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Cerebral Syncope: Insights from Valsalva Maneuver

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Key Words
Cerebral syncope · Valsalva maneuver · Head-up tilt test · Transcranial Doppler · Autoregulation

Abstract
Background and Purpose: Cerebral syncope refers to a loss of consciousness associated with cerebral vasoconstriction in the absence of systemic hypotension. The diagnosis of cerebral syncope could be established by the head-up tilt test (HUT) and transcranial Doppler ultrasonography. Valsalva maneuver (VM) permitted assessment of cerebral autoregulatory function by provoking blood pressure (BP) changes. To develop a path-physiological approach for vasomotor reactivity of cerebral syncope, the authors combined these maneuvers (HUT/transcranial Doppler/VM). ***Methods:*** Using transcranial Doppler ultrasonography, we simultaneously recorded systemic arterial BP in the radial artery and flow velocities in both middle cerebral arteries (MCAFV) in 10 cerebral syncope patients (4 males and 6 females, 35.24 ± 4.5 years old) during the Valsalva maneuver. ***Results:*** The characteristic changes in BP (phases I–IV) were seen in all subjects, accompanying distinct changes in cerebral blood flow velocity. The BP/heart rate responding to VM was within normal limit in all subjects. There was no orthostatic hypotension. Instead, BP increased during the tilting test in 2 subjects (20.00%). The MCAFV dropped 25.4 ± 2.3% from baseline. Abnormal flattening of MCAFV during late phase II (IIb), the paradoxical drop of flow velocity despite restoration of BP, was noted in 9 subjects (90.00%). ***Conclusion:*** During VM there are complex changes in relevant cardiovascular and cerebrovascular variables within a short time span. The paradoxical drop of MCAFV during phase IIb was the result of complex parameters. Among them, a failure in cerebrovascular resistance reduction and even paradoxical vasoconstriction might further compromise cerebral perfusion pressure and lead to syncope.

Background and Purpose

Cerebral syncope refers to a loss of consciousness associated with cerebral vasoconstriction in the absence of systemic hypotension [1]. A diagnosis of cerebral syncope could be established by the head-up tilt test (HUT) with transcranial Doppler ultrasonography [1, 2]. Tilt table testing revealed that the patient lost consciousness without hypotension. Doppler flow measurements of the middle cerebral arteries showed a significant decrease in diastolic velocity during syncope without systemic hypotension [3]. The patient suffered from cerebral blood flow (CBF) dysregulation probably due to abnormal baroreceptor responses triggered during orthostatic stress.

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The proposed mechanism for syncope is that the critical decrease in CBF that leads to fainting is secondary to a hemodynamic collapse mediated by a sudden change in autonomic nervous system activity [1]. However, new evidence suggests that, at least in some patients, the main and primary event is a failure in cerebral vascular self-regulation [4]. Abnormal baroreceptor response and abnormal sympathetic activation are two major standpoints accounting for cerebral syncope.

Valsalva maneuver (VM) permitted assessment of the cerebral autoregulatory function by provoking blood pressure (BP) changes [5]. Cerebral autoregulatory responses during the VM could be confounded by the presence of potent sympathetic activation during the VM elicited by the baroreflex and/or an increase in ICP [6]. Phase IV of the VM is also used to calculate cardiac vagal baroreflex gain. There was no influence of age on mean arterial BP elevation in the late phase II of the VM [7]. To develop a path-physiological approach for vasomotor reactivity of cerebral syncope, the authors combined these maneuvers (HUT/transcranial Doppler/VM).

Methods

Our study was conducted from January 2000 to December 2000. One hundred and sixty-two outpatients with recurrent unexplained syncope were evaluated with the use of an upright tilt table, using transcranial Doppler ultrasonography. We simultaneously recorded systemic arterial BP in the radial artery and flow velocities in both middle cerebral arteries (MCAFV). If subjects fulfilled the sonographic definition of cerebral syncope as 'Doppler flow measurements of the middle cerebral arteries showed a significant decrease in diastolic velocity during syncope without systemic hypotension' [3], diagnosis of cerebral syncope was established and VM was carried out.

