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Age-correlated changes in cerebral hemodynamics assessed by near-infrared spectroscopy

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Abstract

Cerebral hemodynamic responses due to normal aging may interfere with hormonal changes, drug therapy, diseases, life style, and other factors. Age-correlated alterations in cerebral vasculature and autoregulatory mechanisms are the subject of interest in many studies. Near-infrared spectroscopy (NIRS) is widely used for monitoring cerebral hemodynamics and oxygenation changes at the level of small vessels. We believe that the compensatory ability of cerebral arterioles under hypoxic conditions and the dilatatory ability of cerebral vessels due to vasomotion may decline with normal aging. To test this hypothesis we used frequency-domain NIRS to measure changes in cerebral tissue oxygenation and oxy- and deoxy-hemoglobin concentrations caused by hypoxia during breath holding. We also assessed cerebral vasomotion during profound relaxation. Thirty seven healthy volunteers, 12 females and 25 males, ranging from 22 to 56 years of age (mean age 35 ± 11 years) participated in the study. We observed age-correlated changes in the cerebral hemodynamics of normal subjects: diminished cerebral hemodynamic response to hypoxia due to breath holding in middle-aged subjects (38–56 years) and reduced amplitude of cerebral hemodynamic changes due to vasomotion during rest. Snoring related changes in cerebral hemodynamics did not allow us to observe the effect of age in a group of snorers. The prolonged supine position influenced measured changes due to hypoxia. In this investigation NIRS methodology allowed detection of age-correlated changes in cerebral

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oxygenation and hemodynamics. Other variables, such as snoring or posture impacted the observations in our group of healthy volunteers.

Keywords: Cerebral oxygenation; Hypoxia; Vasomotion; Near-infrared spectroscopy; Aging

1. Introduction

Normal aging is associated with marked structural and functional alterations in the cardiovascular and cerebrovascular systems, which are linked to neurophysiological and neuropsychological changes (Kastrup et al., 1998; Matteis et al., 1998; Koshimoto et al., 1999; Buckner et al., 2000; Slosman et al., 2001). To understand the age-related adjustments, several studies using different diagnostic tools have been carried out. Age-correlated changes in regional cerebral blood flow (CBF), cerebral tissue oxygenation, cerebral autoregulation, and cerebrovascular CO_2 reactivity (CCO_2R) were detected in normal subjects by SPECT, transcranial Doppler sonography (TCD), MRI, and near-infrared spectroscopy (NIRS) (Hock et al., 1995; Smielewski et al., 1995; Ross et al., 1997; Kastrup et al., 1998; Matteis et al., 1998; Koshimoto et al., 1999; Buckner et al., 2000; Scheel et al., 2000; Terborg et al., 2000; Niehaus et al., 2001; Slosman et al., 2001; Mehagnoul-Schipper et al., 2002).

A lower CCO_2R was observed in the older adult population (Smielewski et al., 1995; Kastrup et al., 1998; Matteis et al., 1998). Carey et al. (2000) demonstrated lower baroreceptor sensitivity and lower mean cerebral blood flow velocity (BFV) in older subjects compared to young subjects. Watson et al. (2000) reported reduced response in CBF to hyperoxia in elderly subjects compared to young subjects. Several studies have demonstrated age-related alterations in cerebral hemodynamics during the task-activation of the brain (Orlandi and Murri, 1996; Ross et al., 1997; Buckner et al., 2000; Niehaus et al., 2001; Mehagnoul-Schipper et al., 2002) as well as age-related reduction in CBF during rest (Koshimoto et al., 1999; Scheel et al., 2000; Slosman et al., 2001).

Meltzer et al. (2000) report an apparent reduction in mean cortical CBF with healthy aging, which lost significance after correcting the PET data for partial-volume effects deriving from cerebral volume differences among subjects. Therefore, their study questioned the decline in CBF with age in healthy individuals.

Experimental conditions, subjects' gender, hormonal status, congenital or acquired diseases, and complications may interfere with changes due to normal aging and influence on the results of a study. Conflicting data concerning age related changes in male/female cerebral hemodynamics measured by TCD have been reported (Kastrup et al., 1998; Matteis et al., 1998; Carey et al., 2000; Slosman et al., 2001). In men, Kastrup et al. (1998) and Matteis et al. (1998) did not detect any change of CCO_2R with age. Slosman et al. (2001) observed a linear reduction in global CBF as a function of age for both sexes in a healthy population, measured by ^{133}Xe SPECT.

Matteis et al. (1998) and Kastrup et al. (1998) showed that hormonal changes influence cerebrovascular reactivity, resulting in a larger reduction in CCO_2R for postmenopausal women compared to premenopausal women or men of the same age.

Referenced data substantiate that snoring increases the risk for hypertension in both males and females, independent of age, body weight or other lifestyle factors (Lindberg et al., 1998; Hu et al., 2000). Therefore, snoring also may be a factor related to the alteration in cerebrovascular regulation.

Several studies were carried out to quantify postural changes in cerebral oxygenation and systemic hemodynamics in elderly subjects (Mehagnoul-Schipper et al., 2000, 2001; Heitterachi et al., 2002). In the elderly, standing can frequently be accompanied by blood pressure changes and symptoms such as dizziness, lightheadedness, or fainting. Mehagnoul-Schipper et al. (2001) observed standing induced cortical oxygenation declines in healthy elderly subjects, such as a decrease in cerebral oxy-hemoglobin concentration ([O_2Hb]) and an increase in deoxy-hemoglobin concentration ([HHb]), measured over the right frontal cortex by NIRS. Mehagnoul-Schipper et al. (2000), using a continuous-wave NIRS device, demonstrated similar posture change induced cortical oxygenation declines in healthy elderly subjects compared to younger subjects, who did not demonstrate any significant changes.

Hemodynamic factors seem to play an important role in the process of aging and in the pathogenesis of cerebral ischemic events. Terborg et al. (2000) found that reduced CCO_2R measured by NIRS and TCD are related to the severity of cerebral microangiopathy.

