CEREBROVASCULAR EVOKED RESPONSE TO REPETITIVE VISUAL STIMULATION IN SEVERE CAROTID DISEASE – FUNCTIONAL TRANSCRANIAL DOPPLER STUDY

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SUMMARY – Hemodynamic features of the posterior circulation were evaluated by assessing visual evoked response in posterior cerebral artery (PCA) by means of functional transcranial Doppler (fTCD) in 49 patients with high-grade (70%-99%) internal carotid artery (ICA) stenosis or occlusion and 30 healthy subjects. Mean blood flow velocities (MBFV) and mean reaction time (time to peak velocities) (MRT) in each PCA were measured in the dark (closed eyes) and during white light stimulation (opened eyes, looking at the electric bulb), during three consecutive repetitive periods of 1 minute each. In the group of severe carotid disease patients, there was no difference in MRT in PCA during the white light stimulation (P=0.1), whereas in the dark MRT values showed a statistically significantly prolonged visual evoked response (P=0.02), but with no clinical relevance. MBFV values did not differ significantly during white light stimulation (P=0.1), whereas in the dark the difference was also statistically significant (P=0.03), but with no clinical relevance. On the contrary, in the group of healthy subjects, MRT values differed significantly both during white light stimulation (P=0.0005) and in the dark (P=0.00054), showing a significantly prolonged visual evoked response. During white light stimulation, MBFV showed significant decrease and prolonged vasoreactive response (P=0.004). Prolonged vasoreactive response in PCA in healthy subjects during repetitive measurements may indicate exhaustion of the vasoreactive mechanisms. In carotid disease patients, stable vasoreactive response may indicate that the compensatory mechanisms of the posterior circulation are always maximally engaged to compensate for carotid insufficiency.

Key words: Carotid stenosis – ultrasonography; Evoked potentials, visual; Posterior cerebral artery – ultrasonography; Blood flow velocity; Ultrasonography; Doppler, transcranial

Introduction

Functional transcranial Doppler (fTCD) tests are of great value for the assessment of cerebral circulatory reserve since 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. 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.

In patients with significant internal carotid artery (ICA) stenosis or occlusion, attention has been mainly focused on evaluating the hemodynamic effect of ICA stenosis on the middle cerebral artery (MCA)2,3, demonstrating the significantly reduced cerebral vasomotor reactivity (VMR)4, although data on the hemodynamic features of the posterior part of the circle of...
Willis demonstrate that it can play an important role as a collateral channel\textsuperscript{8-10}. Visual stimulation is usually used in testing cerebral vasomotor reserve in the 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 in healthy subjects, have demonstrated increased blood flow velocities in PCA. Aaslid was the first to find that the flow volume in the PCA increased in response to light stimulation of the retina and that the regulation of blood flow velocity was very rapid\textsuperscript{11}. Further investigations showed the percentage of the flow velocity increase to depend on the type of stimuli\textsuperscript{12-16}. Azevedo et al. performed a visual reading test stimulation task and found that an intact cerebral autoregulation compensated for different orthostatic conditions, thus allowing for independent regulation of neurovascular coupling according to the metabolic needs of cortical stimulation\textsuperscript{17}. In order to investigate whether the potent vasodilator agent, acetazolamide (AZ), inhibits the neurovascular coupling, Yonai et al. tested repeated visual stimulus in PCA before and after AZ provocation and indicated an independent regulation of vasodilatation during neurovascular coupling, allowing for the adaptation of cerebral blood flow according to the neuronal activity even if other processes required significant vasodilatation\textsuperscript{18}. Results of the study performed by Zheng et al. demonstrated an increased blood flow velocity in PCA P2 segment due to decreased cerebrovascular resistance during visual stimulation as well as a weakened response with patient aging\textsuperscript{19}. Testing the flow velocity changes in PCA in response to visual stimulation was conducted in pathological states in a few studies. Urban et al. showed that occipital lobe infarction of various sizes led to a reduced visually activated flow increase in the ipsilateral PCA\textsuperscript{20}. 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 presented severe depression of vasoneuronal coupling, increased vulnerability to vasospasm, and a higher risk of stroke\textsuperscript{21}. Smith et al. demonstrated an impaired visual evoked flow velocity response in patients with cerebral amyloid angiopathy, suggesting the pathology of distal resistance vessels as the cause of impairment\textsuperscript{22}.

