Cerebral haemodynamic response to acute intracranial hypertension induced by head-down tilt

Daniele Bosone⁠¹
Vesile Ozturk⁠²
Silvestro Roatta⁠²,⁠¹
Anna Cavallini⁠¹
Piera Tosi⁠¹
Giuseppe Micieli⁠¹

¹ Neurovascular Unit, IRCCS C. Mondino Institute of Neurology, Pavia, Italy
² Dokuz Eylul University, Izmir, Turkey
³ Department of Neuroscience, Physiology Division, University of Turin Medical School, Turin, Italy

Reprint requests to: Dr Daniele Bosone
Neurovascular Unit, IRCCS C. Mondino Institute of Neurology
Via Ferrata, 6 - 27100 Pavia - Italy
E-mail: daniele.bosone@mondino.it

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Summary

The aim of this study was to evaluate, in a context of general inhibition of the sympathetic nervous system, the cerebral haemodynamic response to -30° head-down tilt (HDT), a manoeuvre that produces an increase in intracranial arterial pressure. Nineteen healthy subjects were studied according to the following protocol: 10 min lying in supine position, 10 min HDT, 10 min recovery. Inhibition of the sympathetic system was confirmed by the decrease in heart rate (-3.6 bpm) and arterial blood pressure (-5.9 mmHg, p<0.05) in the late phase of the test. Blood velocity and blood pulsatility index initially increased (+3.2 cm s⁻¹ and +9% respectively, p<0.01) then returned towards baseline before the end of HDT, while the cerebrovascular resistance index (=arterial blood pressure/blood velocity) dropped significantly and remained below control level (-7%, p<0.01) throughout the test. The changes in both these indices were opposite to those reported in several sympathetic activation tests, such as the handgrip and cold pressor tests. Conversely, arterial pressure at cranial level increased during HDT (as it also does during sympathetic activation tests), due to the development of a hydrostatic pressure gradient between heart and brain. Therefore, the effects observed on the pulsatility and resistance indices are not secondary to the increase in intracranial arterial pressure. It is suggested that the changes in these cerebrovascular indices are mediated by a reduction of sympathetic tone that presumably involves the cerebral as well as the peripheral vascular bed.

KEY WORDS: cerebral circulation, head-down tilt, posture, sympathetic nervous system.

Introduction

The high temporal resolution and non-invasiveness of the transcranial Doppler (TCD) technique make it well suited for investigating fast transients occurring in cerebral haemodynamics. TCD has been widely adopted to study the haemodynamic response to acute hypotensive stimuli possibly associated with syncope, both evoked by head-up tilt (1) and by lower body negative pressure (2,3). Conversely, the acute intracranial hypertensive state has been investigated much less. In the few studies published to date, this state was obtained through sympathetic activation tests such as handgrip (4,5), mental stress (6) and cold pressor tests (7). A common finding under these experimental conditions was an increase in cerebrovascular resistance and a decrease in the cerebral artery pulsatility index (PI), the latter probably reflecting a decrease in compliance of the cerebrovascular bed (7-9). Both these effects, as well as the increase in cerebral blood velocity that may also be observed under these circumstances, have often been attributed to an increased constrictive action exerted by the sympathetic system on cerebral vessels.

The aim of this study was to investigate a different model of acute intracranial hypertension: a -30° head-down tilt (HDT). This test produces a hypertensive state that is not mediated by the sympathetic system, but instead related to the development of a hydrostatic pressure gradient between brain and heart. In fact, HDT causes a blood shift from the limbs towards the chest and the head, therein producing increased hydrostatic load of blood. At the same time the sympathetic system undergoes a persistent reflex inhibition due to cardio-pulmonary and baroreceptor loading (10,11).

Comparison of the haemodynamic response to HDT with responses to other sympathetic activation tests, such as the handgrip test and cold pressor test (CPT), will possibly help to clarify which aspects may be attributed to increased sympathetic outflow to cerebral vessels and which may just be secondary to the increase in intracranial arterial pressure (IAP). Particular attention will be paid to the haemodynamic transients occurring at the beginning and at the end of HDT since these may reveal the initial effect of the postural change and the possible occurrence of subsequent corrective mechanisms.

Materials and Methods

Nineteen healthy subjects (11 women, 8 men) with no history of neurological disease or other medical disorder were studied. They were familiarised with the protocol and all gave their informed consent to participate in the study.
All the subjects were tested in the mid-afternoon in a quiet, dimly-lit environment kept at a constant temperature (22°C) and were requested to breathe regularly. Tiltling was performed manually using an Akron 8632 tilt table (Akron Therapy Products Ltd, Ipswich, UK) according to the following protocol: after experiencing the tilting manoeuvre 2-3 times, the subject remained in a supine position for 10 min, before being tilted 30° head-down for 10 min, and then returned to the horizontal supine position for the next 10 min. The tilting manoeuvre was completed in 3-5 s. We chose not to use a faster tilting speed in order to avoid causing the subject discomfort, which would evoke an arousal reaction and thus sympathetic activation.

