Nitrate-potentiated head-up tilt testing (HUT) has a low diagnostic yield in patients with likely vasovagal syncope

Journal:	*Pacing and Clinical Electrophysiology*
Manuscript ID:	PACE-13-0088.R1
Wiley - Manuscript type:	Original
Date Submitted by the Author:	24-May-2013
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Key Words:	Electrophysiology - Clinical, Vagal Syndromes

Nitrate-potentiated head-up tilt testing (HUT) has a low diagnostic yield in patients with likely vasovagal syncope

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Keywords. Vasovagal syncope, Clinical history, Head-up tilt testing

Running head: head-up tilt testing in syncope evaluation

Word count: 3107

ABSTRACT

Background. Vasovagal syncope (VVS) is characterized by a wide spectrum of clinical presentations but the relationship between clinical presentation and response to head-up tilt testing (HUT) has not yet been evaluated in detail. The aim of this study was to assess the relationship between the clinical presentation of VVS and HUT and clinical outcome at long-term follow-up.

Methods. Out of 671 consecutive subjects undergoing nitroglycerin-potentiated HUT for suspected VVS, 369 patients with normal ECG and no structural heart disease were included in our study.

Results. A history suggestive of typical or atypical VVS was obtained in 198 and 171 patients, respectively. The positivity rate of HUT was 65% and 36% in patients with established and likely VVS, respectively ($p < 0.0001$). In patients with established VVS, a time interval of $\leq$28 days between the last syncope and HUT was the only independent predictor of a positive test. In patients with likely VVS, no variable was predictive of a positive HUT. At a mean follow-up of 43 $\pm$ 27 months, the rate of adverse events (all-cause mortality, syncope recurrence, and major diagnostic and/or therapeutic procedures) was similar in patients of both groups, independent of HUT results.

Conclusion. In patients with likely VVS, HUT has a low diagnostic yield and may be inadequate to establish a reliable diagnosis. Similar long-term outcomes were observed in patients with positive or negative test results, suggesting that HUT is of limited value in the management of patients with suspected neurally mediated syncope.

INTRODUCTION

Vasovagal syncope (VVS) is the most frequent cause of transient loss of consciousness both in unselected patients presenting to the emergency department and in those referred to secondary or tertiary centres for syncope.(1-3) A detailed clinical history proved to be crucial in obtaining an accurate etiological diagnosis of syncope.(4) In some patients, VVS is initiated by clear adrenergic stimuli such as fear, pain, emotional distress, or medical instrumentation, whereas in others it develops after prolonged orthostatic stress, or hypovolaemia. However, VVS may also occur without any identifiable trigger or without any warning symptoms. In the latter case, clinical features and interviews are inadequate to identify the cause of syncope, and the diagnosis is established on the basis of a positive response to head-up tilt testing (HUT).(4) Different HUT protocols and provocative pharmacological agents have been introduced into clinical practice to improve HUT positivity rates in unselected populations.(5,6) HUT potentiated with sublingual nitroglycerin (NTG) is one of the recommended test protocols because of its satisfactory positivity rate, specificity and tolerability.(6) However, HUT positivity rates in selected patients with atypical VVS have not yet been investigated in detail. This could be of pivotal importance for clinical decision-making to optimize the diagnostic work-up of syncope patients, to improve examination's diagnostic yield, and to reduce total costs.

On these grounds, the aim of the present study was to assess the clinical presentation of VVS in relation to HUT outcome and to evaluate the long-term (3.5 years) prognosis of syncope, the rate of syncope recurrences and major adverse events in relation to the clinical presentation of VVS and HUT outcome.

METHODS

Study population

All patients with at least one syncopal episode referred to a single tertiary centre for syncope were included consecutively in this prospective, observational study. They underwent a thorough history

using a standardized form , physical examination, 12-lead electrocardiogram (ECG), postural blood pressure testing, and carotid sinus massage according to the recommendations of the European Society of Cardiology Task Force on Syncope.(4) Additional cardiac, neurologic, or psychiatric investigations were performed if clinically indicated. The study was approved by the local Ethics Committee and informed consent was obtained from all patients.

