Cerebral Vasomotor Reactivity and Apnea Test in Symptomatic and Asymptomatic High-Grade Carotid Stenosis

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SUMMARY

Introduction Cerebral vasomotor reactivity (VMR) represents an autoregulatory response of the arterial trunks on the specific vasoactive stimuli, most commonly CO₂.

Objective The aim of this retrospective study was to compare VMR in high-grade symptomatic (SCAS) and asymptomatic carotid stenosis (ACAS), using the apnea test to evaluate the hemodynamic status. **Methods** The study included 50 patients who were hospitalized at the neurology and vascular surgery departments as part of preparation for carotid endarterectomy. We evaluated VMR by calculating the breath holding index (BHI) in 34 patients with SCAS and 16 patients with ACAS, with isolated high-grade carotid stenosis. We evaluated the impact of risk factors and collateral circulation on BHI, as well as the correlation between the degree of carotid stenosis and BHI.

Results A pathological BHI was more frequent in the SCAS group (p<0.01). There was no difference in the range of BHI values between the groups, both ipsilaterally and contralaterally. Only male gender was associated with pathological BHI in both groups (p<0.05). Collateral circulation did not exist in over 60% of all subjects. We confirmed a negative correlation between the degree of carotid stenosis and BHI. **Conclusion** SCAS and ACAS patients present with different hemodynamics. While ACAS patients have stable hemodynamics, combination of hemodynamic and thromboembolic effects is characteristic of SCAS patients.

Keywords: carotid artery diseases; vasomotor system; transcranial Doppler ultrasonography; breath holding

INTRODUCTION

OBJECTIVE

Cerebral hemodynamics is defined by three parameters – cerebral perfusion pressure (CPP), cerebrovascular resistance (CVR) and cerebral blood flow (CBF) – which are in the following relationship: CBF=CPP/CVR. Maintaining a stable CBF with altering CVR, despite changes in CPP, is characteristic of cerebral autoregulation. In case of inadequate development of collateral blood flow, intracerebral arterioles are maximally dilated and become resistant to any vasodilatory stimulus, such as hypercapnia [1, 2].

Autoregulation of blood flow involves mechano- and chemoregulation. Mechanoregulation depends on the gradient of transmural pressure and endothelial vasodilatation, whereas chemoregulation depends on the serum concentration of CO_2 , and changes in arterial pressure do not affect it. Cerebral vasomotor reactivity (VMR), one of the mechanisms of cerebral autoregulation, activates as a response of the arterial trunk and CBF to specific selective vasoactive stimuli, most commonly acetazolamide and CO_2 . Transcranial Doppler with apnea test is considered to be a non-invasive, simple and reproducible method for providing adequate information about cerebral VMR [3, 4]. The aim of the study was to compare cerebral VMR in patients with symptomatic and asymptomatic high-grade carotid stenosis (ACI≥70%) with an assessment of hemodynamic status using the transcranial Doppler (TCD) apnea test. Effects of individual risk factors as well as effects of carotid stenosis degree and collateral blood flow on Breath Holding Index (BHI) were evaluated in two groups of patients, both ipsilaterally and contralaterally to stenosis.

METHODS

The retrospective study included 50 adult patients with internal carotid artery stenosis of over 70%, with 34 patients with symptomatic isolated stenosis and 16 patients with asymptomatic isolated stenosis. The patients were hospitalized due to preoperative diagnostics for carotid endarterectomy and randomly selected at the Clinic for Neurology and Clinic for Vascular Surgery of the Clinical Center of Vojvodina, Novi Sad, from January 2012 to April 2014.

The exclusion criteria in both groups were the following: possible or proved cardioembolic source of stroke (atrial fibrillation, regurgita-

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tion of heart valves, dilatative cardiomyopathy, artificial valves, previous myocardial infarction, patent foramen ovale), contralateral high-grade carotid stenosis or occlusion, significant stenosis or occlusion of vertebrobasilar and intracranial arteries, acute or chronic pulmonary diseases, poor insonation of the temporal bone window and previous stroke and/or carotid surgery.

