Cerebral and cardiovascular dynamics in response to orthostatic stress
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Chapter 4.1

Cerebrovascular and cardiovascular responses associated with orthostatic intolerance and tachycardia

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Introduction

The postural tachycardia syndrome (POTS) (238) (also known as orthostatic tachycardia syndrome (109); or orthostatic intolerance (251)) is characterised by symptoms, including fatigue, light-headedness or dizziness, that occur when the patient (free of orthostatic hypotension or evidence of cardiac or metabolic disease) assumes the standing position (31, 152, 251). POTS has replaced previous labels, such as DaCosta’s syndrome, soldier’s heart, and neurocirculatory asthenia (317). Symptoms of orthostatic intolerance are often found in patients who have chronic fatigue syndrome (237, 251); however, an overt relationship of idiopathic orthostatic intolerance to chronic fatigue syndrome has not been shown (59, 260). Postural tachycardia, an increase in heart rate by >30 beats/min (238), is a typical finding in POTS and is attributed to a compensatory hyperadrenergic orthostatic response to a variety of conditions. Central hypovolemia by excessive gravitational blood pooling, possibly related to or aggravated by selective impairment of sympathetic veno-motor function, has been proposed to explain the tachycardia (109, 153, 264). The associated tachycardia may also be a manifestation of a mild form of acute autonomic neuropathy with decreased norepinephrine clearance during standing and increased sensitivity to adrenergic agonists (110, 127); in a patient with a hyperadrenergic state associated with orthostatic intolerance, an exon 9 mutation of the norepinephrine-transporter gene, with impaired synaptic norepinephrine clearance was identified (251).

In a patient who had orthostatic intolerance, we report the systemic cardiovascular and cerebral hemodynamic changes associated with the patient’s postural symptoms and recovery. A 33-year-old woman with an 8-months history of orthostatic dizziness, fatigue, exertional dyspnea, and palpitations was diagnosed elsewhere as having sympathetic failure and referred for evaluation of this orthostatic disorder. Miction, bowel movements, and sweating were reported to be normal. The patient was examined at admission and after 6 months, when she had regained normal orthostatic tolerance.
Methods

Measurements and Analysis

Transcranial Doppler ultrasound (TCD) determined right middle cerebral artery mean blood flow velocity (MCA $V_{mean}$) was measured (Multidop X2, DWL, Sipplingen, Germany) through the posterior temporal “window” (2). After the optimal signal-to-noise ratio was obtained, the probe was covered with an adhesive ultrasonic gel (Tensive, Parker Laboratories Inc., Orange, NJ, USA) and secured with a head band. The end-tidal carbon dioxide (CO$_2$) tension (P$_{ET}$CO$_2$) was recorded (at the patient’s second examination) as a reflection of the arterial CO$_2$ tension (319) and measured by an infrared CO$_2$ analyser (Hewlett Packard 78345A, Roeblingen, Germany).

Blood pressure was determined at the middle finger of the patient’s non-dominant arm with a Finapres™ model 5 (Netherlands Organisation for Applied Scientific Research, Biomedical Instrumentation, TNO-BMI, Amsterdam) (60, 118). The cuffed finger was placed in the anterior axillary line at the level of the heart. The signals of arterial pressure, the spectral envelope of the MCA velocity, P$_{ET}$CO$_2$ and marker were A/D converted at 100 Hz and stored on hard disk for off-line analysis. Variables were also recorded on a thermo-writer (Graphtec WR7700™, Western Graphtec Inc., Irvine, CA) for on-line inspection.

Heart rate (HR) was obtained from the pulse pressure interval. Beat-by-beat changes in stroke volume (SV) were computed by modelling flow from the arterial pressure simulating a non-linear, time-varying model of the aortic input impedance (303). The flow waveform was integrated during the arterial systole to derive SV (90, 119, 303). The $V_{mean}$ and mean arterial pressure (MAP) were computed as, respectively, the integral of the maximal frequency shifts and of the arterial pressure wave over one beat divided by the corresponding beat interval.