Definitions and diagnostic criteria based on the initial evaluation

The diagnostic criteria for the cause of syncope were established before HUT, taking into account the last syncopal episode. *Established VVS* was defined as syncope preceded by provocative stimuli such as fear, severe pain, emotional stress, instrumentation, or prolonged standing, in association with prodromal symptoms of autonomic activation such as pallor, sweating, nausea, in the absence of other competing causes of syncope. *Likely VVS* was defined as syncope occurring without any identifiable trigger or prodromal symptoms, in the absence of other competing causes of syncope.(4) Therefore, the latter category included patients with syncope of unknown origin and high pre-test likelihood of VVS.

The following patients were excluded from the study:

1) patients with disorders without impairment of consciousness or unexplained falls;
2) patients with structural heart disease, abnormal ECG, syncope during effort or in supine position, or preceded by palpitations or dyspnoea, as all these variables are well known predictors of cardiac syncope.(2,7,8) The ECG was considered abnormal if any of the following were present: sinus bradycardia <50 bpm, first-degree atrioventricular block or higher, bundle branch block, previous myocardial infarction, supraventricular or ventricular tachycardia, left or right ventricular hypertrophy, ventricular preexcitation, long or short QT, Brugada pattern, negative T waves in V1-V3 suggestive of arrhythmogenic right ventricular cardiomyopathy;
3) patients with carotid sinus syndrome, situational syncope or syncope due to orthostatic hypotension. Situational syncope was diagnosed if patients experienced loss of consciousness during or immediately after micturition, defaecation, coughing, swallowing, or sneezing.

Orthostatic hypotension was defined as a drop in systolic blood pressure of ≥20 mmHg and/or a systolic blood pressure value of <90 mmHg associated with syncope or presyncope;

4) patients with delayed orthostatic hypotension during HUT;

5) patients with incomplete evaluation.

Head-up tilt testing

HUT was performed according to the Italian Protocol (6). Blood pressure, heart rate and rhythm were continuously monitored and recorded. Blood pressure was measured using the Finometer Pro device (Finapres Medical Systems, Amsterdam, the Netherlands). After a 5-minute baseline period in the supine position, the patient was tilted up to 60° for 20 minutes. If passive orthostatism did not induce syncope, sublingual NTG spray (300 μg) was administered, followed by additional 15 minutes of tilting. If syncope developed, the tilt table was rapidly lowered to the supine position and the test was stopped. A positive HUT response was defined as the induction of spontaneous syncope associated with hypotension, bradycardia, or both. Positive responses were classified according to the modified VASIS classification.(9)

Treatment

Initial treatment included patient education regarding awareness and avoidance of trigger factors or blood pressure lowering agents. In patients with recognizable prodromal symptoms, physical counterpressure maneuvers were advised. No specific pharmacological therapy for VVS was administered because of the sparse evidence of drug efficacy.(4) Additional treatments (e.g., cardiac pacing) were considered for patients who continued to experience fainting spells despite adequate lifestyle measures. In these cases, the decision on when and how to treat patients was left to the discretion of the attending physician.

Follow-up

Follow-up was obtained by clinic visits or annual telephone interviews. The outcome events were death from any cause, syncope recurrences, and major diagnostic or therapeutic procedures (cardiac pacing, electrophysiologic study, loop recorder implantation, or radiofrequency ablation for

tachyarrhythmias). Events were confirmed by death certificate, hospital charts, and/or physician's records. An independent reviewer, unaware of the patient's clinical history, classified the cause of death.

Statistical analysis

Normally distributed data are expressed as means ± standard deviation. Non-normally distributed variables, as determined by the Kolmogorov-Smirnov test, are expressed as median (range). Student's *t*-test or Mann-Whitney test, chi-square or Fisher exact tests were used for comparison between groups when appropriate. Independent predictors of a positive HUT response were obtained by multivariate logistic regression analysis with stepwise forward selection. Annual event rates were calculated as the number of events divided by the person-years of follow-up. Potential predictors of all-cause mortality and syncope recurrence were first evaluated individually and then analysed by multivariate Cox proportional hazards regression analysis with stepwise forward selection. Survival and syncope recurrence curves were established using Cox regression with adjustment for risk factors. A p value of <0.05 was considered statistically significant. All analyses were performed using SPSS software version 11.5 (SPSS Inc., Chicago, Illinois).

