Cerebral Vasoconstriction in Vasovagal Syncope: Any Link With Symptoms?

A Transcranial Doppler Study

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Background—Cerebral vasoconstriction has been described previously in vasovagal syncope (VVS). This phenomenon appears paradoxical in view of the well-known decrease of systemic vascular resistances taking place during VVS. We aimed to assess (1) whether cerebral vasoconstriction in VVS is an independent paradoxical phenomenon and (2) whether cerebral vasoconstriction has any link with symptoms and/or VVS onsets.

Methods and Results—Seven young patients with recurrent VVS participated in the study. Each patient underwent monitoring of heart rate, blood pressure, cerebral blood flow velocity (by means of transcranial Doppler), end-tidal PCO2, peripheral oximetry, respiratory rate, and tidal volumes both at rest and during head-up tilt. All the subjects experienced tilt-induced VVS. A significant increase of respiratory tidal volumes was observed in each subject 160 seconds before VVS. This deep breathing induced a PCO2 decrease and, consequently, also a decrease in cerebral blood flow velocity and increase in cerebrovascular resistance (expressed by the increase of the pulsatility index). Within 40 seconds, 5 subjects started complaining of discomfort, in the absence of any significant blood pressure drop.

Conclusions—Cerebral vasoconstriction is not a paradoxical phenomenon when it occurs before tilt-induced VVS but rather is only the physiological consequence of the hyperventilation-induced hypocapnia that occurs in habitual fainters. The large lag between the onset of syncope and cerebral vasoconstriction excludes the hypothesis that VVS is dependent on abnormal behavior of cerebral hemodynamics. (Circulation. 2001;104:2694-2698.)

Key Words: syncope ■ cerebrovascular circulation ■ ultrasonics

Neurally mediated or vasovagal syncope (VVS) occurs as a consequence of sudden peripheral vasodilation and inappropriate bradycardia1 due to inhibition of sympathetic efferent activity.2–5 Transcranial Doppler sonography was previously used to study cerebral hemodynamics in VVS induced by a head-up tilt test (HUT).6–12 These studies reported decreases of cerebral blood flow velocity (CBFV) occurring both before any cardiovascular changes and at the onset of hypotension and bradycardia and concluded that this was evidence of an increase in cerebrovascular resistances (CVRs) in HUT-induced syncope. This is an unexpected pattern in view of the observed reduction of vascular resistance in the muscular and splanchnic circulation reported in association with syncope.13,14 Thus, paradoxical reaction in the cerebral microcirculation appears to take place in HUT-induced syncope as an independent phenomenon. Whether this cerebral vasoconstriction is determinant or at least strongly contributes to the onset of VVS cannot be determined on the basis of the previous reports, which are far from being exhaustive15; this intriguing issue remains a matter of debate.

The mechanisms underlying local blood flow regulation differ strongly among the various vascular districts: in the cerebrovascular circulation, the chemical and metabolic stimuli are more important than the autonomic neural control of the vascular tone, contrary to the vascular networks of other organs.16 A correlation between the decrease in CBFV and the lowering of plasmatic carbon dioxide (CO2) that occurs during the HUT has already been demonstrated in healthy subjects as well as in patients suffering from chronic orthostatic intolerance.17,18 Therefore, we reasoned that a cerebral vasoconstriction in VVS can be considered a local paradoxical reaction only if the decrease in CBFV precedes the CO2 decrease or, alternatively, if the drop in CBFV exceeds the expected decrease because of the linear correlation between CBFV and CO2. Furthermore, the assumption that cerebrovascular vasoconstriction accounts for VVS is valid only if a strict link between cerebrovascular vasoconstriction and VVS is demonstrated on temporal series

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The purpose of this study was to assess the links among the cerebral, cardiovascular, and respiratory changes during HUT-induced VVS in VVS-prone patients.

Methods

Subjects
Seven consecutive patients (5 men and 2 women; mean age 21.4 years; range 18 to 25 years), referred for recurrent VVS (≥3 episodes in the previous 9 months), gave their informed consent to participate in the study, which was approved by the local Ethics Committee. Cardiovascular and neurological diseases had previously been excluded on the basis of normal results of clinical history and examinations. Presence of sinus rhythm on the ECG was ascertained in all patients. In addition, current medications, alcohol intake, and smoking also served as exclusion criteria. All patients underwent HUT before the study, which was positive for VVS in all cases.