Cerebrovascular resistance (CVR) was defined as the ratio of MAP to MCA $V_{mean}$. Cardiac output (CO) was defined as the product of SV and HR, and total peripheral vascular resistance (TPR) was MAP divided by CO. MAP, HR, $V_{mean}$, and P$_{ET}$CO$_2$ were expressed in absolute values. The average of the supine resting values for SV, CO and TPR at the first examination were set at 100% (control) and changes from control were expressed in percentages.

At 09.00 hours, after the patient had a light meal without caffeine-containing beverages, the instruments were attached to the patient in a room with an ambient temperature of 22°C. After a test run and ten minutes of rest in the supine position, the patient stood up and remained in that position without leg movements until orthostatic symptoms developed.
Results

A normal HR response to forced breathing indicated intact afferent, central and vagal efferent baroreflex pathways; a normal blood pressure response to standing up indicated preservation of sympathetic arteriolar function (308). Baroreflex sensitivity (as gauged from the initial blood pressure overshoot on standing) was 10.2 ms-mmHg⁻¹. After two minutes of unaided standing, the patient reported dizziness. HR had increased from 66 to 91 beats.min⁻¹ and MAP from 70 to 79 mmHg (+13%) with a large reduction in SV (-59%) and CO (-44%) (Figure 1, left panel). After eight minutes in standing position, the patient became pale with profuse sweating and presyncopal complaints. At that instant, MAP (74 mmHg) was not different from the supine value but HR had increased further to 107 beats.min⁻¹ and the reductions in SV (-69%) and CO (-50%) were larger. The MCA V_mean decreased from 57 to 41 cm·s⁻¹ after two minutes of standing and further to 31 cm·s⁻¹ after eight minutes standing. All values returned to control levels after the patient was in the supine position for one min. A diagnosis of idiopathic orthostatic intolerance was made. The patient was instructed to increase salt intake in her diet and to avoid supine resting during the daytime, and she began a reconditioning program that included leg muscle strengthening exercise. By following these instructions, she regained orthostatic tolerance, with an unrestricted standing time; after six months, she was able to resume her former daily activities, with no further orthostatic symptoms.

At the six-month examination, the supine MCA V_mean was larger (79 cm·s⁻¹), as were MAP (76 mmHg) and CO (+15%) (Figure 1, right panel). The HR increase after eight minutes of standing was normal, (+5 versus +41 beats.min⁻¹) with an increase in MAP (to 93 mmHg; +22%) and a larger pulse pressure (54 versus 35 mmHg). The supine P_ETCO₂ decreased but did not change during standing (29 versus 28 mmHg). The orthostatic reductions in MCA V_mean (–13 versus –26 cm·s⁻¹), SV (–39%) and CO (–33%) were small and the upright CVR was low (1.41 versus 2.39 mmHg·cm·s⁻¹).

Discussion

Orthostatic intolerance is recognised as a disorder of blood pressure regulation with a heterogeneous outcome (127, 222). This report documents the postural systemic cardiovascular and cerebral blood velocity responses in a patient with reversible orthostatic intolerance.

A disproportionately greater effect of postural stress on HR than on blood pressure is the common finding in orthostatic intolerance (31, 152, 251). This greater effect may be an expression of an abnormal functional distribution of central sympathetic tone to the heart and vasculature (63), but, in the current case, the recovery of the patient renders this interpretation
Figure 1.
Postural changes in middle cerebral artery blood velocity and systemic hemodynamics in a patient with orthostatic intolerance

**Left panel**: Note the excessive reduction in CBFV during the initial examination.

**Right panel**: Normal orthostatic tolerance six months after initial examination. **Broken lines**: supine reference values at initial examination.

Rectangle indicate the duration of standing. BP: Blood pressure; CBFV: cerebral artery blood velocity; HR: Heart rate; SV: Stroke volume; CO: Cardiac output; TPR: total peripheral vascular resistance

unlikely. Changes in plasma volume are correlated with orthostatic intolerance (84) and the patient history of physical inactivity and the exaggerated postural decrease in SV suggest hypovolemia as a result of prolonged inactivity, aggravated by loss of lower-extremity muscle tone. Reduced skeletal muscle tone favours orthostatic venous pooling (169) and moderate endurance training improves orthostatic tolerance in deconditioned persons and increases their plasma volume (49, 75, 236). The improvement in this patient supports the idea of a therapeutic role for reconditioning measures in orthostatic intolerance.

