Chapter 36
Asymmetrical Changes in Cerebral Blood Oxygenation Induced by an Active Standing Test in Children with Postural Tachycardia Syndrome

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Abstract Near-infrared spectroscopy enables recognition of various brain conditions based on certain factors, such as oxygenated hemoglobin (oxy-Hb). Since July 2012, we have been trying to determine the mechanisms of autonomic function in Japanese children with orthostatic intolerance (also called orthostatic dysregulation) in Nihon University Itabashi Hospital in Tokyo, Japan. A total of 23 children aged 7–16 years diagnosed with postural tachycardia syndrome (POTS), a subtype of orthostatic dysregulation, were enrolled in the study. We evaluated the relation between asymmetry in frontal cortex activity and the automatic nervous system and compared oxy-Hb changes in the right and left frontal cortices during an active standing test. We observed that during active standing oxy-Hb decreased in the frontal cortex. The oxy-Hb changes were asymmetrical, with a significantly larger decrease in the left frontal cortex than in the right frontal cortex, suggesting that tachycardia during active standing in POTS patients might be caused by activation of the right frontal cortex, which induces sympathetic nervous system activity.

Keywords Cerebral blood oxygenation • Near-infrared spectroscopy • Autonomic function • Orthostatic intolerance

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1 Introduction

Orthostatic intolerance, known as orthostatic dysregulation (OD) in Japan [1], is failure of the autonomic nervous system. It occurs primarily in children and adolescents. Blood flow in part of their brains is abnormal, possibly because of a mismatched reaction to the cardiovascular or neurological system. Unstable regulation of brain blood flow in OD patients, however, has been evaluated by specific modalities including transcranial Doppler flowmetry and near-infrared spectroscopy (NIRS) [2–5]. Continuous-wave NIRS is based on the relative transparency of human tissue to near-infrared light using the modified Beer–Lambert law, which can detect changes in oxygenated Hb (oxy-Hb) and deoxygenated Hb (deoxy-Hb) in brain tissue. Pocket NIRS (Pocket NIRS Duo™; Hamamatsu Photonics, Shizuoka, Japan) is able to evaluate these changes in the form of a remarkable lightweight, mobile application, which can be used during exercise as well as active standing test. In the present study, we observed oxy-Hb and total-Hb changes in the right and left frontal cortices using Pocket NIRS during active standing tests in children with OD.

2 Methods

We studied 23 children or adolescents (14 boys, 9 girls), ranging in age from 7 to 17 years (mean 12.8 ± 2.6 years), who were visited at our outpatient clinic in Nihon University Itabashi Hospital from July 2012 to March 2013. Patients with organic disease were excluded. All of the patients were right-handed. We conducted a medical interview using the OD checklist (Table 36.1) [1] for all of our patients diagnosed as having postural tachycardia syndrome (POTS) based on the Japanese clinical guidelines for juvenile orthostatic dysregulation [5]. The criteria are as following; (1) the heart rate increases by >115 bpm during active standing after arising from the supine position, (2) the heart rate elevates by >35 bpm during active standing compared with that during the supine position. In addition to the patients who met the conditions of criterion (1), (2), we studied subjects whose heart rates were elevated by >21 bpm during active standing, based on Okuni's criteria [1].

The active standing test was performed in the pediatric outpatient clinic under quiet conditions. After resting for 10 min in the supine position, subjects were asked to stand up by themselves and remain standing for 10 min. During active standing, the subjects' blood pressure and heart rate were monitored with a sphygmomanometer.

Pocket NIRS can simulate the conditions of an active standing test. It is a mobile tool that includes a special system consisting of two optical probes with two channels for each and a handy wireless controller (weighing only 100 g) connected to the probes with cables. The optical probes are placed on each side of the forehead above the eyebrows. Each optical probe includes light-emitting diodes (LEDs) as sources and one photo-diode as a detector with 3 cm distance between the detector and LEDs that are able to illuminate the tissue with three wavelengths (SMC735, SMC810, SMC850; Epitex, Inc). The spectroscope continuously provides digital

Table 36.1 Checklist for orthostatic dysregulation (OD) based on Okuni's criteria

