high variability and the relatively small sample size, we did not make the assessment of the ICA stenosis degree above which we expect VMR to be impaired. These data, however, may be somewhat comparable with the findings of others showing that dysfunctional brain perfusion begins to occur when carotid stenosis reaches a value of about 60%.[20] Given the clear correlation between ICA stenosis and vasomotor reserve disorder of the brain vessels on the one hand and the fact that it occurs unilaterally or bilaterally in patients who do not have critical ICA stenosis, other factors may also influence VMR preservation or deterioration. One of the most likely protective mechanisms is the well-developed network of collateral flow that may compensate chronic hypoperfusion due to ICA stenosis up to a certain critical level.[21]

Severe ICA stenosis emerged as an independent risk factor for VMR deterioration; the risk of VMR impairment is about 11 times higher in patients with hemodynamically significant carotid stenosis than in patients without severe ICA stenosis. In an Iranian[22] study, VMR was measured and BHI was calculated in 289 healthy participants. The authors concluded that BHI value was significantly lower in men and in postmenopausal women than in premenopausal women. Our results

Table 7. Distribution of Patients According to VMR and Severity of Carotid Stenosis.

	Preserved VMR, n (%)	Impaired VMR Unilaterally, n (%)	Impaired VMR Bilaterally, n (%)	Total, n (%)
ICA stenosis <70%	26 (66.7)	7 (17.9)	6 (15.4)	39 (100.0)
ICA stenosis ≥70%	2 (18.2)	3 (27.3)	6 (54.5)	11 (100.0)

Abbreviations: ICA, internal carotid artery; VMR, vasomotor rectivity.

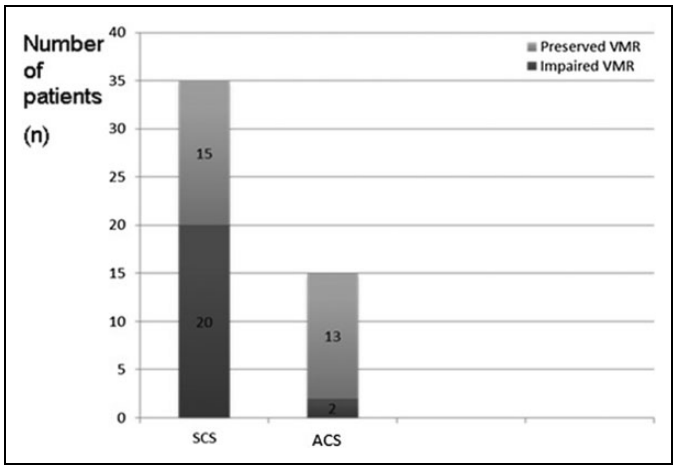

Figure 2. Distribution of patients according to symptoms in relation to VMR. VMR indicates vasomotor reactivity; SCS, symptomatic carotid stenosis; ACS, asymptomatic carotid stenosis.

showed that VMR of the brain vessels is lower in men than in women and although this difference did not reach significance, it may suggest a gender difference in susceptibility to ischemic vascular events. Further investigations involving larger populations are needed.

A previous study investigated VMR in patients with the metabolic syndrome (MetS),[23] as defined by the International Diabetes Federation Consensus of 2006 criteria.[24] Assuming that MetS is a risk factor for cerebrovascular accident, Giannopoulos et al[23] examined VMR in patients with MetS and concluded that MetS is an independent factor for VMR impairment but no disease or condition in this syndrome was highlighted as significant or dominant by itself, indicating that their role in VMR impairment is probably interdependent. In the past, MetS was defined by different criteria according to several international societies and organizations thus leading to incomparable results in clinical studies,[25-29] and further studies should be conducted to clarify this association.

In the present study, the frequency of patients with impaired VMR was significantly higher in the group with SCS than those in the ACS group. Some authors evaluated cerebral hemodynamics in patients with ACS in order to explain how these patients remain asymptomatic despite severe carotid disease.[30,31] They concluded that the patients with ACS having impaired VMR had significantly higher annual risk of stroke than those with preserved VMR and stated that the VMR deterioration is a predictor of ipsilateral stroke. In another study,[32] cerebral hemodynamics in symptomatic and asymptomatic patients before and after CEA for severe ICA stenosis was examined. Preoperatively, there was no VMR difference between symptomatic and asymptomatic patient groups, whereas a significant postoperative VMR improvement was registered only in symptomatic patients. Asymptomatic patients had stable hemodynamics and their vasomotor reserve in response to CEA showed no significant changes. The authors concluded that a better hemodynamic adaptation may be present in these patients and that this does not make them good candidates for surgical treatment.[32] Our results are therefore consistent with the conclusions of those who emphasize the relation between SCS and VMR damage.[33] Several authors stress the role of collateral flow in maintaining cerebral flow homeostasis as a possible mechanism that explains the state of ACS.

One study suggested that patients with ICA occlusion who had impaired VMR may often show an anatomical absence of collateral blood vessels in the circle of Willis or less involvement of collateral flow compared with patients with preserved VMR.[34] Thus, the functional aspect of cerebral hemodynamics was more important in terms of outcomes than a simple anatomical configuration of blood vessels. This could explain our results and also lead to the conclusion that VMR is strongly dependent on the degree of ICA stenosis but if and when it becomes symptomatic and whether the impairment is unilaterally or bilaterally probably depend on the capacity of cerebral collateral circulation and other related factors that require additional research.

Although only severe ICA stenosis was significantly associated with VMR impairment, this does not mean that vascular risk factors should not be treated in these patients.[35] All vascular risk factors in these patients must be treated.

Conclusions

Our study shows that

- The progression of carotid stenosis may cause deterioration of vasomotor reserve of the brain blood vessels;
- severe ICA stenosis is an independent risk factor for VMR impairment and thus may increase the risk of stroke, especially in symptomatic patients.

Authors' Note

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Declaration of Conflicting Interests

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