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Prevalence, timing, and haemodynamic correlates of prodromes in patients with vasovagal syncope induced by head-up tilt test

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Aims To evaluate the prevalence, timing, and haemodynamic characteristics of prodromal symptoms in patients experiencing vasovagal syncope (VVS) during a head-up tilt test (HUT) potentiated with nitroglycerin, and their relationships with those reported before spontaneous episodes.

Methods and results Symptoms preceding HUT-induced syncope were recorded, together with heart rate (HR) and arterial blood pressure (BP) values, in 149 otherwise healthy and drug-free subjects with recurrent unexplained syncope. Head-up tilt test significantly increase the number of patients capable of recognizing the premonitory symptoms of VVS than before spontaneous episodes (96 vs. 79%; $P < 0.001$). The nine most frequent symptoms were stratified into three groups on the basis of their characteristics: headache, hot flashes, and palpitations occurred more than 3 min before syncope, with a very slight reduction in BP; nausea, asthenia, diaphoresis, vertigo, and epigastric discomfort preceded syncope by 1–3 min and were associated with a slight reduction in BP; and blurred vision appeared the last minute before syncope and was characterized by the lowest BP and HR values.

Conclusion In comparison with spontaneous syncopal episodes, HUT allows the more frequent recognition of prodromes also providing useful information in terms of timing and haemodynamic characteristics of symptoms that may allow more tailored patient counselling.

Keywords Vasovagal syncope • Tilt-table test • Signs and symptoms

Introduction

Vasovagal syncope (VVS), the most common cause of fainting, is characterized by a brief loss of consciousness associated with one or more symptoms occurring before, during, and immediately after the event.[1] Clinical prodromes play a major role in the diagnosis of VVS as they correlate with the haemodynamic and autonomic changes leading to it,[2–4] and can also be helpful in clinical management. The initial treatment of all forms of neurally mediated reflex syncope recommended by the current guidelines involves educating patients to recognize triggering events and premonitory symptoms,[5] because those who do so can avert fainting by means of specific manoeuvres, which is even more important, given the frequent inefficacy of medical and electrical therapy.[1]

However, previous studies have shown that a significant percentage of patients are asymptomatic at the time they experience syncope.[4,6] Furthermore, even when symptoms are present, it is often difficult to define their characteristics and correctly estimate their timing before fainting occurs. In this setting, head-up tilt test (HUT), which is considered to be the only appropriate method of diagnosing neurocardiogenic syncope,[5,7] could also be useful as a means of evaluating the occurrence and timing of symptoms before VVS.

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Table 1 Characteristics of patients by the presence of prodromes before at least one episode of spontaneous syncope

	All patients ($n = 149$)	Prodromes before spontaneous syncope		*P*-value
		No ($n = 32$)	Yes ($n = 117$)	
Gender (M/F)	80/69	22/10	58/59	0.054
Age (years)	32 ± 16	35 ± 18	32 ± 15	0.37
No. of syncopal episodes	3.7 ± 3.3	2.5 ± 2.7	4.0 ± 3.4	*0.009*
≥2 syncopal episodes (%)	60	38	66	*0.004*
Body mass index (kg/m^2)	23 ± 4	24 ± 4	23 ± 4	0.13
Systolic blood pressure (mmHg)	115 ± 11	116 ± 12	115 ± 11	0.48
Diastolic blood pressure (mmHg)	77 ± 9	77 ± 9	77 ± 9	0.81
Heart rate (bpm)	69 ± 12	68 ± 12	69 ± 12	0.78

Mean values ± SD. The italicized entries indicate *P*-values that are statistically significant.

The aims of this study were to clarify the clinical features preceding HUT-induced syncope and evaluate their associations with those occurring before spontaneous VVS episodes.

Methods

This study, which complied with the principles of the Declaration of Helsinki, involved 149 consecutive patients with a history of suspected VVS, all of whom gave their informed consent. The exclusion criteria were a history of cardiovascular disease, carotid sinus syndrome, or any disease that might affect the autonomic nervous system, and the use of any medication affecting the cardiovascular system. Before HUT, two of us (C.F. and M.I.) independently interviewed the patients in detail about their medical history and examined them.

Head-up tilt test

The tests were performed between 9:00 and 11:00 a.m. in a temperature-controlled room (23°C) in accordance with the current guidelines[5] by two nurses experienced in the technique (C.B. and M.S.) under the supervision of two physicians (C.F. and M.I.). ECG, systolic blood pressure (SBP), and diastolic BP (DBP) were continuously monitored and recorded using a Task Force Monitor (CNSystems, Graz, Austria).