Arterial blood pressure (ABP) and heart rate (HR) were continuously recorded throughout the experiment, using a photoplethysmographic device (Finapres 2300, Ohmeda, USA); the finger cuff was wrapped around the subject’s right middle finger kept at heart level. A mercury sphygmomanometer was also used to measure systolic and diastolic blood pressure once every 30 s; mean ABP was calculated as (systolicABP + 2*diastolicABP)/3.

A TCD system (DWL Multidop X, Erlingen, Germany) was used to monitor continuously blood velocity in both middle cerebral arteries (V_{MCA}). The device measures the maximum instantaneous blood velocity (cm/s) and does not provide for angle correction. Two pulsed-wave Doppler probes (2MHz) were positioned at the transtemporal acoustic windows by means of a special head device which kept them in place throughout the trial. Both V_{MCA} and ABP signals were digitally acquired by the TCD device (sampling frequency 57.4 Hz) and saved for off-line processing. The device also allowed the operator to set software markers signalling both start (Marker 1) and end (Marker 2) of HDT.

Off-line analysis of the recordings was performed using customised software developed under the LabVIEW programming environment (National Instruments, Austin TX, USA); the off-line processing included computation of the pulsatility index\(^{(1)}\) according to the formula PI=(systolic V_{MCA} - diastolic V_{MCA}) / mean V_{MCA}, estimation of the signal-to-noise ratio, and digital filtering of the signals. Time averages for ABP, HR, V_{MCA}, and PI were computed in four 100 s intervals defined as follows (see also Fig. 1):

i) Baseline: from 130 to 30 s before beginning of HDT;
ii) HDT1: 30-130 s after beginning of HDT;
iii) HDT2: 130-30 s before the end of HDT;
iv) Post: 30-130 s after the end of HDT.

The ABP/V_{MCA} index\(^{(2)}\) was then obtained from the ratio of the ABP and V_{MCA} time averages computed in the same intervals. These estimates were then averaged among all subjects and the values for the last three intervals were compared to baseline. The significance of changes was evaluated by a one-way ANOVA for multiple comparisons, combined with the 2-tail Dunnett’s test. Note that when the subject is in the tilted position (at -30°), IAP can be calculated by adding 12-16 mmHg to ABP. This amount (12-16 mmHg) corresponds to the hydrostatic pressure gradient that develops between the heart and brain in the presence of a 30-40 cm heart-brain distance. The resistance index ABP/V_{MCA} was computed without any correction since the additional hydrostatic pressure applies equally to both the arterial and venous sides of the cerebrovascular bed, and does not affect perfusion pressure.

In order to highlight the haemodynamic transients associated with the change in posture the average blood velocity response was computed from the low-pass filtered V_{MCA} recordings. The cut-off frequency of the low-pass filter was set at 0.5 Hz in order to eliminate, as far as possible, cardiac cycle-related oscillations (freq.>1 Hz) while conserving the slower changes in mean blood velocity.

The experiments were carried out under the approval of the Ethics Committee of the IRCCS C. Mondino Institute of Neurology and in compliance with current national laws.

**Results**

The photoplethysmographic device failed to produce a continuous ABP recording due to movement-related artefacts during the tilting manoeuvres in 6 out of 19 subjects. For this reason the more reliable measures obtained from all subjects through the mercury sphygmonometer were used for the analysis and for the computation of ABP/V_{MCA}; ABP average estimates were obtained from the average of the 3-4 values produced by the mercury sphygmonometer in each interval considered. Figure 1 shows typical recordings from one subject and displays the four phases of the test selected for the analysis i.e., Baseline, HDT1, HDT2 and Post. Average values of each parameter in these different phases, along with significance of the difference from Baseline, are listed in Table I. Average blood pressure usually showed fast and large transients associated with the tilting manoeuvre which resulted in a non significant decrease in the first phase -3.4 mmHg (HDT1, n.s.) reaching significance in the second phase (HDT2: -7%). Due to the development of the hydrostatic pressure gradient, IAP was found to be increased by 9-13 mmHg during HDT1.

Heart rate (HR) showed a slight decreasing trend which did not reach significance (HDT2: -4%, n.s.). Transient increases in HR were observed in the majority of the subjects immediately after the postural changes, i.e., at the beginning and end of HDT.

No difference was observed between blood velocity (V_{MCA}) recordings from left and right MCA, therefore the channel exhibiting no movement artefacts and a better signal-to-noise ratio was chosen for the analysis. The data set used for the analysis thus included 9 velocity recordings from the right MCA and 10 from the left.

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\(^{(1)}\) PI is an empirical index often related to cerebrovascular resistances but potentially affected by other variables, including compliance of the vascular bed (7-9).

