

## Changes in cerebral oxygenation and haemodynamics during postural blood pressure changes in patients with autonomic failure

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Received 22 March 2006, accepted for publication 23 May 2006

Published 14 June 2006

Online at [stacks.iop.org/PM/27/777](http://stacks.iop.org/PM/27/777)

### Abstract

Patients with autonomic failure suffer severe postural hypotension that may be associated with symptoms of cerebral hypoperfusion. This study utilized near-infrared spectroscopy (NIRS) to measure changes in cerebral oxygenation and haemodynamics during the head-up tilt table test in 18 patients with autonomic failure and 10 healthy age-matched volunteers. Heart rate, blood pressure (MAP), oxygen saturation, cerebral tissue oxygen index (TOI) and total cerebral haemoglobin concentration [HbT] were measured continuously. In patients with autonomic failure there was a mean (SD) reduction in MAP of 46.7 (26.5) mmHg ( $p < 0.005$ ) associated with a reduction in TOI of 8.6 (6.2)% ( $p < 0.005$ ) during the head-up tilt table test. In healthy volunteers mean (SD) MAP rose by 12.3 (8.0) mmHg ( $p < 0.005$ ) and TOI fell by 2.6 (3.2)% ( $p < 0.05$ ). There was a mean (SD) reduction in [HbT] of 3.09 (2.82)  $\mu\text{mol l}^{-1}$  ( $p < 0.005$ ) in patients, equivalent to a decrease in cerebral blood volume of 0.2 (0.18) ml/100 g. There were no changes in [HbT] in the healthy volunteers. Postural hypotension in patients with autonomic failure is associated with a substantial decrease in absolute cerebral oxygenation measured by NIRS and this might reflect a critical reduction in cerebral oxygen delivery.

Keywords: near-infrared spectroscopy, cerebral oxygenation, autonomic failure, tilt table test

Blood pressure in the upright posture is maintained via autonomic reflex activity causing an increase in systemic vascular resistance in response to gravitational displacement of blood to the lower part of the body and increased filtration from capillaries into the interstitial space (Lye and Walley 1998). Patients with autonomic failure are unable to modulate vascular tone in response to the upright body position because of the absence of this reflex activity (Mathias 2003). It is still a matter of debate whether, and to what extent, cerebral autoregulation (CA) is disturbed in patients with autonomic failure. In one recent study, CA was not affected in patients with autonomic failure (Hetzl *et al* 2003), although in another CA was preserved in some patients but, in others, there was a linear relationship between mean arterial blood pressure (MAP) and cerebral blood flow (Hesse *et al* 2002). Postural tolerance therefore varies widely between patients. Hypotension associated with autonomic failure may result in syncope if MAP falls below the lower limit of CA, or pre-syncope symptoms such as light headedness and blurred vision that may reflect reduced cerebral perfusion (Van Lieshout *et al* 2003). A number of other symptoms, including neck and back pain, may also occur because of muscle hypoperfusion (Mathias *et al* 1999). Head-up tilt is a significant postural challenge and tilt table testing is an established method to study cardiovascular responses and regulation (Benditt *et al* 1996).

Near-infrared spectroscopy (NIRS) exploits the relative transparency of biological tissue to light between 700 and 1000 nm, and oxyhaemoglobin (O<sub>2</sub>Hb) and deoxyhaemoglobin (HHb) have characteristic absorption spectra in this wavelength range. NIRS is able to monitor changes in cerebral oxygenation and haemodynamics in adults (Owen-Reece *et al* 1999, Elwell *et al* 1992, McLeod *et al* 2003) and has been used in a variety of clinical situations including autonomic failure (Harms *et al* 2000), vasovagal syncope (Colier *et al* 1997), cerebral ischaemia (Kirkpatrick *et al* 1998) and in the elderly (Mehagnoul-Schipper *et al* 2000). Studies using previous generations of NIRS equipment were only able to measure changes in cerebral O<sub>2</sub>Hb and HHb concentrations, variables that are generally unfamiliar to clinicians. Modern NIRS instrumentation is more user friendly and is able to display a measure of absolute cerebral tissue oxygen saturation. The NIRO 300 (Hamamatsu Photonics KK, Japan) uses spatially resolved spectroscopy (SRS) to measure the proportion of O<sub>2</sub>Hb in the field of view, and expresses this as the tissue oxygenation index (TOI), displayed as a simple percentage value (Suzuki *et al* 1999). The application of SRS and the validity of TOI have been described in normal adult volunteers (Quaresima *et al* 2000) and in clinical scenarios (McLeod *et al* 2003, Al-Rawi *et al* 2001) and allows continuous and non-invasive monitoring of cerebral oxygenation.

