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Cerebral oxygenation monitor during head-up and -down tilt using near-infrared spatially resolved spectroscopy*

Koichi Kurihara[1], Azusa Kikukawa[2] and Asao Kobayashi[2]

[1]Self-Defense Force Gifu Hospital, Japan Self-Defense Force, [2]Pharmacochemistry Section, Aeromedical Laboratory, Japan Air Self-Defense Force, Tokyo, Japan

Summary

Reflectance near-infrared spectroscopy (NIRS) has become a suitable and easily manageable method to monitor cerebral oxygenation changes in presyncopal and syncopal symptoms caused by postural changing or standing. A new clinical tissue oxygenation monitor has been recently developed which measures absolute tissue haemoglobin saturation (Tissue Oxygenation Index, TOI) utilizing spatially resolved spectroscopy (SRS). The present study examined the effects of postural changes on cerebral oxygenation as reflected in SRS-NIRS findings. Cerebral oxyhaemoglobin (O_2Hb), deoxyhaemoglobin (HHb), and the TOI were recorded from both sides of the forehead in five healthy male subjects (age range, 28–40 years) during 90° head-up tilt (HUT) and −6° head-down tilt (HDT). Three series of measurements were carried out on separate days. O_2Hb was decreased during HUT. TOI was significantly lower in HUT than in the supine position (SUP). There was no significant change in TOI during HDT. A significant session effect was observed in the left forehead TOI during SUP, but not in the right. SRS-NIRS measurements confirmed sub-clinical alterations of cortical oxygenation during HUT. NIRS data from the left side of the forehead, which may vary with cognitive or emotional activation, were more variable than those from the right side.

Correspondence

Asao Kobayashi, Pharmacochemistry Section, Aeromedical Laboratory, Japan Air Self-Defense Force
1-2-10 Sakae-cho, Tachikawa-shi, Tokyo, 190-8585, Japan
E-mail: nf5a-kbys@jcom.home.ne.jp

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Introduction

Near-infrared spectroscopy (NIRS) can be applied to measure the concentrations of the O_2-carrying chromophores, oxy- and deoxy-haemoglobin (O_2Hb/HHb), in tissues using the principles of light-wave propagation (Jöbsis, 1977; Cope & Delpy, 1988). Reflectance NIRS has become a suitable and easily manageable method for monitoring cerebral oxygenation changes in presyncopal and syncopal symptoms caused by postural changing or standing (Madsen *et al.*, 1995, 1998; Colier *et al.*, 1997; Harms *et al.*, 2000; Mehagnoul-Schipper *et al.*, 2000; van Lieshout *et al.*, 2001). The NIRS devices used in these studies had a light source and detector which were placed a few centimeters apart on the same side of the head, and to changes in O_2Hb/HHb from an arbitrary starting point using a modified Beer–Lambert (MBL) method (Cope & Delpy, 1988). However, the confounding effects of extracranial tissue to MBL-NIRS measurements could not be completely eliminated (Madsen & Secher, 1999; Owen-Reece *et al.*, 1999).

Recently, a new clinical tissue oxygenation monitor has been developed which measures the absolute tissue haemoglobin saturation (Tissue Oxygenation Index, TOI) utilizing NIR spatially resolved spectroscopy (SRS) (Matcher *et al.*, 1995; Suzuki *et al.*, 1999). In SRS, the slope of light attenuation versus distance is measured at a distant point from the light input, from which the TOI is calculated using photon diffusion theory. Al-Rawi *et al.* (2001) evaluated an SRS device for detection of intracranial oxygen changes in the head of adult patients undergoing endarterectomy. They found that the TOI change was closely correlated with changes in transcranial Doppler mean flow velocity of the ipsilateral middle cerebral artery, but not with changes in frontal cutaneous laser-Doppler flowmetry.

Our previous studies (Kobayashi *et al.*, 1999, 2002; Kobayashi & Miyamoto, 2000), which showed continuous cortical oxygenation change during +Gz acceleration exposure, suggested that SRS-NIRS could be a sensitive and specific method for monitoring cerebral oxygenation changes in orthostatic intolerance. The present study investigates the effect of changes in a hydrostatic pressure gradient acting on systemic cerebral circulation as reflected in SRS-NIRS findings.

Methods

Subjects

Five normotensive healthy male volunteers, mean age 32 years (range, 28–40 years), were enrolled in our study. The mean height of the subjects was 169 cm (range, 164–178 cm), and

their mean weight was 68·4 kg (range, 50–95 kg). Each subject was informed of the experimental procedures and signed a written consent form approved by Japan Air Self-Defense Force.