Several studies showed spontaneous fluctuations in cerebral hemodynamics and oxygenation due to vasomotion (Biswal et al., 1997; Zhang et al., 1998; Obrig et al., 2000; Seydnejad and Kitney, 2001). Using TCD, MRI, and NIRS methods, different investigators demonstrated the amplitude and frequency characteristics of these fluctuations during rest and respective changes due to cortex activation and hypercapnia (Biswal et al., 1997; Zhang et al., 1998; Obrig et al., 2000; Seydnejad and Kitney, 2001). Vasomotion fluctuations correlate with three major components of heart rate (HR) variability and blood pressure variation (Obrig et al., 2000; Seydnejad and Kitney, 2001): (1) around 0.25 Hz (the “high” frequency (HF) component), which is synchronized with the respiratory rate; (2) around 0.1 Hz (the “low” frequency (LF) component); and (3) around 0.04 Hz (the “very low” frequency (VLF) component). The origin and frequency spectrum of the slow oscillations (LF and VLF components) in cerebral hemodynamics are unclear. But their investigation may reveal autoregulatory mechanisms of brain vasculature.

With the aid of TCD and photoplethysmography, Zhang et al. (1998) found a strong relationship between the spontaneous changes in arterial blood pressure and cerebral blood flow velocity (mean BFV in the middle cerebral artery) within the frequency range of 0.07–0.30 Hz. This frequency range corresponds to LF and HF oscillations which seem to be systemic and have central origin.

Low frequency fluctuations in capillary blood flow and oxygenation ($<$0.1 Hz) were found in MR signal intensity from the resting human brain (Biswal et al., 1997). The magnitude of these fluctuations was reversibly diminished during hypercapnia. Slow spontaneous oscillations in vascular and metabolic parameters in the adult human brain under the influence of stimulation and hypercapnia were investigated by Obrig et al. (2000) using NIRS. The authors demonstrated that LF (at 0.1 Hz) and VLF (at 0.04 Hz) oscillations (LFO and VLFO, respectively) can be reproducibly detected by NIRS in the human adult visual cortex. In this study of Obrig et al. (2000), LFO were more pronounced in [O_2Hb] than in [HHb]. Spectral contents of VLFO in [O_2Hb] were significantly different during rest and

visual stimulation. They concluded that hypercapnia attenuated the low frequency oscillations while enhancing the respiration induced changes in NIRS parameters (oxygenated and deoxygenated hemoglobin and cytochrome oxidase).

It is well known that NIRS allows evaluation of cerebral tissue oxygenation and changes in oxy- and deoxy-hemoglobin concentrations, which correlate with changes in cerebral blood flow and cerebral blood volume (CBV), thus providing valuable information in understanding age related changes in brain hemodynamics (Elwell et al., 1994; Hock et al., 1995; Smielewski et al., 1995; Mehagnoul-Schipper et al., 2000, 2002; Terborg et al., 2000). NIRS is a non-invasive, non-ionizing technique, which provides unique complementary information about real-time cerebral tissue hemodynamics at the level of small vessels: arterioles, capillaries and venules (Madsen and Secher, 1999; Terborg et al., 2000; Toronov et al., 2000). The TCD method assesses indirectly cerebral perfusion changes through measurement of BFV changes in the larger cerebral arteries, which might not present microangiopathies due to aging or disease. The MRI technique measures relative changes in [HHb], while NIRS provides information about [O_2Hb] as well as [HHb] and therefore [tHb], SO_2, CBF, and CBV. NIRS data may be sufficient to estimate structural and functional alterations in cerebral vasculature.

The main goal of the present study is to compare cerebrovascular hemodynamic responses detected by NIRS in young and middle-aged subjects. In this investigation, we test the hypothesis that aging affects the autoregulatory capacity of the cerebrovascular system to respond to a vasodilatory challenge. Our results suggest that in the brain of healthy older individuals the ability of small arterioles to compensate for changes in oxygen supply (OS) due to hypoxia during voluntary breath holdings may be diminished. The results also indicate that the dilatatory ability of cerebral vessels due to vasomotion may also decline with age.

Previous research (Lindberg et al., 1998; Hu et al., 2000; Mehagnoul-Schipper et al., 2000, 2001; Heitterachi et al., 2002), reports that cerebral perfusion changes, due to factors such as snoring or posture changes during testing, may influence the results of age correlation. In order to address the effect of snoring on cerebral hemodynamic changes measured by NIRS, we separated snorers from non-snorers of our group of the otherwise healthy volunteers. We also examined possible posture effects on age-correlated changes.

Using frequency domain (FD), multi-distant NIRS instrumentation we developed and implemented experimental protocols to assess brain oxygenation and hemodynamic changes in normal subjects (1) during hypoxia induced by voluntary breath holding and (2) attributed to vasomotion during rest.

2. Methods

2.1. Instrumentation

A two-wavelength (690 and 830 nm) multi-distance (MD) FD tissue oximeter (Oxiplex TS; ISS Inc., Champaign, IL) was used to monitor cerebral tissue oxygenation (SO_2) and tissue hemoglobin concentrations (oxy- ([O_2Hb]), deoxy- ([HHb]), and total hemoglobin concentrations ([tHb])) on the left frontal lobe of the brain. We also measured arterial blood hemoglobin oxygen saturation (SaO_2) and heart rate with a standard pulse oximeter (N-200,

Nellcor Inc., Pleasanton, CA) and the respiratory signal (RS) with a respiratory strain gauge (Resp-EZ, Sleepmate, New Life Technologies, Midlothian, VA) simultaneously.

2.1.1. Tissue oximeter

The principals of the multi-distance frequency-domain method and the ISS MD FD tissue oximeter have been described by Fantini et al. (1994, 1999) and Gratton et al. (1997). The tissue oximeter operates at a modulation frequency of 110 MHz, and a cross-correlation frequency of 5 kHz. The eight light sources (four laser diodes per wavelength) are turned ON and OFF in sequence by an electronic multiplexer. The output optical signals, such as average light intensity (dc), amplitude of the intensity wave (ac) and phase shift of the wave (Φ), were averaged over several cycles of the eight light sources resulting in a total acquisition time of 800 ms per measurement.

