Acta Neurol. Belg., 2011, **111**, 195-200

Impact of carotid disease on posterior circulation in patients with vertebral artery occlusion – a functional transcranial Doppler study

M. Bosnar Puretić, A. Lovrenčić-Huzjan, M. Roje Bedeković and V. Demarin

University Neurology Department, Sestre milosrdnice University Hospital Center, Reference Center for Neurovascular Disorders of the Ministry of Health and Social Welfare of the Republic Croatia, Reference Center for Headaches of the Ministry of Health and Social Welfare of the Republic Croatia, Zagreb, Croatia

Introduction

Almost one quarter of all ischemic strokes occur in posterior circulation. Approximately 20% of posterior circulation strokes evolve as a result of vertebral artery (VA) disease (1, 2). The most common causes of vertebral artery occlusion are development of atherosclerotic plaque and embolism, but dissection should also be taken into account, mostly occurring after neck trauma (3). Carotid disease represents an important risk factor for ipsilateral ischemic stroke and TIA in anterior circulation (4, 5, 6). Also, it can be correlated with the occurrence of disturbances in posterior circulation, since in some patients the collateral pathways redirect the posterior blood flow to anterior circulation (7). A study by Delcker and al. showed that a significantly higher rate of TIA in the vertebrobasilar system occurred in patients with combined carotid and vertebral artery disease (8).

Cerebral vasoreactivity and autoregulation are functions of cerebral microcirculation that ensure adequate cerebral blood supply in conditions of altered perfusion pressure and metabolism. It can be precisely estimated in real time using a non-invasive method, functional transcranial Doppler sonography (fTCD) (9). In addition, large artery disease leads to cerebrovascular reactivity impairment, which has been confirmed in patients with severe carotid stenosis and occlusion by means of several fTCD methods. Studies using acetazolamide, CO2, breath-holding, motor tasks and other stimuli showed that reduction of cerebrovascular reactivity in patients with proximal carotid disease is present and corresponds to increased risk of ipsilateral stroke and TIA (10, 11, 12, 13). fTCD detects cerebral blood flow changes during perfusion pressure and metabolic changes and cortical neural activation (neurovascular coupling) (9, 14, 15). For investigations of posterior circulation a simple fTCD method using white light as a stimulus was introduced by Aaslid in 1987 (16). During white light stimulation in healthy subjects, blood flow velocities in the posterior cerebral artery (PCA) significantly increased as a result of neuronal activation and increased metabolism (16). Considering that the visual cortex is almost exclusively supplied by PCA, transcranial Doppler recording during visual stimulation represents a reliable method for cerebral vasoreactivity testing of posterior circulation. But in different pathological neurological conditions this evoked response can be reduced and rarely increased, compared to healthy subjects (17, 18, 19, 20, 21, 22). The results of the fTCD study investigating changes in blood flow velocities in PCA during visual stimuli in patients with vertebral artery occlusion revealed significantly reduced responses (20). This study analyzed visual evoked responses in a group of patients with vertebral artery occlusion regardless of the presence of internal carotid artery stenosis or occlusion in the same patient.

The aim of present study is to evaluate the visually evoked responses in the PCA by means of TCD in patients with isolated VA occlusion and in patients with VA occlusion and carotid disease. The aim is also to compare the extent of these responses between groups of patients and between patients and healthy individuals. The purpose of this study is to explore the range of autonomy of posterior circulation or its dependence on functional status of anterior circulation by means of fTCD.

Subjects and methods

This study was performed at Cerebrovascular laboratory of the University Department of Neurology, Sestre milosrdnice University Hospital Center, Zagreb, Croatia. The Institutional Ethical Committee

