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Breath holding index in episodic primary headaches

Indeks zadržavanja daha u epizodičnim glavoboljama

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Abstract

Background/Aim. Examination of cerebrovascular reactivity in patients with primary headaches is focused mainly on migraine, while the smaller number of studies deals with tension-type and cluster headache, or comparison of cerebral haemodynamic in migraine and tension-type headache (TTH). In this study, we hypothesized that cerebrovascular reactivity differs among different types of episodic primary headaches. In order to prove that we aimed to compare the interictal cerebrovascular reactivity in patients with the episodic form of the three most common types of primary headaches using the breath holding test. **Methods.** Examination was performed in 243 patients, 100 migraineurs with aura (group I), 70 migraineurs without aura (group II), 38 patients with episodic tension-type headache (group III), 35 patients with episodic form of cluster headache (group IV) and 35 healthy controls (group V). The Doppler instrument was used for transcranial doppler (TCD) sonography and breath-holding test performance. Blood flow mean velocities (MV), pulsatility indices (PI) and breath-holding index (BHI) for middle cerebral artery among these groups were analyzed. **Results.** The mean velocities and pulsatility indices were not different in 4 groups of headache patients and controls. The BHI was found to be significantly greater in the migraineurs with aura (1.668 ± 0.269) compared with the patients with migraineurs without aura (1.411 ± 0.358, $p = 0.005$), tension type headache (1.401 ± 0.428, $p = 0.035$), cluster headache (1.203 ± 0.311, $p < 0.01$) and controls (1.195 ± 0.269, $p < 0.01$) showing an exaggerated reactivity to hypercapnia in patients with migraine with aura. **Conclusion.** In conclusion, our finding support the literature data that increased cerebrovascular reactivity is a feature of migraine with aura. Result of unchanged cerebrovascular reactivity in migraine without aura, cluster headache and tension-type headache is expected, still, it is possible that in future, using different technique, we will be able to put more light on vascular changes that are following different headache disorders.

Key words:
migraine with aura; migraine without aura; cluster headache; tension-type headache; breath holding; ultrasonography doppler transcranial.

Apstrakt

Uvod/Cilj. Istraživanja cerebrovaskularne reaktivnosti kod osoba sa primarnim glavoboljama fokusirana su uglavnom na migrenu, dok je manji broj studija bio usmeren na glavobolju tenzionog tipa ili poređenje cerebralne hemodinamike između migrene i glavobolje tenzionog tipa. Cerebrovaskularna reaktivnost kod osoba sa migrenom je dosta ispitivana, primenom različite metodologije i sa različitim zaključcima. Istovremeno, cerebrovaskularna reaktivnost kod osoba sa glavoboljom tenzionog tipa i klaster glavoboljom bila je predmet istraživanja značajno manjeg broja studija. Ovim istraživanjem, cilj nam je bio da uporedimo intraiktalnu cerebrovaskularnu reaktivnost merenu metodom zadržavanja daha kod bolesnika sa epizodičnim formama tri najčešća tipa primarnih glavobolja. **Metode.** Ispitivanje je sprovedeno kod 243 ispitanika, 100 osoba sa migrenom sa aurom (grupa I), 70 osoba sa migrenom bez aure (grupa II), 38 osoba sa epizodičnom glavoboljom tenzionog tipa (grupa III), 35 osoba sa epizodičnom formom klaster glavobolje (grupa IV) i 30 zdravih ispitanika u kontrolnoj grupi (grupa V). Ispitianicima je urađena transkranijalna Doppler sonografija i test zadržavanja daha, pri čemu su analizirane dobijene vrednosti srednjih brzina protoka, indeksa pulsatilnosti i indeksa zadržavanja daha (*Breath-holding index* – BHI), merenih i izračunavanih za srednju cerebralnu arteriju. **Rezultati.** Srednje brzine protoka i indeksi pulsatilnosti nisu se razlikovali među ispitivanim grupama. Vrednosti BHI bile su značajno veće u grupi ispitanika sa migrenom sa aurom (1,668 ± 0,269) u poređenju sa ispitanicima sa migrenom bez aure (1,411 ± 0,358, $p = 0,005$), glavoboljom tenzionog tipa (1,401 ± 0,428, $p = 0,035$), klaster glavoboljom (1,203 ± 0,311, $p < 0,01$) i zdravim kontrolama (1,195 ± 0,269, $p < 0,01$) ukazujući na povećanu reak-

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tivnost na hiperkapniju kod osoba sa migrenom sa aurom. **Zaključak.** Naši rezultati podržavaju hipotezu o post-ojanju interiktalne hipersenzitivnosti i slabosti habituacije kod osoba sa migrenom.