2.1.2. Probe: multi-distance approach

We constructed a comfortable optical probe. The probe is made of soft and flexible polyurethane. This probe design accommodates forehead curvature effects.

Each laser diode of the oximeter is coupled to an optical fiber (400 μm in a core diameter), which provides the light to the illuminated tissue. The optical signals detected at the tissue surface were guided to the photodetector of the oximeter by an optical fiber bundle of 3 mm internal diameter. The source and detector fibers enter the probe parallel to the examined tissue.

Light is directed into and out of the tissue by small, right angle prisms. Each prism is attached to the tips of a pair of fibers (emitting light at wavelengths 690 and 830 nm, respectively). The detector fiber is also coupled to a prism. The four source–detector distances (SDD) of the probe were ranged from 1.98 to 4.08 cm with a mean distance around 3.12 cm.

2.2. Subjects

Thirty seven healthy normal volunteers, 12 females and 25 males, with unremarkable medical history (in particular no personal or family history of cardiovascular or neurological disease) participated in the study. One male and one female were left-handed. The mean age was 35 ± 11 years, ranging from 22 to 56 years. We used such an age range in order to avoid interference with anatomic brain changes in much older subjects. Ten subjects were habitual snorers [three females (30, 31, and 25 years of age) and seven males of age 22–56 (37 ± 12) years]. One young snorer was an occasional smoker. Twenty seven healthy non-snorers, (age 22–55 (35 ± 11) years) constituted the control group.

2.3. Measurement technique

The optical probe was calibrated using a phantom of known optical properties, comparable to the optical properties of brain tissue, prior to the measurements on volunteers. Subjects were measured in the supine position. The optical probe was positioned high on the left side of the forehead where the overlying tissue thickness is at a minimum, the skull is poorly perfused, and the sinuses are avoided. Careful positioning of the NIRS probe minimizes the influence of the superficial tissues on the recovered cerebral oxygenation

and hemodynamics. The probe was firmly attached on the forehead by means of a medical adhesive (*Hollister* #7730). It did not constrict the head and did not block the blood circulation of the scalp. The sensor of the pulse oximeter was attached to the index finger of the subject. A respiratory strain gauge was wrapped around the lower chest or the upper abdominal areas depending on the subject's type of breathing.

2.4. Measurement protocol

We applied NIRS during baseline measurements, voluntary breath holding at functional residual capacity (at the end of a normal expiration), and during rest (profound relaxation). The research protocol received prior approval from the Institutional Review Boards of the University of Illinois at Urbana Champaign and of ISS Inc, Champaign, IL. Written informed consent was obtained from all subjects before testing. Subjects were lying down in a room with dimmed light, comfortable ventilation and temperature. The measurement protocol included several (1–4) stages:

1. Following a complete relaxation for 2 min, baseline measurements of parameters SO_2, [O_2Hb], [HHb], [tHb], SaO_2, HR, and RS were obtained for 3–4 min.
2. Subjects were asked to hold their breath at the end of normal expiration for as long as they felt comfortable (15–30 s) without forcing themselves (to avoid the Valsalva maneuver). After the resumption of breathing and the recovery of the baseline level of SaO_2, subjects were asked to repeat breath holding. Breath holdings with SaO_2 baseline recovery were recorded up to five times.
3. Data were recorded for 7–10 min during rest. Subjects were asked to relax profoundly (or if possible to take a nap) and not to think intensively, in order to minimize the deviation of the vasomotion changes in cerebral hemodynamics, i.e. due to neuronal activation in the frontal lobe during the thinking process.
4. Subjects repeated two to five breath holdings with baseline recovery.

Eleven subjects performed breath holding exercises either before or after the rest period. The remaining 26 subjects followed the complete measurement protocol, with two breath holding periods before and after the rest period.

2.5. Data analysis

The tissue oximeter provides the physiological quantities O_2Hb, HHb, and tHb concentrations ([tHb] = [O_2Hb] + [HHb]), and tissue oxygenation (SO_2 = [O_2Hb]/[tHb]) calculated from the values of the absorption (μ_a) and reduced scattering (μ_s') coefficients obtained at two wavelengths (690 and 830 nm) (Fantini et al., 1994; Gratton et al., 1997).

We analyzed changes in cerebral tissue SO_2, [O_2Hb], [HHb], and [tHb] due to hypoxia during each individual breath holding and changes due to vasomotion during rest.

During breath holding, the maximal changes in the measured hemodynamic parameters were observed from the 8th to the 16th second, from the start of each breath holding period in all the subjects. The mean value of this range is the 12th second. The first type of analysis involved the comparison of the amplitude of the hemodynamic changes on the 12th second of the breath holding (Table 1) and the mean changes during 8–16th second (Table 2),

Table 1
Age-correlated changes in brain oxygenation and hemodynamics during the 12th second of breath holding

Experimental protocol	Subjects ($N = 37$)	Age	Changes in hemodynamic parameters ($\Delta\mu$L), statistics: Pearson coefficient (r_p)				Changes in hemodynamic parameters ($\Delta\mu$L), statistics: Spearman coefficient (r_s)			
			$\Delta[O_2Hb]$	Δ[HHb]	Δ[tHb]	ΔSO_2	$\Delta[O_2Hb]$	Δ[HHb]	Δ[tHb]	ΔSO_2
Breath holding	Non-snorers (27) (18 males, 9 females)	35 ± 11	-0.43 ($P < 0.05$)	0.49 ($P < 0.01$)	-0.27	-0.48 ($P < 0.05$)	-0.44 ($P < 0.05$)	0.59 ($P < 0.01$)	-0.18	-0.57 ($P < 0.01$)
	Male non-snorers (18)	39 ± 12	-0.57 ($P < 0.05$)	0.73 ($P < 0.01$)	-0.37	-0.66 ($P < 0.01$)	-0.62 ($P < 0.01$)	0.77 ($P < 0.01$)	-0.28	-0.73 ($P < 0.01$)
	Snorers (10) (7 males, 3 females)	35 ± 11	-0.027	0.32	-0.16	-0.33 ($P < 0.05$)	-0.23	0.36 ($P < 0.05$)	–	-0.34 ($P < 0.05$)
Before prolonged rest in the supine position	Non-snorers (21) (15 males, 6 females)	35 ± 11	-0.54 ($P < 0.05$)	0.64 ($P < 0.01$)	-0.34	-0.62 ($P < 0.01$)	-0.53 ($P < 0.01$)	0.66 ($P < 0.01$)	-0.3	-0.63 ($P < 0.01$)
	Snorers (5)	37 ± 11	-0.55 ($P < 0.05$)	0.66 ($P < 0.01$)	-0.41	-0.62 ($P < 0.01$)	-0.71 ($P < 0.01$)	0.75 ($P < 0.01$)	-0.45	-0.75 ($P < 0.01$)
After prolonged rest in the supine position	Non-snorers (21)	35 ± 11	-0.3	0.51 ($P < 0.05$)	–	-0.46 ($P < 0.05$)	-0.27	0.62 ($P < 0.01$)	–	-0.51 ($P < 0.05$)
	Snorers (5)	37 ± 11	–	–	–	–	–	0.33	–	-0.32

