Head-down manoeuvre in patients with a high symptom score for orthostatic intolerance reveals impaired right brain frontal lobe vasoreactivity

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Accepted 9 February 2005
Available online 26 March 2005

Abstract

Objective: Autonomic nerve dysregulation produces a sense of impaired well-being and interferes with work performance in affected individuals. In this study, we characterized the pathophysiology of this condition.

Methods: Six patients with high symptom scores for orthostatic intolerance (OI) along with age- and sex-matched normal volunteers were directed to perform a head-down manoeuvre, and the change in cerebral blood flow (CBF) and cerebral oxygen levels (rSO2) in the right and left frontal lobes was measured using near-infrared spectroscopy (NIRS).

Results: The head-down manoeuvre induced a much greater increase in right-sided total haemoglobin concentration (THbl) in normal volunteers (0.51 ± 0.24) when compared to symptomatic patients (0.0 ± 0.04) but had no effect on left-sided THbl (P < 0.05) in either group. Five of 6 patients showed a gradual decrease in right-sided THbl when assuming a sitting position, and all patients with this pattern complained of symptoms of multiple autonomic dysfunction. Further, this pattern of changes in right-sided THbl was not observed in normal volunteers.

Conclusions: The gradual decrease of THbl with the sitting position and the lack of increase during the head-down manoeuvre in symptomatic patients suggest that these patients have impaired vasoreactivity in the right frontal lobes.

Significance: This impaired vasoreactivity likely reflects dysfunction of the right hemisphere and the sympathetic nervous system in patients with OI.

Keywords: Head-down manoeuvre; Orthostatic intolerance; Vasoreactivity; Right hemisphere; NIRS

1. Introduction

Symptoms of autonomic dysfunction include headaches (Goadsby, 2002; Peroutka, 2004; Sliwka et al., 2001), dizziness (Staab et al., 2002; van den Berg et al., 2001), diminished concentration, profuse perspiration (Iwase et al., 1997), and paroxysmal palpitations (Goldstein et al., 2002). Orthostatic intolerance (OI) is also a common feature of autonomic dysfunction and is characterized by adrenergic symptoms occurring with assumption of an upright posture (Jordan et al., 2002). The characteristic symptoms such as headache, concentration difficulties, palpitation of the heart, chest discomfort, blurred vision, dizziness, and nausea, develop when the individual is standing upright and are resolved by a change in position. While the tilt-table test has been established as a standard method for diagnosis of OI (Jacob and Biaggioni, 1999), a questionnaire of 10 items is a simple, reliable, and less expensive method of diagnosing OI (Winkler et al., 2003).

Patients with dizziness show significantly reduced right hemisphere vasoreactivity, as assessed by near-infrared spectroscopy (NIRS) (Shinoura and Yamada, 2005). Since dizziness is a component of OI, we hypothesized that OI might be related to impaired right hemisphere vasoreactivity. Thus, the vasoreactivity of the right and left hemispheres was assessed in patients with a high symptom score.

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for OI. Vasoreactivity was evaluated using the head-down manoeuvre with measurements of the change in total haemoglobin concentration (THbl) and cerebral oxygen levels (rSO2) by NIRS (Shinoura and Yamada, 2005). We found that these patients have impaired right hemisphere frontal lobe vasoreactivity, which possibly reflects dysfunction of the right hemisphere and the sympathetic nervous system.

2. Patients and methods

Six right-handed patients (4 men, two women; 35 ± 1.7 years) with multiple symptoms of autonomic dysfunction (e.g. headache, dizziness, concentration difficulties, profuse perspiration and paroxysmal palpitations) and symptoms scores for OI of greater than 10 were enrolled in this study along with 17 age- and sex-matched right-handed volunteers (11 men, 6 women; mean age, 34 ± 1.6 years) (Fig. 1) (Winkler et al., 2003). Subjects did not exhibit major neurological deficits (e.g. motor or sensory deficits) other than autonomic nervous dysfunction, and none of the subjects were receiving drugs (e.g. sedatives) that could affect autonomic nerve function. All patients underwent magnetic resonance imaging (MRI) or computerized tomography (CT), which failed to demonstrate any discrete lesions. No obvious vascular disorder was observed including blood pressure. Informed consent was obtained from all subjects.

