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BREATH HOLDING INDEX IN THE EVALUATION OF CEREBRAL VASOREACTIVITY

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SUMMARY – The aim of the study was to assess normal values of the middle cerebral artery breath holding index in healthy males and females. Healthy volunteers (180 male and 180 female) were divided into 6 age groups for each sex. All basal cerebral arteries were evaluated by transcranial Doppler in a standardized manner. Breath holding method was used in the evaluation of cerebrovascular vasoreactivity in the middle cerebral artery and 720 values of breath holding index were obtained. The middle cerebral artery mean velocity was continuously monitored for at least 5 minutes to obtain baseline values. Breath was held for 20-30 seconds and mean blood flow velocities during the last 3 seconds of breath hold were taken in calculation as a V_{max} velocity value. Breath holding index was calculated as percent of velocity increase from resting baseline values divided by breath holding time. The values of breath holding index were calculated for all subjects and for each sex separately. Statistical analysis was performed by nonparametric χ^2 and Fisher tests (statistical significance was set at $p<0.05$). Variation coefficient for each age group and Pearson's linear correlation coefficient for mean blood flow velocity and breath holding index values were calculated. The majority (95%) of subjects were in the group of breath holding index values within the range of 1.03-1.65. There was no statistically significant decrease in breath holding index values with age ($p>0.05$), however, an age dependent decrease in the mean blood flow velocity was recorded in all subjects ($p<0.01$). Breath holding index is a nonaggressive, well tolerated, real-time, reproducible screening method to study cerebral hemodynamics.

Key words: *Cerebrovascural circulation – physiology; Respiration – physiology; Blood vessels – ultrasonography*

Introduction

Cerebral autoregulation is the ability to maintain constant cerebral blood flow despite changes in the cerebral perfusion pressure. The first studies of brain perfusion were measurements done at different blood pressures, whereas nowadays transcranial Doppler (TCD) is used to evaluate dynamic cerebral autoregulation in humans[1-3]. The measurement of regional cerebral blood flow (rCBF) by CT Xenon 133 clearance, dynamic susceptibility contrast magnetic resonance imaging (DSC MRI), or more sophisticated methods of positron emission tomography (PET) and single photon emission computed tomography (SPECT) can be performed. Correlation of the results estimated by TCD and previously mentioned less available, time consuming and expensive techniques has demonstrated TCD to be an accurate, specific and sensitive method for cerebral flow evaluation[4-7]. TCD testing of cerebrovascular reactivity measures changes in cerebral blood flow velocities in response to a vasodilatory stimulus such as CO_2 inhalation or acetazolamide administration. Induced hypercapnia estimated by inhalation of CO_2 for at least 30 minutes or acetazolamide injection strongly stimulates vasodilatation of cerebral arterioles, therefore these methods are not suitable in the evaluation of cerebral vasoreactivity in acute stroke patients. In such patients cerebrovascular reserve can be estimated by measuring the change in the cerebral blood flow that occurs in response to endogenous collection of CO_2 such as breath holding method. Studies which compared assessment of vasomo-

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tor reactivity by means of breath holding method, inhalation of CO_2 and acetazolamide injection have shown good correlation between these three methods, and the choice of method to be applied is made depending on the patient's ability to cooperate[8].

Breath holding method was introduced in the early '90s as a nonaggressive, well tolerated, real-time, reproducible screening method to study cerebral hemodynamics. These studies were performed in small groups, mostly dealing with the examination technique and breath holding index (BHI) cutoff values between patients with symptomatic and asymptomatic carotid disease[9-12]. Before establishing this technique in the evaluation of patients with cerebrovascular disorders, standardization of the method in a healthy, cerebral symptom-free population is required.

The aim of the study was to assess normal BHI values in different age groups of both sexes.