Referring to the important role of posterior circulation as a collateral channel in patients with severe carotid disease, the present study was designed to assess visual evoked response as the most powerful and fully noninvasive test of autoregulation in the PCA during white light stimulation and on three repetitive measurements by means of \textit{fTCD} in patients with severe carotid stenosis, in order to determine the hemodynamic effect of severe carotid disease on the posterior circulation.

**Subjects 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 by 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, uncooperative patients (dementia, coma, etc.), heart disease (atrial fibrillation, myocardial infarction, patent foramen ovale, atrial septum aneurysm, mitral valve prolapsed), uncontrolled hypertension, diabetes mellitus and migraine. Patients were abstained from alcohol, caffeine beverages and smoking, as well as drug free (nitrates, $\beta$-blocking agents, calcium channel blockers, anticoagulants and vasodilatatory agents) for at least 24 hours prior to the study.

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 morphological investigation and 5-MHz pulsed Doppler for hemodynamic investigation) according to validated criteria\textsuperscript{23}.

The intracranial arteries were evaluated by TCD (2-MHz hand-held probe; MultiDop X4 DWL, Elektronische Systeme GmbH, Sipplingen). Transcranial Doppler examination was carried out with
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 the P1 segment of the left and right PCA at a depth of 60-70 mm using two 2-MHz probes mounted on an individually fitted headband. The testing was carried out with the patient in supine position, in a dark, quiet room, after an accommodation period of resting and eyes closed for 10 minutes. For visual stimuli, a 100 W electric bulb was used, located 50 cm in front of the head of the subject. After the accommodation period, the mean blood flow velocities (MBFV) and mean reaction time (time to peak velocities; MRT) in each PCA were measured in the dark (closed eyes) and during white light stimulation (opened eyes, looking at the electric bulb). The measurements were performed successively in the dark and during white light stimulation, during three consecutive repetitive periods of 1 minute each. The mean values of MBFV and MRT during a one-minute period with and without visual stimuli were analyzed.

The Ethics Committee of the Sestre milosrdnice University Hospital, Zagreb, approved the study and all study subjects signed an informed consent.

Statistics

For statistical analyses we used statistical program package Statistica for Windows, Kernel release 5.5 A (StatSoft, Inc., Tulsa, OK, USA) (StatSoft, Inc. 2000, STATISTICS for Windows computer program manual, StatSoft, Inc., Tulsa, OK, USA).

We used paired Student’s 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 analyze the correlation of quantitative variables.

From Nonparametric Statistics model we used Pearson $\chi^2$-test to compare distribution of the group qualitative characteristics. To compare the mean reaction time between the two groups, we used Mann Whitney U test as a substitute for Student’s t-test due to the small number of subjects. Results with $P$ values <0.05 were considered statistically significant.

Results

In severe carotid disease patients, MRT values did not differ significantly among the three measurements during white light stimulation ($P=0.1$, Friedman Anova test) (Table 1, Fig. 1). On the contrary, in the group of healthy subjects, during white light stimulation and three consecutive repetitive measurements, MRT was significantly lower on the second (20.67 s ± 16.24 s) and third (25.33 s ± 14.93 s) measurements as compared with the first measurement (13.00 s ± 6.49 s), showing a statistically significantly prolonged vasoreactive response ($P=0.0005$; Friedman Anova test) (Table 1, Fig. 1).

In the group of severe carotid disease patients, MRT values in the dark on the three measurements were statistically ($P=0.02$; Friedman Anova test) but not clinically significantly different (Table 2, Fig. 2). In healthy subjects, the difference in MRT values in

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<th>Table 1. Mean reaction time in posterior cerebral artery during white light stimulation</th>
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*statistically significant; s = second; SD = standard deviation; n = number of subjects; $P$ = statistical significance
In the group of severe carotid disease patients, differences in MBFV values recorded on the three measurements in the dark were statistically significant ($P=0.00054$; Friedman Anova test), but not clinically significant (Table 2, Fig. 2). In healthy subjects, MBFV values in the dark did not yield statistically significant difference among the three consecutive repetitive measurements ($P=0.57$; Friedman Anova test) (Table 4, Fig. 4).