Ključne reči:
migrena sa aurom; migrena bez aure; klaster glavobolja; glavobolja, tenziona; zadržavanje daha; ultrasonografija, dopler, transkranijumska.

Introduction

Migraine and cluster headache, have been considered for the long time to be „vascular headaches“ [1] Today they are known to be „brain diseases“, shifting the primary patological process from vessels to brain tissue [2–4]. Changes in cerebral blood flow, after the period of silence are again in focus, now from the point of epiphenomena, or surrogat markers of headache and its progression [5].

Examination of cerebrovascular reactivity in patients with primary headaches is focused mainly on migraine, while the smaler number of studies deals with tension-type headache, or comparison between cerebral haemodynamic in migraine and tension-type headache (TTH) [6–11].

Cerebrovascular reactivity in patients with migraine have been widely examined by different metodology and different conclusions were brought. [12–18]. The key point of those differences was whether the vasoconstrictor or vasodilator stimuli was used. The results of several studies performed with vasoconstrictor stimuli indicated an increased cerebrovascular reactivity in patients with migraine. These conclusions had been limited by results showing an increased cerebrovascular reactivity exclusively in patients with migraine with aura. The results of the studies using vasodilator stimuli are contradictory, probably due to differences in methodology and patients selection.

Cerebrovascular reactivity in patients with tension-type headache has been the subject of a significantly smaller number of researches [8, 11, 14]. The difference in interictal cerebrovascular reactivity in patients with migraine without aura and episodic TTH was not found [9]. That kind of difference did not show neither by comparison of patients with TTH and healty controls [13, 14].

In patients with cluster headache cerebrovascular reactivity had been examined during the cluster period, after the inhalation of 100% oxygen [19]. In comparison to migrainers, patients with cluster headache had increased response. Comparative data about cerebrovascular reactivity in more than 2 types of episodic primary headaches does not exist.

In this study, we hypothesized that cerebrovascular reactivity differs among different types of episodic primary headaches. In order to prove that, we aimed at comparing the interictal cerebrovascular reactivity in the patients with the episodic form of the 3 most common types of primary headaches using the breath holding test.

Methods

Examination was performed at the Headache Center and Ultrasound Laboratory in the Neurology Clinic, Clinical Center of Serbia, Belgrade, over 5 groups of subjects were treated for the period of two years: migraineurs with aura (group I), migraineurs without aura (group II), patients with episodic TTH (group III), patients with episodic form of cluster headache (group IV) and healthy controls who had no history of headache (group V). Exclusion criteria were cardiovascular, cerebrovascular, or pulmonary disease, arterial hypertension, therapy with beta-adrenoceptor blockers or calcium antagonists in the last three months, comorbidity of 2 types of primary headaches.

All patients and healthy control subjects gave their informed consent to participate in the study and the study was approved by the Ethics Committee of Neurology Clinic, Clinical Center of Serbia, Belgrade.

The diagnosis of episodic primary headache was based on the International Classification of Headache Disorders criteria [20]. The Doppler instrument, RIMED Digi-Lite, a dual-channel transcranial Doppler (TCD) system, was used for TCD sonography and breath-holding test performance. Insonation was performed interictaly, throughout the temporal acoustic bone windows according to a standard approach using 2 MHz transducers to display flow through the middle cerebral artery (MCA). Bilateral monitoring of the MCA, from a depth of 45 mm to 65 mm, was performed with each probe held in place over the temporal bone by the head frame.

Cerebrovascular reactivity has been examined by breath-holding test, based on vasodilatator effect of hypercapnia resulted after 30 seconds of breath holding [21, 22].

Blood flow mean velocities and pulsatility indices were recorded before (MV1, PI1) and after (MV2, PI2) 30 seconds of breath holding.