All subjects were asked to perform positional manoeuvres. The head-down manoeuvre consisted of the patient sitting down for a minute, followed by 3 episodes of dropping their head to their knees for 15 s each time. Over the course of these manoeuvres, THbl and rSO2 were measured using NIRS (TOS-96 monitor, Tostec, Inc., Japan) with the TOS-96 detector placed on both sides of forehead (Litscher et al., 1998). The separation between the light emitting diodes (LEDs) and the photo detector diode was 40 mm, providing an effective monitoring depth of 28 ± 3 mm. THbl was calculated as the sum of oxygenated and deoxygenated haemoglobin, and rSO2 was determined as the percentage of oxygenated haemoglobin in relation to THbl. Initial THbl was designated as 1.0, and thus THbl was not an absolute measure. All subsequent THbl measurements (every 5 s) were expressed as a value relative to this baseline. rSO2 was also measured every 5 s. THbl and rSO2 are represented as mean ± SEM. Mann–Whitney’s U test was used for comparison of THbl and rSO2 between the group of patients and the group of normal volunteers. A statistically significant difference was defined as P < 0.05.

3. Results

Table 1 summarizes the changes in right- and left-sided THbl and rSO2 in patients and normal volunteers during the head-down manoeuvre. Table 2 summarizes the symptoms and scores of OI of the patients. Inclusion/exclusion criteria of patients was as follows; symptom scores for OI of more than 10, no major neurological deficits such as paresis, no discrete lesions in CT or MRI and no reception of drugs such as sedatives. The head-down manoeuvre resulted in significantly lower right-sided THbl in patients with high symptom scores (0.0 ± 0.04) when compared to normal volunteers (0.51 ± 0.24) (P < 0.05) but had no effect on left-sided THbl in either group. The range of right-sided THbl is

<table>
<thead>
<tr>
<th>Questionnaire: In what frequency do you experience any of the following symptoms when standing up for a seated or reclining position, or when standing for long periods of time? Use the scale indicated below to indicate the frequency of each symptom.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
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<tr>
<td>______</td>
</tr>
<tr>
<td>0: never</td>
</tr>
</tbody>
</table>

Fig. 1. Questionnaire for orthostatic intolerance (OI) (Winkler et al., 2003). Subjects rated the frequency of each symptom on a scale from 0 to 4, and cumulative scores were calculated by adding the symptom scale points for each symptom.
Symptom score 15

left-sided THbl and rSO2 when comparing symptomatic R, right; L, left; Mean saturation (%); symptom score, symptom score for orthostatic intolerance; Age (years) 35

Male/female 4/2 11/6

haemoglobin; Initial THbl is designated as 1.0; rSO2, regional oxygen

difficulties

Concentration

Lightheadedness 4 44000

Chest discomfort 0 00300

Profuse
cardia (heart rate increase of at least 30 beats/min while the subject is standing upright); (2) exclusion of symptomatic OI or orthostatic hypotension; and (3) plasma noradrenaline concentrations ≥ 600 pg/ml while the subject is standing upright (Jacob and Biaggioni, 1999). The present study

of autonomic dysfunction (Shinoura and Yamada, 2005), and this pattern was not observed in normal volunteers. Thus, the presented data indicate that the examination of THbl and rSO2 reactivity during head-down manoeuvre would be a valuable screening method for disorders of autonomic dysfunction including OI, although we possibly need to evaluate more number of patients with OI to confirm this hypothesis.