The following risk factors were observed: age, gender, hypertension, diabetes mellitus, hyperlipidemia and smoking, existing and newly-discovered. Previous therapy for hypertension, diabetes mellitus and hyperlipidemia was recorded in the medical file.

Computed tomography and/or magnetic resonance of the brain, computed tomography angiography and/ or digital subtraction angiography were performed in all patients. Doppler ultrasound on Aloka ProSound Alpha 10 device was used for carotid stenosis degree evaluation by combining B-mode imaging (color duplex flow imaging and power Doppler imaging) with Doppler spectral analysis, according to a standardized protocol. The degree of carotid stenosis was determined according to the European Carotid Surgery Trial criteria, verified by already mentioned imaging methods [5, 6, 7]. High-grade carotid stenosis was graded in the following three levels: 70–79%, 80–89% and 90–99%.

Multi-Dop® T device (DWL® Elektronische Systeme GmbH) and manual Doppler pulsing 2 MHz probe were used for insonation od vertebrobasilar arteries and for intracranial arteries through transtemporal window. Mean blood flow velocity (MBFV) was continually recorded in both middle cerebral arteries. We observed the flow direction and MBFV of main collateral blood vessels, anterior and posterior communicating arteries, as an indirect indicator of the presence of collateral blood flow over the anterior and/or posterior flow. Additional suboccipital insonation of vertebro-basilar system was performed, where collateralization was identified by a 100% increase in MBFV in the basilar artery. Finally, the existence of collateral circulation through the external carotid artery was determined by Doppler of the ophthalmic artery flow ipsilateral to a stenosed carotid artery on the same device [8, 9]. These ultrasound methods were performed by several experienced sonographers "blinded" for a duplex and Doppler scans of carotid arteries.

On the same device TCD apnea test was performed by insonating both middle cerebral arteries, by one experienced sonographer. After a normal inspirium, the patient was instructed to hold breath for 30 seconds. In patients who could not hold their breath for the given period, the estimated apnea was calculated in seconds. The MBFV at the beginning of inspirium, after several minutes of normal breathing, was designated as Vmin, whereas the MBFV at the end of the estimated apneic period was designated as Vmax. BHI was calculated using the following formula: BHI=Vmax-Vmin/Vmin×100/seconds. An average of two BHI measurements was taken, and pathological BHI was defined as BHI<0.69 [4, 10].

Obtained data were analyzed and VMR was compared in high-grade symptomatic (SCAS) and asymptomatic carotid stenosis (ACAS), using the TCD apnea test for the evaluation of carotid hemodynamics.

Statistical analysis was performed using the SPSS 21.0 software and included descriptive statistics (mean, range, standard deviation), parametric Student's t-test, as well as the following nonparametric tests: χ^2 test, Pearson's correlation coefficient, univariate and two-way analysis of variance (ANOVA). The p-value lower than 0.05 was considered significant.

The study was approved by the Ethics Board of the Faculty of Medicine in Novi Sad. All patients gave their written, informed consent.

RESULTS

Fifty patients, 39 (78%) men and 11 (22%) women, mean (\pm SD) age 65.1 \pm 7 years (age range, 50-79 years) were divided into two groups: symptomatic carotid artery stenosis (SCAS) with 34 and asymptomatic carotid artery stenosis (ACAS) with 16 patients.

The observed vascular risk factors (age, gender, hypertension, diabetes mellitus, hyperlipidemia and smoking) did not differ significantly between the groups.

Considering the effect of independent risk factors on the VMR in both groups, there was statistical significance only between men and women with men having greater propensity towards VMR reduction (OR 5.075, 95% CI 1.22–21.06, p=0.025). Existence of other risk factors proved not to be associated with the pathological value of the BHI (Table 1).