Breath-holding index (BHI) was calculated for each MCA, using the formula [15]:

$$\text{BHI} = \frac{MV1 - MV2}{MV1} \; x \; \frac{100}{30}.$$

Mean value of BHI was calculated using the formula

$$\text{BHI} = \frac{BH1\,right + BH1\,left}{2}.$$

Blood flow mean velocities (MV), pulsatility indices (PI) and breath-holding index (BHI) for the middle cerebral artery among these groups were analyzed.

Statistical analysis was performed using the SPSS software version 17.0. Distrubution of parameters was assessed by Kolmogorov–Smirnov test. For multiple comparisons among the groups, ANOVA and Kruskal-Wallis test were used, with Tukey honest significance difference (HSD) test and Mann-Whitney test applied in *post hoc* analyses. The significance level was set at 5% ($p < 0.05$).

Results

A total of 243 patients were studied, including 100 migraineurs with aura (group I), 70 migraineurs without aura (group II), 38 patients with episodic tension-type headache (group III), 35 patients with episodic form of cluster headache (group IV) and 35 healthy controls (group V). Demographic features of examined groups are presented in Table 1.

The mean velocities and pulsatility indices were not different in 4 groups of headache patients and controls (Tables 2 and 3).

Mean velocities for MCA in examined groups are presented in Table 2.

Pulsatility indices for MCA in examined groups are presented in Table 3.

BHI was higher in patients with migraine with aura than in migraine without aura, episodic TTH, cluster headache and healthy controls (Table 4). No difference was found among the other groups regarding BHI.

Discussion

Diferent results of cerebrovascular reactivity in migraine might be caused by the diferences in patient selection and methodology. Beside heterogenous data, the result of higher cerebrovascular reactivity in migraine with aura has remained stable over decades of research [23]. Results of our study show that BHI is higher in patients who have migraine with aura than in patients with other types of primary episodic headaches, migraine without aura, episodic

Table 1

Demographic features of the examined groups

Features	MA n = 100	MO n = 70	TTH n = 38	CH n = 35	Controls n = 30
Male, n (%)	29 (29)	9 (12.9)	17 (44.7)	25 (71.4)	17 (56.7)
Age at the time of examination (years), r ± SD	33.75 ± 10.980	38.07 ± 10.136	41.08 ± 12.782	43.74 ± 12.195	35.23 ± 8.386
Age at the time of headache onset, (years) r ± SD	20.04 ± xx.953	20.33 ± 1.134	32.24 ± 1.806	34.23 ± 1.999	–

***MA – migraine with aura; MO – migraine without aura; TTH – tension-type headache; CH – cluster headache.**

Table 2

Mean velocities (MV) in arteria cerebrimedia in the examined groups

Groups	MV (cm/s), r ± SD	*p*-value
MA (n = 100)	56.395 ± 10.817	*vs* MO: 0.500; *vs* TTH: 0.649; *vs* CH: 0.320; *vs* C: 0.552
MO (n = 70)	57.100 ± 10.98	*vs* TTH: 0.789; *vs* CH: 0.157; *vs* C: 0.281
TTH (n = 38)	53.723 ± 11.937	*vs* CH: 0.957; *vs* C: 0.799; *vs*
CH (n = 35)	53.571 ± 11.146	*vs* C: 0.960
C (n = 30)	55.851 ± 11.927	

***MA – migraine with aura; MO – migraine without aura; TTH – tension-type headache; CH – cluster headache; C – controls; r – mean value; SD – standard deviation; MV – mean velocity.**

Table 3

Pulsatility indices (IP) in the examined groups

Groups	IP, r ± SD	*p*-value
MA (n = 100)	0.728 ± 0.175	*vs* MO: 0.061; *vs* TTH: 0.734: *vs* CH: 0.970; *vs* C: 0.552
MO (n = 70)	0.677 ± 0.120	*vs* TTH: 0.209; *vs* CH: 0.168; *vs* C: 0.168
TTH (n = 35)	0.648 ± 0.200	*vs* CH: 0.264; *vs* C: 0.911
CH (n = 35)	0.722 ± 0.117	*vs* C: 0.810
C (n = 30)	0.720 ± 0.155	