The aim of this study was to investigate absolute cerebral oxygenation changes during postural hypotension in patients with autonomic failure using NIRS.

## Methods

### *Subjects*

Eighteen patients with primary autonomic failure and ten aged-matched healthy volunteers (controls) were investigated following local ethics committee approval and written informed consent. The patients suffered from either pure autonomic failure or multiple system atrophy, with severe postural hypotension and clinical features and investigations consistent with the diagnosis (Mathias 2003). For the purpose of this study we combined the patients into a single group because our aim was to investigate changes in cerebral oxygenation during postural hypotension rather than to determine any differential effects between diagnostic groups.

### Systemic measurements

ECG, oxygen saturation (SpO<sub>2</sub>), blood pressure, heart rate and respiratory rate were continuously recorded throughout the study period. Mean arterial blood pressure (MAP) and heart rate (HR) were measured using a non-invasive Portapres<sup>®</sup> system and finger probe (FMS Medical Systems BV, Arnhem, Netherlands). Respiratory rate was measured using a thermistor to analyse airflow via a nasal catheter.

### NIRS measurements

Changes in cranial O<sub>2</sub>Hb and HHb concentrations ( $\Delta[\text{O}_2\text{Hb}]$  and  $\Delta[\text{HHb}]$ ) and absolute TOI were measured continuously using a four-wavelength (775, 813, 853 and 910 nm) NIRO 300 spectrophotometer (Hamamatsu Photonics KK, Japan). Absolute micromolar ( $\mu\text{mol l}^{-1}$ ) changes from baseline of cerebral [O<sub>2</sub>Hb] and [HHb] were calculated using a modified Beer–Lambert law (Elwell *et al* 1994) and age-corrected differential pathlength factor (DPF) of  $5.13 + (0.07 \times A^{0.81})$ , where  $A$  is the age in years (Duncan *et al* 1995). SRS measures scaled absorption coefficients and, assuming a wavelength dependence of light scattering, scaled concentrations of O<sub>2</sub>Hb and HHb can be derived and TOI computed as the ratio of oxygenated to total tissue haemoglobin concentration (Suzuki *et al* 1999):

$$\text{TOI} = \frac{k \cdot [\text{O}_2\text{Hb}]}{k \cdot [\text{O}_2\text{Hb}] + k \cdot [\text{HHb}]} \times 100\%,$$

where  $k$  is a constant accounting for light scattering. Changes in the difference between  $\Delta\text{O}_2\text{Hb}$  and  $\Delta\text{HHb}$  concentrations ( $\Delta[\text{Hb}_{\text{diff}}]$ ) were calculated subsequently. Changes in total cerebral haemoglobin concentration ( $\Delta[\text{HbT}]$ ) were calculated from the sum of  $\Delta[\text{O}_2\text{Hb}]$  and  $\Delta[\text{HHb}]$  and later converted to changes in cerebral blood volume (CBV) using a previously described relationship (Wyatt *et al* 1990):

$$\Delta\text{CBV} = \Delta[\text{HbT}] \times \frac{0.89}{\text{Hb}},$$

where Hb is the systemic haemoglobin concentration.  $\Delta[\text{HbT}]$  is proportional to changes in CBV if blood haemoglobin concentration and cerebral large-to-small vessel haematocrit ratio remain constant during the measurement period, thereby allowing continuous measurement of real-time changes in CBV.