Table 2
Age-correlated of mean changes in brain oxygenation and hemodynamics during 8–16th seconds of breath holding

Experimental protocol	Subjects ($N = 37$)	Age	Changes in hemodynamic parameters ($\Delta\mu$L), statistics: Pearson coefficient (r_p)				Changes in hemodynamic parameters ($\Delta\mu$L), statistics: Spearman coefficient (r_s)			
			$\Delta[O_2Hb]$	Δ[HHb]	Δ[tHb]	ΔSO_2	$\Delta[O_2Hb]$	Δ[HHb]	Δ[tHb]	ΔSO_2
Breath holding	Non-snorers (27) (18 males, 9 females)	35 ± 11	-0.42 ($P < 0.05$)	0.44 ($P < 0.01$)	-0.34	-0.45 ($P < 0.05$)	-0.48 ($P < 0.05$)	0.55 ($P < 0.01$)	-0.31	-0.55 ($P < 0.01$)
	Male non-snorers (18)	39 ± 12	-0.55 ($P < 0.05$)	0.66 ($P < 0.01$)	-0.41	-0.62 ($P < 0.01$)	-0.71 ($P < 0.01$)	0.75 ($P < 0.01$)	-0.45	-0.75 ($P < 0.01$)
	Snorers (10) (7 males, 3 females)	35 ± 11	–	–	–	–	–	–	–	–
Before prolonged rest in the supine position	Non-snorers (19) (13 males, 6 females)	35 ± 11	-0.57 ($P < 0.05$)	0.65 ($P < 0.01$)	-0.41	-0.66 ($P < 0.01$)	-0.45	0.57 ($P < 0.05$)	-0.34	-0.55 ($P < 0.05$)
	Snorers (5)	37 ± 11	-0.49 ($P < 0.05$)	0.52 ($P < 0.01$)	-0.37	-0.55 ($P < 0.01$)	-0.33	0.44 ($P < 0.05$)	-0.28	-0.42 ($P < 0.05$)
After prolonged rest in the supine position	Non-snorers (19)	35 ± 11	-0.17	0.36	–	-0.3	–	0.36	–	-0.32
	Snorers (5)	37 ± 11	-0.14	0.21	–	-0.22	–	0.25	–	-0.2

among subjects. The changes during several (two to eight) breath holdings were averaged for each subject. Age correlation was evaluated with the Pearson linear correlation and the Spearman's rank correlation coefficients by the SPSS statistical package for Windows.

Very low frequency changes, close to 0.04 Hz (0.02–0.06 Hz), in [O_2Hb], [tHb], and SO_2 due to vasomotion were analyzed from the measurements during rest. For the analysis of the vasomotion changes we decomposed the signals ([O_2Hb], [HHb], and SO_2) with the Wavelet toolbox of the Matlab software package. We compared and correlated with the subjects' age the standard deviations of the amplitudes of the VLF changes in [O_2Hb], [HHb], and SO_2 during rest. Statistical analysis was performed by the SPSS statistical package.

3. Results

SaO_2 and HR were used as reference parameters to monitor that changes due to hypoxia were in a normal range. For all control subjects SaO_2 remained above 85% during hypoxic arterial blood desaturation. HR increased due to breath holding, but did not exceed 90 beats/min.

Representative recordings of the auxiliary and NIRS parameters, according to the measurement protocol, of a 30-year-old female non-snorer are presented in Fig. 1. Changes in NIRS parameters are shown with respect to the corresponding baseline values. Hypoxia during breath holding generated a decrease in SaO_2, which is an indication of arterial blood hemoglobin de-oxygenation, and changes in [O_2Hb], [HHb], SO_2, and [tHb] denoting the existence of an autoregulatory mechanism of cerebral tissue oxygenation.

As we expected, and contrary to arterial blood and skin de-oxygenation due to breath holding, in the brain of healthy young non-snorers we observed an increase in [O_2Hb], [tHb], and SO_2 and a decrease in [HHb]. In Fig. 2 we report changes in [O_2Hb] and [HHb] assessed in a control non-snorer during a single breath holding. We observed qualitative and quantitative differences in hemodynamic response to hypoxia in the group of middle-aged subjects (38–56 years old) and the group of snorers compared to young non-snorers (age of 22–36 years).

3.1. Snoring effect

Smaller hemodynamic changes or decreases in Δ[O_2Hb], Δ[tHb], and ΔSO_2, as well as an increase in Δ[HHb] during hypoxic episodes were observed in snorers. In the group of snorers the cerebral hemodynamic response to hypoxia was significantly reduced ($P < 0.05$) compared to the response of non-snorers. Among snorers, the changes in brain hemodynamics and oxygenation during breath holding exercises did not correlate with age.

3.2. Age-correlated changes due to hypoxia

In middle-aged subjects and snorers the changes in cerebral hemodynamic parameters due to hypoxia were reduced in amplitude or even inverted in direction (increase in [HHb] and decrease in [O_2Hb], [tHb], and SO_2).