Measurements

Cerebral oxyhaemoglobin (O_2Hb), deoxyhaemoglobin (HHb), and the TOI (cerebral oxygen saturation) were recorded from both sides of the forehead using two NIRO-300G near-infrared spectrophotometers (Hamamatsu Photonics K.K., Hamamatsu, Japan), according to methods described previously (Kobayashi & Miyamoto, 2000). The optodes (light source and light detector) were set in a black rubber holder at a distance of 4·0 cm. Two sets of the optodes rubber holder were placed on both sides of the forehead, just below the hairline but avoiding the regions of the temporal muscles and sinuses (Kobayashi & Miyamoto, 2000). With the use of three wavelengths (775, 810 and 850 nm), chromophore concentration changes (in $\mu mol\ L^{-1}$) in O_2Hb and HHb were calculated using a modification of the Lamert–Beer law (Delpy *et al.*, 1988): $\Delta C = \Delta OD/\alpha \times L \times B$, where ΔC is concentration changes, ΔOD is the attenuation of light expressed as changes in optical density, α is the extinction coefficient of the chromophore ($mM\ cm^{-1}$), L is the distance between the light source and the detector, and B is a path length factor that takes into account the scattering of light in the tissue (5·92) (van der Zee *et al.*, 1992).

NIRO-300G measures TOI using a spatially resolved technique, which measures the spatial variation of the intensity of retro-reflected light as a function of distance from the light source at large source/detector spacings (Matcher *et al.*, 1995). In NIR-SRS, the slope of light attenuation versus distance is measured at a distant point from the light input, from which the TOI is calculated using photon diffusion theory (Matcher *et al.*, 1995). To allow rapid measurement of the spatial variation of light intensity with respect to source/detector separation, NIRO-300G has been designed and constructed with an NIRS spectrometer incorporating a three-segment photodiode detector array with integral charge amplifiers together with a fiber-optic light delivery cable relaying light from the instrument's laser diode light sources (Matcher *et al.*, 1995; Suzuki *et al.*, 1999). It has been reported that TOI showed an excellent correlation with the data from a blood gas analyzer and a time-resolved spectroscopy apparatus (Suzuki *et al.*, 1999). Data were logged every 0·5 s during the experiment.

Protocol

On the experimental day, the subjects were asked to take their normal breakfast at home, without coffee or tea. Coffee, tea and smoking were prohibited at least 12 h before and during the experiment. All experiments were performed between 9:00 and 11:30 AM, at least 2 h after a light, caffeine-free breakfast, in a quiet, environmentally controlled laboratory having an ambient temperature of 22°C.

Subjects were placed in a supine position (SUP) on an electrically driven tilt table with a foot rest. After 10 min of rest in the SUP, the subjects were tilted to a 90° head-up position for 5 min and were then returned to SUP for 3 min. When the cerebral oxygenation variables were again considered stabilized, the subjects were tilted to a −6° head-down position for 3 min and were then returned to the SUP for 3 min. The rate of change of the tilt was $7{\cdot}8°\ s^{-1}$ for head-up (HUT) and was $6{\cdot}7°\ s^{-1}$ for head-down tilt (HDT). After this first head-up and -down tilt cycle, two identical cycles were performed. Three sessions, each of which included three cycles of HUT and HDT, were carried out on separate days to assess the reproducibility of alterations in cerebral oxygenation variables.

The NIRS data were continuously recorded during the session. Arterial pressure (BP) and the heart rate (HR) were measured on the right arm using an autosphygmomanometer (BP-203i; Nippon Colin, Komaki, Japan) in SUP and HUT at the first tilt cycle in each session to confirm that the subject could tolerate the HUT.

Data analysis

All NIRS variables were analysed using an IBM computer and NIRO-300G software (Hamamatsu Photonics K.K., Japan). In the SUP, baseline values for O_2Hb, HHb, and TOI were taken as an average over 2 min before the postural change. The changes of O_2Hb (ΔO_2Hb) and HHb (ΔHHb) from the baseline were calculated as an average over 2 min before the postural change. In HUT and HDT, TOI was averaged over 1-min period before the postural change. The paired Student's *t*-test was used to compare the bilateral data collected from the left and right machines. The paired *t*-test was also used to compare mean TOI values in SUP and HUT. The variability of the baseline TOI in the session was assessed using a two-way (subjects × baseline measurements; 5 × 6) ANOVA with repeated measures on both factors. Correlation coefficients between BP and COS indices were computed using the Pearson correlation analysis method. For all statistical contrasts, a *P*-value of 0·05 was considered to be statistically significant.