Standing induces a sympathetically mediated increase in HR and systemic vasoconstriction with a reduction in MCA V_{mean} (22, 89, 150, 213). A reduced MCA V_{mean} can be interpreted either as a decrease in cerebral blood flow or as an increase in the diameter of the MCA. The MCA diameter is reported stable over a range of arterial pressures by orthostatic stress, as simulated by lower body negative pressure, suggesting that the MCA is not involved in regulation of CVR (250). We therefore consider that, in the conditions of this study, the
changes in MCA $V_{\text{mean}}$ may be interpreted to reflect changes in cerebral blood flow. The postural reduction in MCA $V_{\text{mean}}$ is larger in the young than noted for elderly subjects (150), with cerebral oxygenation following this pattern, suggesting that the postural reduction in cerebral perfusion in young persons is not negligible (89). Orthostatic dizziness was associated with trivial changes in blood pressure but with a large reduction in CO (50%) and a 46% reduction in MCA $V_{\text{mean}}$, compatible with an increase in CVR. An increased CVR associated with syncope may occur in the absence of overt hypotension (79). In contrast, functional derangement in vasovagal syncope is a withdrawal of muscle sympathetic nerve activity (297) with a decrease in blood pressure and followed by a decrease in cerebral blood flow at a reduced CVR (239). In subjects with orthostatic intolerance a postural increase in CVR is a consistent finding (80, 152, 185, 239). Expression of CVR as the ratio of MAP to MCA $V_{\text{mean}}$ assumes that the cerebral blood velocity reflects changes in the smaller cerebral vessels rather than in the MCA, implying cerebral arteriolar vasoconstriction (79) with a reduction in cerebral perfusion. This assumption is supported by observation of healthy subjects during orthostatic stress, in which it is found that cerebral oxygenation is related to cerebral perfusion (as determined by transcranial Doppler), also with an insignificant reduction in blood pressure (89, 162).

A slight decrease in $P_{ET\text{-}CO_2}$ during orthostatic stress is common (171). The reduction in supine $P_{ET\text{-}CO_2}$ in this patient may account for approximately 15% of the reduction in MCA $V_{\text{mean}}$ (221). Although at the second examination $P_{ET\text{-}CO_2}$ did not change when the patient stood, we cannot exclude the possibility that at the first examination a postural reduction in $P_{ET\text{-}CO_2}$ may have contributed to compromising cerebral perfusion.

In orthostatic intolerance, the symptoms of dizziness and light-headedness are indicative of cerebral hypoperfusion (185). The greater postural increase in CVR and HR in orthostatic intolerance was proposed to reflect an increased sympathetic tone (63) with impaired cerebrovascular autoregulation or triggering of abnormal baroreceptor responses during orthostatic stress (80, 108, 152). The reduction in MCA $V_{\text{mean}}$, together with the patient’s complaints and symptoms indicated a compromised cerebral perfusion, and although MAP was within the range associated with cerebral autoregulation, the lower MAP at the first examination may have contributed to the lower MCA $V_{\text{mean}}$ (93). Cerebral blood flow may also be affected when CO decreases to less than half the supine value when there is competition for perfusion between different organs (94). The effect of a limitation of the ability to increase CO on MCA $V_{\text{mean}}$ was demonstrated in patients with atrial fibrillation (101) and in healthy persons with cardio-selective $\beta$-adrenergic blockade (102). Also, when healthy persons stand, CO decreases approximately 20%, and cerebral blood velocity and oxygenation decrease even though the changes in MAP, even at the level of the brain, are trivial (89). Therefore, cerebral blood flow is controlled by autoregulation, partial pressure of arterial CO$_2$ tension and local metabolic activity (142); but CO seems to be equally important. In this patient who had intact baroreflex control and no postural decrease in blood pressure, the low MCA $V_{\text{mean}}$ at the
first examination seemed to be related to excessive postural reduction in CO rather than to a lower MAP. This suggests that the symptomatic reduction in cerebrovascular conductance is to be interpreted as being an adaptive response to a critical limitation of systemic blood flow, rather than to a derangement of cerebral autoregulation. These changes may be reversed by reconditioning measures.