Data Collection
Each subject was lying on a tilt table in a quiet room at constant temperature (20°C to 22°C), breathing room air, in the absence of external visual and acoustic stimuli. The peaks of the QRS complexes (R waves) on the ECG tracings (90603 A, Spacelabs) were used for beat-to-beat measurements of RR interval and its inverse, heart rate. Systolic, mean (MAP), and diastolic arterial blood pressure values were monitored noninvasively by means of a volume-clamp photoplethysmograph (Finapres, Ohmeda). Continuous respiratory activity signal was recorded by means of a piezoelectric transducer (OS-9000TRS, GoldStar) connected to an elastic band that was fastened around the bottom of the chest. The respiratory tracing had been preliminarily calibrated by having the subjects exhale and inhale to fill and empty an 800-ml spirometer bag, thus allowing us to calculate the variations in tidal volume during the test. Continuous end-tidal CO2 (PETCO2) was measured with a capnographic monitor (Capnographe, Novametrics). Recordings of CBFV were performed with a 2-MHz probe (Multidop L, DWL) on the middle cerebral artery on the dominant hemisphere; the position of the probe was kept constant by means of a mechanical holder equipped with an elastic band that was fastened around the skull. The insonation depth was set between 51 and 57 mm, depending on the optimization and stability of the signal. The values of diastolic (dCBFV), mean (mCBFV), and systolic (sCBFV) blood flow velocities were recorded, together with the pulsatility index (PI), computed as (sCBFV−dCBFV)/mCBFV. Oxiometry (PO2) was measured with a transcutaneous laser (Spacelabs 90603 A). All signals were sampled at 256 Hz/channel with a multifunction input/output board (AT-MIO-16F5, National Instruments) and stored on a personal computer for subsequent offline analysis.

Protocol
After a 10-minute rest, the tilt table was turned up to 60° for 2 minutes twice, at 5-minute intervals, to let the subjects become acquainted with the test and minimize the emotional influence. After a further 20 minutes of rest in the horizontal position, the table was turned up again to 60° for data collection. Monitoring was performed for 45 minutes per subject, unless symptoms of incipient syncope and/or a vasovagal reaction occurred earlier, with subsequent termination of HUT. We decided to mark online the moment at which the patients eventually started complaining of symptoms different from incipient syncope.

Previous studies reported that patients can complain of “discomfort” (fatigue, nausea, muscular pain, anxiety, breathing difficulty) during HUT before suffering from VVS and also before symptoms of incipient syncope occur.18,19 The moment at which the patients eventually started complaining of the above-mentioned symptoms different from incipient syncope was therefore marked online to examine eventual associations between this discomfort and the cardiovascular or cerebrovascular changes during HUT. The termination of HUT due to the onset of presyncope or syncope was also marked online.

Calculations
Offline analysis was performed on the temporal series of HUT starting from second 181 of HUT, thus excluding from analysis the first 3 minutes of HUT, when signals are not stable, because of the dynamic and reflex changes that occur in that period.

The change in cardiac and respiratory signals cannot be accurately assessed, owing to point modifications, but can be defined by characteristic changes over subsequent time periods. Because we wished to concentrate on evaluating these same changes over time, namely the onset of change in one parameter with respect to another, we decided to calculate each signal as an average over a predefined time period, with the aim of reducing any variation that single point changes can confer on the overall signal. Thus, for all the parameters, the averaged values for each 20-second interval were calculated: the values from all the consecutive 20-second intervals were expressed as a percentage with respect to the average of the first interval (from 181 to 200 seconds after the beginning of HUT). Significant changes of the monitored parameters during a 20-second interval with respect to previous intervals were evaluated, and a trend for each parameter was defined when there was no return to the baseline in the following intervals. In this way, we could identify the beginning of the changes of respiratory tidal volumes, PETCO2, CBFV, blood pressures, and heart rate. Furthermore, we evaluated whether different signals changed simultaneously (ie, in the same 20-second box) and also the latency of VVS onset. We chose to average over 20-second intervals to reduce the bias due to the increased low-frequency oscillations of CBFV values induced by HUT.20 In contrast to other studies,6,10,18 CVRs were not computed, because the proposed formula (CVR=MAP/mCBFV) does not consider the fact that CBFV and arterial pressure values oscillate spontaneously with a significant time shift:20 this could introduce a misleading error to evaluate the behavior of cerebral hemodynamics.

Nonparametric statistics (Mann-Whitney U test) were used to assess the statistical significance of paired (subsequent 20-second boxes within the time series of a signal) and unpaired (different signals at the same time interval) data. Regression analysis evaluated the relation between variations of relative mCBFV (%) and PETCO2 absolute (mm Hg) values. Statistical significance was set at a value of P<0.05.

