Original articles

Cerebral vasoconstriction in neurally mediated syncope: relationship with type of head-up tilt test response

Silvano Silvani, Giovanni Padoan*, Anna Rita Guidi*, Giovanni Bianchedi*, Aleardo Maresta

*Cardiology Division, *Neurology Division, S. Maria delle Croci Hospital, Ravenna, Italy*

Key words:
Autonomic nervous system; Blood pressure; Echo-Doppler; Pathophysiology; Syncope.

Background. **The pathophysiology of neurally mediated syncope (NMS) is unclear. Cerebral vasoconstriction has been observed in NMS patients during tilt testing. To shed light on the pathophysiology of NMS, we attempted to establish whether the degree of cerebral vasoconstriction changes with the tilt test positivity type, scored in accordance with Sutton's classification.**

Methods. **Twenty-one patients (12 males and 9 females, mean age 41 ± 15 years) consecutively admitted to tilt test evaluation were studied through simultaneous recordings of their electrocardiogram, blood pressure, electroencephalogram and transcranial Doppler sonography (TCD) of the middle cerebral artery. TCD allowed computation of the Gosling's pulsatility index [PI = (systolic velocity - diastolic velocity)/mean velocity], as an index of cerebrovascular resistance.**

Results. **In the 13 tilt-positive patients (62%), TCD revealed a significant PI increase at the onset of prodromic symptoms in comparison with baseline (2.01 ± 0.94 vs 0.77 ± 0.20, p < 0.001, paired-sample Student's t-test). No significant TCD alterations were seen in tilt-negative patients. Furthermore, the percentage change in the PI from baseline was significantly higher in cardioinhibitory types (254 ± 51%, 5 patients) than in mixed and vasodepressor types (101 ± 22%, 8 patients, p < 0.001, independent-sample Student's t-test).**

Conclusions. **Our data show that the degree of cerebral vasoconstriction at the onset of prodromic symptoms changes with the tilt test positivity type. We suggest that in NMS patients the degree of cerebral vasoconstriction may depend on the amount of sympathetic activation. The sympathetic modulation of cerebral vasoconstriction may therefore be a turning point in the explanation of the pathophysiology of NMS.**

(Ital Heart J 2003; 4 (11): 768-775)

Received May 20, 2003; revision received August 4, 2003; accepted August 18, 2003.

Address:
Dr. Silvano Silvani
Via Busmanti Dario, 21
48100 Ravenna
E-mail:
snsilvani@jumpy.it

Introduction

It has been suggested that a neurally mediated mechanism is involved in most cases of unexplained syncope. However, the pathophysiology of neurally mediated syncope (NMS) is still poorly understood despite the great number of studies that have addressed this issue[1]. Various theories have attempted to explain this complex pathophysiological entity. One of the most recent is the "cerebral blood flow dysregulation" theory. The role of the sympathetic nervous system in regulating the cerebral blood flow has been a source of controversy in the literature[2,3]. Cerebral blood vessels are richly innervated with adrenergic nerve fibers, but, under resting conditions, these nerves probably play only a lesser role in controlling cerebral blood flow[4], at least in non-primate species. However, in conditions of acute hypertension[5] or hypercapnia[6], sympathetic activation clearly constricts the cerebral blood vessels and is probably important in protecting the brain from severe hypertension[7-10]. This effect of sympathetic activation is probably greater in large than in small blood vessels[11]. Moreover, there appears to be an important species difference in the response of the cerebral blood flow to sympathetic stimulation. In summary, there appears to be adequate experimental evidence to suggest that sympathetic stimulation in primates, including humans, may cause arteriolar, as well as large-vessel, cerebral vasoconstriction, shifting both the upper and lower limits of the autoregulation curve to the right. Although protective during acute hypertension, this shift may be detrimental during hypotension. Indeed, if the lower limit of the autoregulation curve is shifted to the right, modest degrees of hypotension, which would otherwise be well tolerated, may compromise the cerebral

blood flow, which decreases much more than when the autoregulation curve is normal. Some recent studies have focused on the cerebrovascular hemodynamics during head-up tilt test (HUT)-induced syncope or during lower body negative pressure (LBNP)-induced presyncope. Cerebral vasoconstriction has been observed in NMS patients during HUT[12,13] and in healthy humans during LBNP[14,15]. The aim of our study was to determine whether the degree of cerebral vasoconstriction changes with the tilt test response, scored in accordance with Sutton's classification[16].

Methods

Twenty-one patients (12 males and 9 females, mean age 41 ± 15 years) were consecutively submitted to HUT with simultaneous recording of their electrocardiogram (ECG), blood pressure, electroencephalogram (EEG) and transcranial Doppler sonography (TCD) of the middle cerebral artery. All patients had formerly undergone clinical and instrumental examinations, including EEG and two-dimensional echo-Doppler, with negative diagnostic work-up. In accordance with the VASIS study indications[17], all tilt-positive patients were classified on the basis of the type of HUT response, using Sutton's classification (Table I)[16]. After written consent had been obtained, each patient was submitted to HUT in the fasting state in a quiet room. After 10 min of baseline measurement of heart rate and blood pressure, the tilt table was positioned at an angle of 60° from the horizontal for up to 45 min. If syncope or presyncope occurred during HUT, the table was rapidly lowered to the supine position and the study halted. If the test was negative, 0.3 g of sublingual nitroglycerin were administered[18] and the test was prolonged for 20 min. Heart rate was recorded by means of a 6-limb or precordial lead ECG, using a Siemens Mingograf 7 device (Siemens AG, Munich, Germany). The seventh trace was utilized for blood pressure recording by means of a connection with the Ohmeda Finapres System (Ohmeda, Lousville, CO, USA). The accuracy and reliability of this technique of blood pressure measurement (by the photoplethysmographic method in the finger) have been reported in previous studies[19,20]. The paper speed was 10 mm/s. The blood pressure trace was set at 100 mmHg = 2 cm from the 0 line. EEG was performed with a Nihom Kohdem 8-channel device (Nihom Kohdem, Tokyo, Japan), with a paper speed of 15 mm/s. TCD was performed with a TC 2-64 B EME device (Nicolet Vascular, Madison, WI, USA) via the transtemporal approach with a 2-MHz pulsed wave. The Doppler probe was adjusted for optimal signal recording and positioned by means of a proper head device. TCD allowed us to determine cerebral blood flow velocity during HUT.