approved the study. All subjects read and signed an informed consent document. We included adult hospitalized patients as well as subjects from the outpatient department; three groups of examinees were formed: patients with isolated extracranial or intracranial VA occlusion; patients with extracranial or intracranial VA occlusion and unilateral significant internal carotid artery (ICA) stenosis or occlusion, and a control group. We included asymptomatic carotid stenosis patients with no history of neurological symptoms arising from supplying territory of ICA and symptomatic patients with neurological symptoms arising from ICA territory, ie. TIA, amaurosis fugax or stroke 3 or more months before entering the study, since in this period of time after an incident cerebral vasoreacitivity improves (23, 24). Exclusion criteria were: limited temporal ultrasound window, stenosis or occlusion of intracranial arteries other than VA, bilateral severe ICA stenosis or occlusion to avoid the interference of this condition on intracranial hemodynamics by developing extensive anterior and posterior compensatory pathways, severe visual field or other visual deficit, non-compliance (dementia, disturbance of consciousness), recent TIA or stroke (< 3 months), non-regulated hypertension (irregular taking of antihypertensive medications, blood pressure more than 140/90 mmHg) and non-regulated diabetes mellitus (data from clinical chemistry and a clinical history), severe heart condition that could influence cerebral hemodynamics (atrial fibrillation, myocardial infarction, severe heart failure, patent foramen ovale, atrial septum aneurysm, and mitral valve prolapse). None of the patients used vasoactive medications. Patients had abstained from alcohol, caffeinated beverages and smoking, as well as drugs that may alter blood pressure or cause vasodilatation (nitrates, β-blocking agents, calcium channel blockers, anticoagulants and vasodilatatory agents) for at least 24 hours prior to the study.

We examined the extracranial part of carotid and VA using a Color Doppler Flow Imaging device with a 7,5 MHz linear probe for morphological investigation and a 5 MHz probe for hemodynamic investigation. The degree of ICA stenosis and occlusion was assessed according published ultrasonographic criteria (25). The VA occlusion was diagnosed according validated ultrasonographic criteria (25, 26). Trancranial Doppler sonography of Willis circle and vertebrobasilar system was performed in accordance with validated criteria (27, 28). Values of mean blood flow velocities (MBFV) in PCAs recorded while examinees' eyes were open, but without additional light stimulation were considered as MBFV in basic conditions.

For assessment of visual evoked responses in PCA we used the MultiDopX4 DWL device, Elektronische system GmbH, Sipplingen with 2 MHz probe with incorporated original DWL software for evoked flow. Simultaneous bilateral recording of PCAs at P1 segment by two Doppler channels through temporal window was performed and changes of mean blood flow velocities were registered using the software application for the evoked flow. For white light stimulation a lamp of 100 W was used, at a distance of 50 cm from the subject's eyes. Examinees were tested in a supine position in a quiet, dark room. They were instructed to relax and not to speak or move during the investigation. The first phase of the investigation was a 10-minute accommodation period while examinees were left to rest in a supine position with eyes closed. After the accommodation period we performed three consecutive tests, each consisting of one minute of recording MBFV in PCAs while the examinee's eyes were closed and one minute of recording while the examinee was looking at white light. For analysis we used mean value of these three recordings, separately for the right and for the left PCA.

As an outcome measure of response in PCA we defined the percentage of MBFV changes in PCA during light stimulation compared with MBFV in PCA with the subject's eyes closed.

For statistical analysis we used the statistical program package Statistica for Windows, Kernel release 5,5 A (StatSoft, Inc. Tulsa, OK) (StatSoft, Inc. (2000). Results are presented as mean values with standard deviations and in percentages. The differences in responses between groups were assessed using the T-test and Kolmogorov-Smirnov test. Statistical significance was defined as p value < 0,05.

Results

The study included 17 patients with isolated occlusion of VA, 15 patients with occlusion of VA and unilateral severe ICA stenosis or occlusion, and 26 age and sex matched subjects in the control group. All groups were matched also according major vascular risk factors (hypertension, diabetes mellitus, hyperlipidemia, smoking, previous TIA or stroke) since these conditions have an impact on cerebral vasoreactivity (29, 30). The demographic data of study subjects are presented in Table 1. In 26 patients we found unilateral VA occlusion and in 6 patients both VA were occluded. Bilateral VA occlusion was found in 2 patients with coexisting carotid disease. Out of 38 occluded VA, 23 were occluded in the extracranial part and 15 VA the intracranial. Out of 15 patients with carotid disease, 10 had significant