The NIRS optodes (transmitting and receiving devices) were placed on the scalp over the frontal region below the hairline, approximately 4 cm above the supra-orbital ridge. A purpose built holder was used to maintain a constant inter-optode separation of 50 mm and light shielding was provided by a black cloth wrapped around the head.

### Protocol

Patients and volunteers were strapped to an electrically operated tilt table in the horizontal position and all the monitors were connected. Following a ‘run-in’ period to allow the measured variables to become stable, the study began with a 10 min period of recording with the patient/volunteer lying supine with the tilt table in the horizontal position (supine). The table was then rapidly moved (over 15 s) to a 60° head-up tilt for a further 10 min period (head-up). The head-up tilt was reversed immediately if any patient complained of severe symptoms or if syncope was imminent.

**Table 1.** Demographics of the study population.

|                          | Patient group ( $n = 18$ ) | Normal volunteers ( $n = 10$ ) |
|--------------------------|----------------------------|--------------------------------|
| Mean (range) age (years) | 61 (42–79)                 | 60 (46–68)                     |
| Sex (M:F)                | 13:5                       | 5:5                            |

**Table 2.** Summary values of HR, MAP, SpO<sub>2</sub> and TOI for supine and head-up position in patients with autonomic failure and healthy aged-matched controls. Results are expressed as mean ( $\pm$ SD). Significant changes between supine and tilt are indicated by \* ( $p < 0.005$ ) and # ( $p < 0.05$ ). A difference between patient and control groups for the supine or tilt positions is indicated by  $\sim$  ( $p < 0.005$ ) against the control data.

|                      | Patients    |              | Controls         |                     |
|----------------------|-------------|--------------|------------------|---------------------|
|                      | Supine      | Tilt         | Supine           | Tilt                |
| MAP (mmHg)           | 99.1 (19.2) | 52.3 (20.2)* | 75.3(6.6) $\sim$ | 87.6 (11.9)* $\sim$ |
| HR (bpm)             | 72.4 (11.0) | 81.2 (9.2)*  | 66.5 (8.8)       | 76.7 (10.0)*        |
| SpO <sub>2</sub> (%) | 96.5 (1.7)  | 96.5 (1.6)   | 95.8 (1.7)       | 95.3 (0.7)          |
| TOI (%)              | 72.3 (6.7)  | 63.8 (8.1)*  | 69.3 (4.8)       | 66.8 (4.6)#         |

**Table 3.** Changes in [O<sub>2</sub>Hb], [HHb], [Hb<sub>diff</sub>] and [HbT] and cerebral blood volume during head-up tilt in patients with autonomic failure and healthy aged-matched controls. Results are expressed as mean ( $\pm$ SD). Significant changes during head-up tilt are indicated by \* ( $p < 0.005$ ) and # ( $p < 0.05$ ). A difference between patient and control groups is indicated by  $\sim$  ( $p < 0.005$ ) against the control data.

