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Visual Evoked Response in Patients with Severe Carotid Disease – Functional Transcranial Doppler Study of Posterior Circulation

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ABSTRACT

The goal of this study was to evaluate the visual evoked response in posterior cerebral artery (PCA) by means of functional transcranial doppler in patients with severe carotid disease and to determine the hemodynamic effect of severe carotid disease on posterior circulation. Measurements were performed successively in the dark and during the white light stimulation in 49 patients with high-grade (70–99%) internal carotid artery (ICA) stenosis or occlusion and compared with 30 healthy age and sex matched subjects. Mean blood flow velocities (MBFV) (cm/s±2SD) and mean reaction time (MRT) (s±2SD) during three consecutive repetitive periods of 1 minute each were analyzed. MBFV in PCA during the white light stimulation and in the dark between the two groups didn't differ. MRT in patients showed a significantly prolonged visual evoked response in both affected (light: patients 29.36±14.46, controls 19.67±11.25, respectively, $p<0.046$; dark: patients 35.25±11.9, controls 21.89±10.31, respectively, $p<0.002$ and unaffected side (dark: patients 33.13±11.12, controls 23.89±11.23, respectively, $p<0.032$) of ICA. This data showed that MRT is the principal restrictive factor in the case of carotid stenosis suggesting the independence of cerebral vascular reserve capacity of the posterior part of Willis circle that is necessary to be considered separately.

Key words: *carotid stenosis, visual evoked response, posterior cerebral artery, transcranial doppler, functional*

Introduction

Estimation of impaired cerebral vascular reserve by means of transcranial doppler (TCD) in patients with severe carotid disease can be achieved by the assessment of cerebral blood flow changes in response to various vasodilatatory stimuli[1–4]. In patients with high-grade stenosis or occlusion of the internal carotid artery (ICA) significantly reduced cerebral vasomotor reactivity (VMR) have been demonstrated[5–7] yet, attention has been mainly focused upon evaluating the hemodynamic effect of ICA stenosis on the middle cerebral artery (MCA)[8,9]. The data on the hemodynamic features of the posterior part of the circle of Willis, which can play an important role as a collateral channel in patients with significant ICA stenosis, are still sparse.

Brain function, neuronal metabolism and regional blood perfusion are in close physiological relationship called vasouneuronal coupling. During various cognitive, motor activities and sensor stimulation metabolic demands of the involved region become more pronounced and consecutively the regional cerebral blood flow of the involved area increases[10]. Vascular response to neuronal activation has been well documented by various imaging techniques[11–13]. Since these techniques have a reasonable spatial but poor temporal resolution they fail to assess the dynamic properties of vasoneuronal coupling, which is likely to be impaired in different stages of cerebrovascular disease. TCD offers the opportunity to evaluate rapid changes of vasomotor reactivity according to metabolic demands during various functional conditions[14].

Visual stimulation is usually used in testing cerebral vasomotor reserve in posterior cerebral artery (PCA) territory feeding the occipital lobe and most of the supplied tissue being involved in the visual system. Studies testing the visually evoked response in PCA, conducted mostly on healthy subjects, have demonstrated increased

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blood flow velocities in PCA. Aaslid first found that the flow volume in the posterior cerebral artery increased 20.2% in response to light stimulation of the retina, while flow velocity in the same artery increased 16.4%[15]. The regulation of blood flow velocity was very rapid; only 2.3 seconds elapsed from application of the light stimulus to 50% of full response. Full regulation (90% of full response) took 4.6 seconds. Further investigations showed that percentage of the flow velocity increase depends of the type of the stimuli[16–20]. Azevedo et al. performed a visual reading test stimulation task and found that an intact cerebral autoregulation compensates the different orthostatic conditions thus allowing an independent regulation of neurovascular coupling according to the metabolic needs of cortical stimulation[21]. Testing the flow velocity changes in PCA in response to a visual stimulation was conducted in pathological states only in few studies. Urban et al. showed that occipital lobe infarction of various size leads to a reduced visually activated flow increase in the ipsilateral PCA[22]. Becker et al. studied visually evoked cerebral blood flow velocity changes in different states of brain dysfunction and suggested that in aneurysmal subarachnoid hemorrhage decreased metabolic flow response presents severe depression of vasoneuronal coupling, increased vulnerability to vasospasm and a higer risk for stroke[23].