Results
The basal values of the monitored parameters and the changes during HUT are displayed in Table 1: the different time periods of the changes of respiratory pattern (deep breathing), general feeling (discomfort), pressure control (MAP), and syncope are reported. All the subjects experienced syncope or presyncope during HUT. The latency of VVS with respect to both these changes and the onset of discomfort is listed in Table 2: time values are approximated at 20 seconds. The vasovagal reaction took place 13 minutes after the beginning of HUT (range 8 to 19 minutes). Five patients started complaining of discomfort during HUT 2 minutes before VVS (range 1 to 4 minutes), without requesting HUT interruption. In each subject, the cardiovascular changes at the onset of vasovagal reaction were preceded by 2 periods characterized by significant changes of other parameters (Figure 1). At first, the breathing pattern became irregular for both the frequency and duration of single breaths (Figure 2): there was a significant increase in the average tidal volumes (Table 1), which persisted throughout the test. This phase was therefore labeled “deep breathing” in Tables 1 and 2. As shown in Table 1, significant decreases of PETCO2, mCBFV,
and dCBFV began at the same time. Table 2 makes evident that the time between the onset of these changes and VVS varied with each patient by an average 160 seconds (range 120 to 200 seconds) but that for each patient, the alterations in respiratory pattern (deep breathing), PETCO₂, and CBFVs all occurred in the same period: their relationships are shown in Figure 3. Subsequently, in the absence of significant blood pressure change, discomfort was reported by 5 patients (Table 2). At that time, tidal volumes and PI showed significant further increases, whereas mCBFV, dCBFV, and PETCO₂ showed further significant decreases (Table 1). A second remarkable change in systemic hemodynamics occurred 100 seconds (range 80 to 140 seconds) after the beginning of the deep-breathing phase and consisted of continuous, significant decreases in MAP and sCBFV values. No significant changes in PO₂ values were observed throughout the test.

Finally, it is evident that PETCO₂ and mCBFV changes occurred with minimal time lag, because of the strict relationship between the 2 parameters. A significant association between mCBFV and PETCO₂ (r=0.745; P<0.001), lasting until VVS onset, with a constant of 3.52 (mCBFV%/mm Hg PETCO₂), was observed on linear regression analysis.

Discussion

The main feature of this study is represented by important changes in cerebral hemodynamics, consisting of significant reductions of mCBFV and dCBFV, occurring much earlier than the vasovagal reaction. There is consistent agreement between our data and the previous reports concerning CVR increase before VVS, thus confirming that the phenomenon is reproducible in selected patients. Our data show that CBFV changes occurred at the same time as significant changes in the respiratory pattern and, consequently, in PETCO₂ values. These changes occurred with a range between 120 and 200 seconds before VVS (Table 2). Therefore, the present data confirm that in our patients as well, cerebral vasoconstriction took place before syncope independently of a significant blood pressure drop, as already stated previously.

Indeed, this behavior of CVR appears paradoxical in VVS, mostly in the vasodepressive and mixed forms, because hypotension secondary to peripheral vasodilation is determinant for syncope in these cases. Peripheral vasodilation, even when it occurs locally in some peripheral circulatory networks of the body, has been considered determinant for the onset of hypotension. A neural mechanism, represented by the suppression of sympathetic outflow to the resistance vessels, has been suggested as the underlying determinant of hypotension. Therefore, a different mechanism of vascular regulation must be hypothesized to explain the cerebral vasoconstriction in VVS. The observed mCBFV decreases in our series were evidently independent of any severe arterial blood pressure drop undergoing the lower limit of autoregulation, because hypotension occurred ≥160 seconds later. Figure 1 shows that the sequence of changes involves first tidal volume, then PETCO₂, and finally systolic arterial pressure. This finding was consistent in all our patients and, in contrast to what has previously been observed in a different group of patients, supports the hypothesis that an independent mechanism is likely to act on the CVR vessels. The finding of a strict temporal link (ie, changes occurring in the same 20-second box) among changes in respiratory pattern, PETCO₂, and cerebral hemodynamics can offer a likely explanation for this cerebrovascular behavior. In fact, CO₂ is a well-known powerful vasomotor agent in the cerebral circu-
luation: its increase induces vasodilation and its decrease induces vasoconstriction. The observed hyperventilation (Table 1: increase of tidal volumes), physiologically leading to hypocapnia, is likely to represent the determinant of cerebral vasoconstriction in our patients. In fact, linear regression analysis showed a significant correlation between PETCO₂ and mCBFV decreases, in agreement with the behavior previously reported in healthy subjects during HUT. The present data on CO₂ reactivity do not differ greatly from those described during orthostatic stress and before the onset of syncope in our patients. As already stated, a decrease in CO₂ leads to concurrent mCBFV and dCBFV decreases, with slight or absent sCBFV decrease, therefore inducing an increase in PI. Because a PI increase has been considered a suitable index of increased CVR, our PI data further stress the already described CVR increase. Therefore, cerebral vasoconstriction preceding VVS was not a paradoxical local phenomenon in our study but rather represented the physiological response of the cerebral circulation to hyperventilation.