Analysis of variance (two-way ANOVA) showed significant correlation between both gender and pathological BHI mean values in both groups (F=4.562, p=0.039) (Table 2).

 Table 1. Univariate analysis of individual risk factors for breath holding index ipsilateral to stenosis in both groups

	5 1		
Risk factors	OR	95% CI	р
Gender (male – female)	5.075	1.22–21.06	0.025
Age (1-year interval)	0.98	0.90–1.06	0.63
HTA (Yes – No)	0.97	0.16–5.89	0.97
DM (Yes – No)	1.62	0.43–6.17	0.48
HLP (Yes – No)	0.50	0.14–1.74	0.28
Smoking (Yes – No)	1.70	0.48–6.09	0.41

HTA – hypertensio arterialis; DM – diabetes mellitus; HLP – hyperlipidemia; OR – odds ratio; CI – confidence interval; p – statistical significance

Table 2. The influence of gender on the pathological breath holding
index value between symptomatic and asymptomatic carotid stenosis
groups ipsilateral to carotid stenosis

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Group	Gender	X	SD	N
Symptomatic	Female	0.68	0.22	6
	Male	0.61	0.38	28
	Total	0.62	0.36	34
Asymptomatic	Female	1.27	0.53	5
	Male	0.64	0.35	11
	Total	0.84	0.50	16
Total	Female	0.95	0.48	11
	Male	0.62	0.37	39
	Total	0.69	0.42	50

 \overline{X} – mean value; SD – standard deviation; N – number of patients

	Group						
BHI ipsilateral	Symptomatic		Asymptomatic		Total		
	Ν	%	Ν	%	Ν	%	
Normal values	7	20.6	10	62.5	17	34.0	
Pathological values	27	79.4	6	37.5	33	66.0	
Total	34	100.0	16	100.0	50	100.0	

Table 3. Distribution of breath holding index (BHI) values ipsilateral to stenosis in the two groups

Observing the influence of both genders on the mean value of BHI, in females there was a significant reduction of BHI only in SCAS group (Mann–Whitney test, U=3000; p=0.028), while in males there was no difference between the groups (t-test, t=0.222, p=0.36).

There was no significant difference in BHI values between the two groups; SCAS: 0.04–1.64, ACAS: 0.05–1.93. The presence of pathological values of BHI (<0.69) was significantly more frequent in the SCAS group (27 [79.4 %] vs six [37.5%] patients [p<0.01]) (Table 3).

We examined the presence and distribution of collateral pathways. There was no collateral circulation in 33 (66%) patients in the SCAS and ACAS groups, and no significant influence on the BHI values ipsilateral to stenosis (Pearson's correlation, r=-0.250, p>0.05) (Graph 1).

In the remaining 17 (34%) patients in both groups, the secondary collateral pathway was dominant (via arteria ophtalmica [AIO]) in SCAS group, while the primary collateral pathway (via anterior communicating arteries) was dominant in the ACAS group, but with no statistical significance (p>0.05).

Regarding the degree of carotid stenosis, most of the patients (42%) were in the second group with 80-89% stenosis. There was a statistically significant negative correlation between the degree of stenosis and BHI values in both SCAS and ACAS groups (p<0.05) (Graph 2).

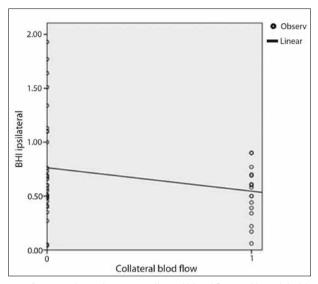
Contralateral to carotid stenosis, there was no significant difference in BHI between the groups (SCAS: 0.30– 2.06, ACAS: 0.50–1.95) (p>0.05), or in the distribution of pathological BHI (p>0.05).