Since the intracerebral effects of carotid occlusive disease were studied mostly in the anterior part of the circle of Willis, this present study was designed to assess visual evoked response as the most powerful and fully non-invasive test of autoregulation in the PCA during white light stimulation by means of functional transcranial doppler (fTCD) in patients with severe carotid stenosis, in order to determine the hemodynamic effect of severe carotid disease on the posterior circulation.

Patients and Methods

The study cohort consisted of 49 consecutive patients (mean age±SD 67±8; 37 men) with high-grade (70–99%) ICA stenosis or occlusion as measured by Doppler ultrasonography and 30 healthy volunteers (mean age±SD 67±7; 22 men) with normal ICAs. The two groups were comparable in age ($p<0.91$) and sex ($p<0.52$).

Inclusion criteria were: symptomatic or asymptomatic severe unilateral stenosis or occlusion of the ICA.

Exclusion criteria were: limited ultrasound temporal window, detectable stenosis or occlusion of any of the arteries of the Willis circle, incooperative patients (dementia, coma, etc.), heart disease (atrial fibrillation, myocardial infarction, patent foramen ovale, atrial septum aneurysm, mitral valve prolapse), uncontrolled hypertension, diabetes mellitus and migraine.

In two patients with ICA occlusion and in 1 patient with high grade ICA stenosis mild stenosis (<50%) of contralateral ICA was found.

Carotid artery disease was assessed and defined using the color Doppler flow imaging (CDFI) and power doppler imaging (PDI) (ALOKA Prosound 5500, 7,5 linear array transducer for morphologic investigation and 5 MHZ pulsed Doppler for hemodynamic investigation) according to validated criteria[24].

The intracranial arteries were evaluated by TCD (2 MHz hand-helded probe; MultiDop X4 DWL, Elektronische Systeme GmbH, Sipplingen). The TCD examination was carried out with the patient in a supine position according to validated criteria[25]. It included transtemporal insonation of the MCA, ACA (anterior cerebral artery) and PCA and transoccipital insonation of the VA (vertebral artery) and BA (basilar artery).

Visual evoked response was obtained by means of TCD (MultiDop X4 DWL, Elektronische Systeme GmbH, Sipplingen) using a special application for evoked flow. It included transtemporal simultaneous insonation of P1 segment of LT and RT PCA at a depth of 60–70 mm using two 2 MHz probes mounted on an individually fitted head band. The testing was carried out with the patient in a supine position, in a dark, quiet room, after an accomodation period of resting and closed eyes for 10 minutes. For the visual stimuli a 100W electric bulb was used, located 50 cm in front of the head of the examinee. After the accomodation period mean blood flow velocities (MBFV) and mean reaction time (time to peak velocities) (MRT) in each PCA were measured, in a dark (closed eyes) and during a white light stimulation (opened eyes, looking at a electric bulb). The measurements were performed successively in the dark and during the white light stimulation, during three consequtive repetitive periods of 1 minute each. Mean values of MBFV and MRT during a one minute period with and without visual stimuli were analised.

The ethics committee of the University Hospital »Sestre milosrdnice«, Zagreb, approved the study and all patients signed informed consent.

Statistical analyses

For statystical analyses we used statistical program package Statistica for Windows, Kernel release 5,5 A (StatSoft, Inc. Tulsa, OK) (StatSoft, Inc. (2000); STATISTICS for Windows (Computer program manual). Tulsa, OK: StatSoft, Inc.

We used paired Student t-test to compare quantitative variables between the two groups, t-test for dependent variables to compare values of repetitive measurements within the same group and linear regression analyses to analise the corelation of quantitative variables.