OI is characterized by headache, concentration difficulties, palpitations, dizziness and nausea when an upright posture is assumed (Winkler et al., 2003). Patients with OI comprise the majority of those with autonomic disorders (Jacob and Biaggioni, 1999). Diagnostic criteria for OI include: (1) adrenergic symptoms associated with orthostatic tachycardia (heart rate increase of at least 30 beats/min while the subject is standing upright); (2) exclusion of symptomatic OI or orthostatic hypotension; and (3) plasma noradrenaline concentrations ≥ 600 pg/ml while the subject is standing upright (Jacob and Biaggioni, 1999). The present study
utilized a questionnaire of 10 items that was validated by Winkler et al. as a screening test for OI. They claim that the questionnaire showed high validity: applying logistic regression, 93.48%. This indicates that subjects could be classified correctly into healthy and OI group by this questionnaire, possibly without any other measurement. However, in future, we plan to use recordings such as ECG spectroscopy or EEG that would allow to show any or a specific change in cerebral activation during the head-down manoeuvre.

Fig. 2. Changes in total haemoglobin (THbl) and regional oxygen saturation (rSO₂) in a 23-year-old healthy man (A) and a 40-year-old healthy man (B) during a head-down manoeuvre. The ordinate indicates changes in THbl relative to baseline (designated as 1.0) and changes in rSO₂ (%). The vertical arrows indicate the peak of changes in THbl. Note that right ΔTHbl is positive in panels A and B.

Fig. 3. Changes in total haemoglobin (THbl) and regional oxygen saturation (rSO₂) in a 35-year-old man (A = Patient 1 in Table 2) and a 39-year-old man (B = Patient 2 in Table 2) with high symptom scores for OI during a head-down manoeuvre. The ordinate indicates changes in THbl relative to baseline (designated as 1.0) and changes in rSO₂ (%). Note that THbl gradually decreases and that right ΔTHbl is zero during a head-down manoeuvre in panels A and B.
Sympathetic cardiovascular control is lateralized to the right hemisphere (Hilz et al., 2001; Yokoyama et al., 1987; Yoon et al., 1997), and massive right Sylvian fissure subarachnoid hemorrhage is associated with electrocardiographic changes (Hirashima et al., 2001). Several studies suggest that idiopathic OI results from enhanced sympathetic activation (Jordan et al., 2002; Robertson et al., 1999) mediated by the right hemisphere (Witting, 1997). It should be noted that all the patients complained of multiple autonomic dysfunction, while they did not complain of dysregulation of cardiovascular control such as hypertension or angina pectoris, possibly because they were relatively young and duration of autonomic dysfunction was relatively short. Additional concurrent recording of respiration, ECG and skin conduction might assist interpretation of this study. Further, stress-regulating coping strategies are mediated preferentially by the right hemisphere (Henry, 1997; Schore, 1997, 2002; Spivak et al., 1998; Witting, 1997), and the right medial prefrontal cortex is highly activated by stress and modulates autonomic function in rats (Sullivan and Gratton, 1999). Interestingly, in the present study, all patients with a high symptom score for OI complained of stress for work or home. This may indicate persistent activation of the sympathetic system that may ultimately lead to habituation, which could explain the low vasoreactivity in right hemisphere of patients with OI. Indeed, right hemisphere damage in children result from repeated psychological trauma (stress) during development, and they lose critical social skills of human bonding, in which the right hemisphere plays a critical role (Henry, 1997; Witting, 1997). Alternatively, the marked decrease in the rSO2 in the right hemisphere may lead to suppression of right hemispheric function, resulting in autonomic dysfunction by dysregulation of the sympathetic nervous system. Further study to characterize the relationship between suppression of vasoreactivity in the right hemisphere and autonomic dysfunction would be of benefit.

In conclusion, the lack of increase in right-sided THbI in patients with high symptom scores for OI suggests impaired vasoreactivity in response to pressure and may reflect dysfunction of the right hemisphere and the sympathetic nervous system.

References