Results

All of the subjects completed the experimental protocol without presyncopal or syncopal symptoms. O_2Hb was observed to decrease during HUT and to increase slightly during HDT (Fig. 1, Table 1). The latency of cortical oxygenation changes after the postural change was not observed in the 0·5-s interval measurements. The mean and SD values of the O_2Hb change (ΔO_2Hb) between the two sides of the subjects' foreheads were not significantly different (Table 1) for either HUT or HDT. A significant difference between the two sides of the forehead was observed in ΔHHb during HUT. The baseline TOI value (SUP) was not significantly changed in the session [right, $F(5,60) = 0{\cdot}255$; left, $F(5,60) = 0{\cdot}116$]. TOI was significantly lower in HUT than in SUP (Fig. 1, Table 1). TOI decreased

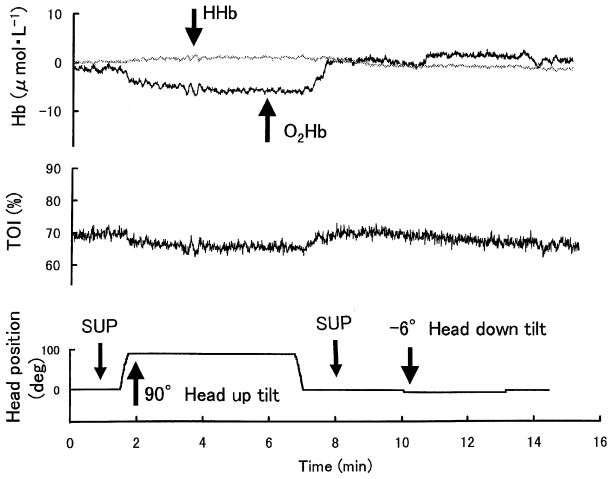

Figure 1 Representative continuous recording of oxyhaemoglobin (O_2Hb), deoxyhaemoglobin (HHb), and tissue oxygen index (TOI, cerebral oxygen saturation) in the left forehead during supine position (SUP), head-up tilt, and head-down tilt.

more in the right forehead than in the left forehead. There was no significant change in TOI during HDT.

Figure 2 shows the mean TOI in SUP at each of the three sessions. The left forehead TOI in SUP was significantly changed across the sessions [$F(2,75) = 26{\cdot}177$, $P<0{\cdot}01$]. No significant session effect was observed in the right forehead TOI [$F(2,75) = 0{\cdot}517$]. TOI was significantly higher in the left forehead ($75{\cdot}2 \pm 5{\cdot}7$) than in the right ($71{\cdot}4 \pm 5{\cdot}6$) at the third session in SUP. Although the baseline TOI in the left was significantly higher at the third session, significant TOI decrement during HUT was observed in each side of the forehead at each session ($P < 0{\cdot}01$). There was no significant session effect in ΔO_2Hb during HUT [right, $F(2,30) = 0{\cdot}52$; left, $F(2,30) = 2{\cdot}08$].

A significantly higher diastolic blood pressure and higher HR were observed in HUT compared with SUP (Table 2). No significant correlation was observed between BP changes and ΔO_2Hb in HUT.

Discussion

In the present study, O_2Hb and TOI, which are measurements of frontal cortical oxygenation using MBL and SRS respectively, decreased during the postural change from SUP to HUT without presyncopal or syncopal symptoms. The lack of a significant cortical oxygenation change during 6° HDT was comparable with the result obtained from MBL O_2Hb measurement during 10° HDT (Madsen *et al.*, 1998). Haemodynamic responses to HUT, such as HR and BP increments (Smith & Porth, 1991), were also observed in the present study.