RESULTS

Patient characteristics

Out of 671 patients evaluated, 302 patients were excluded according to the criteria described previously. The remaining 369 patients formed the population of the present study (Fig. 1). According to the diagnostic criteria based on the initial evaluation, 198 patients were diagnosed with established VVS and 171 with likely VVS. The demographic and clinical characteristics of the two groups are reported in Table 1. The clinical features of syncope in the two groups of patients are showed in Table 2.

Diagnostic yield of HUT

From the total of 369 patients, 191 (52%) had a positive HUT. In 173 subjects (91%), positive

responses occurred during the pharmacologic phase and were more frequently observed in patients with established VVS (128/198, 65%) than in those with likely VVS (62/171, 36%) ($p < 0.0001$). The hemodynamic pattern of positive responses was similar between groups. In patients with recurrent syncope (≥2 syncopal episodes), the positivity rate was 67% (103/154) in patients with established VVS and 41% (42/102) in those with likely VVS ($p < 0.0001$). The clinical features of patients with likely VVS in relation to HUT results are reported in Table 3. The only difference between patients with positive or negative HUT results was a higher prevalence of major trauma in the latter.

Predictors of a positive response to HUT

The results of univariate logistic regression analysis for prediction of a positive HUT response are shown in Table 4. On multivariate logistic regression analysis, a history suggestive of typical VVS and a time interval between the last syncopal episode and HUT of ≤ 28 days were identified as predictors of a positive response to HUT in the overall population (Table 4). In patients with established VVS, the time from the last spontaneous syncope to test remained the only independent predictor of a positive HUT response [Wald $\chi 2 = 11.694$, $p < 0.001$, Exp (β) 3.289, 95% confidence interval (CI) 1.662–6.508]. In this group, the positivity rate decreased from 76% to 53% ($p < 0.001$) if the test was performed after 28 days from the last syncopal episode. In patients with likely VVS, no pre-test or intra-test variable was predictive of a positive HUT, and the rate of positive results was 41% and 31% if the test was performed within or after 28 days from the last syncopal episode, respectively ($p = 0.27$).

Adverse events (all-cause mortality, syncope recurrence and major diagnostic and/or therapeutic procedures)

Patients were prospectively followed for a mean period of 43 ± 27 months (median 44 months). Only nine patients were lost to follow-up. The annual all-cause mortality rate was 1.0% in patients with established VVS and 2.2% in those with likely VVS ($p = 0.07$). On univariate Cox proportional regression analysis, age at first syncope >65 years ($\chi^2 = 17.62$, $p < 0.0001$),

hypertension (χ^2 = 9.16, p <0.002) and co-morbidities (χ^2 = 6.895, p <0.01) were found to be predictive of all-cause mortality. On stepwise multivariate analysis, age at first syncope >65 years [Wald χ^2 = 17.624, p <0.0001, Exp (β) 1.113, 95% CI 1.059–1.169] emerged as the only independent predictor of mortality. No patient died of sudden death. The 1-year recurrence rate of syncope was 4.6% and 4.0% in patients with established and likely VVS, respectively (p = 0.88). On univariate Cox analysis, the number of previous syncopal episodes ≥ 3 (χ^2 = 20.894, p <0.001) and diabetes (χ^2 = 8.120, p <0.005) were identified as predictors of syncope recurrence. On stepwise multivariate analysis, the number of previous syncopal episodes was an independent predictor of syncope recurrence [Wald χ^2 = 19.968, p <0.0001, Exp (β) 1.073, 95% CI 1.074–1.125]. Cumulative syncope recurrence-free curves as a function of HUT results after adjustment for the number of previous syncopal episodes are shown in Figure 2. The clinical characteristics and HUT results of the eight patients who underwent a major therapeutic procedure are shown in Table 5. At follow-up, a potential cardiac cause of syncope was documented in only 2 patients (supraventricular tachycardia due to a concealed accessory pathway in one and infra-hisian conduction abnormalities in the other). A non-syncopal cause of loss of consciousness was identified in 2 patients with likely VVS, who were diagnosed with epilepsy (HUT response was positive in one and negative in the other). The rate of major clinical events in relation to the clinical presentation of syncope and HUT results is shown in Figure 3.