Subjects and Methods

Data on 360 healthy volunteers (180 men and 180 women, mean age 67±12 years, 720 MCA values) were evaluated. Subjects were divided into 6 age groups (I-VI) for each sex: 20-29, 30-39, 40-49, 50-59, 60-69 and >70 years. Patients aged >70 were analyzed as a separate group together because we did not expect any statistically significant differences in the mean blood flow velocity (MBFV) or BHI. All subjects were free from cerebral symptoms, stroke or signs of transient ischemic attack (TIA). Stroke risk factors such as arterial hypertension, high levels of serum cholesterol and triglycerides, ischemic heart disease, atrial fibrillation or diabetes mellitus were under control. Alcohol consumption was none or moderate. Cigarette smokers were included in the study. Patients with moderate or severe atherosclerotic changes of the main head and neck blood vessels were not included in the study. Evaluation of extracranial blood vessels was performed by the method of color Doppler flow imaging (CDFI) and power Doppler imaging (PDI) on an Aloka 5500 Prosound with a 7.5 MHz linear probe.

TCD examination was performed on a TCD DWL Multidop X4 instrument with a 2 MHz hand-held pulsed wave Doppler probe. TCD was performed in supine position after 5-minute bedrest. The probe was placed over each transtemporal window, the circle of Willis arteries were insonated by standard protocol and MBFV were recorded. Blood vessels of the vertebrobasilar system were insonated by standard protocol through the suboccipital window with the same probe, in the sitting position.

Mean velocity of MCA was continuously monitored during the breath holding test. Baseline was defined as a continuous mean velocity over 30 seconds after an initial 5-minute resting period (V_{mean}). Subjects were asked to hold their breath for 30 seconds after normal inspiratory breath to exclude Valsalva maneuver. Subjects who could not hold their breath for 30 seconds held breath as long as they could and that time was taken in subsequent calculations. MBFV of last 3 seconds of breath hold period were recorded and taken as V_{max}. This procedure was repeated after a 2-minute resting period and the mean value of both measurements was taken for calculation. For further analysis BHI was calculated as percentage increase in MBFV occurring during breath holding divided by the time (seconds) for which the subject held his/her breath (Fig. 1): V_{max}-V_{mean}/seconds x 100. Statistical analysis of different groups of subjects was performed by nonparametric χ^2 and Fisher's tests (statistical significance was set at $p<0.05$). Variation coefficient was calculated for BHI values as a measure of data dispersion for each group. MBFV and BHI values were compared using Pearson's linear correlation coefficient.

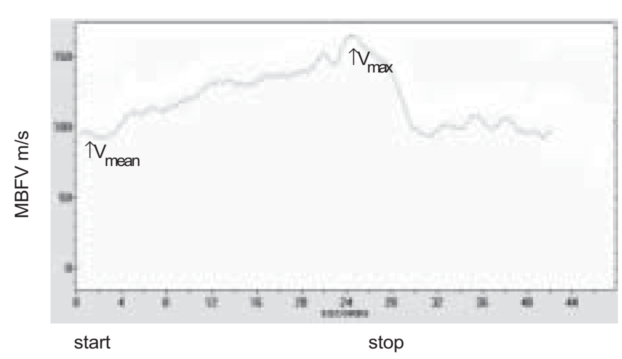

Fig. 1. Transcranial Doppler data on the mean flow velocities (MBFV) in the middle cerebral artery (MCA) of a young female subject during the breath holding test.

Results

All cerebral arteries were insonated in basal conditions in a standardized manner. The depth of insonation at which the signal was of the best quality is presented in Table 1. Comparison of MBFV in basal cerebral arteries between males and females in each age group, MBFV values and standard deviation (SD) in the MCA, ACA, PCA, BA and VA are also presented in Table 1. Data did not show any statistically significant differences between the left and right branches of Willis circle, and this distinction was excluded from the model.