In the last decade, NIRS has become a suitable and easily manageable method for monitoring cerebral cortical oxygenation during orthostatic stress (Madsen *et al.*, 1995, 1998; Colier *et al.*, 1997; Harms *et al.*, 2000; Krakow *et al.*, 2000; Mehagnoul-Schipper *et al.*, 2000; van Lieshout *et al.*, 2001). Several studies have shown that the NIRS-MBL method showed a decrease in cerebral O_2Hb concentration during HUT or standing in patients with presyncopal symptoms. Some of these studies also showed an O_2Hb decrease in healthy control subjects during postural changes (Madsen *et al.*, 1995, 1998; Harms *et al.*, 2000; Krakow *et al.*, 2000; van Lieshout *et al.*, 2001). However, several studies have reported the absence of an effect of postural stress on cerebral O_2Hb in healthy subjects (Madsen *et al.*, 1995, 1998; Colier *et al.*, 1997; Mehagnoul-Schipper *et al.*, 2000). An asymptomatic decrease in frontal cortical oxygenation has been reported in healthy elderly subjects (age range, 70–83 years) after active standing, but not in healthy young subjects (<45 years) (Mehagnoul-Schipper *et al.*, 2000). The present study found O_2Hb changes in non-syncopal young subjects (age range, 28–40 years) during postural change (90° HUT). The NIRS using the MBL method was therefore potentially capable of detecting sub-clinical alterations of cerebral blood oxygenation.

Table 1 Mean changes (Δ) cerebral haemoglobin and tissue oxygen index (TOI) from the baseline (supine position) in 90° head up and −6° head down tilt.

	Head up tilt (HUT)		Head down tilt (HDT)	
	Right	**Left**	**Right**	**Left**
Δ O_2Hb (μmol L^{-1})	$-4{\cdot}9 \pm 2{\cdot}8$	$-5{\cdot}4 \pm 3{\cdot}0$	$1{\cdot}0 \pm 1{\cdot}0$	$1{\cdot}1 \pm 1{\cdot}0$
Δ HHb (μmol L^{-1})	$1{\cdot}8 \pm 1{\cdot}6$	$1{\cdot}3 \pm 1{\cdot}4$[a]	$0{\cdot}3 \pm 0{\cdot}5$	$0{\cdot}3 \pm 0{\cdot}5$
Δ TOI(%)	$-3{\cdot}2 \pm 2{\cdot}5$	$-2{\cdot}2 \pm 2{\cdot}8$[a]	$-0{\cdot}3 \pm 1{\cdot}0$	$-0{\cdot}2 \pm 0{\cdot}8$
TOI(%)	$67{\cdot}9 \pm 4{\cdot}7$***	$70{\cdot}6 \pm 4{\cdot}7$***	$71{\cdot}4 \pm 4{\cdot}9$	$73{\cdot}1 \pm 6{\cdot}3$
(Supine)	$(71{\cdot}0 \pm 4{\cdot}8)$	$(72{\cdot}8 \pm 4{\cdot}7)$	$(71{\cdot}7 \pm 4{\cdot}7)$	$(73{\cdot}3 \pm 6{\cdot}5)$

[a]Head up tilt Δ TOI and Δ HHb significantly different between both sides of the forehead ($P<0.01$). Baseline value was taken in supine position as an average over 2 min before postural change. The changes of haemoglobin and TOI from the baseline were calculated as an average over 2 min before the postural change.
Δ O_2Hb: change in oxyhaemoglobin concentration from the baseline.
Δ HHb: change in deoxyhaemoglobin concentration from the baseline.
TOI: Tissue oxygen index (cerebral oxygen saturation).
TOI significantly different compared with supine position (***$P<0.001$). All values are given as mean ± SD.

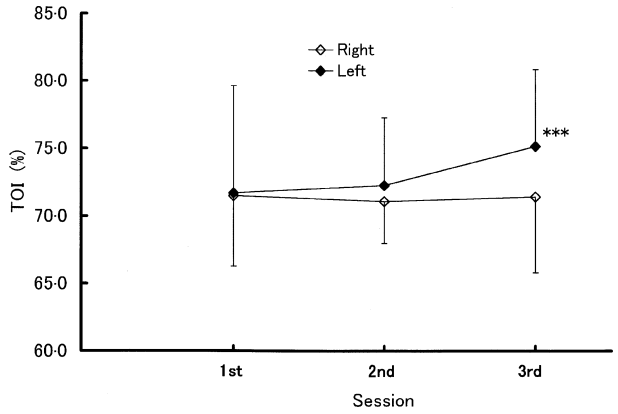

Figure 2 Mean values of supine (SUP) TOI from both sides of the forehead in each session. TOI significantly different between both sides of the forehead at the 3rd session (***P<0.001). Values are mean ± SD.

Table 2 Blood pressure and heart rate response to head up tilt (90°).