DISCUSSION

Main findings

This study shows that the positivity rate of HUT is significantly lower in patients with likely VVS than in those with established VVS. Typical vasovagal fainting is commonly triggered by typical predisposing factors,(4) and the loss of consciousness is preceded by prodromal symptoms such as pallor or sweating, indicating transient alterations in autonomic nervous system activity. (10)

However, the classic markers of VVS can often be absent, in particular in elderly individuals. (7) Atypical VVS was reported to be the most frequent clinical presentation either in unselected patients referred to the emergency department (1) or in selected patients referred to secondary or tertiary centers for syncope.(7) At present, HUT is the only clinical laboratory test recommended to determine susceptibility to vasovagal fainting in patients with unexplained syncope.(4,5) In our study, although different mechanisms other than neurally mediated syncope (e.g., sick sinus syndrome, paroxysmal atrioventricular block of supraventricular tachycardia) may be responsible for the loss of consciousness in patients with likely VVS and negative test results, the diagnostic yield of HUT was very poor in this patient subset.

Our study population included patients with a low probability of having cardiac syncope because those with clinical features suggestive of a cardiac etiology were excluded.(2,7) In a previous investigation, abnormal ECG and structural heart disease were the most powerful predictors of cardiac syncope, whereas in the absence of structural heart disease cardiac etiology was unlikely unless syncope was preceded by palpitations.(2) The predictive value of abnormal ECG and/or structural heart disease for an arrhythmic cause of syncope has recently been confirmed by prolonged ECG monitoring.(8) During follow-up, a cardiac cause of syncope, undetected at initial evaluation, was identified in only 2 patients with likely VVS and a negative HUT (paroxysmal supraventricular tachycardia in one and atrioventricular conduction disturbance in the other). In addition, patients with established or likely VVS shared similar clinical characteristics, independent of HUT results. Finally, during follow-up, comparable rates of syncope recurrence, major diagnostic and/or therapeutic procedures and death were observed in patients with a positive or negative HUT.

A shorter time interval between the last syncopal episode and HUT is a well known predictor of a positive response to the test (11-12) and may explain the lower positivity rates in patients with likely VVS. However, in this group, the time from the last syncopal episode to HUT, although slightly longer than that of patients with established VVS, was not associated with a positive HUT

and cannot account for the low positivity rates recorded in our study.

In our study a low recurrence rate of syncope was observed. This can be due to the selection of patients: recurrence of VVS is predicted by the frequency of events in the preceding year and by the total number of historical spells. (13) In our population 30% of patients did not have a history of previous syncope. Finally we cannot exclude the effect of treatments (physical contermaneuvres, reduction or cessation of vasoactive drugs, cardiac pacing). Also in the EGSYS 2 follow-up study a low recurrence rate of syncope was observed in treated patients with neurally-mediated syncope. (14)

VVS is one of the most common causes of convulsive syncope, which may render the differential diagnosis with epilepsy challenging.(15) Information obtained from a witness or other bystanders is crucial, but when history alone does not point to any specific etiology, HUT is currently recommended as a diagnostic tool.(4) At follow-up, epilepsy was confirmed as the cause of loss of consciousness in 2 patients with likely VVS, one of whom had a positive HUT. Although the possibility of a misdiagnosis cannot be excluded, this may lead us to hypothesize that two different causes of fainting were concomitantly present in these patients. No patient had non-syncopal conditions, such as pseudo-syncope or cataplexy.