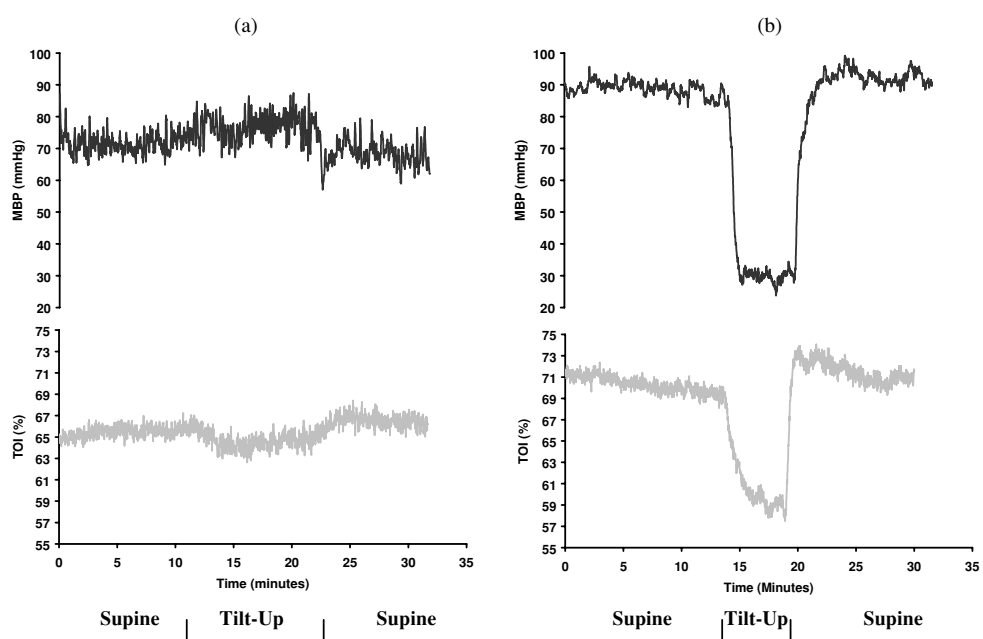
|   | Patients       | Controls            |
|---|----------------|---------------------|
| O <sub>2</sub> Hb ( $\mu\text{mol l}^{-1}$ )  | -7.26 (4.35)*  | -0.70 (1.94) $\sim$ |
| HHb ( $\mu\text{mol l}^{-1}$ )                | 4.17 (2.65)*   | 1.06 (0.99)# $\sim$ |
| Hb <sub>diff</sub> ( $\mu\text{mol l}^{-1}$ ) | -11.43 (6.63)* | -1.77 (1.89) $\sim$ |
| HbT ( $\mu\text{mol l}^{-1}$ )                | -3.09 (2.82)*  | 0.36 (2.43) $\sim$  |
| CBV (ml/100 g)                                | -0.20 (0.18)*  | 0.02 (0.15) $\sim$  |

### Data acquisition and analysis

Physiological data were monitored continuously and downloaded onto a personal computer for later analysis off-line. The mean of the values for TOI,  $\Delta$ [O<sub>2</sub>Hb],  $\Delta$ [HHb], MBP and HR recorded during the final 2 min at each position (supine and head-up) was used as the summary variable. Inter-group differences in baseline variables were compared using a non-paired Student's *t*-test and within group changes between supine and head-up tilt with a paired *t*-test. Significance was taken at  $p < 0.05$ .

### Results

Patient and control demographics are shown in table 1. The summary MAP, HR, SpO<sub>2</sub> and TOI values for supine and head-up positions are shown in table 2 and the changes in [O<sub>2</sub>Hb], [HHb], [HbT] and CBV are shown in table 3. A typical real-time change in TOI and MAP in one volunteer and a symptomatic patient is illustrated in figure 1.



**Figure 1.** Representative data collected from (a) a healthy volunteer and (b) a symptomatic patient with severe postural hypotension. For illustrative purposes data have been smoothed using 1 s non-overlapping averaging. Mean arterial blood pressure (MAP) and cerebral tissue oxygenation (TOI) are shown in real-time during head-up tilt.

The supine MAP was lower in the control group compared to the patient group, but there were no significant inter-group differences in the other measured variables in the supine position. There were no significant changes in SpO<sub>2</sub> or respiratory rate during the study period in either group. The tilt test was terminated before 10 min in three patients because of the imminent onset of syncope. These patients were included in the study and the last 2 min of data prior to return to supine were used as the summary variables for these patients.

MAP rose in every control during head-up tilt, with a mean rise ( $p < 0.005$ ) of 12.3 mmHg (range 3 to 30 mmHg). MAP decreased in every patient during head-up tilt ( $p < 0.005$ ) with a mean fall of 46.7 mmHg (range 1 to 98 mmHg). There was a rise in HR of 10.2 bpm (range 5 to 20 bpm) and 8.7 bpm (range -6 to +23 bpm) during head-up tilt in the control and patient groups respectively ( $p < 0.005$ ). There was a rise in HR in all controls during head-up tilt, whereas HR rose in only 14 patients, with no change in two and a reduction of 5 and 6 bpm in a further two.