\(^{(2)}\) ABP/V_{MCA} normally indicated with the acronym CVR for cerebrovascular resistance, is a resistance index based on the assumptions that blood velocity is proportional to blood flow, i.e., the cross-sectional area of the insonated vessel does not change, and the ABP is a good approximation of the perfusion pressure of the vascular bed.
MCA. $V_{\text{MCA}}$ exhibited, on average, a mild increase in HDT1 (+4%) that lasted several minutes and then slowly returned towards baseline. Attention was then focused on the transient $V_{\text{MCA}}$ changes occurring immediately after the tilting manoeuvres. At HDT onset, the average $V_{\text{MCA}}$ trace exhibited a clear transient increase of about +5 cm s$^{-1}$, recovered within 15-25 s (Fig. 2A). Instead, a diphasic response (+5, -6 cm s$^{-1}$) lasting about 40 s occurred when returning to the horizontal position, followed by a slow return to baseline lasting 2-3 minutes (Fig. 2B). The PI also exhibited a mild increase (HDT1: +8.7%) while ABP/$V_{\text{MCA}}$ significantly decreased during both phases of HDT (HDT1: -7.2%; HDT2: -7.6%).

**Discussion**

In the present study, HDT was adopted as a model of acute intracranial hypertension in a context of inhibition of the sympathetic nervous system. This manoeuvre was shown to increase IAP and to affect the cerebral circulation, producing an increase in PI and a decrease in ABP/$V_{\text{MCA}}$. Inhibition of the sympathetic system during HDT is documented by several studies in the literature that have reported decreased muscle sympathetic nerve activity and total peripheral resistance (11), as well as decreases in plasma norepinephrine (10) and in HR (12,13); here, this inhibition was confirmed by a slight decrease in ABP while the increase in IAP, provoked by the development of the hydrostatic pressure gradient between heart and brain, was found to be in the range 9-13 mmHg.

It is interesting to compare these results with those previously observed during the CPT (7) which, in a context of generalized sympathetic activation, produced a comparable increase in IAP (18 mmHg) but opposite...
changes in the haemodynamic parameters, namely a considerable decrease in PI accompanied by a marked increase in ABP/V_{MCA}. This haemodynamic pattern is not peculiar to CPT, on the contrary it has been found in several other sympathetic activation tests (5,6,14).

The results of these comparisons have several implications: i) changes observed in PI and ABP/V_{MCA} are not secondary to the increase in IAP, which was of comparable magnitude in the two tests (CPT and HDT); ii) consequently, the decrease in PI and increase in ABP/V_{MCA} observed in sympathetic activation tests (CPT) are likely to be effects of increased sympathetic drive to cerebral vessels as suggested elsewhere (7); iii) accordingly, the increase in PI occurring during HDT, suggests an increased compliance of the cerebrovascular bed, probably mediated by a decrease in sympathetic tone; a similar effect has been observed during -80° HDT, although the authors interpreted it as an effect of increased cerebrovascular resistance, possibly mediated by the myogenic mechanism (13).

The HDT is, in fact, a complex stimulus and the involvement of other mechanisms (namely, metabolic and myogenic) in the cerebral haemodynamic response must be considered. When HDT is performed starting from the horizontal (supine) position, blood pressure increases by 12-16 mmHg (in the -30° case), with respect to the values at heart level, in both the arterial and the venous sides of the cerebrovascular bed; therefore cerebral perfusion pressure (CPP=IAP-IVP), is not primarily influenced by the hydrostatic gradient itself and cerebral blood flow should remain largely unaffected. Consequently, the metabolic mechanism is not thought to play a major role in the cerebral hemodynamic adaptation to HDT. In addition, no influence on the results is expected from arterial pCO\_2 since end-tidal pCO\_2 was shown to remain unchanged throughout a 20-minute -30° HDT (15), as well in response to a milder HDT (16); moreover, the increase in pCO\_2 is known to produce the opposite effect on PI, i.e., a decrease rather than an increase, as we observed during HDT (17).

As for the myogenic mechanism, the same hydrostatic gradient that affects the arterial and venous blood streams also affects the cerebrospinal fluid, thereby contributing to the rise in intracranial pressure during HDT (18-20). This effect counteracts the variation in transmural pressure in brain vessels (18), which means that the involvement of the myogenic mechanism (dependent on transmural pressure changes) is also likely to be small.

Averaging V_{MCA} recordings proved useful to unmask haemodynamic transients, lasting several tens of seconds, occurring at the beginning and end of the manoeuvre. These transients, provoked by the imposed postural perturbation, revealed the lack of a feed-forward control of cerebral circulation. In fact, due to the rather slow speed of tilting adopted, they were rather small in amplitude and could simply reflect the passive response of the vascular network to the blood displacement that affects ABP and cardiac output (11,21).

However, the involvement of cerebral blood flow autoregulatory mechanisms has also been suggested (13,22) and cannot be entirely excluded. Finally, the possibility that the observed changes in V_{MCA} simply reflect a small change in cross-sectional area of the MCA at the level of insonation rather than any real change in underlying cerebral blood flow should also be considered (23).

In conclusion, these results suggest that cerebral sympathetic pathways, as well as extracranial pathways, are inhibited during HDT and that the haemodynamic changes recorded are mostly due to passive mechanisms; moreover, the results indirectly support the idea that the decrease in PI associated with the increase in ABP/V_{MCA} found during CPT may be an indicator of the sympathetic activation at cerebral level.

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References

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