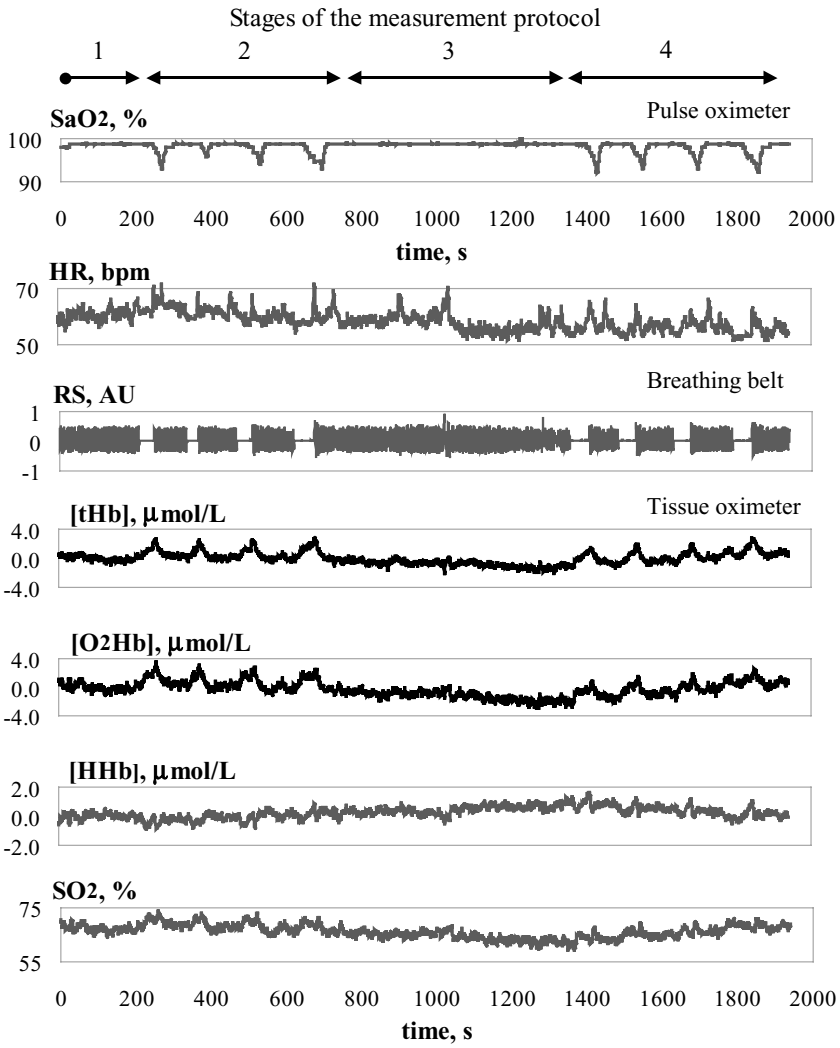

Fig. 1. Recording of auxiliary and NIRS parameters according to the measurement protocol: 1, baseline; 2 and 4, breath holding exercises and respective recoveries to the baseline; 3, prolonged rest. Changes (Δ) in hemodynamic parameters are presented with respect to baseline.

We found a significant age correlation of the changes in cerebral hemodynamic parameters, averaged over all breath holdings of each subject. Age correlation of Δ[HHb] and ΔSO_2 on the 12th second in the entire group of subjects and age correlation of $\Delta[O_2Hb]$, Δ[HHb], and ΔSO_2 on the 12th second and during the 8–16th second in the group of 27 non-snorers and the group of 18 male non-snorers are reported in Tables 1 and 2. Age dependence of the averaged changes in brain hemodynamics and oxygenation observed in 27 non-snorers on the 12th second of breath holding is shown on Fig. 3. Changes in [HHb]

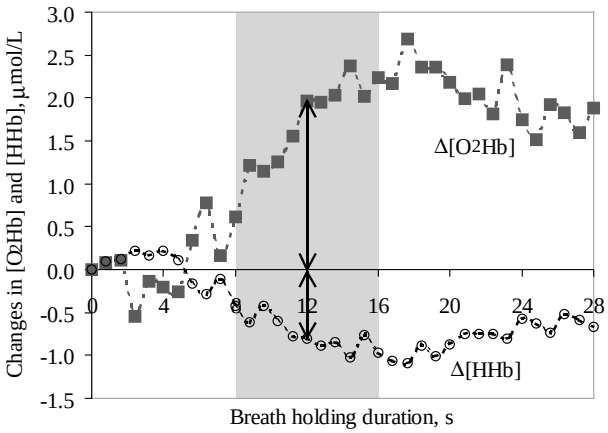

Fig. 2. Changes in oxy-[O_2Hb] and deoxy-hemoglobin [HHb] concentrations assessed in a control non-snorer during breath holding. The amplitude of the changes on the 12th second of the breath holding and the mean changes during 8–16th seconds (shaded area) were compared among subjects.

due to hypoxia were smaller than the changes in [O_2Hb], but the age correlation of [HHb] was stronger and more significant than the correlation of [O_2Hb].

We found a strong correlation of the cerebral hemodynamic parameters with age in the group of non-snorers and a much stronger one in the group of male non-snorers (Tables 1

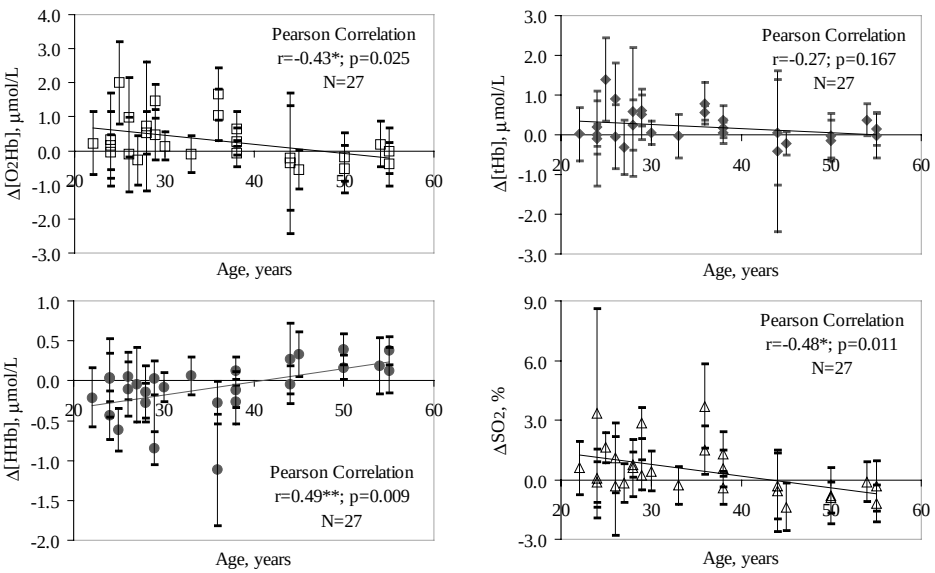

Fig. 3. Age dependence of averaged changes in brain hemodynamics and oxygenation observed in 27 non-snorers on the 12th second of breath holding.