Some previous reports are strongly suggestive of general cerebral suffering preceding VVS: aura phenomena, abnormal electroencephalographic changes, and impaired hemoglobin oxygen saturation have all been described before VVS onset. Cerebral vasoconstriction might account for these findings if it leads to significant reduction of oxygen supply to the brain. Unfortunately, our data cannot be considered exhaustive for solving this question, because we recorded only peripheral oxygen saturation: this did not change in any patient throughout the test. Although local impairment of oxygen supply secondary to cerebral vasoconstriction cannot be excluded, the hypothesis of cerebral vasoconstriction as the cause of HUT-induced syncope cannot be supported by our data, because the delay of VVS with respect to CVR increase (≥160 seconds) does not support cerebral vasoconstriction as the determinant of syncope in our patients.

Changes of the respiratory pattern have already been described during orthostatic stress and before the onset of HUT-induced syncope, also in association with reports of a concomitant hypocapnia-induced CVR increase. Furthermore, a 3-minute lag of VVS with respect to the beginning of hyperventilation during HUT was shown recently. It is undoubtedly difficult to assume a pivotal role for hyperventilation in HUT-induced VVS only on the basis of these reports, because the patients studied were not homogeneous for clinical history and underlying diseases (eg, primary and secondary autonomic dysfunction, recurrent or occasional VVS). Because sympathetic activity and sympathetic withdrawal in HUT-induced VVS differ between habitual and

### Table 1. Cardiovascular, Cerebrovascular, and Respiratory Parameters During HUT

<table>
<thead>
<tr>
<th>Patient</th>
<th>HR, bpm</th>
<th>Deep Breathing, %</th>
<th>Discomfort, %</th>
<th>MAP Decrease, %</th>
<th>Syncope, %</th>
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<tbody>
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<td>89±6</td>
<td>101±10*</td>
<td>113±10*</td>
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<td>125±4*</td>
<td>134±5†</td>
<td>136±10*</td>
<td>144±11*</td>
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</tbody>
</table>

HR indicates heart rate; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; and NM, not measurable.

### Table 2. Latency of Syncope Onset With Respect to the Beginning of Changes of the Monitored Signals

<table>
<thead>
<tr>
<th>Patient</th>
<th>Deep Breathing</th>
<th>PETCO₂ Decrease</th>
<th>dCBFV Decrease</th>
<th>mCBFV Decrease</th>
<th>PI Increase</th>
<th>Discomfort</th>
<th>sCBFV Decrease</th>
<th>MAP Decrease</th>
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Values are expressed in seconds.
occasional fainters, the present study was performed on a homogeneous group of young habitual fainters.

A significant increase in heart rate (Table 1) was associated with the already described changes of respiration and cerebral hemodynamics, presumably as a reflex compensatory phenomenon in response to blood pooling in the lower veins, consisting of a baroreceptor-mediated increase in sympathetic activity. It would be hazardous to hypothesize that increased sympathetic activity could also contribute to an increase in CVR, because so far, HUT-induced sympathetic modulation of cerebral hemodynamics has been demonstrated to operate only on the spontaneous CBVF oscillations, but not on absolute CBVF values, and only in the absence of significant CO₂ changes.

Hyperventilation is likely to represent the link between the relative hypovolemia due to blood pooling in lower venous beds (ie, abdomen and lower limbs) and the cardiac inhibitory reflex during HUT in this group of patients. In fact, tidal volume increase could represent a sort of “respiratory pump” as a physiological response attempting to increase the blood volume afferent to the intrathoracic veins, thus aiming to compensate for the amount of blood otherwise pooled in the lower venous beds. Conversely, hyperventilation-induced hypocapnia accounted for cerebral vasoconstriction, this presumably leading to a slightly impaired cerebral perfusion responsible for the discomfort referred to by most patients, largely before presyncope. In fact, 5 of 7 patients started complaining of discomfort soon (ie, 20 to 40 seconds) after the onset of cerebral vasoconstriction (ie, PI increase), in the absence of any significant blood pressure drop: this occurred ≥100 seconds after discomfort. This is in agreement with a previous report of the slow progressive decrease and the final disappearance of sympathetic nerve efferent traffic during HUT-induced syncope in patients with recurrent VVS. A further similarity with the above-mentioned observations might be represented by the slow, progressive, although not yet significant, blood pressure decrease observed in our series since the beginning of hyperventilation (Figure 1).

In conclusion, our data demonstrate that previously reported cerebral vasoconstriction is not a paradoxical phenomenon when it occurs before HUT-induced VVS in habitual fainters but rather the physiological consequence of hyperventilation-induced hypocapnia. Furthermore, the temporal lag between the onsets of discomfort and presyncope with respect to cerebral vasoconstriction, not excluding the fact that minor discomfort might depend on a slightly impaired cerebral perfusion, demonstrates that VVS is due simply to an arterial pressure drop and bradycardia as signs of a full-blown vasovagal reaction. The large time lag between the onset of syncope and a PI decrease found in our study excludes the hypothesis that VVS is dependent on abnormal cerebral hemodynamics.

References
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