Gosling's pulsatility index (PI) was computed as (systolic velocity - diastolic velocity)/mean velocity. The baseline PI value was defined as the value assessed at initial HUT. The increase in the PI from the baseline value to the value just before syncope (tilt-positive patients) or to the value at the end of tilt testing (tilt-negative patients) was computed and divided by the baseline PI value to obtain a percentage PI increase (ΔPI). Previous studies[21,22] have shown that the PI is a reliable index of cerebrovascular resistance modifications, with a specificity of 98-100% in the diagnosis of cerebrovascular vasospasm. Indeed, the PI increases in case of arteriolar vasoconstriction and decreases in case of arteriolar vasodilation[23]. The differences in the ΔPI among the three groups of patients described in the results section were analyzed via one-way analysis of variance (ANOVA). The difference in the ΔPI between each combination of two groups of the three groups was analyzed using the Student's t-test with the Bonferroni correction for *post hoc* comparison.

Statistical analysis. Data are presented as mean ± SD, with n indicating the number of cases. The paired-sample Student's t-test was used to compare the baseline PI values with those registered just before syncope (tilt-positive patients) or with those registered at the end of tilt testing (tilt-negative patients). Differences in the ΔPI were analyzed by one-way ANOVA and the Student's t-test with the Bonferroni correction for *post hoc* comparison. Differences were considered statistically significant at $p < 0.05$.

Results

Thirteen patients (62%) were tilt-positive. In 2 patients, the response was type 3 pure vasodepressor, in 6

Table I. Proposed classification for tilt-induced vasovagal syncope[16].

Type 1 - Mixed
Heart rate initially increases and then falls but the ventricular rate does not fall to < 40 b/min or falls to < 40 b/min for < 10 s with or without asystole for < 3 s.
Blood pressure initially increases and then falls before heart rate decreases.

Type 2A - Cardioinhibitory
Heart rate initially increases and then falls to a ventricular rate < 40 b/min for > 10 s or asystole occurs for > 3 s.
Blood pressure initially increases and then falls before heart rate decreases.

Type 2B - Cardioinhibitory
Heart rate initially increases and then falls to a ventricular rate < 40 b/min for > 10 s or asystole occurs for > 3 s.
Blood pressure initially increases and only falls to systolic hypotensive levels < 80 mmHg at or after the onset of a rapid and severe decrease in heart rate (as defined above).

Type 3 - Pure vasodepressor
Heart rate rises progressively and does not fall by more than 10% from peak at the time of syncope.
Blood pressure falls to cause syncope.

patients it was type 1 mixed, in 2 patients cardioinhibitory type 2A, and in 3 patients cardioinhibitory type 2B. Nitrates were administered to 12 subjects with a negative HUT out of the total group of 21 patients studied. Four patients became tilt-positive after this procedure. The type of positive response in these 4 patients was type 3 pure vasodepressor in 1 patient, type 1 mixed in 2 patients and type 2A cardioinhibitory in 1 patient.

In accordance with our previous study[24], the EEG patterns showed different degrees of alterations, depending on the type of tilt test positivity: in the 2A and 2B types, during the prodromic phase, a slowdown and reduction in the amplitude of cerebral electrical activity; in type 1 mixed, the EEG remained unmodified with respect to baseline. During syncope, in the 2A and 2B types, pseudorhythmic and then polymorphic delta activities were recorded, followed by a "flat" EEG; polymorphic and pseudorhythmic delta activities were then recorded in inverse sequence. In type 1 mixed, the electrical activity did not disappear during the syncopal phase, but theta activity and then polymorphic delta activity were recorded, followed by theta activity again.

In the post-syncope phase, in types 2A and 2B, a slowed-down activity and a reduced amplitude of alpha waves were recorded (similar to those of the prodromic phase); in type 1 mixed, the EEG returned to baseline.

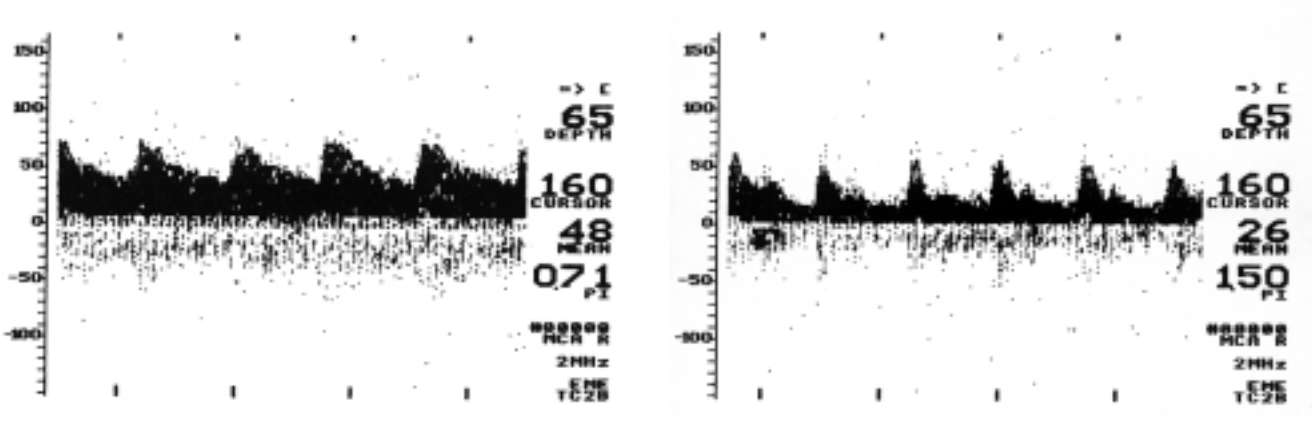
Finally, in type 3 patients, the EEG remained unmodified with respect to baseline during all phases of tilt testing. No EEG alterations were found in the 8 tilt-negative patients.