and 2). Pearson's type correlation of changes in [tHb] was found only for mean changes during the 8–16th second of the breath holdings, which were performed after rest in the group of 27 subjects (6 snorers and 21 non-snorers) (the correlation coefficient was $r_p = -0.43^*$, $P = 0.026$) and in the group of 21 non-snorers ($r_p = -0.45^*$, $P = 0.043$).

3.3. Prolonged supine position effect

A group of 26 subjects, 5 snorers and 21 non-snorers, performed breath holding exercises before and after rest in the supine position (profound relaxation/napping). We compared age correlation of hemodynamic responses to hypoxia before and after rest. Two of these subjects were not able to hold their breath up to 16 s. We found differences in cerebral hemodynamic changes during breath holdings performed before and after rest. Changes due to breath holdings performed before rest correlated with age, while changes due to breath holdings made after rest did not show age correlation at all or showed lower correlation (Tables 1 and 2). Similar results were found for all subjects divided in two groups: 28 subjects who carried out breath holdings before rest and 35 subjects who did breath holdings after rest.

3.4. Age-correlated changes due to vasomotion

Time traces of SO_2, [O_2Hb], and [HHb] with respect to their baseline values and the decomposed vasomotion changes in cerebral SO_2, [O_2Hb], and [HHb] observed on the left forehead of a 24-year-old female and a 50-year-old male control non-snorers are presented in Fig. 4. The frequency of VLFO varied among subjects in a range of 0.02–0.06 Hz. Reduced amplitudes of slow changes in [O_2Hb], [HHb], and SO_2 due to vasomotion were observed in the middle-aged subjects, non-snorers (Fig. 5) as well as snorers. We found age correlation of cerebral hemodynamic changes ([O_2Hb], [HHb], and SO_2) due to vasomotion with the Pearson correlation coefficient $r_p \leq -0.5$ and the level of significance $P \leq 0.002$, in all subjects, snorers and non-snorers, who participated in the study. The Spreaman criterion gave stronger and more significant correlation for [O_2Hb] ($r_s = -0.58$, $P = 0.000$) and [HHb] ($r_s = -0.52$, $P = 0.001$).

4. Discussion

Using the FD multi-distant NIRS instrumentation (OxiplexTS, ISS Inc.) we found a reduced response to induced hypoxia and diminished amplitude of VLFO in the middle-aged subjects (38–56 years old) compared to younger subjects (22–36 years of age). Snorers (22–56 years old) demonstrated a reduced response to hypoxia independent of age. Rest in the supine position influenced the cerebral hemodynamic response to breath holdings, and more pronounced changes were observed in snorers and in older subjects. Therefore, there was no significant correlation with age or a decreased correlation with age of the changes in cerebral hemodynamics and oxygenation due to breath holdings after rest in the supine position. We did not compare sex differences or age correlation of changes in

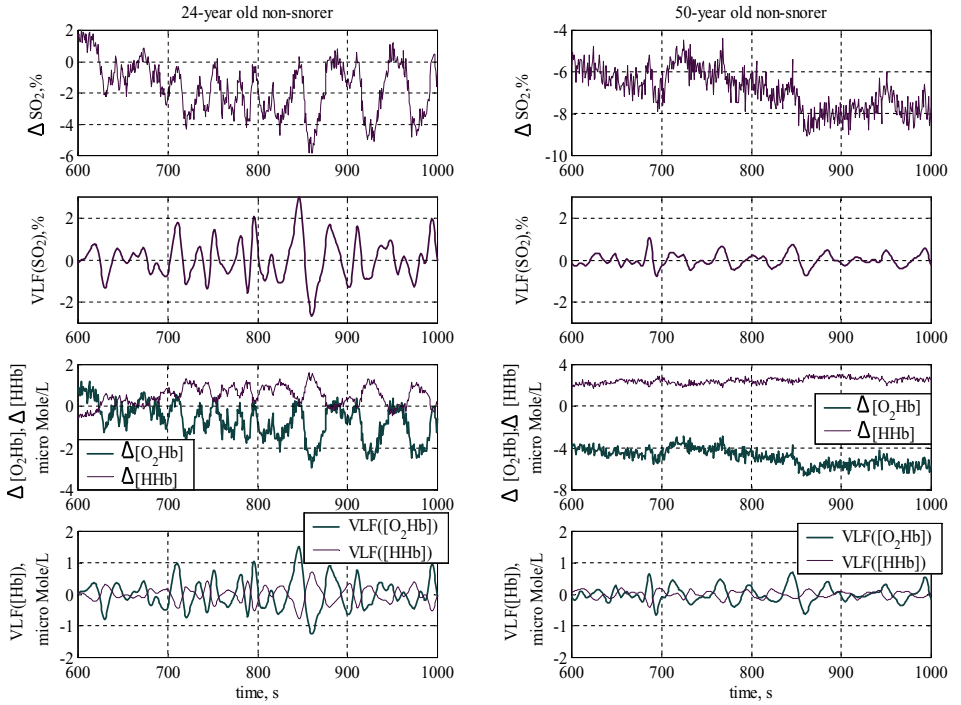

Fig. 4. Changes in cerebral SO_2, [O_2Hb], and [HHb] due to vasomotion (very low frequency changes: VLF(SO_2), VLF([O_2Hb]), and VLF([HHb]), respectively) observed on the left forehead in a 24- and a 50-year-old control non-snorers during prolonged rest in the supine position. ΔSO_2, Δ[O_2Hb], and Δ[HHb] indicate changes in the hemodynamic parameters with respect to the baseline.

women because of the restricted female age range in our study (from 24 to 38 years). Our findings correlate with the results of other studies.