Table 1

Demographic data of study subjects

	VA occlusion	VA occlusion + carotid disease	Controls
Sex, n (%) M F	 13 (76,5) 4 (23,5)	 12 (80) 3 (20)	 17 (65,4) 9 (34,6)
Age, y, mean ± SD	58,9 ± 11,4	61,5 ± 10,5	58,4 ± 11,9
Arterial hypertension, n (%)	5 (29,4)	5 (33,3)	8 (30,1)
Hyperlipidaemia, n (%)	4 (23,5)	4 (26,7)	6 (23,1)
Diabetes mellitus, n (%)	1 (5,8)	1 (6,7)	2 (7,7)
Smoking, n (%)	2 (11,7)	2 (13,3)	3 (11,5)
Previous TIA or stroke, (> 3 months), n (%)	1 (5,8)	2 (13,3)	0 (0)

ICA stenosis and in 5 patients ICA was occluded. The study included 18 hospitalized patients, and since only for these patients brain CT or MRI was eligible, these data weren't used in further analysis.

In physiological conditions (eyes opened, no additional light stimulation) MBFV in PCA in control group were 36,35 ± 12,44 cm/s in the right and 35,61 ± 13,38 cm/s in the left PCA, in the group of patients with isolated VA occlusion 35,58 ± 12,52 cm/s in the right PCA and 34,52 ± 11,96cm/s in the left PCA and in the group of patients with VA occlusion and carotid disease 36,59 ± 11,47 cm/s in the right and 35,83 ± 11,07 cm/s in the left PCA. We found no significant difference in MBFV in PCAs in physiological conditions between groups. During visual stimulation in all three groups, an increase of MBFV occurred. While looking at white light, MBFV in the control group increased by 22,85 ± 20,9% in the right PCA and by 20,67(cm/s) ± 15,31% in the left PCA compared to MBFV for the same group with the eyes closed ($p < 0,001$). In the group of patients with vertebral artery occlusion, MBFV in PCA increased significantly while looking at white light; 15,15 ± 15,98% in the right PCA and 12,57 ± 15,52 in the left PCA ($p < 0,001$). Also in patients with VA occlusion and carotid disease MBFV in PCA during light stimulation significantly increased; 8,57 ± 14,4% for right PCA ($p < 0,001$) and 10,07 ± 14,56% for left PCA($p = 0,001$). In figure 1. MBFV in PCAs before and after white light stimulation for all three groups are presented. Figure 2 shows the comparison of PCA MBFV increase during white light stimulation for all three groups; data are presented in percentages. This analysis revealed a significantly larger visually evoked response for both PCAs in the control group than in the group with isolated VA occlusion ($p < 0,05$ for both PCAs). A comparison between the control group and the group of patients with VA occlusion and carotid disease shows an especially remarkable difference ($p = 0,01$ for the right PCA, $p < 0,01$ for the left PCA). We recorded weaker visually evoked response in the group of patients with VA occlusion and carotid disease compared to the group with isolated VA occlusion. But a statistically significant difference was present only for the right PCA ($p = 0,027$) and not for the left PCA ($p = 0,377$).

Discussion

We recorded a significant increase of MBFV in PCA during white light stimulation in all groups, which is in concordance with the results of previous studies indicating that fTCD using visual stimuli is a reliable and reproducible method for posterior circulation cerebral vasoreactivity assessment (16, 31). As in the presented study, previous studies have shown impairment of neurovascular coupling and cerebral autoregulation distally to severe VA disease (20, 32). We found impairment of microcirculatory function (neurovascular coupling) in the occipital lobe in patients with VA occlusion using visual stimuli. Also, in conditions of reduced systemic blood pressure in patients with bilateral VA disease, autoregulatory mechanisms fail to maintain sufficient blood supply in posterior circulation (32). Our results as well as results from previous studies involving anterior and posterior circulation suggest that although neurovascular coupling is a function of cerebral microcirculation, large artery disease affects greatly this function (12, 33, 34). The study comparing sonographic findings of VA and internal carotid arteries and frequency of TIA in vertebrobasilar system demonstrated significant rate of TIAs in the same region in patients with combined carotid and vertebral artery disease (71%). On the contrary, a group of patients with isolated vertebral artery disease showed TIAs in only 13% (8). The results of our investigation are in accordance with the last study as we found more attenuated visual evoked responses in patients with combined VA occlusion and carotid disease than in patients with isolated VA disease.