**Discussion**

Recent studies have demonstrated the existence of an independent cerebral vascular reserve capacity of the posterior circulation as compared with the anterior part of the circle of Willis in patients with severe carotid stenosis. 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 VA by TCDH and Diamox test. They found a significantly lower MCA VMR percentage on the side of carotid stenosis in all study patients, whereas the VA VMR percentage remained similar regardless of carotid stenosis and a symptomatic or asymptomatic course of carotid occlusive disease. They conclude that vasomotor response in the posterior circulation remains constant regardless of the side of ICA stenosis and refers to an independent cerebral vascular reserve capacity of the posterior circulation as compared with the anterior part of the circle of Willis25,26. Roje-Bedeković et al. in their study showed that visual evoked response of the PCA did not differ between the stenosed and nonstenosed side of ICAs in severe carotid disease patients, suggesting the existence of an independent cerebral vascular reserve capacity of the posterior part of the Willis circle that is necessary to be considered separately from the anterior part27.

Table 3. Mean blood flow velocities in posterior cerebral artery during white light stimulation

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<th>Mean blood flow velocities in posterior cerebral artery – light (cm/s ± 2SD)</th>
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<td>PATIENTS (n=49)</td>
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<tr>
<td>1</td>
<td>32.65±11.69</td>
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<tr>
<td>2</td>
<td>32.14±11.81</td>
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<tr>
<td>3</td>
<td>31.14±10.91</td>
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<td>HEALTHY (n=30)</td>
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<tr>
<td>1</td>
<td>31.33±8.24*</td>
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<td>2</td>
<td>30.47±8.44*</td>
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<td>3</td>
<td>29.87±8.66*</td>
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*statistically significant; s = second; SD = standard deviation; n = number of subjects; P = statistical significance

Considering the cerebrovascular response to repetitive visual stimulation, Nedeltchev et al. found the migraineurs with aura to exhibit a larger cerebrovascular response to repetitive visual stimulation compared to headache-free subjects, suggesting a reduced adaptation to environmental stimuli in migraine, since there was no habituation in migraineurs in contrast to healthy controls28. In her long term follow-up of unilateral ICA occlusion including repeated tests of vasomotor reactivity by TCD, Zbornikova found that MBFV in the PCA increased on the occluded side compared with that at the start of the follow up29. Olah et al. demonstrated impaired repetitive visually evoked flow velocity response in otherwise healthy
chronic young cigarette smokers, suggesting that impaired cerebral vasodilatory mechanism together with atherosclerosis may influence stroke occurrence and outcome in chronic smokers\textsuperscript{30}.

We found that in the group of severe carotid disease patients, MRT values did not differ among the three measurements during white light stimulation, whereas in the dark MRT values showed a statistically significantly prolonged visual evoked response, but with no clinical relevance, either because of the small number of subjects or because of the measurement error. Regarding MBFV, these values did not differ significantly among the three measurements during white light stimulation, whereas in the dark the difference was also statistically significant, but with no clinical relevance. On the contrary, in the group of healthy subjects, MRT values differed significantly both during white light stimulation and in the dark, showing a significantly prolonged visual evoked response in PCA on the second and third measurements as compared with the first measurement. During white light stimulation, MBFV values recorded on the second and third measurements showed a significant decrease as compared with the first measurement, indicating again a prolonged vasoreactive response in PCA during the three repetitive measurements in healthy subjects.

Considering that in the group of severe carotid disease patients, there was no difference either in MRT or in MBFV in PCA during white light stimulation, we can conclude that in severe carotid disease patients the vasoreactive response in PCA remained stable over the three stimulation cycles. The unchanged vasoreactive responses in PCA during the repetitive measurements pointed to compensatory mechanisms of their posterior circulation, which most probably are constantly maximally engaged in maintaining their cerebral blood stable. The mild prolongation in MRT as well as the mild decrease in MBFV in PCA on the second and third measurements as compared to the first measurement in the dark, which were of no clinical relevance, could be interpreted as a habituation, but also as a sign of exhaustion of the vasomotor reserve during the three repetitive measurements. In the group of healthy subjects, a decrease in MBFV as well as the prolonged vasoreactive response in PCA during repetitive measurements and white light stimulation indicated exhaustion of the vasoreactive mechanism in healthy subjects, which was not shown in the group of patients because their posterior circulation compensatory mechanisms were obviously maximally engaged in overcoming carotid insufficiency. Severe carotid disease patients exhibited a larger cerebrovascular response to repetitive visual stimulation as compared with healthy subjects.