In the control group head-up tilt was associated with a small mean fall in TOI of 2.6% ( $p < 0.05$ ), but in two volunteers TOI did not change and in one it increased by 3%. There were no significant changes in [Hb<sub>diff</sub>] and [HbT] but [Hb<sub>diff</sub>] decreased in eight volunteers and increased in two, and [HbT] decreased in six and increased in the remainder.

During head-up tilt in the patient group, postural hypotension was associated with a reduction in TOI in every patient ( $p < 0.005$ ), with a mean reduction of 8.6% (range 0.2–23.0%). There was also a significant decrease in mean [Hb<sub>diff</sub>] and [HbT] of 11.43 and 3.09  $\mu\text{mol l}^{-1}$  respectively ( $p < 0.005$ ). The small decrease in [HbT] is equivalent to a reduction in CBV of 0.2 ml/100 g. [Hb<sub>diff</sub>] decreased in 17 patients by 3.24 to 22.0  $\mu\text{mol l}^{-1}$

and rose in one by  $1.31 \mu\text{mol l}^{-1}$ . [HbT] also decreased in the same 17 patients by 0.54 to  $7.93 \mu\text{mol l}^{-1}$  and rose in the other by  $2.29 \mu\text{mol l}^{-1}$ .

## Discussion

In healthy subjects, the normal cardiovascular response to head-up tilt is a rise in MAP, HR and peripheral vascular resistance and a fall in cardiac output and stroke volume (Van Lieshout *et al* 2003, Chandler and Mathias 2002). The MAP and HR changes observed in the control group in our study are in keeping with these known responses. Primary autonomic failure encompasses a range of disease entities whose common feature is severe postural hypotension associated with a minimal rise in heart rate (Mathias 2003, Chandler and Mathias 2002). Significant reductions in blood pressure were observed in our patient group during head-up tilt, although there was an associated rise in HR.

The modest rise in MAP during head-up tilt in the control group was associated with a small reduction in TOI, which is almost certainly of no physiological or clinical significance. During head-up tilt, gravitational effects induce a rapid shift of blood to the lower parts of the body and, in healthy humans, neural reflexes come into play to maintain blood pressure and cerebral perfusion (Wieling *et al* 1998). These regulatory responses are primarily mediated via the sympathetic nervous system (Cencetti *et al* 1999) and, because cerebral blood vessels are richly innervated with adrenergic fibres, sympathetic activation causes a balanced large-vessel vasoconstriction and arteriolar/venule vasodilatation (Stewart 2002). This results in a net decrease in the arterial:venous cerebral blood volume ratio and is likely to account for the small reduction in TOI in the controls.

In the patient group, we observed a substantial fall in TOI that was temporally related to the reduction in blood pressure during head-up tilt. This is likely to represent an increase in oxygen extraction by the brain in an attempt to maintain oxygenation during a period of relative hypoperfusion (Van Lieshout *et al* 2003). If arterial oxygen content remains constant, cerebral tissue oxygen supply is predominantly a function of CBF. Although we did not measure CBF in this study, previous work has shown that, during postural hypotension, middle cerebral artery flow velocity (FV) measured using transcranial Doppler falls to a greater degree in patients with sympathetic failure compared to normal volunteers (Wieling *et al* 1998). Furthermore, symptomatic patients had greater postural reductions in MAP than asymptomatic patients, and this was associated with greater changes in middle cerebral FV and in cerebral oxygenation measured by NIRS. These data suggest that, during postural hypotension, symptomatic patients suffer a decrease in CBF close to the critical lower level of cerebral perfusion and that further reductions in blood pressure are sufficient to elicit symptoms of cerebral hypoperfusion.

