ASSESSMENT OF BREATH HOLDING INDEX DURING ORTHOSTASIS

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SUMMARY – The aim of the study was to assess differences in cerebrovascular reactivity in healthy subjects during orthostasis. Twenty healthy volunteers (11 men and 9 women) with no atherosclerotic risk factors were evaluated by use of transcranial Doppler. The breath holding index (BHI) was obtained in supine and upright posture using standardized procedure. Student's t-test was used on comparison of the mean blood flow velocities (MBFV) and BHI between supine and upright posture and between the left and right side of the body. The middle cerebral artery MBFV in supine posture was 66.6 cm/s on the right side and 68.5 cm/s on the left side and in upright posture 60.6 cm/s on the right side and 62.3 cm/s on the left side. There was no significant MBFV difference either between supine and upright posture or between male and female subjects. The mean BHI in supine posture was 1.59 on the right side, 1.65 on the left side, and in upright posture 1.63 on the right side and 1.7 on the left side, without significant sex difference. There was no statistically significant differences in BHI between supine and upright posture (P=0.81 and P=0.68 for the right and left side, respectively) or between the two sides of the body in supine (P=0.71) and upright posture (P=0.8). In conclusion, evaluation of cerebrovascular reactivity yielded no significant difference in BHI values during orthostatic stress.

Key words: *Posture – physiology; Cerebrovascular reactivity; Cerebrovascular circulation – physiology; Hemodynamic processes – physiology*

Introduction

The ability to assume upright posture depends crucially on adequate perfusion of the brain[1,2]. Blood flow to the brain can be influenced through adjustments in systemic hemodynamics (i.e. perfusion pressure), or through local vascular modulation (i.e. cerebral autoregulation)[3]. Cerebral autoregulation refers to the inherent ability of cerebral blood vessels to keep cerebral blood flow constant over a wide range of systemic blood pressure[4].

Transcranial Doppler (TCD) is a noninvasive ultrasonic technique that measures local blood flow velocity and direction in the proximal portions of large intracranial arteries[5,6]. TCD evaluation of large basal conducting vessels, which remain relatively constant in diameter during moderate pressure fluctuations or changes in microcirculatory function, can provide an index of relative flow changes in response to small blood pressure changes and physiologic stimuli to assess autoregulation and vasomotor reactivity of distal cerebral arteriolar bed[7]. Techniques used on vasomotor reactivity testing of static (i.e. at rest) or dynamic (i.e. after provocative stimuli) cerebral autoregulation include measuring changes in flow velocities following 1) hemodynamic stimuli (rapid leg cuff deflation, Valsalva maneuver, deep breathing, ergometric exercise, head-down tilting, orthostasis and lower body negative pressure, and beat-to-beat spontaneous transient pressor and depressor changes in the mean arterial

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pressure); 2) CO_2 inhalation (hypercapnia/hyperventilation, hypocapnia); 3) breath-holding index (BHI); 4) acetazolamide injection; and 5) transient hyperemia response and its variants[8-10]. BHI is a nonaggressive, well-tolerated, real-time and reproducible screening method to study cerebral hemodynamics[11-13].

Several studies have reported a marked decrease in the steady-state mean cerebral blood flow velocity during orthostatic stress with head upright tilt and lower-body negative pressure in normal subjects, despite maintenance of a relatively constant mean arterial blood pressure[14-18]. These findings suggest the presence of a paradoxical cerebral vasoconstriction, which may be induced by a reduction in arterial CO_2 and/or sympathetic activation elicited by orthostatic stress[19-22]. Moreover, a significant increase in the gain of the transfer function estimates between spontaneous beat-to-beat fluctuations in the mean arterial blood pressure and mean cerebral blood flow velocity has been reported at high levels of lower body negative pressure[22], suggesting impaired dynamic cerebral autoregulation. In addition, dynamic cerebral autoregulation was found to be dependent on end-tidal CO_2 level and impaired during head upright tilt by analyzing transfer function estimates between the mean arterial blood pressure fluctuations and beat-to-beat cerebrovascular resistance[23]. Arterial CO_2 tension is one of the strongest physiologic modulators of cerebral blood flow[24], and a number of studies have examined dynamic effects of $PaCO_2$ changes on the mean cerebral blood flow velocity (cerebral vasomotor reactivity) by employing step CO_2 changes[25,26], controlled breathing protocols[27], and spontaneous breath-to-breath $PaCO_2$ fluctuations along with the mean arterial blood pressure fluctuations[28]. Arterial, end-tidal, and transcutaneous CO_2 levels have been shown to fall significantly in normal subjects immediately after head upright tilt[20,28-31], whereas Cencetti *et al.*[20] demonstrated a significant link between declines in the cerebral blood flow velocity and CO_2 after head upright tilt. Despite the cerebral blood flow velocity decrease during orthostatic stress, its effect on dynamic cerebral autoregulation is unclear, with both intact[19,32-34] and impaired[23,35] cerebral autoregulation being reported in normal subjects. It remains controversial whether dynamic cerebral autoregulation is altered under orthostatic stress[19,22,23,34,36,37]. The aim of this study was to assess cerebrovascular reactivity during orthostasis in healthy subjects using the breath holding method.