Results of this study suggest a reduced adaptation to visual stimuli in severe carotid disease patients, since there was no habituation in severe carotid disease patients in contrast to healthy controls. The cerebral vasomotor response in the PCA in severe carotid diseased patients is not changed, demonstrating the effectiveness of switching the circulation from the vertebrobasilar to the carotid system via PCA and posterior communicant artery (PCoA), keeping the cerebral perfusion satisfactory and suggesting an independent cerebral posterior circulation mechanism that compensates very successfully for the anterior circulation insufficiency in severe carotid disease. Evaluation of the vascular reserve capacity of the posterior circulation using visual stimuli in patients with severe carotid disease gives an excellent insight into the hemodynamic effect of carotid stenosis and takes into account the key role of the posterior collateral circulation in intracerebral hemodynamics. We believe that

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<tr>
<td>1</td>
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<td>22.24±10.17*</td>
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understanding the effect of severe carotid stenosis on the posterior circulation can be of great help in selecting patients who are at a higher risk of stroke, and may also represent the way of selecting out those patients that will benefit most from interventional procedures. The findings obtained in this study warrant further trials in order to evaluate the clinical significance and the role of repetitive visual evoked response testing of the posterior circulation in the management of severe carotid disease. In addition, these findings may prove useful in further study of the pathogenesis and management of stroke.

Acknowledgment

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Sažetak

CEREBROVASKULARNI EVOCIRANI ODGOVOR NA OPETOVANI VIDNI PODRAŽAJ KOD UZNAPREDOVALE KAROTIDNE BOLESTI – ISPITIVANJE POMOĆU FUNKCIJALNOG TRANSKRANIJSKOG DOPLERA

M. Roje-Bedeković, M. Bosnar-Puretić, A. Lovrenčič-Huzjan i V. Demarin

Mjerenjem vidnog evociranog odgovora stražnje moždane arterije (ACP) funkcionalnim transkranijskim doplerom (FTCD) procjenjivala su se hemodinamska zbivanja u stražnjem dijelu moždanog krvotoka u 49 bolesnika s uznapredovalom karotidnom stenozom (70%-99%) ili okluzijom i usporedila s rezultatima u 30 zdravih ispitanika. Mjere su se srednje brzine strujanja krvi (SBK) i srednje vrijeme reagiranja (SVR) u ACP u mraku (zatvorene oči) i tijekom podraživanja bijelim svjetlom (otvorene oči, gledanje u električnu žarulju) tijekom tri opetovana mjerenja u slijedu u trajanju od 1 minute svaki. U skupini bolesnika s uznapredovalom karotidnom bolešću tijekom podraživanja bijelim svjetlom nije bilo statistički značajne razlike u SVR (P=0,1), dok su rezultati u mraku pokazali statistički značajno produljen vidni evocirani odgovor (P=0,02), ali bez kliničkog značenja. SBSK se nisu statistički značajno razlikovalo tijekom podraživanja bijelim svjetlom (P=0,1), dok su u mraku rezultati pokazali statistički značajnu razliku (P=0,03), ali bez kliničkog značenja. Naprotiv, u skupini zdravih ispitanika vrijednosti SVR pokazale su statistički značajnu razliku i tijekom podraživanja bijelim svjetlom (P=0,0005) i u mraku (P=0,00054), što upućuje na značajno produljenje vidnog evociranog odgovora u ACP. Tijekom podraživanja bijelim svjetlom SBSK pokazale su značajno smanjenje vrijednosti i produljen vazoreaktivni odgovor u ACP (P=0,004). Produljen vazoreaktivni odgovor u ACP u skupini zdravih ispitanika tijekom opetovanih mjerenja može upućivati na iscrpljenost vazoreaktivnih mehanizama. U bolesnika s uznapredovatom karotidnom bolešću stabilan vazoreaktivni odgovor može upućivati na maksimalnu uključenost kompenzacijskih mehanizama stražnjega moždanog krvotoka u prevladavanju karotidne insuficijencije.

Ključne riječi: Karotidna stenozna – ultrazvuk; Evocirani potencijali, vidni; Stražnja moždana arterija – ultrazvuk; Brzina krvnog protoka; Ultrazvuk; Doppler, transkranijski

M. Roje-Bedeković et al. Repetitive visual stimulation in severe carotid disease