***MA – migraine with aura; MO – migraine without aura; TTH – tension-type headache; CH – cluster headache; C – controls; r – mean value; SD – standard deviation; MV – mean velocity.**

Table 4

Breath-holding index (BHI) in the examined groups

Breat-holding index	MA n = 100	MO n = 70	TTH n = 38	CH n = 35	Controls n = 30	*p* value
BHI (ACM), r ± SD	1.668 ± 0.269	1.411 ± 0.358	1.401 ± 0.428	1.203 ± 0.311	1.195 ± 0.269	< 0.01*

***MA – migraine with aura; MO – migraine without aura; TTH – tension-type headache; CH – cluster headache; BHI – breath-holding index; ACM – *a. cerebri media*; **Mann-Whitney Test, Asymp. Sig. (2-tailed): MA and MO, 0.005; MA and TTH, 0,35, MA and CH, < 0.01, MA and control, < 0.01; MO and TTH, 0.971, MO and CH 0.059, MO and control 0.080, TTH and CH 0.075, TTH and control 0.088, CH and control 0.912.**

TTH and cluster headache. These data confirm results of previous studies reporting an increased cerebrovascular reactivity exclusively in patients with migraine with aura in comparison with migraineurs without aura [12, 14]. Also, our data do not confirm literature reports of increased vasodilatatory response in migraine without aura [12]. This difference is just one among other, epidemiological and clinical differences between these two entities imposing the question older more than thirty years, whether the migraine with and without aura are two kinds of headache disorder [24]. In our group of patients with migraine with aura, one third of them had migraine without aura as well. Beside that, the cerebrovascular reactivity was significantly higher in this group of patients.

Potential explanation for increased cerebrovascular reactivity in migraine, particulary with aura, lies in hypersensitivity and impaired habituation to stimuli [23, 25]. Literature data, in accordance with our results, suggest that the autoregulation disorder leading to inadequate, increased response of intracranial arteries to metabolic stimuli could be the key feature for increased cerebrovascular reactivity [25]. According to neurovascular coupling theory [26, 27] cerebral blood flow varies due to local cortical activity. Intraictally impaired cerebrovascular reserve could point to disfunction of vascular elements of neurovascular unit, meaning pericits, muscle and endothelial cells contained in the wall of small vessels [28]. Endothelial dycfunction in migraine is the new question arrised just few years ago, with increasing number of ongoing researches dealing with it [29].

To our best knowledge, this is the first study on cerebrovascular reactivity covering and comparing, at the same time, the episodic forms of the 3 most common types of primary headaches.

There are studies showing no difference in cerebrovascular reactivity in patients with migraine without aura in comparison to patients with tension-type headache and healthy controls[14]. Our study showed the same result, overcoming the limitation of broad overlap between migraine and TTH data that were presented in a report of Arjona et al. [14], with strict patient selection.

The results considering interictal cerebrovascular reactivity in patients with cluster headache, being significantly lower in comparison to migraine with aura, and showing no difference to migraine without aura, tension-type headache and healty subjects, are in accordance with conclusions of other authors [19] who found significant difference in vasomotor reactivity between CH patients and controls in response to hypocapnia only during the headache phase, with difference disappearing 30 min after the attack. Recent study showed that the BHI mesured after the oxygen inhalation is significantly higher in the cluster patients compared to the migraine patients which is the conclusion that our study could not support. Opposite to CO_2, a powerful vasodilatatory stimulus, oxygen is a powerful vasocontrictor and its inhalation just before the testing of cerebrovascular reactivity by breath-holding test, without doubt affects the test results. Beside vasoconstriction, with direct impact on vessels, 100% oxygen influence the cerebral blood flow indirectly, by inhibition of neurons in the trigeminocervical complex. This „oxygen inhibition“ of neuronal activation in the trigeminocervical complex is shown on an animal model for cluster headache, developed in order to reveal therapeutic effect of oxygen in cluster headache [30].

Conclusion

In conclusion, our finding support the literature data that increased cerebrovascular reactivity is a feature of migraine with aura. Result of unchanged cerebrovascular reactivity in migraine without aura, cluster headache and tension-type headache is expected, still, it is possible that in future, with different technique, we will be able to put more light on vascular changes that follow different headache disorders.

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