However, several studies described independence of posterior circulation. In patients with carotid occlusive disease assessment of cerebral vasoreactivity with acetazolamide showed impaired reaction in the middle cerebral artery while the vertebral artery

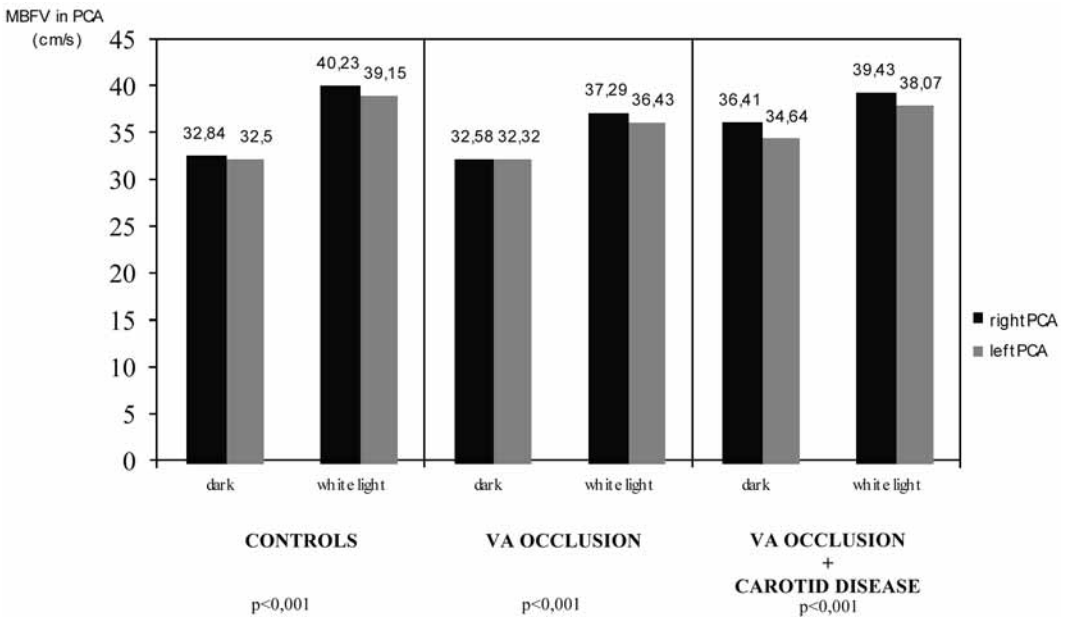

FIG. 1. — The comparison of mean blood flow velocities (MBFV) in PCA with subject's eyes closed and during looking at white light for control group, patients with VA occlusion and patients with VA occlusion and carotid disease.