Comparison with previous studies

Sheldon et al. compared the demographic characteristics and historic features of syncope patients with a positive HUT to those of syncope patients with a negative HUT and no obvious cause of syncope.(12) Patients with either negative or positive test results shared similar clinical characteristics and actuarial probabilities of remaining free of syncope, suggesting that they may be part of the same population. However, HUT outcome was not analysed as a function of the clinical presentation of syncope. Our results are consistent with those of the ISSUE study, which showed that patients with isolated unexplained syncope with either a negative or positive HUT have similar clinical characteristics and outcomes (a low annual recurrence rate and a low risk of injury or adverse events). These findings may suggest a neurally mediated cause of syncope in patients of

both groups.(16) It can therefore be assumed that patients with established or likely VVS share similar pre-test characteristics and post-test outcomes despite remarkable differences in HUT response.

Pathophysiological implications

Usually, typical VVS starts at a young age, and in most subjects it occurs as an isolated manifestation not associated with cardiovascular, neurologic or other diseases.(17-18) Atypical VVS is more common in older individuals and may frequently be associated with cardiovascular or neurological disorders. Several mechanisms may account for the different clinical presentations of atypical VVS, including a displacement of blood from the thorax to the lower extremities,(19) impaired baroreflex sensitivity,(20) decreased parasympathetic activity,(21) and decreased cardiac responsiveness to β-adrenergic stimulation.(22) All these mechanisms may prevent the activation of the cardioinhibitory response eliciting reflex bradycardia and decreased sympathetic drive (the Bezold-Jarisch reflex).(23) Recently, Giese et al. (24) showed that older patients tolerated upright posture for a longer period before syncope than did younger patients. In this respect, it is likely that higher baseline blood pressure values provide the elderly with a greater blood pressure "reserve" for maintenance of consciousness compared with younger patients. These mechanisms may contribute to lower positivity rates of HUT in elderly patients with atypical VVS.

Study limitations

Several limitations should be acknowledged. First, alternative diagnoses to VVS could not be excluded in every case because of the current lack of a gold standard test. As a consequence, in patients with likely VVS, positivity rates of HUT may not reflect the real sensitivity of the test. Second, the sample selection is another limitation. It has been estimated that only a minority of patients with syncope seek medical attention.(25) We are aware that the inclusion of patients with a broad range of clinical and hemodynamic features is a potential source of selection bias. However, it should to be noted that this is the exact population most often referred for HUT. Accordingly, our findings should be interpreted within the context of the study sample, and NTG-potentiated HUT

results cannot be compared with those of other series using different protocols.

The ISSUE 2 study (26) showed that in some patients with recurrent suspected neurally mediated syncope arrhythmias may cause loss of consciousness. Indeed, primary tachyarrhythmias and paroxysmal atrioventricular blocks with concomitant increase in sinus rate were detected using implantable loop recorders in 21% of cases. It is worth noting, however, that data from the ISSUE 2 study refer to a population of severely symptomatic patients that strongly differs from our study sample.

Conclusions

The findings of the present study suggest that in patients with high pre-test likelihood of neurally mediated syncope HUT may provide diagnostic evidence of susceptibility to vasovagal reactions in patients with typical VVS. However, in patients with an atypical presentation of syncope (in particular in the elderly) HUT outcome alone may be inadequate to establish a reliable diagnosis. The low diagnostic yield of HUT limits its diagnostic value, and test results should always be interpreted cautiously in patients with other potential causes of loss of consciousness.

Contributorship.

Nunzia Rosa Petix:conception and design, statistical analysis

Attilio Del Rosso:conception and design, statistical analysis

Raffaello Furlan:drafting the article and revising

Guarnaccia Vincenzo:drafting the article and revising

Andrea Zipoli:conception and design, drafting the article and revising

Conflict of Interest: None declared.

Funding: this research received no specific funding.

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FIGURE LEGENDS

Figure 1. Flow diagram of the study patients undergoing head-up tilt testing potentiated with sublingual nitroglycerin**.** Of the 671 eligible patients (pts), 302 were excluded from the analysis on the basis of well established criteria. The remaining 369 patients formed the population of the present study.