In tilt-positive patients (n = 13), the PI values just before syncope were compared with those at baseline to assess changes in cerebrovascular resistance. The PI values were significantly higher than those at baseline just before syncope or presyncope (2.01 ± 0.94 vs 0.77 ± 0.20, $p < 0.001$, paired-sample Student's t-test). On the other hand, in tilt-negative patients (n = 8) no significant variations with respect to baseline were found in the PI values at the end of tilting (0.89 ± 0.18 vs 0.86 ± 0.13, p = NS, paired-sample Student's t-test). In patients with a positive tilt test the pattern of change of the PI did not vary following nitrate administration. After nitrate administration, the ΔPI was 84% in 1 patient with a type 3 pure vasodepressor response, 107 and 112% respectively in 2 patients with a type 1 mixed response and 218% in 1 patient with a type 2A cardioinhibitory response. Such ΔPIs were within the range of values measured in patients who showed the same type of tilt test positive response without nitrate administration.

We divided our study population into three groups on the basis of the HUT response: 1) tilt-negative patients (n = 8), 2) type 1 mixed and type 3 tilt-positive patients (prevalent and pure vasodepressor types, n = 8), 3) type 2A and type 2B tilt-positive patients (cardioinhibitory types, n = 5). The differences in the ΔPI among the three groups were highly significant ($p < 0.001$). Even the differences in the ΔPI between each combination of two groups of the three groups described above were highly significant ($p < 0.001$).

The main finding of the present study was that the ΔPI was significantly higher in cardioinhibitory types (254 ± 51%, 5 patients) than in mixed and vasodepressor types of NMS (101 ± 22%, 8 patients) ($p < 0.001$, independent-sample Student's t-test).

Figure 1A shows the TCD pattern of a type 1 mixed patient on initial tilting: the PI was 0.71. Just before syncope, the pattern changed abruptly (Fig. 1B): the diastolic velocity decreased while the systolic velocity remained unchanged; the PI therefore increased from 0.71 to 1.50 (increase of 111%). The sequence of cerebral blood flow velocity changes in type 2A patients differed from that seen in type 1 mixed patients. Figure 2A shows the TCD pattern of a type 2A patient: the initial PI was 0.54. Just before syncope there was a dramatic change; the diastolic velocity fell abruptly, while



A B

Figure 1. *Transcranial Doppler sonography pattern of a type 1 "mixed" patient at initial tilt* (panel A). *Just before syncope* (panel B), *a decrease in diastolic velocity may be observed, while the systolic velocity remains unchanged. Therefore, the pulsatility index (PI) increases from 0.71 to 1.50 (ΔPI of 111%).*

the systolic velocity remained unchanged. The PI therefore increased from 0.54 to 1.83 (increase of 238%) (Fig. 2B). In the type 2B patient the sequence of TCD patterns was different from that seen in the type 2A patient. On initial tilting, the PI was 0.77 (Fig. 3A). When bradycardia and hypotension abruptly developed, the diastolic component almost completely disappeared, whereas the PI increased from 0.77 to 3.39 (increase of 340%) (Fig. 3B). The cerebral vasoconstriction lasted for a total of about 1 min, beginning to decrease after the patient had been replaced in the supine position (Fig. 3C) (20 s after the beginning of syncope). Figure 4A reports the pattern observed after 40 s: although on the decrease, the vasospasm was still present in conditions of persisting hypotension and restored cardiac rhythm. The TCD pattern then returned to that seen during initial tilting (after 60 s) (Fig. 4B).

In figure 5, heart rate and blood pressure recordings of the above patient are shown.

Discussion

The study was designed to investigate the profile of the cerebral blood flow velocity during HUT performed in patients who presented with a history of syncope and/or presyncope.

Our TCD findings yielded indirect evidence of cerebral vasoconstriction in tilt-positive patients, in that the PI values significantly increased just before syncope with respect to those observed at baseline. Similar results have been reported by other authors[12-15].

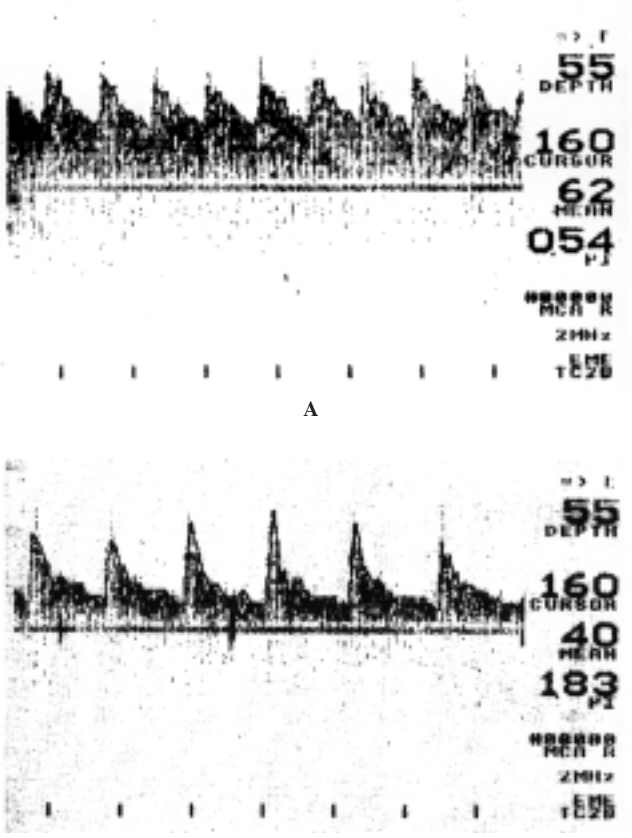


Figure 2. *Transcranial Doppler sonography pattern of a type 2A patient at initial tilt* (panel A)*. Just before syncope* (panel B)*, a dramatic change may be observed; the diastolic velocity falls abruptly, while the systolic velocity remains unchanged. Therefore, the pulsatility index (PI) increases from 0.54 to 1.83 (ΔPI of 238%).*