After 10 min of supine rest, the patients were tilted to 70° using an electronically operating tilt-table with a footboard. If VVS had not occurred after 20 min, 300 μg of nitroglycerin was administered sublingually, and the test was continued for a further 20 min.[5] The syncope was classified by two of us (C.F. and M.I.) on the basis of the modified Vasovagal Syncope International Study (VASIS) classification as type 1 (mixed), type 2A (cardioinhibition without asystole), type 2B (cardioinhibition with asystole), or type 3 (vasodepressive).

Symptom assessment

Reports of prodromes just before spontaneous syncope were collected before HUT. Each symptom was considered present when referred to as prodromes of one spontaneous fainting episode.

The symptoms occurring before VVS episodes during HUT were recorded, together with heart rate (HR), SBP and DBP at the time of symptom onset; clinical manifestations reported during or after syncope were not considered. The assessed symptoms were anxiety, asthenia, blurred vision, chest pain, diaphoresis, dyspnoea, epigastric discomfort, headache, hot flashes, nausea, palpitations, paraesthesia, tinnitus, tremor, vertigo, vomiting, or weakness. Any symptom reported by <5% of the patients before spontaneous or HUT-induced episodes was excluded from analysis.

Statistical analysis

The data are given as mean values ± standard deviation (SD) unless otherwise specified; categorical variables are described as frequencies and percentages. The timing and haemodynamic characteristics of the prodromal symptoms were evaluated using mean values and their 95% confidence intervals (CIs) in order to take into account the different number of patients experiencing each symptom. Within-group comparisons were made using Student's *t*-test for dependent variables, and between-group comparisons by means of Student's *t*-test for independent samples. The non-parametric Mann–Whitney *U*-test was used when appropriate. Frequencies were compared using the χ^2 or Fisher's exact test, and paired proportions using McNemar's test. The statistical analyses were made by one of us (P.G.) using Statistica 6.1 software (StatSoft Inc., Tulsa, OK, USA).

Results

One hundred and forty-nine out of 239 patients (62%) were HUT positive and included in the analysis. Prodromes before spontaneous syncopal episodes occurred in 117 (79%) patients and were not present in 32 (21%). *Table 1* shows the characteristics of the patients divided into those with and without symptoms before at least one spontaneous syncope episode. Those with prodromes had experienced a significantly higher number of episodes in general, and a significantly greater proportion of them had experienced two or more. There were no demographic or clinical differences between the two groups.

The frequency of patients recognizing prodromes before HUT-induced syncope was significantly higher than those at spontaneous episode (96 vs. 79%, $P < 0.001$). *Figure 1* shows the prevalence of prodromal symptoms before spontaneous and HUT-induced syncope. Blurred vision, nausea, asthenia, and headache were significantly more frequent before HUT-induced than spontaneous syncope. Symptoms occurred before spontaneous episode were reproduced by HUT with the following percentages: 72% for blurred vision, 74% for nausea, 65% for asthenia, 49% for vertigo, 31% for diaphoresis, 60% for headache, 20% for epigastric discomfort, and 60% for palpitations. Among the six patients who reported hot flashes before spontaneous syncope, nobody referred the aforementioned symptom before HUT-induced syncope.

Table 2 shows the symptoms occurring immediately before HUT-induced VVS, their timing, and the patient's haemodynamic characteristics at the time of onset. Blurred vision was the most frequent symptom observed followed by nausea, asthenia, diaphoresis, vertigo, headache, hot flashes, epigastric discomfort, and palpitations. In the case of all of the symptoms except palpitations, there was a significant reduction in both mean SBP and DBP in comparison with the values measured after the first minute of