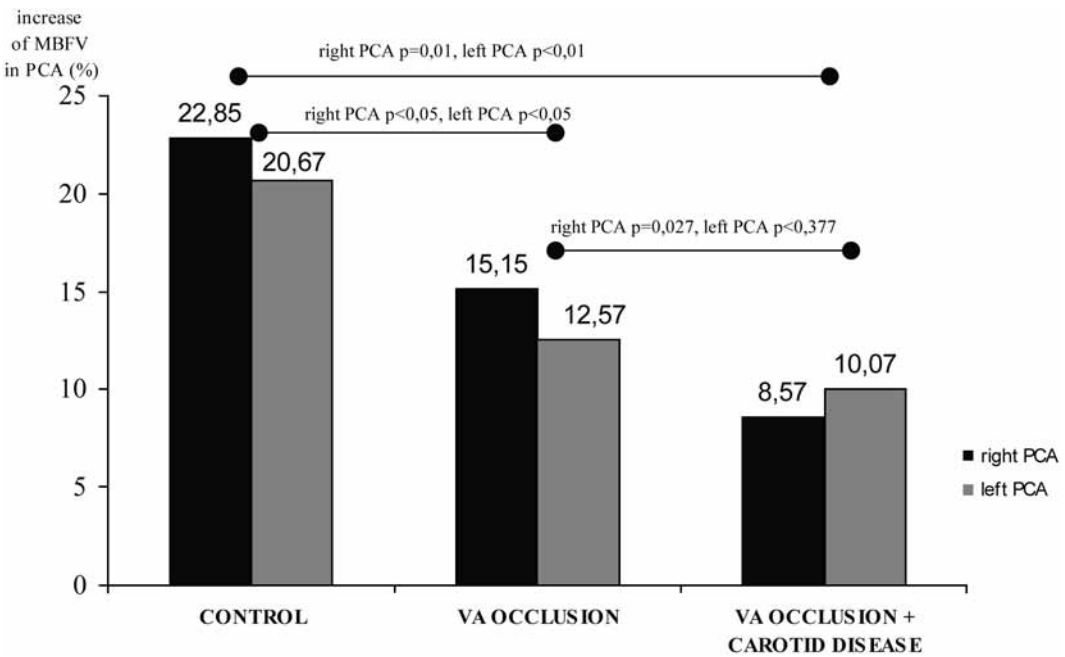

FIG. 2. — The comparison of the percentages of PCA mean blood flow velocities (MBFV) increase during white light stimulation between control group, patients with VA occlusion and patients with combined VA occlusion and carotid disease.

remained normal (12, 35). Similar results were obtained in the study of Roje Bedeković *et al*. testing cerebrovascular reactivity in PCA using visual stimulation. Yet, the same study revealed significantly prolonged mean reaction time in PCAs during visual stimulation in patients with carotid disease (36).

We found several limitations of our study. fTCD is a reliable method for recording a changes in blood flow in real time. But insonation techniques still cannot indisputably overcome collateral variations of Willis' circle, which has to be taken into consideration in discussion of collateral pathways (37. We

found reduced visual evoked response in patients with VA occlusion and carotid disease compared to patients with isolated VA occlusion, but statistically significant only for right PCA. Possibly, it could be explained by asymmetry in visual processing in the occipital lobe in humans, but this question remains open. Analysis of the evoked response in PCA would be more precise parallel to data of brain CT or MR findings for all patients, as well as to data of ipsilateral or contralateral carotid disease in patients with VA occlusion. We compared visual evoked responses between patients with isolated VA occlusion and patients with coexisting carotid disease, but also in these two groups heterogeneity exists regarding unilateral vs. bilateral VA occlusion, intracranial vs. extracranial VA occlusion and internal carotid significant stenosis vs. occlusion. Although the literature on this topic is scarce we presume that different locations and degrees of occlusive diseases could have different effect on cerebral vasoreacitivity. We considered this heterogeneity as a study limitation since the study population's size is too small for further subanalysis of possible effects of these conditions on cerebral vasoreactivity due different collateral pathways.

We can conclude that our results demonstrate that autonomy of posterior circulation cannot be taken for granted regarding condition of carotid arteries. We found reduced visual evoked response in PCA in patients with VA occlusion and in patients with VA occlusion and carotid disease, with a weaker response in the last group. It suggests that carotid disease in patients with occlusive changes of vertebrobasilar arteries still has an additional effect on posterior circulation. Probably due to the anatomical position of VA and limited diagnostic and therapeutic possibilities, there are a limited number of studies dealing with physiology and pathophysiology of posterior circulation. The results of our study could contribute to better comprehension of cerebral hemodynamics in carotid and vertebral artery occlusive disease as well in the clinical approach to this kind of patient. We also demonstrated fTCD testing by visual stimulus as a relevant tool for evaluation of functional vasomotor reserve of the posterior circulation. For more precise information about the autonomy of posterior and anterior cerebral circulation in pathological conditions, further studies using other functional imaging methods are needed.