Table 1. Transcranial Doppler evaluation of basal cerebral arteries according to sex and age groups

		Insonated basal cerebral artery MBFV (cm/s)				
Age group (yrs)		MCA (M1)	ACA (A1)	ACP (P1)	AV	AB
20-29	male*	69 ±10	50 ± 7	42 ± 9	39 ± 7	40 ± 9
	female	64 ± 8	47 ± 7	39 ± 8	36 ± 8	38 ± 8
30-39	male*	65 ± 8	49 ± 9	34 ± 6	35 ± 7	37 ± 7
	female	60 ± 8	45 ± 8	30 ± 7	32 ± 8	34 ± 7
40-49	males	59 ±10	49 ± 8	33 ± 8	33 ± 6	33 ± 8
	females	58 ± 8	47 ± 8	32 ± 7	30 ± 7	31 ± 7
50-59	males	58 ± 9	40 ± 8	30 ± 8	29 ± 5	29 ± 8
	females	57 ± 8	39 ± 8	30 ± 8	30 ± 6	28 ± 8
60-69	males	56 ±10	39 ± 9	31 ± 8	28 ± 6	28 ± 7
	females	56 ±10	39 ± 7	27 ± 8	29 ± 7	27 ± 8
>70	males	48 ± 9	36 ± 8	29 ± 6	27 ± 8	29 ± 7
	females	47 ± 8	35 ± 6	26 ± 8	26 ± 7	26 ± 8
Insonation depth (mm)		50 – 55	65 – 70	60 – 65	60 – 65	85 – 90

MBFV, mean blood flow velocity; *p<0.05

The decrease in MBFV values with age in males and females is presented in Table 1 ($p<0.05$). A statistically significant sex difference in MBFV was only recorded in the age 20-29 and 30-39 age groups ($p<0.05$). There was no sex difference in the mean BHI values. Data are presented as mean BHI value and SD for each sex and pool (Table 2). BHI values showed an age dependent decreasing tendency ($p<0.05$), however, all values remained within the 1.03-1.65 range because of data dispersion in each age group (variation coefficient around 20) (Fig. 2).

Discussion

Our results showed a decrease in MBFV depending on age, but no changes in BHI with age were observed. In order to evaluate cerebral vasoreactivity we measured only BHI values in MCA because previous studies have shown that anterior (MCA, ACA) and posterior (ACP, BA, VA) circulation in a population without atherosclerotic changes of the main head and neck arteries have similar cerebrovascular reserve capacities[10]. In case of occlusive carotid disease, anterior circulation (MCA) showed changes in vasomotor reactivity, while posterior circulation (VA, ACP) remained similar irrespective of the symptomatic/asymptomatic course, suggesting an independent cerebrovascular reserve in the posterior circulation[13].

We did not compare different duration of BHI examination because previous studies have shown that there is no difference between short (<27) and long (27>) breath holding times[9].

There was no statistically significant difference between the measured MBFV and standardized normal MBFV values for the corresponding age groups[14-17]. We

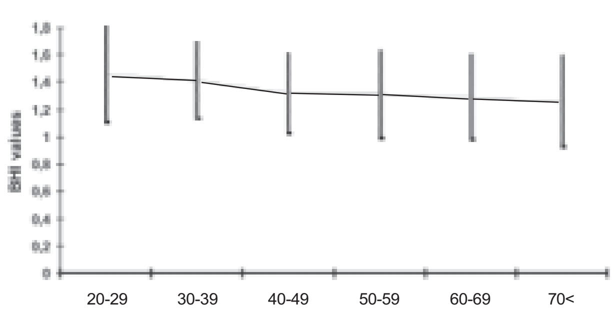

Fig. 2. Breath holding index (BHI) values according to age groups (pooled results for both sexes).

Table 2. Breath holding index according to sex and age groups, and pooled values

Age group (yrs)	Pooled value	Male	Female
20-29	1.46 ± 0.35	1.46 ± 0.34	1.45 ± 0.29
30-39	1.41 ± 0.25	1.44 ± 0.29	1.43 ± 0.25
40-49	1.32 ± 0.29	1.32 ± 0.31	1.32 ± 0.29
50-59	1.31 ± 0.32	1.31 ± 0.30	1.31 ± 0.32
60-69	1.29 ± 0.31	1.28 ± 0.22	1.27 ± 0.21
>70	1.13 ± 0.33	1.15 ± 0.35	1.13 ± 0.32

found a decreasing trend in MBFV values depending on age, probably due to normal physiologic changes that are present as part of cardiovascular aging[8,18,19], and include lower cardiac baroreceptor sensitivity, decline in blood pressure and cerebral blood flow, and also widening of the cerebral arterial vessel diameter.