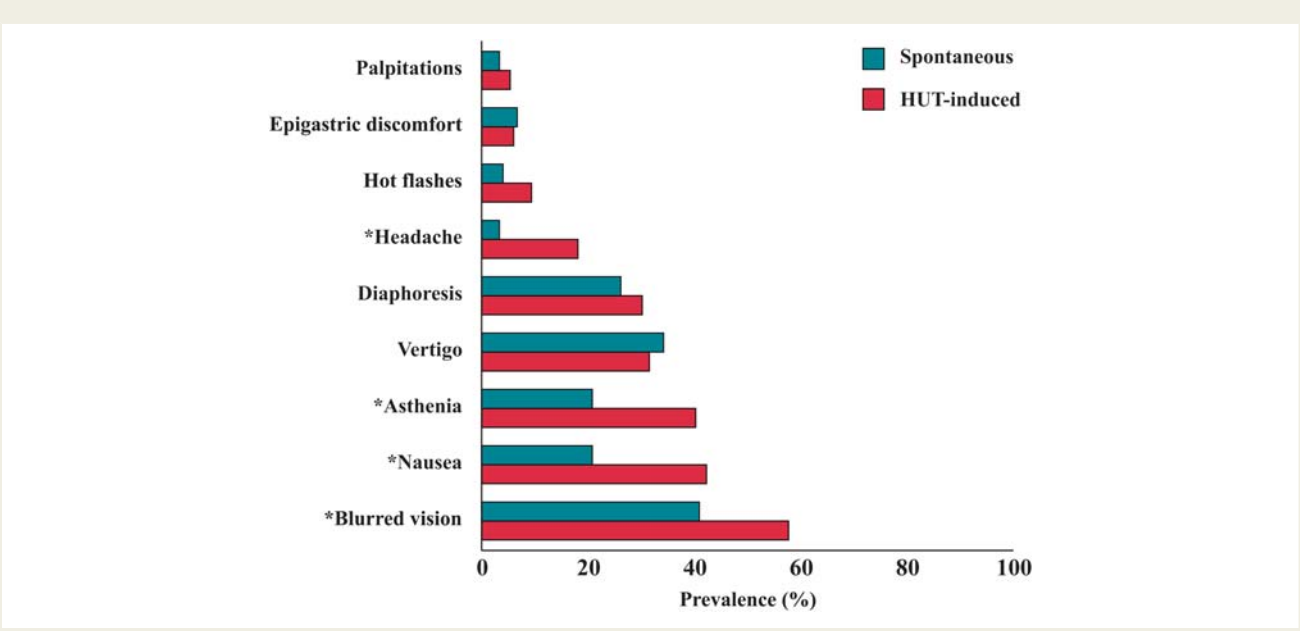

Figure 1 Prevalence of prodromal symptoms before spontaneous and HUT-induced syncope. *Significantly different ($P < 0.05$) using McNemar's test for paired proportions. Blurred vision ($P = 0.002$), nausea ($P < 0.001$), asthenia ($P < 0.001$), and headache ($P < 0.001$) were significantly more frequent before HUT-induced than spontaneous syncope.

Table 2 Frequency of symptoms before HUT-induced syncope, their timing, and the patients' cardiovascular parameters at the time of onset

	N	Onset (min before VVS)	SBP (mmHg)	DBP (mm Hg)	HR (bpm)
Blurred vision	86	0.7 (0.5–0.9)	82 (78–85)*	56 (53–58)*	74 (68–80)
Nausea	63	1.8 (1.0–2.5)	92 (88–96)*	63 (60–67)*	81 (74–87)
Asthenia	60	1.6 (0.8–2.5)	94 (89–99)*	66 (61–70)*	*85 (78–92)*†
Vertigo	47	2.3 (0.8–3.7)	96 (91–101)*	64 (61–67)*	83 (74–92)
Diaphoresis	45	1.8 (0.5–3.1)	89 (84–95)*	62 (57–66)*	78 (69–86)
Headache	27	4.6 (2.0–7.2)	110 (102–117)*	74 (68–79)*	97 (88–107)†
Hot flashes	14	3.7 (0.1–7.4)	113 (101–125)*	75 (65–85)*	86 (75–97)
Epigastric discomfort	9	1.0 (0.5–1.6)	94 (83–105)*	60 (48–71)*	79 (71–87)
Palpitations	8	2.4 (1.0–3.8)	108 (91–124)	78 (65–91)	121 (102–140)†

Mean values (95% CIs). HUT, head-up tilt test; VVS, vasovagal syncope; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.
*Significantly lower ($P < 0.05$) than those after the first minutes of HUT; †significantly higher ($P < 0.05$) than those after the first minutes of HUT.

HUT (SBP and DBP mean values were 118 ± 13 and 81 ± 10 mmHg, respectively). Heart rate was higher at the time of onset of asthenia, headache, and palpitations than those after the first minute of HUT (mean value was 78 ± 13 bpm). The symptom occurring closest to syncope was blurred vision, which was associated with the lowest SBP, DBP, and HR values.

Table 3 shows the prevalence of prodromes observed before HUT-induced syncope, the frequency of VASIS type, and the percentage of patients receiving nitroglycerin by the presence/absence of prodromes before spontaneous syncope episodes. There were no differences in the overall number of symptoms or the occurrence of each prodrome.

There were no differences in symptom frequency by VASIS type (*Figure 2A*) or nitroglycerin use (*Figure 2B*) except in the case of headache, which occurred more frequently in the patients who fainted only after receiving nitroglycerin.