REFERENCES

1. Bernasconi A, Bogusslavsky J, Basseti C, Regli F. Multiple acute infarcts in the posterior circulation. J Neurol Neursurg Psychiatry. 1996;60:289-296.
2. Khan S, Cloud GC, Kerry S, Markus HS. Imaging of vertebral artery stenosis: a systematic review. J Neurol Neurosurg Psychiatry. 2007;78(11):1218-1225.
3. Wityk RJ, Chang HM, Rosengart A, Han WC, DeWitt LD. *et al*. Proximal extracranial vertebral artery disease in the New England Medical Center Posterior Circulation Registry. Arch Neurol. 1998;55(4):470-478.
4. Blaser T, Hoffmann K, Buerger T, Effenberger O, Wallesch C-W. Risk of Stroke, Transient Ischemic Attack, and Vessel Occlusion Before Endarterectomy in Patients With Symptomatic Severe Carotid Stenosis. Stroke. 2002;33:1057-1062.
5. Lanzino G, Tallarita T, Rabinstein AA. Internal carotid artery stenosis:natural history and management. Semin Neurol. 2010;30(5):518-527.
6. Demarin V, Lovrenčić-Huzjan A, Bašić S, Bašić Kes V, Bielen I. *et al*. Recommendations for the management of patients with carotid stenosis. Acta Clin Croat 2010;49:101-118.
7. Bogousslavsky J, Regli F. Vertebrobasilar transient ischemic attacks in internal carotid artery occlusion or tight stenosis. Arch Neurol. 1985;42(1):64-68.
8. Delcker A, Diener HC, Timmann D, Faustmann P. The role of vertebral and internal carotid artery disease in the pathogenesis of vertebrobasilar transient ischemic attacks. Eur Arch Psychiatry Clin Neurosci. 1993;242(4):179-183.
9. Demarin V, Bosnar Puretić M. Funkcionalno ispitivanje moždnog krvotoka transkranijskim doplerom. In: Demarin V, Lovrenčić-Huzjan A, eds. Neurosonologija. Zagreb, Školska knjiga;2009.
10. Rundek T, Demarin V, Despot I, DeSyo D, Podobnik-Šarkanji S. Value of cerebral vasoreactivity testing in patients with carotid artery disease before and after carotid endarterectomy. Acta Clin Croat. 1993;32: 141-150.
11. Silvestrini M, Troisi E, Cupini LM, Matteis M, Pistolese GR. *et al*. Transcranial Doppler assessment of the functional effects of symptomatic carotid stenosis. Neurology. 1994;44(10):1910-1914.
12. Gur AY, Bornstein NM. Cerebral vasomotor reactivity of bilateral severe carotid stenosis:is stroke unavoidable? Eur J Neurol. 2006;13(2):183-186.
13. Reinhard M, Gerds TA, Grabiak D, Zimmermann PR, Roth M. *et al*. Cerebral dysautoregulation and the risk of ischemic events in occlusive carotid artery disease. J Neurol. 2008;255(8):1182-1189.
14. Lohmann H, Ringelstein EB, Knecht S. Functional transcranial Doppler sonography. Front Neurol Neurosci. 2006;21:251-260.
15. Béné R, Lovrencić-Huzjan A, Azman D, Strineka M, Budisić M. *et al*. Blood flow velocity in middle cerebral artery during visuo-motor tasks using a mirror: a transcranial Doppler study. Acta Clin Croat. 2009;48(3):305-310.
16. Aaslid R. Visually evoked dynamic blood flow response of the human cerebral circulation. Stroke. 1987;18:771-775.