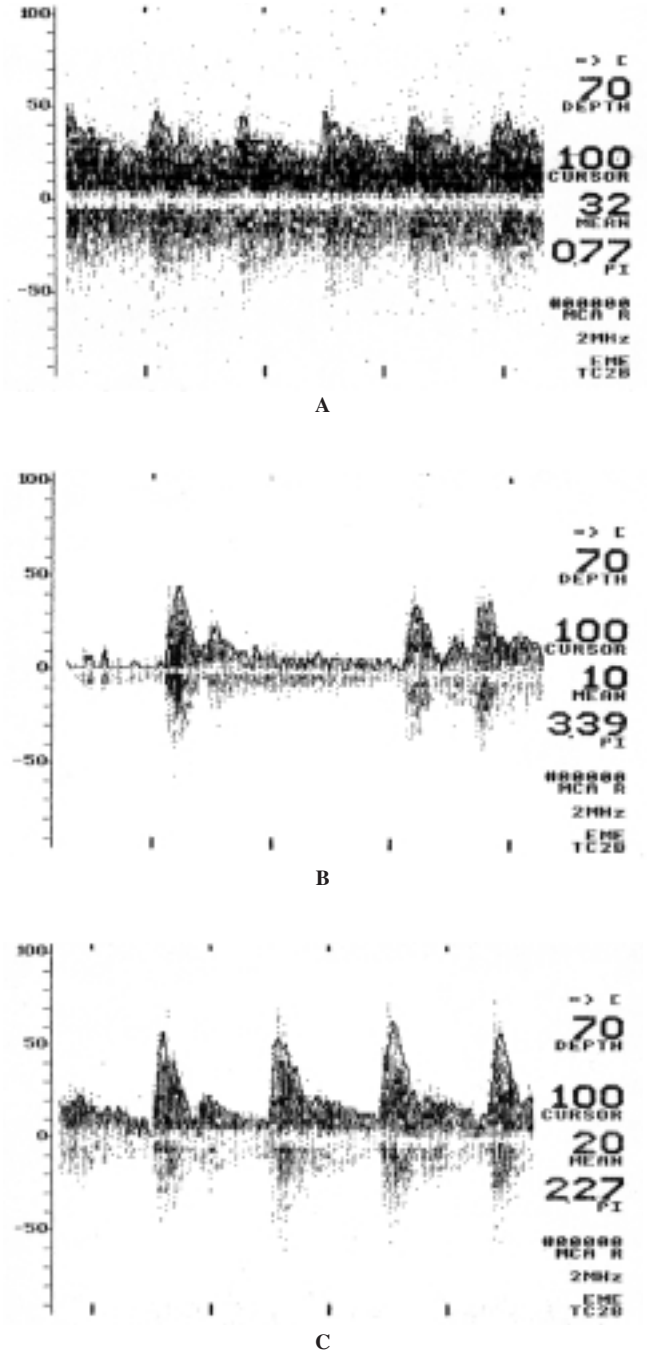
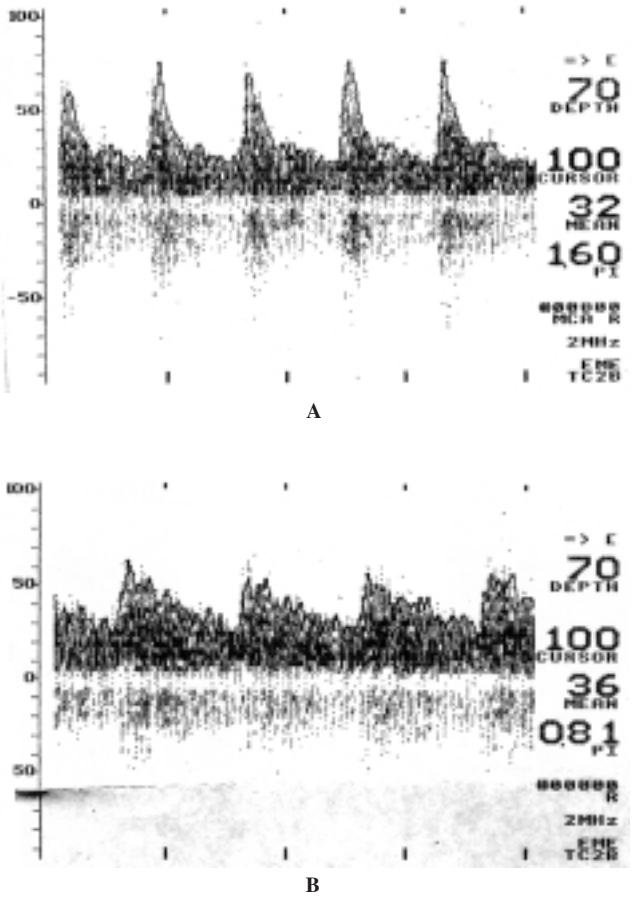