Major manifestations
A. Dizziness on standing
(Frequent: including standing up slowly; sometimes: once a week; rare: less than once a week)
B. Fainting on standing
(Frequent: once a week; sometimes: once a month; rare: once every 2 months)
C. Nausea when taking a hot bath
(Frequent: does not enter a hot water bathtub or takes lukewarm baths; sometimes: more than half of the total; rare: once every 2 months)
D. Palpitations
(Frequent: 2/3 or more when moving a little; half of the times when moving a little; rare: once every 2 months)
E. Difficulty in getting out of bed
(Frequent: more than three times a week; sometimes: 1–2 times a week; rare: less than 1–2 times a week)
Minor manifestations
a. Pallor, b. Anorexia; c. Colic pain; d. Fatigue; e. Headaches
(Frequent: more than three times a week; sometimes: 1–2 times a week; rare: once 2 months)
f. Car-sickness
(Frequent: every time or once week or including cannot get on a car; sometimes: more than half the times; rare: once every 2 months)
Schellong test
g. Pulse pressure narrows by 16 mmHg or more during a standing test
h. A fall in systolic blood pressure of 21 mmHg or more during a standing test
i. Increase in the pulse rate of 21 beats per minute or more during a standing test
j. T_{II} depression of 0.2 mV or more on a standing EEG
(When test cannot be endured, the patients are assumed to be positive)

signals from the cerebral oxy-Hb, deoxy-Hb, and total-Hb based on the modified Beer–Lambert law in which changes in hemoglobin chromophore concentrations, which is in a relation of simultaneous linear equation with light absorbance divided by the extinction coefficients of the chromophores and the optical path length in the tissue, which is the average distance that light travels between the source and detector through the tissue. The system is controlled from a standard laptop personal computer through a wireless connection provided by Bluetooth, which is enable to acquire up to 60 data per second. Time-concentration courses of cerebral oxy-Hb, deoxy-Hb, and total-Hb are monitored simultaneously on the personal computer panel while the examination is being performed. We measured changes in the oxy-Hb level and the total-Hb level in both supine and active standing postures. To evaluate laterality in both postures, the average oxy-Hb level and total-Hb level were calculated for a selected 60 s during which those variability rate was almost stable between 60 s (1 min) and 540 s (9 min). Because of avoiding terrible artifact originating from patients' motional or mental stress, we thought it was necessary to exclude unstable periods including first and last 1 min for the reasons of a tense atmosphere or getting tired. The oxy-Hb and the total-Hb were included, and the deoxy-Hb was excluded in the present study.

Data are given as the mean ± SD. The Mann–Whitney U test was used for comparison of oxy-Hb and total Hb changes between the right and left sides. A value of $p < 0.05$ was considered to indicate a significant difference. Informed consent was obtained from the patients and their legal parents.

3 Results

Oxy-Hb (Fig. 36.1, Table 36.2)

From the onset of standing, the oxy-Hb level decreased, falling markedly on the left with a mean level of –118.7 ± 72.6 μmol/L·cm (range –244.5 to 28.1 μmol/L·cm). In contrast, on the right side it fell only a mean level of –41.8 ± 56.9 μmol/L·cm (range –121.6 to 83.6 μmol/L·cm) ($p = 0.0003$).

Total-Hb (Table 36.3)

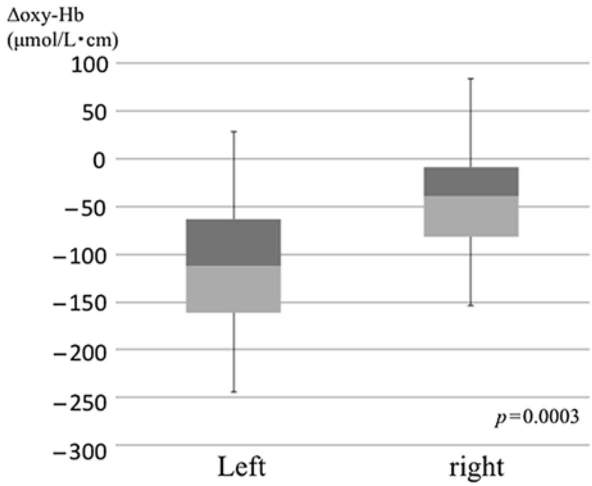

Fig. 36.1 Comparison oxy-Hb changes between the right and left frontal cortices. Oxy-Hb decreased during active standing, decreasing more markedly on the left, with a mean value of −118.7 ± 72.6 μmol/L·cm (range −244.5 to 28.1 μ mol/L·cm), than on the right, with a mean value of −41.8 ± 56.9 μmol/L·cm (range −121.6 to 83.6 μmol/L·cm) ($p = 0.0003$)