From Nonparametric Statistics model we used Pearson χ^2-test to compare a distribution of qualitative characteristics of the group. To compare a mean reaction time between two groups we used Mann Whitney U test as a sabstitute for Student t-test due to the small number of the subjects. Results with p-values of <0.05 were considered statistically significant.

TABLE 1
MEAN BLOOD FLOW VELOCITIES (MBFV) IN POSTERIOR CEREBRAL ARTERY (PCA) IN THE GROUP OF PATIENTS WITH ADVANCED CAROTID DISEASE

MBFV in PCA (cm/s±2SD)				
Patients (n=49)				
MBFV light	Affected side	32.6±11.49	p<0.69	t=1.86
	Unaffected side	29.88±8.61		
MBFV dark	Affected side	23.44±10.84	p<0.15	t=1.48
	Unaffected side	21.32±7.08		

TABLE 2
MEAN REACTION TIME (MRT) IN PCA IN THE GROUP OF PATIENTS WITH ADVANCED CAROTID DISEASE

MRT in PCA (s±2SD)				
Patients (n=49)				
MRT light	Affected side	29.38±14.46	p<0.09	t=1.79
	Unaffected side	26.33±12.41		
MRT dark	Affected side	35.25±11.9	p<0.35	t=0.97
	Unaffected side	33.13±11.12		

Results

In the basal conditions (opened eyes) mean values of MBFV didn't differ between the two groups (cm/s±2SD): right (RT) PCA patients 29.08±10.46, controls 25.8±7.32, respectively (p<0.14, NS); left (LT) PCA patients 28.65± 9.58, controls 25.93±8.67, respectively (p<0.21, NS).

This study showed no statisticall difference in MBFV (Table 1) or in MRT (Table 2) between affected and unaffected side within the patients group neither during the white light stimulation nor in the dark.

Following the visual evoked response test, difference between MBFV in PCA during the white light stimulation and in the dark was found to be 9.16±4.08 cm/s±2SD on the affected side and 8.56±3.74 cm/s±2SD on the unaffected side, respectively (p<0.33; t=0.98; t-test for dependent variables, NS).

The difference between MRT in PCA during the white light stimulation and in the dark was found to be –5.88± 7.12 s±2SD on the affected side and –6.79±9.1 s±2SD on the unaffected side, respectively (p<0.49; t=0.70; t-test for dependent variables, NS).

During the white light stimulation mean value of MBFV in PCA on the affected side of ICA in the patients group was 32.6±11.49 cm/s±2SD, while in ipsilateral PCA in controls it was 30.56±8.34 cm/s±2SD (p<0.4, NS). Mean value of MBFV during the white light stimulation in PCA on the unaffected side of ICA in the patients group was 29.88±8.6 cm/s± 2SD, while in ipsilateral PCA in controls it was 29.99±9.5 cm/s±2SD (p<0.96, NS). In the dark also, mean values of MBFV in PCA neither on the affected (patients 23.44±10.84 cm/s±2SD; controls 21.40±7.32 cm/s±2SD; p<0.37; NS) nor on the unaffected side (patients 21.32±7.08 cm/s±2SD; controls 20.12±8.33 cm/s±2SD; p<0.5) didn't show statistical difference.

Difference between mean values of MBFV in PCA during the white light stimulation and mean values of MBFV in PCA in the dark between affected side in the patients group (9.16±4.06 cm/s±2SD) and ipsilateral side in controls (9.16±4.38 cm/s±2SD), respectively (p<0.99, NS) and between unaffected side in the group of patients (8.56±3.74 cm/s±2SD) and ipsilateral side of ICA (left and right) in the controls (9.87±4.13 cm/s±2SD) respectively (p<0.16, NS) was not found.

On the contrary, MRT during the white light stimulation on the affected side in patients group was found to be 29.36±14.46 s, while on the ipsilateral side of ICA in the controls it was significantly lower (19.67±11.25 s), respectively (u=69.5; z=2.00; p=0.046; Mann Whitney U--test). MRT in the dark on the affected side in patients group was 35.25±11.9 s and on the ipsilateral side in the controls it was also significantly lower 21.89±10.31 s, respectively (u=43.5; z=3.02; p=0.002; Mann Whitney U--test).