Discussion

To the best of our knowledge, this is the first study that has analysed the association between the symptoms preceding spontaneous VVS and those preceding HUT-induced VVS, as well as the timing of symptom onset before HUT-induced VVS.

The relevance of these results lies in the generally recognized usefulness of symptoms in the diagnosis and clinical management of VVS. Various studies have demonstrated the diagnostic value of the symptoms preceding spontaneous episodes of VVS,[3,4] as well as their capacity to predict HUT outcomes[8–11] and VVS recurrence.[12] This value is mainly due to their association with the significant decrease in BP caused by the initial changes in autonomic balance leading to fainting[13] and, on the basis of this, it is currently recommended that patients should be counselled to recognize prodromal symptoms as a first step to preventing VVS, because this can allow them to make appropriate postural manoeuvres to reduce the recurrence of syncope. This approach to the management of VVS has proved to be effective,[14] and is even more relevant given the conflicting results of most therapeutic measures.[1]

Table 3 Prodromes before HUT-induced syncope, VASIS classification, and nitroglycerin use by the presence of prodromes before at least one episode of spontaneous syncope

	Prodromes before spontaneous syncope		*P*-value
	No (*n* = 32)	Yes (*n* = 117)	
Prodromes before HUT-induced syncope			
Mean number	2.4 ± 1.3	2.5 ± 1.2	0.95
Blurred vision (%)	59	57	0.83
Nausea (%)	28	46	0.07
Asthenia (%)	44	39	0.65
Vertigo (%)	22	34	0.18
Diaphoresis (%)	44	26	0.06
Headache (%)	16	19	0.68
Hot flashes (%)	13	9	0.50
Epigastric discomfort (%)	9	5	0.40
Palpitations (%)	3	6	0.46
VASIS classification, no. (%)			0.83
1	8 (25)	35 (30)	
2A–2B	13 (41)	47 (40)	
3	11 (34)	35 (30)	
Nitroglycerin provocation (%)	53	57	0.68

Mean values ± SD.

Our findings extend those of previous studies insofar as they demonstrate that HUT can significantly increase the number of patients capable of recognizing the premonitory symptoms of VVS. Head-up tilt test is therefore not only a useful means of confirming that the symptoms are related to the vasovagal origin of syncope, but can also increase the patients' sense of control over them. This seems to be supported by the fact that the patients who had experienced more VVS episodes were those who more frequently reported symptoms before spontaneous syncope, which strengthens the potential usefulness of HUT in increasing patients' awareness of their prodrome.

The usefulness of HUT in patient education is further supported by two other factors. First, we identified the most frequent symptoms preceding HUT-induced VVS, which had also a good correlation with the symptoms referred before spontaneous episodes. Moreover, we defined timing, and haemodynamic characteristics of symptoms, and found that they could be divided into three groups. Headache, hot flashes, and palpitations were characterized by the fact that they appeared more than 3 min before the onset of syncope and were accompanied by a very slight drop in BP; nausea, asthenia, diaphoresis, vertigo, and epigastric discomfort appeared 1–3 min before the onset of syncope and were accompanied by a slight drop in BP; and blurred vision frequently appeared <1 min before the onset of syncope and was accompanied by a considerable drop in BP. This differentiation is in line with the findings of previous studies showing that VVS is not a sudden-onset phenomenon because BP reduction is already evident at the beginning of the prodromes, 3 min before the impending syncope.[15]

The definition of groups of symptoms with an early, intermediate, and late onset, and different changes in BP could be extremely useful in patient counselling. In particular, patients should be educated to recognize the prodromal symptoms that appear first, thus giving them time to make appropriate postural manoeuvres in an attempt to prevent fainting. This hypothesis is supported by the findings of Krediet *et al.*,[16] who have shown that informed and instructed patients can correctly recognize prodromes and promptly perform counter-manoeuvres (leg crossing and muscle tensing) to prevent vasovagal reactions.

Our results also demonstrated that the prevalence of symptoms before HUT-induced VVS is not related to the VASIS type of syncope. The administration of nitroglycerin does not modify the frequency of symptoms except for headache which is more frequently observed. Considering that headache is the most common side effect of nitrates,[17] its occurrence after nitroglycerin