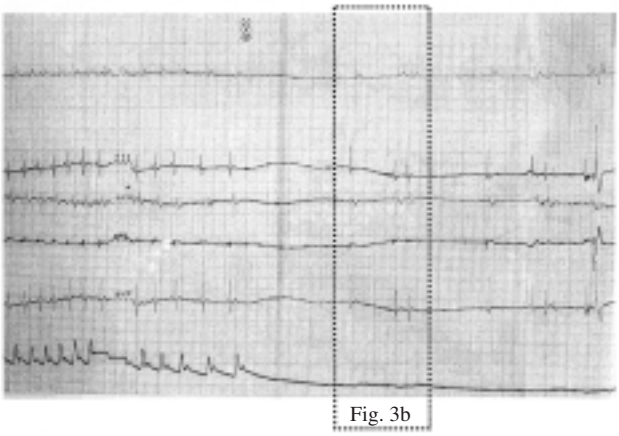
Figure 3. *Transcranial Doppler sonography pattern of a type 2B patient.* Panel A *shows the pattern at initial tilt, with a pulsatility index (PI) of 0.77. When bradycardia and hypotension abruptly develop* (panel B)*, the diastolic component almost completely disappears, whereas the PI increases to 3.39 (ΔPI of 340%). The cerebral vasoconstriction lasted for a total of about 1 min and started to decrease when the tilt bed was lowered to the supine position.* Panel C *shows the pattern after 20 s, with the PI decreased from the peak value of 3.39 to a value of 2.27.*



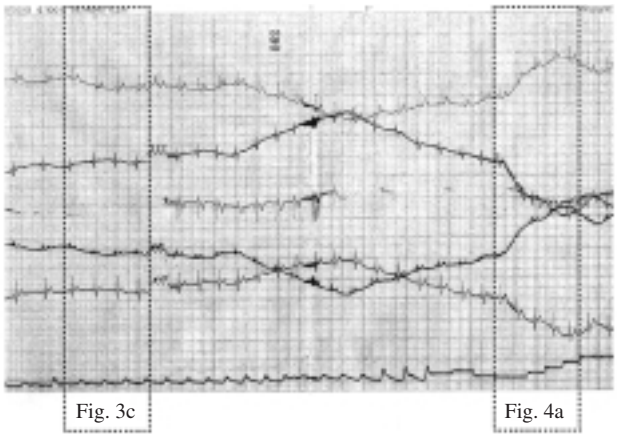
A

B

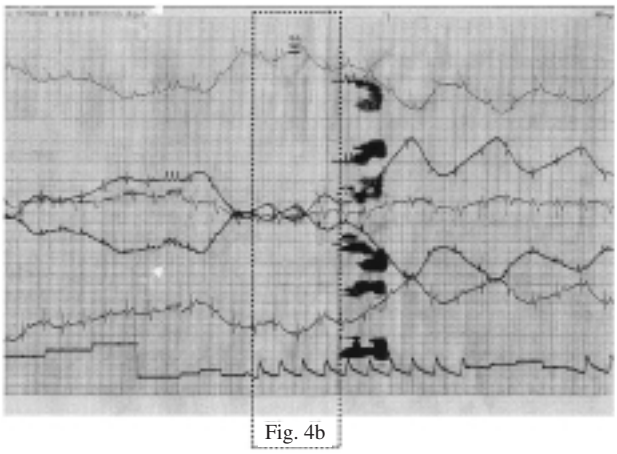
Figure 4. *Same patient as figure 3.* Panel A *shows the transcranial Doppler sonography pattern 40 s after the beginning, with persisting vasospasm, although in a decreasing phase, in conditions of hypotension and restored cardiac rhythm. The pattern then returns to that seen during initial tilting 60 s after the beginning* (panel B). *PI = pulsatility index.*



A



B



C

Figure 5. *Tilt recording of the above patient.* Panel A *shows heart rate as recorded on the electrocardiogram* on top *(leads I, III, aVR, aVL, aVF) and blood pressure* below. *It is important to note that blood pressure starts decreasing at the onset of rapid and severe heart rate fall and finally becomes no longer perceptible. The transcranial Doppler shown earlier in figure 3B is the pattern corresponding to the beats enclosed in the rectangle.* Panel B *shows the subsequent tilt recording. Note the restored cardiac rhythm in the presence of persisting hypotension. The transcranial Doppler patterns shown in figure 3C and 4A respectively correspond to the first and second groups of beats enclosed in the rectangles.* Panel C *shows the subsequent tilt recording. Note that now even blood pressure is progressively restored. The transcranial Doppler pattern shown in figure 4B corresponds to the beats enclosed in the rectangle.*

The novelty of our study lies in the fact that we computed the percentage increase in PI (ΔPI) to determine whether it (and thus the degree of cerebral vasoconstriction) changes with the tilt test response. We demonstrated that the differences in the ΔPI variation among the three groups into which we divided the patients studied (tilt-negative, tilt-positive types 1 mixed and 3, tilt-positive types 2A and 2B) were statistically significant; we also demonstrated that the difference in the ΔPI between any two of the three groups was highly significant. We were therefore able to demonstrate that cerebral vasoconstriction is significantly more marked in cardioinhibitory types than in mixed and pure vasodepressor types of NMS. Thus, we can affirm that there is a relationship between the degree of cerebral vasoconstriction and the type of tilt-positive response. Such findings have never been reported in the literature and deserve some pathophysiological scrutiny. The cerebral circulation in humans has been assessed in previous physiology studies[25]. The cerebral vessels are influenced by metabolic and neural factors, and respond to changes in arterial pressure by means of autoregulatory adjustments. They are also unusual-

ly responsive to chemical stimuli, in that hypercapnia produces marked vasodilation, whereas hypocapnia produces vasoconstriction, thereby increasing the cerebrovascular resistance. In contrast, the responses to neural stimuli are circumscribed: in most conditions, the function of sympathetic nerves is not relevant, but in case of an acute increase in arterial pressure they have an important protective role. Recently, Levine et al.[14,15] speculated that, during low-level orthostatic stress (induced by means of graded LBNP in healthy humans), a modest amount of sympathetic activation occurs and that, through the mechanism of cerebral autoregulation, the ensuing large-vessel vasoconstriction is counterbalanced by arteriolar vasodilation; thus, the cerebral blood flow and velocity – as measured in the middle cerebral artery – remain constant. However, during greater orthostatic stress, the reduction in cardiac filling and central blood volume may produce intense sympathetic activation resulting in arteriolar as well as large-vessel cerebral vasoconstriction. It has been hypothesized that sympathetic activation causes a dynamic shift to the right in the autoregulatory range (Fig. 6)[14]; although protective during acute hypertension, this shift may be detrimental during hypotension, leading to presyncope. This hypothesis may also hold true for our data.