Subjects and Methods

Twenty healthy volunteers (11 men and 9 women) were included in the study. An informed consent was obtained before the study entry. All subjects were free from cerebral symptoms, stroke, or signs of transient ischemic attack, and also free from stroke risk factors such as arterial hypertension, hyperlipidemia, ischemic heart disease, atrial fibrillation or diabetes mellitus. All subjects had negative history of orthostatic hypotension and syncope. 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. Extracranial blood vessels were evaluated 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.

Cerebrovascular reactivity to hypercapnia was evaluated by use of BHI[13] on a TCD Sonara TEC (Vyasis Healthcare). Two dual 2-MHz transducers fitted on a headband and placed on the temporal bone windows were used for bilateral continuous measurement of the mean blood flow velocity in middle cerebral arteries. The depth of insonation ranged from 48 to 52 mm. BHI is obtained by dividing the percentage increase in the mean flow velocity occurring during breath holding by the length of time (seconds) the subjects hold their breath after normal inspiration (mean flow velocity at the end of breath holding minus mean flow velocity at rest divided by mean flow velocity at rest) multiplied by 100 divided by seconds of breath holding). The mean flow velocity at rest was obtained by continuous recording of 1-minute normal breathing. Subjects were asked to hold their breath for 30 seconds after normal inspiration to avoid Valsalva maneuver. Subjects that could not hold their breath for 30 seconds held breath as long as they could and that time was taken in subsequent calculation. Before proceeding to definitive recording, subjects were trained to perform the procedure correctly. The procedure was performed in supine posture and then in upright posture. Student's t-test was used to compare the mean blood flow velocity and BHI between su-

Table 1. Mean blood flow velocities (MBFV) and breath holding index according to side and supine or upright posture

		Right	Left
MBFV in middle cerebral artery (cm/s)	Supine	66.6	68.5
	Standing	60.6	62.3
	Supine after 20 s	88.9	91.7
	Standing after 20 s	81.1	84.2
Breath holding index	Supine	1.59	1.65
	Standing	1.63	1.7
P value		0.81	0.68

pine and upright posture. It was also used for side to side comparison. The level of significance was set at $P<0.01$.

Results

Twenty healthy volunteers (11 men and 9 women), mean age 35, nine of them nine smokers, were included in the study. There was no significant difference in the mean blood flow velocity between supine and upright posture (Table 1) or between male and female subjects (Table 2). The mean BHI in supine posture was 1.59 on the right side and 1.65 on the left side, and in upright posture 1.63 on the right side and 1.7 on the left side, without any significant sex difference. There was no statistically significant difference in BHI between supine and upright posture (P=0.81 and P=0.68 for the right and left side, respectively), or between the sides in supine (P=0.71) and upright posture (P=0.8) (Tables 1 and 2).

Discussion

During orthostasis, the mean blood flow velocity values were slightly reduced as compared with supine

Table 2. Breath holding index according to sex and supine or upright posture

Breath holding index	Male	Female	*P* value
Supine	1.65	1.57	0.65
Standing	1,68	1.63	0.78