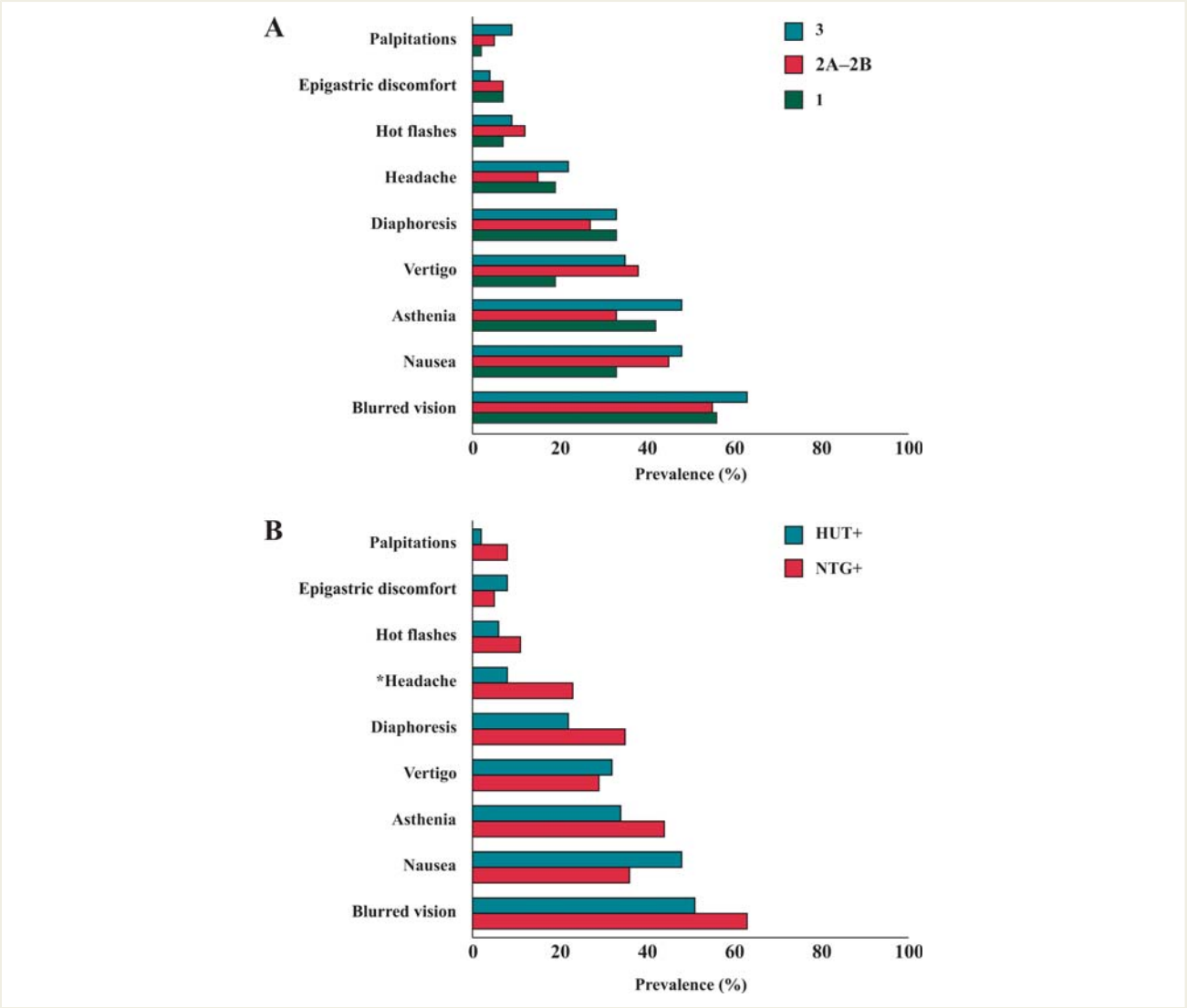

Figure 2 (*A*) Prevalence of prodromal symptoms during HUT by VASIS classification. There were no significant between-group differences. (*B*) Prevalence of prodromal symptoms during HUT by test phase (HUT+: patients who fainted before nitroglycerin administration; NTG+: patients who fainted after nitroglycerin administration). Headache was significantly more frequent in the patients who fainted after nitroglycerin administration (*$P = 0.015$).

administration and before VVS occurrence should be considered less specific than the other symptoms.[17]

Clinical perspectives

Further studies should be designed to evaluate whether the analysis of individual symptoms preceding syncopal episodes during HUT reduces spontaneous VVS recurrence, improving the prodrome recognition of an impending syncopal episode. Moreover, the HUT ability in reproducing the same symptoms occurring before spontaneous syncope should be prospectively evaluated in order to confirm our results.

In conclusion, our study shows that it is possible to characterize the symptoms occurring before a spontaneous episode in patients with HUT-induced VVS, which could be useful in increasing the patients' sense of control over their symptoms and ensuring more effective counselling aimed at averting fainting.

Conflict of interest: none declared.

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