Smielewski et al. (1995), using a NIRO 1000 instrument on 50 volunteers (19–68 years of age), observed that changes in [O_2Hb] and Hbdif = [O_2Hb] − [HHb] demonstrated a significant decrease in CO_2 reactivity beyond the ages of 35 years. The correlation coefficients were $r = -0.31$ ($P < 0.039$) and $r = -0.38$ ($P < 0.009$), respectively. In these results, a higher correlation coefficient of Hbdiff indicates a better age correlation of changes in [HHb] with respect to age correlation of changes in [O_2Hb]. In our study we also found a stronger age correlation of changes in [HHb] due to hypoxia as compared to changes in [O_2Hb] and SO_2. A lower CCO_2R in the older adult population was observed by Smielewski et al. (1995), whereas the findings of Kastrup et al. (1998) and Matteis et al. (1998) correlate with our findings: a lower cerebrovascular response to voluntary induced hypoxia due to breath holdings.

Several studies with NIRS and functional MRI (fMRI) demonstrated decreased task-related cerebral hemodynamics and oxygenation responses in elderly subjects (Hock et al., 1995; Smielewski et al., 1995; Ross et al., 1997; Buckner et al., 2000; Mehagnoul-Schipper et al., 2002). The slow hemodynamic response to stimulus activation using fMRI and NIRS,

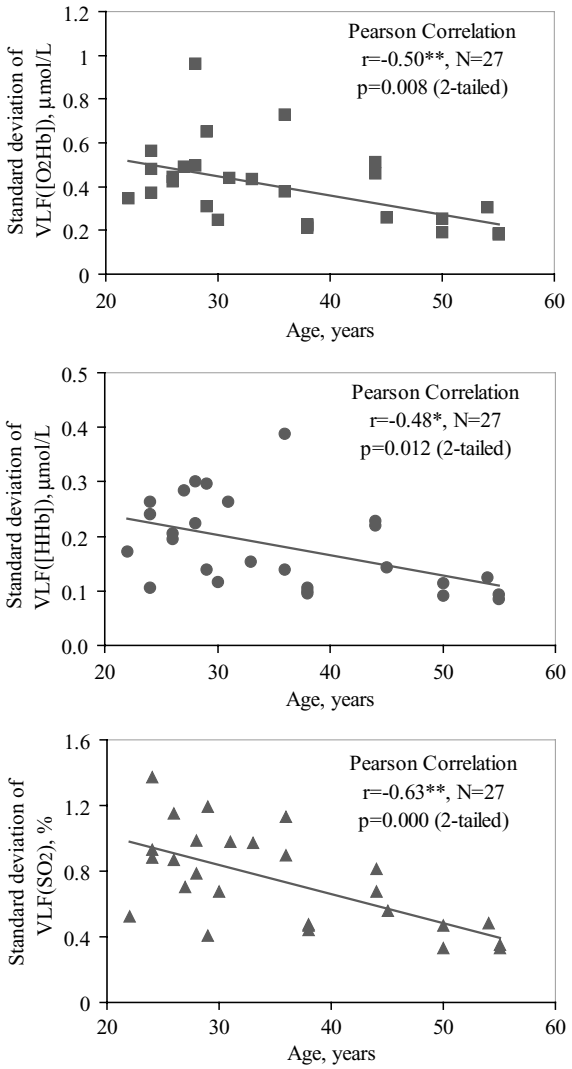

Fig. 5. Age correlation of the changes in oxy- and deoxy-hemoglobin concentrations and cerebral tissue oxygenation due to vasomotion, standard deviations of VLF([O_2Hb]), VLF([HHb]), and VLF(SO_2) observed on the left forehead of 27 non-snorers.

reported in the literature, is smaller in amplitude than the response to induce hypoxia. Since these authors have found an age correlation for smaller signals, our goal was to see age correlation for larger signals expecting better statistical results.

During the present study of age-correlated changes in cerebral hemodynamics and oxygenation, we invited the participants to perform breath holding (instead of task-related activation), because changes due to induced by hypoxia, when the protective autoregula-

tory mechanism is switched on, are larger in amplitude than changes induced by cortical activation. The task-related changes detected by Toronov et al. (2000) in hemoglobin concentrations were in a range of 1 μmol/L, which is comparable to changes due to vasomotion in our study. In the group of younger non-snorers, we observed that changes due to hypoxia were 1.5–3 times larger.

Because of the layered structure of the human head, the main question in NIRS is the degree of the relative contribution of superficial and deep tissues to the measured values. Generally it has been considered that the information derived from source–detector distances less than 2.5 cm, would mostly reflect changes in the superficial layers, namely the skin and the skull (Rolfe, 2000). Changes in the deeper layers, such as brain tissue, are interrogated by longer (>2.5 cm) separation distances (Owen-Reece et al., 1996; Rolfe, 2000; Young et al., 2000). Using FD multi-distant NIRS instrumentation in a two-layer phantom model, Franceschini et al. (1998) showed that a superficial layer, up to 6 mm thick, does not influence the recovery of the optical properties of the underlying layer. In the presence of a thin (<6 mm) superficial layer, the change in μ_a of an underlying layer was more accurately determined with the multi-distance method than with the single-distance methods.

Quantitative data on brain atrophy in adults measured by computed tomography suggest that between 20 and 60 years there is only minor brain atrophy and that pronounced brain atrophy begins after the age of 60 years (Hock et al., 1995). Since the protective autoregulatory mechanism exists only in cerebral tissue to prevent tissue desaturation during hypoxia, we believe that qualitative changes in hemodynamics and tissue oxygenation observed during this investigation reflected changes at the brain level.