Table 36.2 List of changes in oxy-Hb level

No.	Left oxy-Hb	Right oxy-Hb	No.	Left oxy-Hb	Right oxy-Hb
1	−113.6	−78.4	13	−241.8	−106.5
2	−164.3	−154.3	14	−157.7	−13.2
3	−45.3	−11.8	15	−79.7	−11.0
4	−27.0	−47.0	16	28.1	10.4
5	−54.8	83.6	17	−77.0	−15.0
6	−62.8	−6.5	18	−148.6	−107.5
7	−237.3	−12.9	19	−159.4	−70.6
8	−51.5	13.1	20	−194.4	−80.5
9	−244.5	−102.7	21	−112.6	14.0
10	−170.9	−82.8	22	−85.4	−40.0
11	−158.8	−46.1	23	−106.7	−121.6
12	−64.6	25.2	Mean	−118.7 ± 72.6	−41.8 ± 56.9

Values are expressed in μmol/L·cm

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Table 36.3 List of changes in total Hb level

No.	Left total-Hb	Right total-Hb	No.	Left total-Hb	Right total-Hb
1	78.0	22.2	13	–246.7	–71.1
2	–32.1	–21.0	14	–74.0	33.2
3	4.3	24.2	15	32.5	102.4
4	55.0	22.7	16	130.3	61.4
5	–24.6	221.5	17	2.2	21.7
6	5.6	26.7	18	–47.2	–87.1
7	–259.1	32.9	19	48.5	6.1
8	–17.4	40.0	20	1.2	–20.3
9	–318.5	–113.9	21	–55.7	42.7
10	–137.0	–69.5	22	–63.3	2.7
11	–118.0	–18.0	23	54.6	–3.0
12	–18.7	65.5	Mean	–43.5 ± 110.4	14.0 ± 68.5

Values are expressed in μmol/L·cm

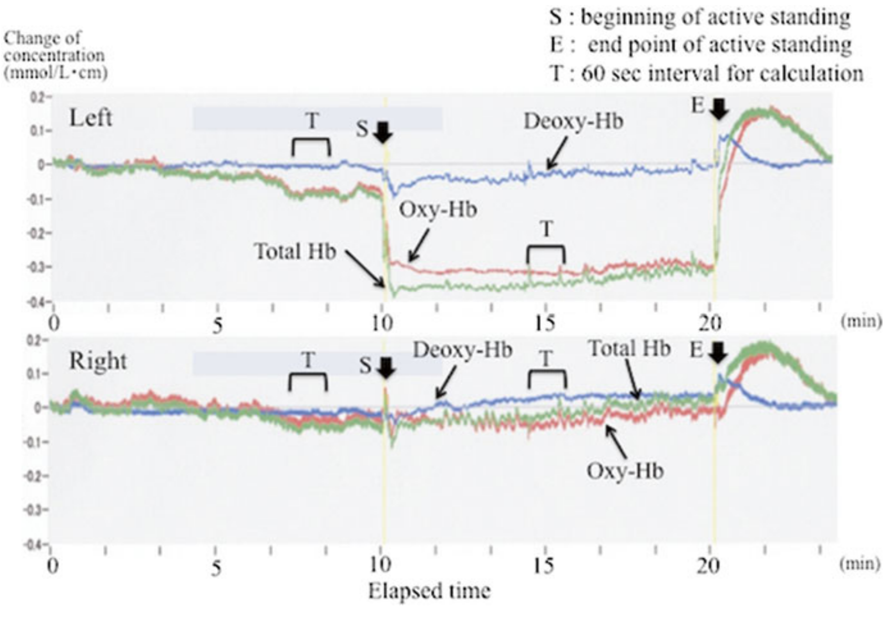

Fig. 36.2 13 Year-old male typical example of changes in NIRS parameters. Example of the variability of oxy-Hb in our study in patients with postural tachycardia syndrome. The rate of oxygen concentration changes on the *left* and *right sides* are shown in the *upper* and *lower graphs*, respectively. Oxy-Hb decreased during active standing, falling more markedly on the *left side* than on the *right. Arrow S* indicates the beginning of active standing. *Arrow E* indicates the end of active standing. Interval T with a *square bracket* means selected 60 s for calculation of oxy-Hb and total Hb level

From the onset of standing, total-Hb level on the right side slightly increased with a mean level of 14.0 ± 68.5 μmol/L·cm (range –113.9 to 221.5 μmol/L·cm). Total-Hb level on the left side decreased with a mean level of –43.5 ± 110.4 μmol/L·cm (range –318.5 to 130.3 μmol/L·cm) ($p = 0.04$).