MRT during the white light stimulation on the unaffected side in patients group was 26.33±12.41 s, while on the ipsilateral side of ICA in the controls it was also lower (18.67±9.09 s), respectively (u=76.5; z=1.72; p=0.09, Mann Whitney U test, NS). MRT in the dark on the unaffected side in patients group was 33.13±11.12 s, while on the ipsilateral side in the controls was 23.89±11.23 s, respectively (u=66.0; z=2.13; p=0.03; Mann Whitney

TABLE 3
MRT IN THE GROUP OF PATIENTS WITH ADVANCED CAROTID DISEASE AND IN HEALTHY VOLUNTEERS

	MRT in PCA (s±2SD)						
			Patients (n=49)	Healthy (n=30)	u	z	p
Time	Affected side	Light	29.36±14.46*	19.67±11.25*	69.5	2.00	0.046*
		Dark	35.25±11.9*	21.89±10.31*	43.5	3.02	0.002*
	Unaffected side	Light	26.33±12.41	18.67±9.09*	76.5	1.71	0.085
		Dark	33.13±11.12*	23.89±11.23*	66.0	2.13	0.032*

p<0.05 statisticaly significant

U-test). The findings of the MRT on the unaffected side in the dark differed significantly between the groups (Table 3).

Discussion

Our study found that in basal conditions mean values of MBFV in the PCA didn't differ between a group of severe carotid disease patients and healthy subjects referring to an important role of posterior circulation as a collateral channel in patients with severe carotid disease.

Moreover, the findings according to MBFV and MRT in this study also showed that visual evoked response of the PCA remains similar both on the stenosed and the unstenosed side of ICAs in the case of more pronounced metabolic demands of the region, suggesting a cerebral posterior circulation mechanism that compensates very successfully the anterior circulation insufficiency in severe carotid disease.

Gur and Bornstein evaluated the hemodynamic features of the posterior circulation in patients with severe carotid stenosis by assessing and comparing cerebral vasomotor reactivity (VMR) in the MCA and vertebral arteries (VA) by transcranial Doppler and Diamox test. They found a significantly lower MCA VMR percentage value on the side of the carotid stenosis in all the studied patients while VA VMR percentage remained similar regardless of carotid stenosis and a symptomatic or asymptomatic course of carotid occlusive disease. They concluded that vasomotor response in the posterior circulation remains constant regardless the side of ICA stenosis and refer to an independent cerebral vascular reserve capacity of the posterior circulation as compared with the anterior part of the circle of Willis[26,27].

Considering the similarity of MBFV in PCA during the white light stimulation and in the dark between the patients group and healthy subjects, as well as between the affected and unaffected side of ICA in the carotid stenosis patients, our study suggests that posterior circulation compensatory mechanism is highly effective and works independently. Hemodynamic effect of ICA stenosis on the MCA with significantly reduced VMR of the MCA highly correlating with the grade of the stenosis has been demonstrated in patients with high-grade stenosis or occlusion[28–31]. On the contrary, again, our study findings show that the cerebral vasomotor response in the PCA in carotid diseased patients is not changed, demonstrating the effectiveness of switching the circulation from vertebro-basilar to carotid system via PCA and posterior communicant artery (PCoA) keeping the blood flow velocities satisfactory.

In contrast, the MRT data showed a significantly prolonged visual evoked response in PCA in both affected and unaffected side of ICA in the severe carotid stenosis patients. Our findings refer to a remarkably lower mean reaction time on the affected side of ICA in carotid disease patients that is prolonged vasoreactive response both during the white light stimulation and in the dark (Table 3). The difference in MRT on the unaffected side between the patients and controls during the white light stimulation was clinically but not statistically significant, possibly because of the low number of subjects, but there is a clear trend towards a prolonged vasoreactive response on the unaffected side of ICA in carotid disease patients as well (Table 3). The findings of the MRT on the unaffected side in the dark differed significantly between the groups. Concerning the similarity of MBFV in PCA and the significantly prolonged vasoreactive response in severe carotid disease patients, we can conclude that MRT is the principal restrictive factor and indicator of compromised cerebral circulation in the presence of hemodynamic significant carotid stenosis.