Every patient was monitored by means of standard electrocardiography, continuous (beat-to-beat) noninvasive BP measurements (Finapres, Ohmeda; Louisville, Colo., USA), pulse oximetry and nasal capnography (Ohmeda 4700 OxiCap, Ohmeda), and noninvasive near-infrared cerebral spectrophotometry (Invos 3100 Cerebral Oximeter, Somanetics; Troy, Mich., USA) with the sensor placed on the patient's forehead. After the baseline period, during which the patient had been supine for 10 min, he or she was positioned at 80° from horizontal on a tilt table with a weight-bearing footboard. The test continued for a maximum of 40 min; if no response (cardioinhibitory, vasodepressor, or mixed) was observed, a threat of doing venipuncture was made and the procedure was eventually performed. If no response was elicited in 5 min, the test result was deemed negative. If a response was present, the patient was repositioned in Trendelenburg's position until there was a total resolution of the symptoms. The patient was then placed in the supine position.

This instrument is based on the volume clamp method of Peñáz and the physical criteria of Wesseling, which have been shown to accurately reflect intra-arterial BP changes [3]. The data were transferred to and recorded on an IBM-compatible computer and analyzed offline by a person who was blind to the other results. Patients were asked to initiate and maintain the straining for 15 s after normal inspiration by blowing into a tube that was connected to a sphygmomanometer. A tiny air leak was placed in the tube to ensure that airway pressure was produced from the thoracic cavity and not the pharynx. Prior to the measurements, the patients were carefully instructed in performing the VM and they practiced the maneuver. The straining pressure was controlled so that it would be 30 mm Hg.

Data Analysis

A two-sided p value of less than 0.05 was considered to indicate statistical significance. SPSS soft software (version 10.0, SPSS, Chicago, Ill., USA) was used for statistical analysis.

Results

The diagnosis of cerebral syncope was established in 10 patients (4 males and 6 females, 35.24 ± 4.5 years old). Besides, 10 age- and sex-matched healthy subjects were recruited as a control group. 'Doppler flow measurements of the middle cerebral arteries showed a significant decrease in diastolic velocity during syncope without systemic hypotension' [3] (fig. 1). Instead, BP increased during the tilting test in 2 subjects. The maximal MCAFV drop of these 10 victims measured 25.4 ± 2.3% from baseline. Ten subjects became syncopal during the HUT test. The time lag between HUT and syncope was 7.2 ± 2.3 min.

The characteristic changes in BP (phases I–IV) were seen in all subjects, accompanying distinct changes in CBF velocity. The BP/heart rate responding to VM in all subjects was within normal limits.

During phase I, BP increased, whereas CBF velocity did not change. During phase IIa, mean and diastolic CBF velocities were reduced by 32.8%. During phase IIb, mean and diastolic pressures increased above the baseline level, and CBF velocity returned to the baseline before the VM. Abnormal flattening of MCAFV during late phase II (IIb), the paradoxical drop of flow velocity despite restoration of BP, was noted in 9 subjects (90.00%) (fig. 2a, b). During phase III, BP was reduced, whereas CBF velocity did not change. During phase IV, overshoots of systolic, mean, and diastolic CBF velocities were all greater than those in BP. Of note, these overshoots returned quickly to baseline levels in almost 10 s.

Abnormal flattening of MCAFV during late phase II (IIb), the paradoxical drop of flow velocity, despite restored BP, was noted in 9 subjects (90.00%). The MCA