posture. Assessment of cerebrovascular reactivity in healthy subjects on supine and upright posture yielded no significant BHI differences. These findings confirmed the results of previous studies showing the mean cerebral blood flow velocity to decline in normal subjects after passive head upright tilt[14-18,36]. Zhang *et al.* used lower body negative pressure to demonstrate that dynamic cerebral autoregulation may deteriorate in normal subjects during high levels of orthostatic stress[22]. The same results were shown in some other studies[21,36]. The sympathetic neural activity was found to have a constraining effect on cerebral blood flow responses to CO_2 stimuli during head upright tilt[21,24]. Leftheriotis *et al.* showed the dynamic cerebral autoregulation to be preserved in normal subjects at low levels of orthostatic stress[32]. Carey *et al.* assessed dynamic cerebral autoregulation responses in normal subjects and patients with recurrent vasovagal syncope and showed that cerebral autoregulation was preserved initially after head upright tilt in both groups[36]. In some studies, dynamic autoregulation was found to remain unchanged in normal and neurally mediated syncope patients during head upright tilt[19,34]. One reason for these discrepancies is likely to be different experimental methods used (lower body negative pressure *vs.* head upright tilt), as well as timing of assessment (before or during the throes of syncope induced by orthostatic stress). The amount of orthostatic stress during head upright tilt may not be equivalent to high levels of lower body negative pressure. Moreover, head upright tilt stimulates the vestibulosympathetic reflex, which may elicit cerebral hemodynamic responses different to those during lower body negative pressure[38,39].

Cerebral blood flow is particularly difficult to measure because of its complex vascular supply and control mechanisms that result in a heterogeneous regional distribution of flow[40]. The present study of cerebral blood flow in humans required a technique that is safe and noninvasive while allowing for repeatable estimates of changes in global flow on a beat-to-beat basis. To meet these requirements, we used the TCD developed by Aaslid *et al.*[6], which takes advantage of the ability of ultrasound at relatively low frequencies (2 MHz) to penetrate the skull. The middle cerebral artery is ideally suited for this technique because its axis makes a relatively small angle with that of the Doppler beam, optimizing the opportunity to obtain true maximum velocities. Furthermore, this angle remains constant throughout the study, thus ensuring that Doppler signals are proportional to the true blood velocity. Because of its safety, ease of use, and ability to monitor rapid changes in global cerebral blood flow from the velocity, TCD has become a standard clinical tool in the evaluation of cerebral circulation[6,12,41].

The results of this study showed changes in cerebral hemodynamics during orthostasis. In healthy subjects, there were no significant differences in BHI during orthostatic stress. We used the simple, noninvasive and well tolerated breath holding method to assess cerebrovascular reactivity[13,42]. To our knowledge, it was the first time that it was used in assessing cerebrovascular reactivity during orthostasis in healthy subjects. These results can be used in further studies to measure cerebral hemodynamics during orthostatic stress in specific groups of patients (patients with syncope, autonomic failure, cerebrovascular disease, arterial hypertension, etc.).

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Sažetak

PROCJENA INDEKSA ZADRŽAVANJA DAHA TIJEKOM ORTOSTAZE

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Cilj ovoga istraživanja bio je ispitati postojanje razlike cerebrovaskularne reaktivnosti u zdravih ispitanika tijekom ortostaze. Metodom transkranijskog doplera pregledano je 20 zdravih ispitanika (11 muškaraca i 9 žena) bez prisutnih čimbenika rizika za razvoj aterosklerotske bolesti. Vrijednosti indeksa zadržavanja daha (IZD) određene su u ležećem i stojećem stavu na standardiziran način. Studentov t-test primijenjen je za usporedbu srednjih brzina strujanja krvi i IZD između ležećeg i stojećeg stava te u odnosu strana. Srednja brzina strujanja krvi u srednjoj cerebralnoj arteriji u ležećem stavu ispitanika bila je 66,6 cm/s desno i 68,5 cm/s lijevo, a u stojećem stavu 60,6 cm/s desno i 62,3 cm/s lijevo. Nije bilo značajne razlike u vrijednosti brzine strujanja krvi između ležećeg i stojećeg stava ispitanika kao niti između spolova. Prosječna vrijednost IZD u ležećem stavu bila je 1,59 desno, 1,65 lijevo, a u stojećem stavu 1,63 desno te 1,7 lijevo, podjednaka za oba spola. Statističkom obradom nije nađena razlika u vrijednosti IZD uspoređujući ležeći i stojeći stav (P=0,81 za desnu stranu, P=0,68 za lijevu stranu), a niti uspoređujući dvije strane u ležećem (P=0,71) i stojećem stavu (P=0,8). Nisu zabilježene značajne razlike IZD u procjeni cerebrovaskularne reaktivnosti tijekom ortostatskog stresa.

Ključne riječi: *Položaj tijela – fiziologija; Cerebrovaskularna reaktivnost; Cerebrovaskularni krvotok – fiziologija; Hemodinamski procesi – fiziologija*