Functional tests are of great value for the assessment of cerebral circulatory reserve. Critically reduced perfusion pressure in the cerebral arteries may lead to functional ischemic impairment or even ischemic tissue damage in certain vulnerable areas of the brain. The main reason for a reduction of cerebral perfusion pressure is severe extracranial occlusive disease. The perfusion pressure of the brain cannot be measured directly and a parameter indirectly reflecting cerebral perfusion pressure can be measured by using functional tests[32]. Evaluation of vascular reserve capacity of the posterior circulation using visual stimuli in patients with severe carotid disease gives an excellent insight in hemodynamic effect of carotid stenosis and takes into account the key role of the collateral circulation in intracerebral hemodynamics.

All together, posterior circulation in patients with severe carotid stenosis was tested using two different methods and two different arteries from the posterior part of the circle of Willis. The findings originating from Gur and Bornstein[26,27] study by Diamox test and our findings with completely non-invasive testing of visual evoked response in the PCA in patients with severe carotid disease both suggest the existence of an independent cerebral vascular reserve capacity of the posterior part of Willis circle that is necessary to be considered separately from the anterior part. Understanding the effect of carotid stenosis on the posterior circulation can be of a great help in selecting the patients who are at higher risk for stroke and may also represent the way of selecting out those patients who will benefit most from interventional procedures. We believe that the findings obtained in this study warrant further trials in order to evaluate the clinical significance and the role of visual evoked response testing the posterior circulation in the carotid disease management and may prove useful in further study of the pathogenesis and management of stroke.

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VIDNI EVOCIRANI ODGOVOR U BOLESNIKA SA ZNAČAJNOM KAROTIDNOM BOLESTI – ISPITIVANJE STRAŽNJEG KRVOTOKA FUNKCIONALNIM TRANSKRANIJSKIM DOPLEROM

SAŽETAK

Cilj istraživanja bio je procijeniti vidni evocirani odgovor u stražnjoj moždanoj arteriji (ACP) funkcionalnim transkranijskim doplerom u bolesnika sa uznapredovalom karotidnom bolesti i utvrditi hemodinamski učinak uznapredovale karotidne bolesti na stražnji moždani krvotok. Mjerenja su izvršena naizmjence u mraku i tijekom podraživanja bijelim svjetlom u 49 bolesnika sa značajnom stenozom (70–99%) ili okluzijom unutarnje karotidne arterije (ACI) i uspoređena s vrijednostima dobivenim u 30 zdravih dobrovoljaca odgovarajuće dobi i spola. Analizirane su srednje brzine strujanja krvi (SBSK) (cm/s±2SD) i srednje vrijeme reagiranja (SVR) (s±2SD) tijekom tri uzastopna ponavljana mjerenja u trajanju od 1 minute svaki. SBSK u ACP tijekom podraživanja bijelim svjetlom i u mraku nisu se statistički značajno razlikovale između dvije skupine. SVR u bolesnika je pokazalo statistički značajno produljen vidni evocirani odgovor i na bolesnoj (svjetlo: bolesnici 29,36±14,46, zdravi 19,67±11,25, $p<0,046$; mrak: bolesnici 35,25±11,9, zdravi 21,89±10,31, $p<0,002$ i na zdravoj strani ACI (mrak: bolesnici 33,13±11,12, zdravi 23,89±11,23, $p<0,032$). Rezultati pokazuju kako je SVR glavni ograničavajući čimbenik u bolesnika sa značajnom karotidnom stenozom i upućuju na neovisnost rezerve stražnjeg dijela Willisovog kruga. Odvojeno proučavanje prednjih i stražnjih dijelova Willisovog kruga kod bolesnika sa značajnom stenozom ili okluzijom ACI u procjeni moždane hemodinamike je neizbježno.