We suggest that the degree of cerebral vasoconstriction in tilt-positive patients may be determined by the sympathetic activation induced by the deactivation of the cardiopulmonary receptors as a result of the orthostatic stress-mediated reduction in central blood volume. The behavior of the autonomic nervous system during orthostatic stress has been investigated by several authors[26-31]. Furlan et al.[27] studied the cardiac autonomic changes preceding occasional vasovagal reactions in healthy humans by means of time-variant power spectral analysis of heart rate variability; these authors found two different and opposite patterns in syncopal patients, suggesting that NMS in subjects with occasional episodes of loss of consciousness may be promoted by an alternative pathophysiological mechanism independent of an excessive enhancement of sympathetic activity to the heart. Attempts to quantify the sympathetic activity before syncope have yielded variable, and sometimes opposite, results. For instance, the plasma norepinephrine concentrations have been found to be elevated or diminished before syncope. Moreover, studies based on conventional power spectral analysis of heart rate variability have indicated increased, reduced, or unchanged values of the markers of cardiac modulation before a vasovagal event. These discordant results were thought to be due to the methods used, which were not adequate for the continuous assessment of the cardiac autonomic changes that precede neurogenic syncope. Our opinion, however, is that the effects of sympathetic activation on the heart (in response to orthostatic stimuli) do not necessarily reflect the effects of sympathetic activation on other vascular beds[32], and therefore on the cerebrovascular circulation. This may explain the discrepancies seen among the results of each method used to date.

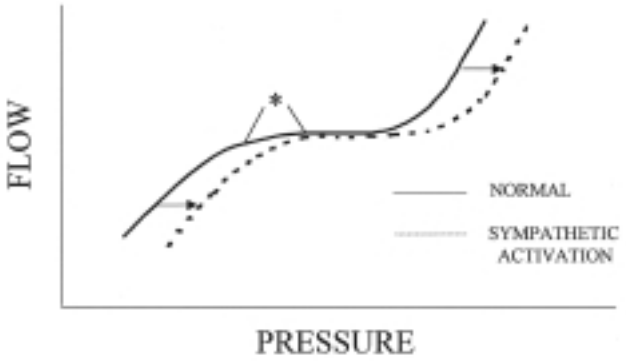


Figure 6. *Hypothetical autoregulatory curves relating the arterial pressure to the cerebral blood flow, in normal conditions* (solid line)*, and during sympathetic activation during lower body negative pressure* (dashed line)*. * the lower limit of autoregultion, which, during sympathetic activation, is likely to be shifted to the right. This shift may compromise the cerebral autoregulation during hypotension induced by orthostatic stress, thus contributing to the symptoms of presyncope. From Levine et al.[14], with permission.*

We believe that the hypothesis of Levine et al.[14,15] is applicable to our findings because LBNP is a recognized technique of mimicking and modulating the effects of gravity, particularly on the central venous pressure and arterial pressure. Recently, Mano et al.[33] have shown a graded, linear relationship between the degree of orthostatic stress during HUT (sine of the tilt angle) and sympathetic nervous activity. The relationship we found between the degree of cerebral vasoconstriction and the type of tilt-positive response may therefore be explained on the basis of the different amounts of sympathetic activation resulting from the different orthostatic stress-mediated reductions in the central blood volume during HUT. Our hypothesis may also explain one of the most debated aspects of NMS, i.e. the presence of different types of tilt test response in the same patient undergoing repeated HUT examinations. It has been reported that a patient who has had a cardioinhibitory type positive response at the first HUT may have a type 1 mixed or a vasodepressor type positive response at the second HUT, or may even have a tilt-negative response[34-36]. This behavior, according to our hypothesis, may be explained by the amount of sympathetic activation that changes in the same patient in subsequent HUT examinations because the orthostatic stress-mediated reduction in the central blood volume, and therefore the deactivation of the cardiopulmonary receptors, may change from one occasion to another. It should be pointed out that Levine's study, which was performed on healthy humans, revealed a modest percentage increase (17%) in the PI from rest to maximal LBNP before the onset of symptoms or systemic hypotension, thus suggesting a mild degree of cerebral small-vessel vasoconstriction[14]. In contrast, we found a greater ΔPI in our patients (159 ± 84%, 13 patients). However, Levine him-

self has pointed that the regulation of the cerebral blood flow in patients with neurocardiogenic syncope may be quite different to that occurring in healthy individuals. Therefore, we may hypothesize that the cerebral vasoconstriction induced by sympathetic activation increases to a much greater extent in NMS patients than in healthy subjects, and that it reaches its highest level in cardioinhibitory type 2B NMS (followed by cardioinhibitory type 2A, type 1 mixed with a prevalent vasodepressor component, and type 3 pure vasodepressor, in descending order). This really may represent a means of "modulation" of cerebral vasoconstriction through sympathetic activation.