Before concluding that the fall in TOI in the patients represents a reduction in oxygen delivery to the brain, it is important to exclude other potential causes. TOI is dependent on arterial oxygen content, but because  $\text{SpO}_2$  remained constant during the measurements, changes in arterial oxygen content can be excluded. A reduction in CBV would also explain the fall in TOI and, although the decrease in CBV recorded during our study was statistically significant, the actual reduction was modest (approximately  $0.2 \text{ ml}/100 \text{ g}$ ). We do not believe therefore that this could explain the substantial reductions observed in TOI. An increase in cerebral metabolic rate without a commensurate increase in oxygen delivery will also result in a reduction in TOI. Although, it is unlikely that cerebral metabolic rate changed during the period of our measurements, or that it is affected by posture, we cannot exclude this possibility. Finally, it is also possible that the brain may move downwards during head-up tilt and therefore less brain volume is interrogated by NIRS compared to the supine position.

Although we cannot exclude this possibility in this study, it seems an unlikely explanation because there were only modest changes in TOI in the volunteers during head-up tilt.

In our patient group, postural hypotension was associated with a reduction in  $[O_2Hb]$  ( $7.26 \mu\text{mol l}^{-1}$ ) similar in magnitude to that observed previously. In a study of patients with sympathetic failure, changes of  $-8.2$  and  $-5.9 \mu\text{mol l}^{-1}$  were recorded in symptomatic and asymptomatic patients respectively during the first 30 s after standing (Harms *et al* 2000). In association with the fall in  $[O_2Hb]$ , we observed a  $4.17 \mu\text{mol l}^{-1}$  rise in  $[HHb]$  and this change is also similar to that recorded previously (Harms *et al* 2000). Several studies have demonstrated that the changes in  $[O_2Hb]$  and  $[HHb]$  are related to changes in systemic blood pressure (Harms *et al* 2000, Colier *et al* 1997, Mehagnoul-Schipper *et al* 2000) and this has been confirmed by our study.

Previous studies have also demonstrated changes in cerebral oxygenation measured by NIRS during symptoms suggestive of cerebral hypoperfusion (Harms *et al* 2000, Colier *et al* 1997, Mehagnoul-Schipper *et al* 2000), but none have used TOI as the oxygenation variable. Colier *et al* (1997) measured a four-fold reduction in  $[Hb_{\text{diff}}]$  that was associated with fainting following head-up tilt in hypovolaemic volunteers, and suggested that this reflected a mismatch between cerebral oxygen supply and demand. Of note in this study is the predictive value of changes in  $[Hb_{\text{diff}}]$  for the onset of symptoms. In another study, the pattern and degree of change in  $[HbO_2]$  were able to predict vasovagal syncope (Szufladowicz *et al* 2004). The reduction in  $[Hb_{\text{diff}}]$  during head-up tilt in our controls was  $1.77 \mu\text{mol l}^{-1}$ , similar to the  $1.6 \mu\text{mol l}^{-1}$  change previously recorded in volunteers (Colier *et al* 1997). However, the fall in  $[Hb_{\text{diff}}]$  during postural hypotension in our patient group was  $11.43 \mu\text{mol l}^{-1}$ , more than three times greater than the changes recorded in symptomatic, hypovolaemic volunteers during head-up tilt (Colier *et al* 1997). This supports the hypothesis that the changes that we recorded during head-up tilt represent a mismatch between cerebral oxygen supply and demand. Changes in cerebral  $[Hb_{\text{diff}}]$  have previously been used to define a cerebral ischaemic threshold, when a change in  $[Hb_{\text{diff}}] > 6.8 \mu\text{mol l}^{-1}$  was associated with cerebral ischaemia identified by reductions in transcranial Doppler FV and typical EEG changes (Kirkpatrick *et al* 1998). Although the  $[Hb_{\text{diff}}]$  change in our patients was almost double this value, we cannot conclude that this indicates cerebral ischaemia because ischaemic thresholds have not been defined in this patient population. A study in elderly volunteers suggested that regulation of cerebral oxygenation changes with age (Mehagnoul-Schipper *et al* 2000) and it is equally likely that such compensatory changes occur in patients subjected to regular and profound postural stress. The relatively greater reduction in  $[Hb_{\text{diff}}]$  in our patient group compared to that observed previously in symptomatic healthy volunteers (Colier *et al* 1997) supports this notion.

