CEREBRAL PERFUSION IN SUBJECTS WITH ORTHOSTATIC INTOLERANCE

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INTRODUCTION
Orthostatic intolerance is characterized by symptoms of lightheadedness, tiredness, palpitations, blurred vision and occasionally, by loss of consciousness during standing, which are relieved upon recumbency. These symptoms are suggestive of cerebral hypoperfusion, yet they occur in the absence of orthostatic hypotension. We therefore evaluated cerebral vasoregulation in patients with OI. The specific objectives were 1) to evaluate if excessive cerebral vasoconstriction occurs in OI during head-up tilt 2) to find out whether hypocapnia could be the mechanism for this phenomenon 3) to investigate whether an impaired cerebral autoregulation (CA) is present in these patients. We hypothesized that cerebral hypoperfusion is present and related to changes in CO₂ and is not due to impaired CA. Therefore, we undertook a series of studies to evaluate the effect of head-up tilt on respiration, CO₂, cerebral blood flow and systemic cardiovascular responses in OI patients and healthy controls. We also evaluated the effect of correction of CO₂ on the recorded abnormalities. Finally, we evaluated CA using the Valsalva maneuver (VM) combined with a new analytical method.

CURRENT STATUS OF RESEARCH

Methods

Subjects: Thirty patients suffering from orthostatic intolerance (OI) and seventeen healthy subjects participated in the study. OI was defined as an excessive orthostatic heart rate (HR) increment of at least 30bpm and an absolute standing HR of at least 100bpm for >60% of the duration of the 10 min tilt-table test associated with symptoms of OI including dizziness, lightheadedness and blurry vision.

Protocols: After a period of rest, participants underwent a head-up tilt to 80° for 10 minutes. Eight patients underwent an additional tilt study with hyperventilation for 4 minutes, followed by CO₂ rebreathing for 5 minutes. Participants also performed three VM in the supine position with recovery periods of at least 3 minutes between maneuvers.

Data Acquisition and Analysis: Time series of RR-intervals, systolic (SBP), diastolic (DBP) and mean (MBP) blood pressure (BP) were acquired beat-to-beat. HR was calculated from RR-intervals. BP was measured from the finger using a photoplethysmographic method (Finapres). Impedance Cardiography was measured using BOMED NCCOM3 R-7, Irvine, CA. Respiration was measured using a nasal thermistor and sampled at 4 Hz. Endtidal CO₂ was derived from the expiratory air flow using Puritan Bennett 254 airway gas monitor calibrated with 5% CO₂.

Cerebral blood flow velocity (CBFV) was measured using transcranial Doppler (TCD) (Multigon Industries, New York). The left middle cerebral artery was insonated from the anterior temporal window. The TCD-probe (2 MHz) was positioned to record the maximal velocity and fixed in the desired angle using a specially designed teflon probe holder. Systolic (CBFV_S), diastolic (CBFV_D) and mean (CBFV_M) CBFV were detected from the analog signal on a beat-to-beat basis. Cerebrovascular resistance (CVR) was estimated as MBP/CBFV_M.

CA was assessed using a new analytical method: The resistance area product (RAP) of cerebral vascular resistance was calculated on a beat-to-beat basis from the slope of the best linear fit between the upstroke of the raw signal of BP and CBFV of each cardiac cycle. An autoregulatory index (ARI) was then calculated as the slope of the linear fit between beat-to-beat values of RAP and MBP during the VM. A higher ARI stands for a greater change of RAP with the same change of BP and therefore better CA.

Results

Clinical Characteristics: Gender and age distribution of patients (25 women and 5 men, aged from 21 to 44 years; mean 31.3±1.2 years) and controls (13 women and 4 men; aged from 20 to 41 years; mean 30±1.6 years) were statistically not different. All patients experienced typical symptoms of orthostatic intolerance such as dizziness, lightheadedness and fatigue. None of the controls reported symptoms of orthostatic intolerance during head-up tilt.
Head-up Tilt: All OI patients had increased supine HR (p<0.001) and cardiac output (CO, p<0.01) when compared with the control group. In response to head-up tilt, OI patients had a significantly greater HR (p<0.001), CO (p<0.001), and lower CO$_2$ (p<0.01) than controls. CBFV was significantly lower during tilt in OI. In contrast, CVR increased during tilt in OI patients (p<0.01), but not in controls. TPR significantly increased with tilt in controls (p<0.05) but not in OI and TPR values during tilt were lower (p<0.01) than in controls.

In controls, respiratory frequency and CO$_2$ did not significantly change during tilt. In contrast, OI patients underwent a significant degree of hypocapnia during tilt (p<0.01). The mean respiratory frequency during tilt of 0.25 Hz in OI did not differ significantly from that of controls (0.23 Hz), although the range of respiratory frequencies was wider during tilt in OI (from 0.06 to 0.39 Hz) than in controls (0.12 to 0.31 Hz). In OI patients, spontaneous rhythmic breathing was interrupted by episodes of deep breaths, faster respiratory rate, irregular respiration or apneas.

To quantify the relationship between CO$_2$ and CBFV and HR we regressed changes in CO$_2$ against changes in CBFV$_M$ and in HR in these patients with OI and in controls. CBFV$_M$ significantly correlated with the level of CO$_2$ with coefficient of determination >0.8 (p<0.0001) in all patients. Linear regression was used to quantitate the relationship. For OI, the relationship between CBFV$_M$ and CO$_2$ had a coefficient of determination of 0.93, and the slope was 1.46 cm/s/mmHg. A significant regression was also found between HR and CO$_2$; coefficient of determination was 0.86, and slope -0.54 cm/s/mmHg. Corresponding values for controls were: CBFV$_M$ vs CO$_2$: R$^2$ = 0.86, p<0.001; HR vs CO$_2$, R$^2$ = 0.72, p<0.0001. There was no significant difference in the slopes for OI and controls.

Hyperventilation during head-up tilt induced significant reductions of CBFV and CO$_2$ and a significant increase in HR and CVR. BP was not significantly different. CBFV and CVR rapidly improved within the first 2 minutes of CO$_2$ rebreathing. HR was also significantly lower during CO$_2$ rebreathing.

Cerebral Autoregulation: Changes of RAP closely followed changes of MBP during the VM in all participants except for one control with poor correlation between these parameters who was excluded from further analysis. R$^2$ was greater than 0.5 for all other participants (R$^2$ = 0.75±0.14). The correlation was significantly better in patients (R$^2$ = 0.81±0.08) than controls (R$^2$ = 0.64±0.15, p<0.05). ARI was not significantly different between patients (0.0131±0.0063 cm$^{-1}$s) and control group (0.0140±0.0040 cm$^{-1}$s).

Conclusion
Cerebral vasoconstriction occurs in OI during orthostasis, which in significant part is due to hypocapnia resulting from hyperventilation with an increase in depth but not rate of respiration. CA however is not impaired in patients with OI.

FUTURE PLANS
We plan to further explore mechanisms of cerebral vasoregulation in patients with orthostatic intolerance and to further validate our improved method to evaluate dynamic CA.

INDEX TERMS
OI, POTS, cerebral autoregulation, vasoregulation, hypocapnia, blood flow velocity, hyperventilation, transcranial Doppler, head-up tilt

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