With regard to the presence of a causal link between cerebral vasoconstriction and bradycardia/asystole and/or hypotension, we only found a chronological succession of the two events, which does not allow us to conclude that there is a causal relationship. However, our EEG and TCD results clearly demonstrated the presence of cerebral hypoxia and of cerebral vasoconstriction respectively, in the absence of bradycardia/asystole and/or systemic hypotension during the prodromic and the early post-syncope phases of types 2A and 2B tilt-positive patients. We can therefore exclude that cerebral vasoconstriction is caused by bradycardia/asystole. In addition, having demonstrated that cerebral vasoconstriction precedes the development of bradycardia and/or asystole, we can hypothesize that the former may be the cause of the latter. Moreover, the degree of cerebral vasoconstriction may determine the extent of bradycardia/asystole, since in our study the greatest ΔPI was found in types 2A and 2B positive patients, i.e. in the positivity types characterized by the most severe bradycardic/asystolic responses during HUT. Finally, with regard to the relationship between hypotension and cerebral vasoconstriction, by applying a mathematical method of analysis to several indexes of cerebral blood flow (including the PI) Dan et al.[37] recently demonstrated that the cerebral blood flow velocity declines before the arterial pressure in patients with orthostatic vasovagal presyncope during HUT. Their results showed that the changes in several indexes of cerebral blood flow precede the reductions in arterial pressure during vasovagal presyncope and, therefore, cannot be caused by changes in arterial pressure. These data are important because they provide a mathematical validation for our findings. In conclusion, we agree with Dan's suggestion that "the earliest changes in the cascade of events culminating in vasovagal syncope result from a central nervous system trigger, whatever that trigger may be".

Limitations of the study. As reported by other authors[38], the TCD technique allows for an extremely accurate assessment of the cerebral blood flow and is instrumental in the diagnosis of cerebral vasospasm. However, these measurements depend on the assumption that the diameter of the middle cerebral artery remains constant. Although several studies[39-41] have shown that changes in the diameter of the middle cerebral artery itself are negligible compared with those of the cerebral arterioles, it is possible that some large-vessel vasoconstriction due to sympathetic activation does occur at higher levels of orthostatic stress. If so, a reduction in the diameter of the middle cerebral artery might increase the velocity measured at TCD and therefore mislead us into underestimating the reduction in blood flow and/or the degree of small-vessel vasoconstriction. Another potential limitation of the study is that alterations in carbon dioxide levels may have influenced the results[42]; however neither hyperventilation nor hypoventilation occurred during tilt testing in any subject in our study. Moreover, as reported by Dan et al.[37], this may not be a major problem, as Levine et al.[14] have shown that hypocapnia secondary to hyperventilation does not cause presyncope, even though it decreases the cerebral blood flow velocity more than LBNP, which does cause presyncope.

Moreover, we asked our patients to perform voluntary hyperventilation and hypoventilation before tilt testing, and found an increase in the PI during hyperventilation and a decrease in this index during hypoventilation. These data are in contrast with the observations of Grubb et al.[12], who affirmed that no significant change in velocity was found during voluntary hyperventilation or hypoventilation before tilting. Thus, our patients appear to have a normal cerebral metabolic regulation of blood flow.

Finally, a recent study[43] has demonstrated that alterations in respiration do not play any role in the vasomotor instability preceding tilt-induced syncope.

In conclusion, our data show that the degree of cerebral vasoconstriction at the onset of prodromic symptoms changes with the positivity type of the tilt test. We suggest that the degree of cerebral vasoconstriction may depend on the degree of sympathetic activation in NMS patients. The sympathetic modulation of cerebral vasoconstriction may constitute a turning point in the explanation of the pathophysiology of NMS.

References

1. Mosqueda-Garcia R, Furlan R, Tank J, Fernandez-Violante R. The elusive pathophysiology of neurally mediated syncope. Circulation 2000; 102: 2898-906.
2. Heistad DD, Marcus ML. Evidence that neural mechanisms do not have important effects on cerebral blood flow. Circ Res 1978; 42: 295-302.
3. Purves MJ. Do vasomotor nerves significantly regulate cerebral blood flow? Circ Res 1978; 43: 485-93.
4. Alm A, Bill A. The effect of stimulation of the cervical sympathetic chain on retinal oxygen tension and on uveal, retinal and cerebral blood flow in cats. Acta Physiol Scand 1973; 88: 84-94.
5. Bill A, Lindner J. Sympathetic control of cerebral blood flow in acute arterial hypertension. Acta Physiol Scand 1976; 96: 114-21.