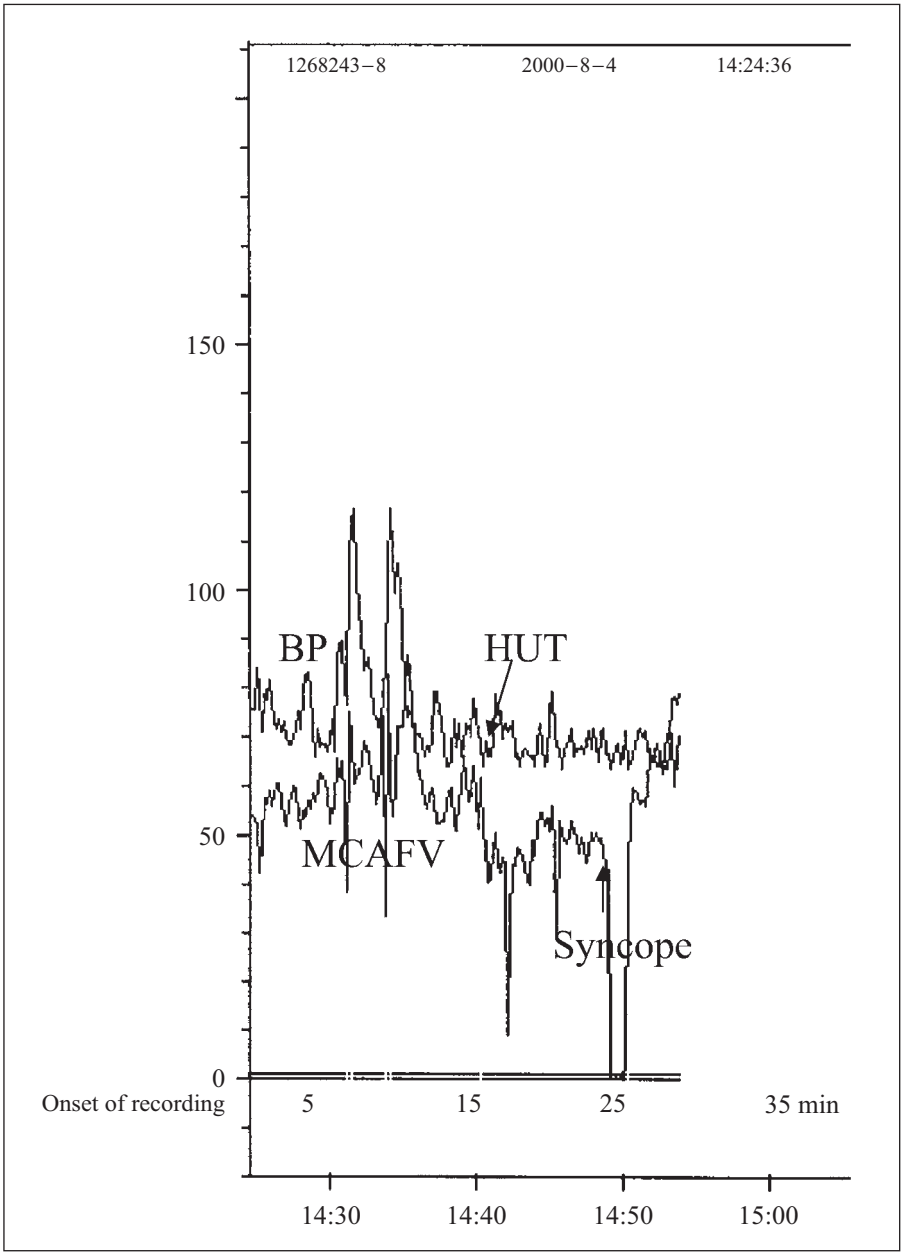


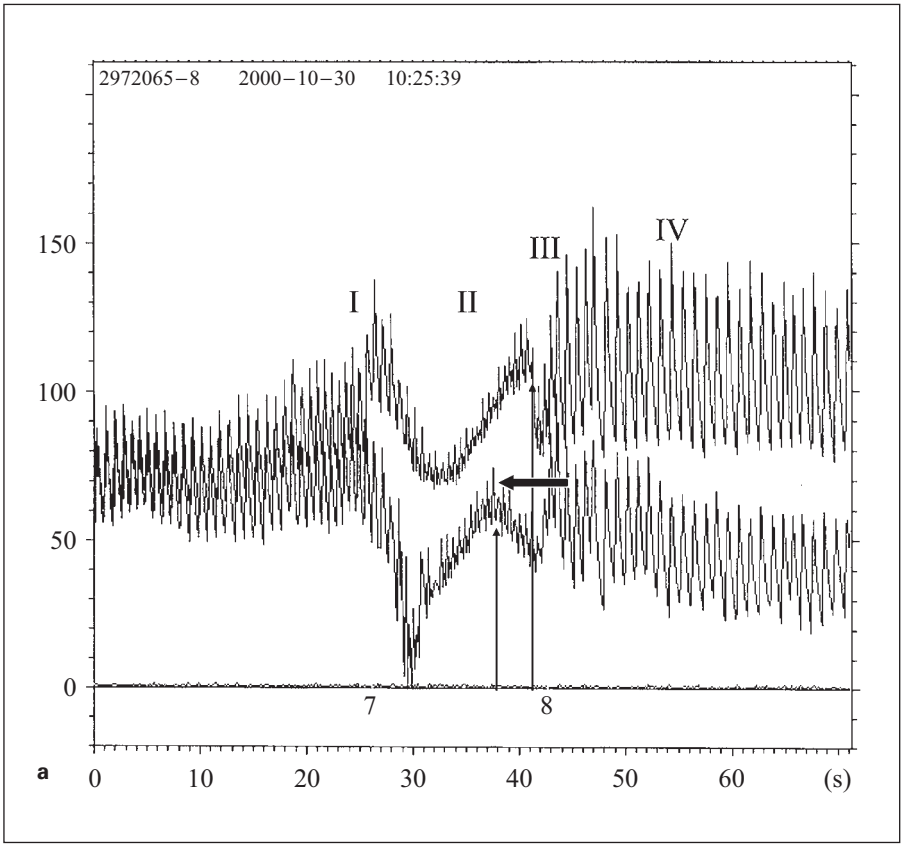
Fig. 1. A characteristic picture of the tilting table study: HUT provoked no significant BP alteration but a paradoxical drop of blood flow velocity (BP: upper curve; MCAFV: lower curve; long arrow: time of HUT; short arrow: time of syncope). The MCAFV dropped 42% from baseline in this case. An average of 10 subjects became syncopal during the HUT test. The time lag between HUT and syncope measured 7.2 ± 2.3 min.

blood flow dropped before the BP curve with a time lag. The time lag measured 3.3 ± 1.5 s in 9 subjects (fig. 2a). In contrast, the abnormal flattening during phase IIb was seen in only 2 control subjects ($p < 0.05$). The MCAFV of these two individuals (28-year-old female and 32-year-old male) dropped by 20 and 15% from baseline on tilting, respectively, without systemic hypotension. They complained only of giddiness during tilting rather than syncope. The VM/HUT study of the other control subjects was within the normal limit (fig. 2b).

Discussion

Cerebral Syncope: A Hypo-α-Adrenergic State?

The frequency of an abnormal phase IIb attenuation in cerebral syncope subjects was statistically higher than that in the control group. Sandroni et al. [8] described a similar phenomenon during intravenous phentolamine administration (α-adrenergic antagonist). In their pharmacological study, they concluded that the phase II was mainly under α-adrenergic regulation [8, 9]. Based on this, we would like to postulate that a hypo-α-adrenergic