We did not estimate anatomic differences between subjects and related functional response properties to anatomic differences. Based on the discussion above and the NIRS instrument characteristics, we compared the absolute changes in [O_2Hb], [HHb], [tHb], SO_2, and in the amplitude of VLFO between the groups of subjects of different age under following assumptions:

(1) Using FD NIRS multi-distant instrumentation and the appropriate source–detector distances, the hemodynamic changes measured by NIRS mostly reflect changes at the brain cortex.
(2) There was no significant brain atrophy with aging in the group of tested healthy subjects ranging from 22 to 56 years of age.
(3) The qualitative differences in hemodynamics due to hypoxia between groups are independent of the pathlength of the transmitted light, the forehead curvature, and measured brain volume differences between subjects.

In our study, for the group of non-snorers (27 subjects, age 22–55 years) we found significant age correlation of changes in [O_2Hb], [HHb], and SO_2, but no correlation between age and changes in [tHb] (see Tables 1 and 2) during breath holdings without the Valsalva maneuver. Stronger correlation with age was found for changes in [HHb]. Increased CO_2 concentration in arterial blood is a vasodilator for cerebral vessels. Therefore, during breath holdings we observed the cerebral autoregulation mechanism which consists of an increase in CBF and CBV and ideally can be observed as an increase in [O_2Hb], [tHb], and SO_2 and a decrease in [HHb] of the cerebral tissue (Mehagnoul-Schipper et al., 2002). We recorded quantitative and qualitative differences in changes due to hypoxia among different subjects.

A smaller decrease in [HHb] or even an increase in [HHb] was observed in the middle-aged subjects and snorers. Assuming there was no change in oxygen consumption (OC) during breath holding exercises, an increase in [HHb] in cerebral tissues indicated a reduced oxygen supply (OS) and an altered autoregulatory mechanism with age and snoring. Reduced cerebrovascular response to hypoxia due to breath holding and diminished amplitude of VLFO during rest, observed in 38–56 years old subjects and snorers, might suggest: (1) structural vascular alterations (altered elasticity); (2) functional vessel changes (enduring dilation of vessels); (3) systemic changes (altered blood pressure, arteriosclerosis); (4) changes in cardio- and/or cerebrovascular regulatory mechanisms.

During the study, we observed the influence of snoring and the prolonged relaxation in the supine position on the age correlation of NIRS parameters. Therefore, the quantification of physiological changes in the cerebral hemodynamics and oxygenation with aging using NIRS requires the knowledge of possible experiment-, sex-, pathology-dependent differences in cerebrovascular reactivity.

Lindberg et al. (1998) and Hu et al. (2000) substantiate that snoring increases the risk for hypertension in both males and females, independent of age, body weight or other lifestyle factors. Based on of our data, we can conclude that snoring affects the cerebral hemodynamic response to hypoxia in young subjects as well as in middle-age subjects. Therefore, snoring also may be a factor related to the alteration of cerebrovascular regulation.

Changes in the observed cerebrovascular response to hypoxia due to prolonged laying in the supine position in elderly subjects in this study are in agreement with the findings of Mehagnoul-Schipper et al. (2000, 2001) and Heitterachi et al. (2002). They reported and quantified postural changes in cerebral oxygenation and systemic hemodynamics in elderly subjects. We also observed the interference of postural state with the age correlation of the hemodynamic parameters. Prolonged supine position improved cerebral hemodynamics and eliminated the age correlation of the investigated response. Further studies are required to estimate posture induced cerebral hemodynamic changes, qualitatively and quantitatively, in different age groups.

Biswal et al. (1997), Zhang et al. (1998), Obrig et al. (2000), and Seydnejad and Kitney (2001) showed spontaneous fluctuations in cerebral hemodynamics and oxygenation due to vasomotion. We also recorded low frequency oscillations (in the frequency range 0.02–0.06 Hz) due to vasomotion in our subjects during rest via cerebral NIRS. We found an age correlation of the amplitude of these fluctuations. These findings confirm our hypothesis that vasomotion fluctuations may be used as an indicator of cerebrovascular changes (i.e. elasticity) due to normal aging or possibly due to pathological changes. We investigated only the very low frequency range of vasomotion fluctuations because this component of our signal was more stable in amplitude and frequency in our recorded data. The origin and significance of these oscillations are still open to questions we did not (or could not) attempt to answer in this study.

In order to decrease the number of formulated assumptions and to improve the objectivity of the age-correlation analysis, it might be advisable to compare relative changes across different experimental conditions between groups of subjects, such as relative changes of the amplitude of VLFO from baseline values to those during hypercapnic conditions. We tested two control non-snorers of 30 and 55 years of age. We confirmed decreases in amplitude of VLFO in [O_2Hb], [HHb], and SO_2 due to slight hypercapnia induced

by breathing into a paper bag for 7 min. Relative decreases in [O_2Hb] and [HHb] VLFO amplitudes were larger in the young subject compared to the older subject. Regarding SO_2 changes, a relative decrease in the VLFO amplitude was bigger in the older subject. Since hypercapnia stimulates cerebrovascular dilation, we can hypothesize that in the older subject this effect is less pronounced due to eventual structural and/or functional changes in the cerebral vasculature. We hypothesize that with the proposed above measurement of relative across-condition changes one can register age-dependent changes in cerebral hemodynamics which correlate to those we demonstrated with the absolute changes.

To stengthen the findings of this study it is necessary to increase the number of measured subjects, to expand the age range of subjects up to 70–80 years, and to provide an even distribution of subjects of both genders over the different age categories.

5. Conclusion

Using NIRS frequency-domain methodology, we have detected age-correlated changes in cerebral oxygenation and hemodynamics in a group of healthy volunteers. In the group of snorers, age correlation of the hemodynamic parameters was masked by a reduced hemodynamic response to induced hypoxia.

On the basis of our results, we hypothesize that NIRS measurements are sensitive to age-correlated impaired cerebral hemodynamics. These data can be used to investigate the influence of drug (hormonal) therapy, of diseases, or of lifestyle on cerebrovascular reactivity, capacity for capillary vasodilatation, susceptibility to ischemic damage in elderly subjects. We believe that via NIRS it is possible to constitute a normative dataset that could be used later to identify individuals at risk for cerebrovascular degenerative processes.

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