	Supine	Head up tilt
Blood pressure (mmHg)		
Systolic	125.3 ± 6.1	127.4 ± 7.8
Diastolic	72.4 ± 6.2	78.5 ± 9.7[a]
Heart rate (bpm)	59.9 ± 9.2	70.1 ± 8.1[a]

[a]Head up position significantly different compared with supine position ($P<0.001$).
All values are given as mean ± SD.

Currently available MBL-NIRS instruments measure changes in reflected light intensity, placing the light source and one detector several centimeters apart on the surface of the head. While the effects of extracranial tissue on these measurements cannot be completely eliminated, these effects have been demonstrated to be relatively small as long as the interoptode distance is at least 5·0 cm (Madsen & Secher, 1999; Owen-Reece *et al.*, 1999). The NIRO-300G used in the present study measures chromophore (O_2Hb and HHb) concentration changes using the MBL method and also provides an absolute measurement of tissue haemoglobin saturation (TOI) by the SRS method (Matcher *et al.*, 1995; Suzuki *et al.*, 1999). The NIRO-300G incorporates three segment detectors housed in a single probe which is placed 4–5 cm from the source. Combining these multi-distance measurements of optical attenuation with the usual multi-wavelength spectroscopy data allows calculation of the relative concentrations of Hb and O_2Hb in the illuminated tissue and therefore an absolute measurement of TOI. Simultaneous measurement by the NIRO-300 and NIRS devices based on time-resolved spectroscopy on the human arm supported the accuracy of the scattering coefficient (Suzuki *et al.*, 1999). Al-Rawi *et al.* (2001) evaluated the NIRO-300 for detection of intracranial oxygen changes in the head of adult patients undergoing endarterectomy. They demonstrated that forehead TOI from the frontal region territory decreased with chromophore changes during clamping of the internal carotid arteries, but not with the changes induced by clamping the external carotid arteries. They also showed that TOI change was closely correlated with changes in transcranial Doppler mean flow velocity of the ipsilateral middle cerebral artery, but not with changes in frontal cutaneous laser-Doppler flowmetry. They concluded that TOI change was largely derived from the intracranial vascular bed.

In the present study, HUT reduced TOI, suggesting that cerebral oxygenation decreased on the cerebral cortical tissue level during HUT. Transcranial Doppler sonography (TCD) provides an indirect estimation of changes in cerebral tissue perfusion by assessing blood flow velocity changes and has also become an accepted non-invasive method for monitoring cerebral haemodynamics during orthostatic stress (Harms *et al.*, 2000). Many studies have demonstrated that HUT reduces TCD-determined middle cerebral artery blood velocity in both healthy subjects and patients with orthostatic hypotension (Levine *et al.*, 1994; Bondar *et al.*, 1995; Cencetti *et al.*, 1997; Novak *et al.*, 1997; Schondorf *et al.*, 1997; Harms *et al.*, 2000; Lipsitz *et al.*, 2000; Blaber *et al.*, 2001; Carey *et al.*, 2001). The TOI decrease found in the present study suggests that NIRS-SRS provides a reliable and sensitive method for monitoring cerebral oxygenation changes during postural change. However, it may be difficult to define the most common territorial distribution of the major cerebral arteries because of NIRS sampling from a composite tissue of arteries, capillaries, and veins. Quaresima *et al.* (2000) concluded that TOI measured by the SRS method predominantly reflected the saturation of the intracranial venous compartment in their venous occlusion study. It is therefore likely that TOI changes are not directly correlated with BP during HUT.

The present findings suggest that TOI is more variable on the left side of the forehead in SUP, while no significant change was observed on the right side. Several NIRS studies have reported a significant difference between the two sides of the forehead during cognitive activation (Hoshi & Tamura, 1993; Takeuchi, 2000). A flight simulator study revealed a higher O_2Hb increment in the left forehead during landing in a cross-wind condition (Takeuchi, 2000). The same left frontal O_2Hb change was also observed in normal subjects during emotional stress and during a language task. The left prefrontal cortex is related to various higher brain functions. Recent functional magnetic resonance imaging studies have demonstrated that the left prefrontal cortex outside the classic 'Broca's area' is also activated by language processing, associated with activation of language centers (Binder *et al.*, 1997). Significantly higher TOI was observed in the left forehead, suggesting that cognitive or emotional activation may be produced in the left prefrontal cortex. Further studies are needed to identify and quantify differences in psychological effects on TOI between the two sides of the forehead.

In conclusion, MBL- and SRS-NIRS measurements confirmed sub-clinical alterations of frontal cortical oxygenation during HUT.

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