Oxy-Hb variability rate indicated markedly clearer laterality rather than total-Hb during active standing.

4 Discussion

Changes in cerebral blood flow in patients with OD can now be determined by NIRS. Mehagnoul-Schipper et al. [6] reported that a decrease in oxy-Hb following an orthostatic change was found. Kim et al. [4] demonstrated that children with abnormal circulatory responses during active standing had significantly reduced oxy-Hb compared with their normal counterparts. However, asymmetrical changes in cerebral blood flow were not well documented in their report. We focused on bilateral cerebral oxygen levels in patients with OD during active standing.

Several NIRS monitoring systems are available clinically for evaluating cerebral oxygen levels. Because we thought that the NIRS application should be portable, lightweight and wireless during active standing, we believed that the Pocket NIRS Duo™ (Hamamatsu Photonics, Shizuoka, Japan) was best for our study. Mobile NIRS is expected to become useful in several fields. For example, it can monitor the muscle oxygenation level during exercise, which would be helpful in the sports science field. Additionally, seizure status can be monitored in infants who are in constant motion, which would be useful in brain research [7, 8]. Pocket NIRS provides data on serial changes in oxy-Hb, deoxy-Hb, and total-Hb levels as the rate of change from the beginning of the examination. Thus, it can record these levels for any turn of events. We found a significant difference in the response of oxy-Hb and total-Hb in the frontal cortices between the right and left sides, with a decreasing response during active standing. The results of oxy-Hb changes were asymmetrical, with a significantly greater decrease in the left frontal cortex than in the right frontal cortex during active standing.

We believe asymmetrical cerebral oxygen levels are related to some unstable situation during active standing. It has been reported that during mental stress tasks right frontal cortex activity plays a greater role in sympathetic nervous activity than the left frontal cortex [9–11]. Also, according to some reports describing laterality of sympathetic nervous activity, the right hemisphere plays a greater role than the left hemisphere, especially influencing cardiac performance [12–15]. We enrolled patients with POTS, in whom it is postulated that excessive blood pooling exaggerates acceleration of sympathetic nervous activity, resulting in tachycardia. In fact, we found typical asymmetrical cerebral oxy-Hb changes in patients with POTS, suggesting that the right frontal cortex during active standing by POTS patients has a greater role in cerebral regulation of the heart rate by virtue of the increased sympathetic nervous activity. Thus, tachycardia during active standing in POTS patients might be caused by activation of the right frontal cortex.

Oxy-Hb indicated major changes with typical laterality rather than total-Hb during active standing. It is said that the oxy-Hb level is better marker to evaluate cerebral oxygenation rather than total-Hb level according to some previous reports [4, 16], although total-Hb is excellent marker to estimate cerebral blood volume.

Clinical parameters including blood pressure and partial pressure of carbon dioxide in arterial blood ($PaCO_2$) might be related to our observed changes evaluated by NIRS. Tachtsidis et al. [17] reported changes in blood pressure are present in the superficial layer of the head which is sampled when using a traditional NIRS measurement principle. On the other hand, some papers [18, 19] describe that orthostatic stress in humans can decrease $PaCO_2$ measured by end-tidal carbon dioxide. $PaCO_2$ changes effects derived from NIRS signals significantly reported by Scholkmann et al. [20]. Furthermore, the observed decreased in oxy-Hb in patients with OD might also reflect changes in systemic parameters, especially in $PaCO_2$ based on these previous studies.

4.1 Study Limitations

Because there were no controls in our study, there could be no comparison about the laterality of cerebral oxygen levels between POTS patients and normal controls. However, it might be possible to verify a causal relation between asymmetrical cerebral oxygen levels and the laterality of sympathetic nervous activity.

Although it is said that cerebral blood flow cannot be measured by NIRS application directly, the motion of cerebral blood flow corresponded to the oxy-Hb changes during active standing in this study. Thus, we believe that cerebral blood flow can be evaluated by Pocket NIRS. The Pocket NIRS device is also susceptible to superficial blood flow and oxygenation changes. We speculate that the oxy-Hb signal is only partially originating from the cortex/cerebral layers, maybe only to a very small percentage.

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