17. Lisak M, Trkanjec Z, Mikula I, Demarin V. Mean blood flow velocities in posterior cerebral arteries during visual stimulation. Mt Sinai J Med. 2005; 72(5):346-350.
18. Urban PP, Allardt A, Tettenborn B, Hopf HC, Pfennigsdorf S. *et al*. Photoreactive flow changes in the posterior cerebral artery in control subjects and patients with occipital lobe infarction. Stroke. 1995;26(10):1817-1819.
19. Becker VU, Hansen HC, Brewitt U, Thie A. Visually evoked cerebral blood flow velocity changes in different states of brain dysfunction. Stroke 1996; 27:446-449.
20. Bosnar Puretić M, Lovrenčić Huzjan A, Roje Bedeković M, Demarin V. The influence of vertebral artery occlusion on visual evoked responses in posterior cerebral artery. Rad Hrvatske akademije znanosti i umjetnosti. 2007;497:103-113.
21. Smith EE, Vijayappa M, Lima F, Delgado P, Wendell L. *et al*. Impaired visual evoked flow velocity response in cerebral amyloid angiopathy. Neurology. 2008;71(18):1424-1430.
22. Wolf ME, Jäger T, Bäzner H, Hennerici M. Changes in functional vasomotor reactivity in migraine with aura. Cephalalgia. 2009;29(11):1156-1164.
23. Widder B, Kleiser B, Krapf H. Course of cerebrovascular reactivity in patients with carotid artery occlusions. Stroke. 1994;25(10):1963-1967.
24. Aries MJ, Elting JW, De Keyser J, Kremer BP, Vroomen PC. Cerebral autoregulation in stroke: a review of transcranial Doppler studies. Stroke. 2010; 41(11):2697-2704.
25. Lovrenčić Huzjan A. Ultrazvučni pregled karotidnih arterija. In: Demarin V, Lovrenčić-Huzjan A, eds. Neurosonologija. Zagreb, Školska knjiga;2009.
26. Lovrenčić Huzjan A, Vuković V, Bosnar Puretić M, Dematin V. Sonographic features of vertebal artery occlusion (the role of color and power Doppler flow imaging). Acta Clin Croat. 1999;38:279-285.
27. Alexandrov AV, Demarin V. Insonation techniques and diagnostic criteria for transcranial Doppler sonography. Acta Clin Croat. 1999;38:97-108.
28. Alexandrov AV, Sloan MA, Wong LK, Douville C, Razumovsky AY *et al*. American Society of Neuroimaging Practice Guidelines Committee. Practice standards for transcranial Doppler ultrasound: part I – test performance. J Neuroimaging. 2007;17(1):11-8.
29. Last D, Alsop DC, Abduljalil AM, Marquis RP, de Bazelaire C. *et al*. Global and regional effects of type 2 diabetes on brain tissue volumes and cerebral vasoreactivity. Diabetes Care. 2007;30(5):1193-1199.
30. Ficzere A, Valikovics A, Fülesdi B, Juhász A, Czuriga I. *et al*. Cerebrovascular reactivity in hypertensive patients: a transcranial Doppler study. J Clin Ultrasound. 1997;25(7):383-389.
31. Wiedensohler R, Kuchta J, Aschoff A, Harders A, Klug N. Visually evoked changes of blood flow velocity and pulsatility index in the posterior cerebral arteries: a transcranial Doppler study. Zentralbl Neurochir. 2004;65(1):13-17.
32. Haubrich C, Kohnke A, Diehl RR, Moller-Hartmann W, Klotzsch C. Impact of vertebral artery disease on dynamic cerebral autoregulation. Acta Neurol Scand. 2005;112(5):309-316.
33. Markus H, Cullinane M. Severely impaired cerebrovascular reactivity predicts stroke and TIA risk in patients with carotid artery stenosis and occlusion. Brain. 2001;124:457-467.
34. Lin WH, Hao Q, Rosengarten B, Leung WH, Wong KS. Impaired neurovascular coupling in ischaemic stroke patients with large or small vessel disease. Eur J Neurol. 2010 Nov 30. [Epub ahead of print].
35. Gur AY, Bornstein NM. Cerebral vasomotor reactivity of the posterior circulation in patients with carotid occlusive disease. Eur J Neurol. 2003;10(1):75-78.
36. Roje Bedeković M, Bosnar Puretić M, Lovrencić Huzjan A, Demarin V. Visual evoked response in patients with severe carotid disease – functional transcranial doppler study of posterior circulation. Coll Antropol. 2009;33(4):1353-1357.
37. Hoksbergen AW, Legemate DA, Ubbink DT, Jacobs MJ. Collateral variations in circle of Willis in atherosclerotic population assessed by means of transcranial color-coded duplex ultrasonography. Stroke. 2000;31(7):1656-1660.

dr Marijana Bosnar Puretić,
University Department of Neurology,
Sestre milosrdnice University Hospital,
Vinogradska cesta 29,
10 000 Zagreb
E-mail: mbos-puretic@inet.hr
mbpuretic@gmail.com