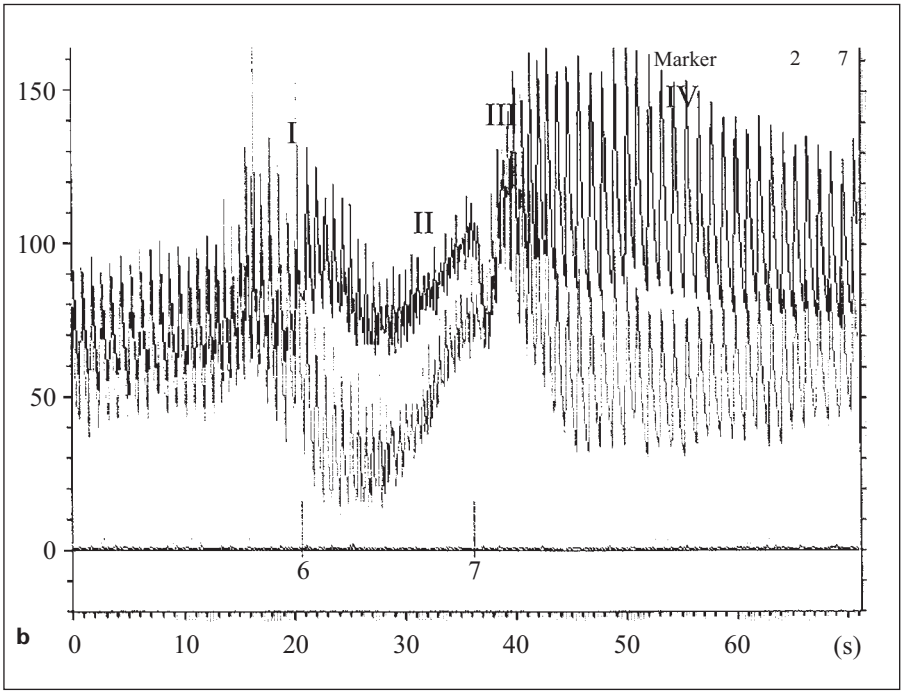


Fig. 2. a Abnormal attenuation of MCAFV was noted over late phase (short arrow; BP: upper curve; MCA CBF: lower curve). The MCA blood flow dropped before the BP curve with a time lag of 4.5 s (long arrows). The average time lag of our 9 subjects measured was 3.3 ± 1.5 s. **b** The VM study of healthy control subjects showed a parallel BP and MCA blood flow curve in the whole phase II.

state might contribute to cerebral syncope [8–10]. Oshita et al. [11] described the intracranial vasoconstriction after an acquired hypo-α-adrenergic state. Abnormal intracranial vasoconstriction was the proposed pathophysiology of cerebral syncope [1–3]. Given the relationship between the hypo-α-adrenergic state and abnormal intracranial vasoconstriction, our results supported the hypothesis of Grubb [2]. Nevertheless, in the absence of pulsatile index (PI) measurements on recording, it makes our results lack direct evidence of cerebral vasoconstriction. Actually, different adrenergic subtypes variably affect peripheral and intracranial vessels. α_{1B}- and α_{2C}-adrenoceptors mainly affect the intracranial vessels rather than the peripheral ones [12]. In the work of Sandroni et al. [8], phentolamine was a nonspecific adrenergic blocker. α-Adrenergic agonists had been reported to be highly effective for some refractory neurocardiogenic syncope [9]. Do our results have a therapeutic implication of α-adrenergic agonists in cerebral syncope? α-Adrenergic agonist may raise peripheral BP to very high levels without necessarily having an intracranial effect. The net effect is unknown. Further studies with PI plotting and specific α-adrenergic subtype exploration are necessary. In their work Grubb et al. [2] hypothesize that MCA vasoconstriction leads to a cerebral hypoxia from a single case EEG recording. Pleiotropy of α-adrenergic receptor manifestation may make a further exploration of cerebral syncope possible.

Bisharat et al. [4] described that β-blockers were effective for cerebral syncope in their single case report. An underlying hyper-β-adrenergic state was suggested. However, β-adrenergic regulation mainly affected the phase IV rather than the phase II [6]. There was no evidence of phase IV abnormality in our work on cerebral syncope. β-Adrenergic regulation seemed intact among our cerebral syncope subjects. Our results did not support the observation of Bisharat et al.

Nevertheless, attenuation of phase IIb and a significant MCAFV drop on HUT coexisted in 2 control subjects. There was a giddiness rather than syncope. It appears that nearly 20% of the presumably asymptomatic controls may have a similar response, confounding the interpretation of our data somewhat. However, Kimmerly et al. [13] described a similar observation that cerebral vasoconstriction without concurrent BP alteration could occur in both norms and those with orthostatic intolerance. VM/HUT-demonstrated abnormalities might contribute to a broad spectrum of phenotype from subclinical giddiness to a recurrent syncope.

In conclusion, VM may offer evidence of α-adrenergic dysregulation of cerebral syncope. Based on the conclusions made from our work, we would like to ask whether the α-adrenergic agonist could reverse phase II attenuation on VM. Pleiotropy of α-adrenergic receptor manifestation may make a more comprehensive exploration of cerebral syncope possible. Further study with the use of PI plotting during HUT and VM would be helpful to reflect the degree or presence of vasoconstriction. Reliance on CBF velocity alone can be misleading since it is only a very approximate measure of CBF. A larger scale with the use of VM with beat-to-beat PI plotting was necessary to verify the reproducibility and specificity of our points.

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