There was no statistically significant difference in BHI values between males and females. We found an age dependent decreasing tendency in BHI, however, most of BHI values remained within the range of 1.03-1.65 because of dispersion of data in each age group. Therefore we took this range as a standard range of BHI values for both males and females, which can be introduced in daily evaluation of the cerebrovascular reserve[6,7,9,20]. We hypothesized that cerebral vasoreactivity could be impaired during breath holding test in older age groups, but results showed good correlation with previous studies suggesting that there is no deterioration of cerebral autoregulation with age[8,18,19]. Higher BHI values in younger age groups (20-29 and 30-39 years) and the decreasing tendency of BHI values in older age groups (>70) is probably a consequence of longterm impact of atherosclerosis risk factors, which we could not completely exclude from our study[1-3,17,21,22].

In Croatia, acute stroke is the leading cause of death and disability, whereas in industrialized countries stroke is the second cause of death. In order to reduce stroke incidence we tried to introduce new screening methods in the everyday cerebrovascular evaluation of stroke risk patients[22-24]. In normal individuals, a decline in cerebral perfusion pressure does not influence the regional cerebral blood flow because of cerebral blood flow autoregulation[25-27]. This cerebral blood flow compensatory mechanisms are exhausted in pathologic conditions, resulting in acute cerebrovascular incident as a sequel. Clinical trials suggest that carotid endarterectomy can significantly lower the stroke risk in symptomatic patients[6,7,20,25,26]. Previous studies have shown that measurement of cerebrovascular vasoreactivity is a reliable assessment of the hemodynamic effects of a severe carotid stenosis[28-30]. BHI proved to be a reliable prognostic factor for the assessment of stroke risk in symptomatic carotid stenosis[30-33].

Before evaluation of pathologic conditions, we tried to standardize normal BHI values. This study proved the TCD breath holding method to be a nonaggressive, well tolerated, real-time, reproducible screening method to study cerebral hemodynamics.

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Sažetak

INDEKS ZADRŽAVANJA DAHA U PROCJENI MOŽDANE VAZOREAKTIVNOSTI

I. Zavoreo i V. Demarin

Mjerenje moždane vazoreaktivnosti pomoću transkranijskog doplera (TCD) metodom zadržavanja daha pokazalo se jednostavnim i neinvazivnim načinom izdvajanja populacije bolesnika koji su pod rizikom za obolijevanje od moždanog udara. Prije uvođenja ove metode u svakodnevnu praksu pokazala se potreba za standardizacijom indeksa zadržavanja daha (IZD), mjerenog u arteriji cerebri mediji (ACM). Zdravi ispitanici podijeljeni su po spolu, a zatim po dobi u 6 skupina: 1 skupina 20-29 godina, 2 skupina 30-39 godina, 3 skupina 40-49 godina, 4 skupina 50-59 godina, 5 skupina 60-69 godina, 6 skupina >70 godina. Svi ispitanici su podvrgnuti standardnom TCD pregledu i mjerenju indeksa zadržavanja daha u obje ACM (720 vrijednosti). Srednja brzina strujanja krvi (SBSK) u ACM je mjerena prije, tijekom i nakon zadržavanja daha te je IZD izračunat kao postotno odstupanje srednje brzine od nulte linije podijeljeno s vremenom trajanja testa. Nije pronađena statistički značajna razlika između muškaraca i žena kao niti razlika između desne i lijeve strane Willisova kruga ($p<0.05$). Pronađen je statistički značajni pad SBSK u svim ispitivanim žilama ovisno o dobi ispitanika($p<0,01$). Nije pronađen statistički značajan pad IZD vrijednosti ovisno o dobi ispitanika ($p<0,05$). Većina ispitanika imala je vrijednosti IZD u rasponu od 1,03 do 1,65. Mjerenje moždane vazoreaktivnosti pomoću IZD pokazalo se kontinuiranom, neinvazivnom, jednostavnom i lako ponovljivom metodom probira.

Ključne riječi: *Cerebrovaskularna cirkulacija – fiziologija; Respiracija – fiziologija; Krvne žile – ultrasonografija*