The small reduction in  $[HbT]$  during head-up tilt in our patient group was similar to that measured in elderly patients subjected to postural stress (Mehagnoul-Schipper *et al* 2000), although the reduction in  $[HbT]$  (around  $3 \mu\text{mol l}^{-1}$  in our study) represents a very small fall (3–4%) compared to the estimated total cerebral blood volume of  $70\text{--}100 \mu\text{mol l}^{-1}$  (Levine *et al* 1994). However, these findings do suggest that compensatory vasodilatation (which would have resulted in an increase in  $[HbT]$ ) did not occur in response to the hypotension-induced reduction in cerebral perfusion, a finding also noted previously (Colier *et al* 1997).

Previous studies using NIRS to measure cerebral oxygenation during postural challenges have used older generations of NIRS equipment and there has been concern that these measurements might include a significant contribution from the extracranial circulation (Germon *et al* 1994). A recent study used the NIRO 300 to investigate cranial oxygenation changes during carotid surgery and demonstrated that the sensitivity of TOI to intracranial

changes was 87.5% with a specificity of 100% (Al-Rawi *et al* 2001). In contrast, the sensitivity and specificity to extracranial changes were 0%. These data confirm that TOI is a measure of cerebral tissue oxygenation and is a superior measure of cerebral oxygenation than the variables measured by previous generations of equipment, i.e. relative changes in [O<sub>2</sub>Hb] and [HHb]. We have therefore confirmed that there is a significant decrease in cerebral oxygenation during postural hypotension in patients with autonomic failure.

Another advantage of TOI over other methods of measurement of cerebral oxygenation is that it is a relatively focal measurement. In this study we measured TOI only in the frontal cortex and are therefore unable to comment about oxygenation changes that might have occurred in other parts of the brain. It is possible that these changes are not replicated throughout the whole brain and that the decrease in frontal cortical oxygenation occurred as a result of blood being diverted to other areas of the brain to preserve vital functions during postural hypotension. Although there is the option of multi-site monitoring with the NIRO 300, NIRS is unable to interrogate deeper areas of brain and we are therefore currently unable to investigate this hypothesis further.

NIRS allows measurement of dynamic changes in cerebral oxygenation and haemodynamics and we have confirmed that it is a reliable monitor during head-up tilt table testing in patients and healthy volunteers. Under many circumstances it would be preferable to make real-time measurements of changes in CBF, but the options for such measurements are very limited during head-up tilt table testing. It is not possible to use established techniques, such as positron emission tomography or magnetic resonance imaging, because of the inability to change the table angle in the scanner. Although changes in FV can be measured using transcranial Doppler, these offer only a surrogate for changes in CBF. In the absence of reliable measures of CBF, NIRS therefore provides a useful measure of real-time changes in cerebral oxygenation and haemodynamics during dynamic changes, such as head-up tilt table testing.

NIRS is a simple, non-invasive technique that can measure continuously cerebral oxygenation and haemodynamics. TOI represents a measure of the balance between oxygen supply and demand in the superficial cortex with a high degree of sensitivity and specificity. We have demonstrated that postural hypotension in patients with primary autonomic failure is associated with a greater reduction in absolute cerebral tissue oxygen saturation than in healthy age-matched controls subjected to the same postural stress. NIRS is a useful clinical tool in the evaluation of this patient group and may also assist assessment of the efficacy of therapeutic interventions.

#### *Conflicts of interest*

None

#### *Ethics approval*

This study was approved by the Joint Research Ethics Committee of the Institute of Neurology and the National Hospital for Neurology and Neurosurgery.

#### **Acknowledgment**

Ilias Tachtsidis was funded by an MRC/EPSRC Interdisciplinary Research Collaboration.

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