DISCUSSION

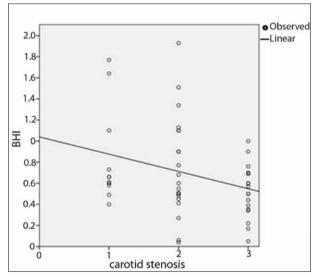
Evaluation of cerebral VMR may have a prognostic value for patients with steno-occlusive carotid disease. This is based on the relationship between exhausted cerebral hemodynamics and the development of stroke, with hemodynamic phenomena possibly differing in SCAS and ACAS patients [10, 11].

Although precise mechanism of brain circulation control is still unknown, several biological variables should be addressed: larger CBF in women with blood flow velocity in medial cerebral artery 3-5% faster than in men, and considerable interindividual difference between PaCO₂ and blood flow velocity [12, 13]. In our study, reduced VMR is more common in men regardless of which study group they belong to, which confirms the literature data about low vascular sensitivity for applied vasoactive stimuli in men. VMR in men was significantly reduced in the





Graph 1. Correlation between collateral blood flow and breath holding index (BHI) ipsilateral (0 – no collateral blood flow; 1 – with collateral blood flow)



Graph 2. Correlation between the degree of carotid stenosis and breath holding index (BHI) (1=70–79%; 2=80–89%; 3=90–99%)

SCAS compared to the ACAS group. Male gender represented an important risk factor for stroke, which has been confirmed in previous studies [13, 14, 15].

Other risk factors (age, hypertension, diabetes mellitus, hyperlipidemia and smoking) showed no significant influence on the VMR in either group. In their study, Krdžić et al. [16] using TCD apnea test also did not found association between those risk factors and VMR reduction in patients with SCAS. In our study most of the patients were metabolically well regulated with drugs and effect of multiple risk factors during a longer period of time has to be considered.

Collateral circulation through the extra- and intracranial collaterals is important for maintaining a normal CPP, as well as a compensatory mechanism in the process of infarction development. If it is insufficient or absent, hemodynamics of cerebral circulation is compromised [17, 18, 19]. In our study, more than 60% of all subjects did not have a developed collateral circulation; in the SCAS group secondary type prevailed via AO, and in the ACAS group primary pathway prevailed via anterior communicating arteries, although without statistical significance. This may explain an ipsilateral cerebrovascular event in a number of SCAS subjects. In the SCAS group, carotid microembolization hypothesis together with the absence of collateral circulation could explain the emergence of stroke. Carotid microemboli become symptomatic with the CPP lowering and with lack of time for activation of collateral circulation, which would otherwise have a protective hemodynamic role. In this way hemodynamics equalizes microembolic mechanism of carotid disease [18, 19, 20].

In the remaining SCAS patients, existing secondary collateral circulation was probably hemodynamically afunctional and, as such, it represents a specific indicator of impaired hemodynamics. It has been shown previously that in ACAS patients intracranial hemodynamic status is better preserved than in SCAS patients. The role of the circle of Willis in preservation of the intracranial hemodynamic status via primary collateral flow in this group was confirmed by other authors [21-24].

Our results showed that the SCAS group had a lower BHI value ipsilateral to stenosis compared to the ACAS group. These results confirm the previous findings: a lower BHI value (<0.69) represents a higher risk of stroke, and a higher grade of carotid stenosis is associated with a lower BHI value [4, 25, 26, 27]. Almost half of the patients (44.1%) in the SCAS group had a high level carotid stenosis (90-99%), while 50% of the patients in the ACAS group had a medium level stenosis (80-89%). Our results confirm negative correlation between the degree of carotid stenosis and VMR. Other authors reported similar results by using different vasoactive tests and methods. Levine et al. [28] found reduced VMR in 18 patients with transient ischemic attack and negative correlation between carotid stenosis degree (50-99%) and VMR by using 5% CO, inhalation and positron emission tomography. Gooskens et al. [29] and Reinhard et al. [30] used different methods and also reported negative correlation between carotid stenosis degree and a loss of hemodynamic regulation, concluding that normal function of collateral circulation is necessary for the preservation of brain autoregulation.