6. Harper AM, Deshmukh VD, Rowan JO, Jennet WB. The influence of sympathetic nervous activity on cerebral blood flow. Arch Neurol 1972; 27: 1-6.
7. Busija DW, Heistad DD, Marcus ML. Effects of sympathetic nerves on cerebral vessels during acute, moderate increases in arterial pressure in dogs and cats. Circ Res 1980; 46: 696-702.
8. Heistad DD, Marcus ML. Effect of sympathetic stimulation on permeability of the blood-brain barrier to albumin during acute hypertension. Circ Res 1979; 45: 331-3.
9. Edvinsson L, Owman C, Siesjo B. Physiological role of cerebrovascular sympathetic nerves in the autoregulation of cerebral blood flow. Brain Res 1976; 117: 519-23.
10. Gross PM, Heistad DD, Strait MR, Marcus ML, Brody MJ. Cerebral vascular responses to physiological stimulation of sympathetic pathways in cats. Circ Res 1979; 44: 288-94.
11. Baumbach GL, Heistad DD. Effects of sympathetic stimulation and changes in arteriolar pressure on segmental resistance of cerebral vessels in rabbits and cats. Circ Res 1983; 52: 527-33.
12. Grubb BP, Gerard G, Roush K, et al. Cerebral vasoconstriction during head-upright tilt-induced vasovagal syncope. A paradoxic and unexpected response. Circulation 1991; 84: 1157-64.
13. Grubb BP, Samoil D, Kosinski D, et al. Cerebral syncope: loss of consciousness associated with cerebral vasoconstriction in the absence of systemic hypotension. Pacing Clin Electrophysiol 1998; 21: 652-8.
14. Levine BD, Giller C, Lane LD, Buckey JC, Blomqvist CG. Cerebral versus systemic hemodynamics during graded orthostatic stress in humans. Circulation 1994; 90: 298-306.
15. Zhang R, Zuckerman JH, Levine BD. Deterioration of cerebral autoregulation during orthostatic stress: insights from the frequency domain. J Appl Physiol 1998; 85: 1113-22.
16. Sutton R, Petersen M, Brignole M, et al. Proposed classification for tilt-induced vasovagal syncope. European Journal of Cardiac Pacing and Electrophysiology 1992; 3: 180-3.
17. Raviele A, Brignole M, Sutton R, et al, for the Vasovagal Syncope International Study (VASIS) Investigators. Effect of etilefrine in preventing syncopal recurrence in patients with vasovagal syncope: a double-blind, randomized, placebo-controlled trial. Circulation 1999; 99: 1452-7.
18. Raviele A, Menozzi C, Brignole M, et al. Value of head-up tilt testing potentiated with sublingual nitroglycerin to assess the origin of unexplained syncope. Am J Cardiol 1995; 76: 267-72.
19. Imholz BP, Settels JJ, Van der Meiracker AH, Wesseling KH, Wieling W. Non-invasive continuous finger blood pressure measurement during orthostatic stress compared to intra-arterial pressure. Cardiovasc Res 1990; 24: 214-21.
20. Omboni S, Parati G, Frattola A, et al. Spectral and sequence analysis of finger blood pressure variability: comparison with analysis of intra-arterial recordings. Hypertension 1993; 22: 26-33.
21. Lennihan L, Petty GW, Fink ME, Solomon RA, Mohr JP. Transcranial Doppler detection of anterior cerebral artery vasospasm. J Neurol Neurosurg Psychiatry 1993; 56: 906-9.
22. Patty G, Wiebers D, Meissner I. Transcranial Doppler ultrasonography: clinical applications in cerebrovascular disease. Mayo Clinic Proc 1990; 65: 1350-64.
23. Woodcock JP, Gosling RG, Fitzgerald DE. A new non-invasive technique for assessment of superficial femoral artery obstruction. Br J Surg 1972; 59: 226-31.
24. Silvani S, Ciucci G, Verità E, et al. Correlazione tra tipo di positività del tilt test ed elettroencefalogramma simultaneo: risultati preliminari. Ital Heart J Suppl 2000; 1: 103-9.
25. Heistad DD, Kontos HA. Cerebral circulation. In: Shepherd JT, Abboud FM, eds. Handbook of physiology. Section 2: The cardiovascular system III. Bethesda, MD: American Physiological Society, 1983: 137-82.
26. Victor RG, Leimbach WN Jr. Effects of lower body negative pressure on sympathetic discharge to leg muscles in human. J Appl Physiol 1987; 63: 2558-62.
27. Furlan R, Piazza S, Dell'Orto S, et al. Cardiac autonomic patterns preceding occasional vasovagal reactions in healthy humans. Circulation 1998; 98: 1756-61.
28. Furlan R, Jacob G, Palazzolo L, et al. Sequential modulation of cardiac autonomic control induced by cardiopulmonary and arterial baroreflex mechanisms. Circulation 2001; 104: 2932-7.
29. Furlan R, Porta A, Costa F, et al. Oscillatory patterns in sympathetic neural discharge and cardiovascular variables during orthostatic stimulus. Circulation 2000; 101: 886-92.
30. Jacob G, Shannon JR, Costa F, et al. Abnormal norepinephrine clearance and adrenergic receptor sensitivity in idiopathic orthostatic intolerance. Circulation 1999; 99: 1706-12.
31. Furlan R, Jacob G, Snell M, et al. Chronic orthostatic intolerance: a disorder with discordant cardiac and vascular sympathetic control. Circulation 1998; 98: 2154-9.
32. Floras JS, Butler GC, Ando SI, Brooks SC, Pollard MJ, Picton P. Differential sympathetic nerve and heart rate spectral effects of nonhypotensive lower body negative pressure. Am J Physiol Regul Integr Comp Physiol 2001; 281: R468-R475.
33. Mano T, Iwase S, Watanabe T, Saito M. Age-dependency of sympathetic nerve response to gravity in humans. Physiologist 1991; 34 (Suppl): S121-S124.
34. Ector H. Neurocardiogenic, vasovagal syncope. Eur Heart J 1999; 20: 1686-7.
35. de Buitleir M, Grogan EW, Picone MF, Casteen JA. Immediate reproducibility of the tilt-table test in adults with unexplained syncope. Am J Cardiol 1993; 71: 304-7.
36. Brooks R, Ruskin JN, Powell AC, Newell J, Garan H, McGovern BA. Prospective evaluation of day-to-day reproducibility of upright tilt-table testing in unexplained syncope. Am J Cardiol 1993; 71: 1289-92.
37. Dan D, Hoag JB, Ellenbogen KA, et al. Cerebral blood flow velocity declines before arterial pressure in patients with orthostatic vasovagal presyncope. J Am Coll Cardiol 2002; 39: 1039-45.
38. Sloan MA, Haley EC, Kassel NF, et al. Sensitivity and specificity of transcranial Doppler ultrasonography in the diagnosis of vasospasm following subarachnoid hemorrhage. Neurology 1989; 39: 1514-8.
39. Lindegaard KF, Lundar T, Wiberg J, Sjoberg D, Aaslid R, Nornes H. Variations in the middle cerebral artery blood flow investigated with noninvasive transcranial blood velocity measurements. Stroke 1987; 18: 1025-30.
40. Huber P, Handa J. Effect of contrast material, hypercapnia, hyperventilation, hypertonic glucose and papaverine on the diameter of the cerebral arteries. Invest Radiol 1967; 2: 17-32.
41. Giller CA, Bowman G, Dyer H, Mootz L, Krippner W. Cerebral arterial diameters during changes in blood pressure and carbon dioxide during craniotomy. Neurosurgery 1993; 32: 737-41.
42. Hainsworth R. Fainting. In: Bannister R, ed. Autonomic failure: a textbook of clinical disorders of the autonomic nervous system. Oxford: Oxford University Press, 1988: 142-5.
43. Lipsitz LA, Morin R, Gagnon M, Kiely D, Medina A. Vasomotor instability preceding tilt-induced syncope: does respiration play a role? J Appl Physiol 1997; 83: 383-90.