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According to the literature, there is still controversy regarding the symmetry or asymmetry of VMR between the SCAS and ACAS groups. Silvestrini et al. [25] pointed to a different VMR in symptomatic and asymptomatic patients with significant carotid stenosis. Nighoghossian et al. [31] and Lucertini et al. [32] reported opposite results. Literature data show a combined action of hemodynamic and thromboembolic effects on stroke, and a special emphasis is given to the role of the morphological structure of a carotid plaque as a possible source of microemboli [25, 33], which may explain our results.

Our study has some limitations that have to be considered in the interpretation of the results. First, limited number of patients in both groups; second, influence of number of activated collateral paths on VMR in certain groups; and third, the fact that only one sonographer performed the TCD apnea test. This emphasizes the need for expanded research with more patients, thus adding to better evaluation of the mechanism of stroke and therapy algorithm.

CONCLUSION

Hemodynamic effects of symptomatic and asymptomatic high-grade stenosis on VMR are different. Combined hemodynamic and thromboembolic effects of carotid plaque could contribute to the occurrence of stroke in SCAS patients. More stable hemodynamics is characteristic of ACAS patients. The occurrence of secondary collateral pathway, via AO, indicates disturbed intracranial carotid hemodynamics, when brain tissues receive insufficient blood supply from the primary collaterals, thereby providing patients a valuable, but limited, compensation. The results of this study revealed an important implication for clinical practice. It suggested that early evaluation of cerebral hemodynamics in a symptomatic and asymptomatic carotid disease are essential for determining optimal therapeutic strategies. Understanding the value of TCD apnea test as a simple and fast method that can be used in the carotid hemodynamics follow-up is important for every neurologist and vascular surgeon, especially in our circumstances, where other, more expensive methods are hardly accessible or even unavailable.

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Церебрална вазомоторна реактивност и апнеа тест код симптоматске и асимптоматске високостепене каротидне стенозе

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КРАТАК САДРЖАЈ

Увод Церебрална вазомоторна реактивност (ВМР) је одговор артеријског стабла на дејство специфичних вазоактивних стимулуса, најчешће угљен-диоксида (*CO*₃).

Циљ рада Циљ овог ретроспективног истраживања било је поређење ВМР код високостепене симптоматске (СКАС) и асимптоматске каротидне стенозе (АКАС) применом апнеа теста у процени хемодинамског статуса.

Методе рада Истраживање је обухватило 50 болесника хоспитализованих на Клиници за неурологију и васкуларну хирургију у оквиру преоперационе припреме за каротидну ендартеректомију. Процењивана је BMP израчунавањем индекса задржавања даха (енгл. *breath holding index – BHI*) између 34 болесника са СКАС и 16 болесника са АКАС и изолованом високостепеном каротидном стенозом. Процењен је утицај фактора ризика на вредности *BHI*, те упоређен степен каротидне стенозе и колатералног крвотока са *BHI*. Резултати Патолошка вредност *BHI* била је чешћа у СКАС групи (*p*<0,01). Није било разлике у опсегу вредности *BHI* међу групама ипсилатерално и контралатерално. Једино се код мушкараца обе групе испољио значајан утицај на патолошку вредност *BHI* (*p*<0,05). Колатерална циркулација није постојала код више од 60% испитаника обе групе. Потврђена је негативна корелација између степена каротидне стенозе и вредности *BHI*.

Закључак Болесници са СКАС и АКАС имају различиту каротидну хемодинамику. Док се код особа са АКАС уочава стабилна каротидна хемодинамика, комбинација хемодинамског и тромбоемболијског ефекта је одлика болесника са СКАС.

Кључне речи: болести каротидне артерије; вазомоторни систем; транскранијална доплер ултрасонографија; задржавање даха

Примљен • Received: 08/08/2014

Ревизија • Revision: 10/03/2015