Figure 2. Cumulative syncopal recurrence free-survival in patients with established VVS and likely VVS in relation to HUT results. Comparison of 4-year syncopal recurrence free- survival curves of patients with established (top panel) and likely VVS (bottom panel) in relation to HUT results. *Solid lines* represent HUT-positive patients and *dotted lines* represent HUT-negative patients. Note that no significant differences in syncope recurrence in relation to HUT results were found between groups.

HUT, head-up tilt test; VVS, vasovagal syncope.

Figure 3. Rate of major clinical events in relation to the clinical presentation of syncope and HUT results**.** Comparison of the rate of major clinical events between patients with established and likely VVS in relation to HUT results.

Syncope rec. = syncope recurrence rate; Major proc. = Major diagnostic and/or therapeutic procedure.

HUT, head-up tilt test; VVS, vasovagal syncope.

Table 1. Baseline characteristics of the study population

	Established VVS (n=198)	Likely VVS (n=171)	p Value
Age, yrs (mean ± SD, median)	50 ± 20 (55)	61 ± 20 (67)	0.0001
Male gender, n (%)	79 (40)	82 (48)	0.14
Age at first syncope, yrs (mean ± SD)	45 ± 21	58 ± 20	0.0001
Syncopal episodes (mean ± SD)	4.5 ± 4.7	2.7 ± 3.1	0.0001
Recurrent syncope, n (%)	149 (75)	105 (61)	0.005
Syncopal episodes ≥ 3, n (%)	109 (55)	56 (33)	0.0001
Presyncopal episodes (mean ± SD)	3.2 ± 4.5	2.0 ± 4.0	0.005
Traumatic syncope, n (%)	80 (40)	87 (51)	0.05
Major trauma, n (%)	17 (9)	31 (18)	0.01
Fractures, n (%)	13 (7)	24 (14)	0.02
Prodromal symptoms, n (%)	198 (100)	63 (37)	0.0001
Time interval between the last syncopal episode and HUT, days (mean ± SD)	47 ± 87	88 ± 133	0.19
Associated diseases, n (%)			
Hypertension	52 (26)	67 (39)	0.01
Diabetes	7 (4)	18 (11)	0.01
Neurological disorders	2 (1)	9 (5)	0.09
Other	8 (4)	11 (6)	0.08

HUT, head-up tilt test; VVS, vasovagal syncope.

Table 2. Clinical features of syncope in patients with established and likely VVS

	Established VVS (n = 198)	Likely VVS (n = 171)	p Value
Prolonged orthostasis	126 (64%)	0 (0%)	0.0001
Warm/crowded place	13 (6%)	0 (0%)	0.001
Fear/pain/emotion	45 (23%)	0 (0%)	0.0001
Instrumentation	14 (7%)	0 (0%)	0.001
Nausea/vomiting	129 (65%)	0 (0%)	0.0001
Blurred vision	40 (20%)	22 (13%)	0.08
Dizziness	59 (30%)	41 (24%)	0.09
Sweating preceding syncope	153 (77%)	2 (1%)	0.0001
Pallor	37 (19%)	0 (0%)	0.0001
Epigastric discomfort	52 (26%)	1 (0.5%)	0.0001
Asthenia	19 (10%)	16 (9%)	0.9
Hot flashes	11 (5%)	0 (0%)	0.006
Incontinence	2 (1%)	11 (6%)	0.005
Slow recovery	10 (5%)	34 (20%)	0.0001
Confusion	2 (1%)	26 (15%)	0.0001
Nausea/vomiting after syncope	16 (8%)	7 (4%)	0.1
Retrograde amnesia	7 (4%)	68 (40%)	0.0001

VVS, vasovagal syncope.

Table 3. Clinical features of patients with likely VVS in relation to head-up tilt test results

	Positive HUT (n=62)	Negative HUT (n=109)	p Value
Age, yrs (mean ± SD)	62 ± 18	60 ± 20	0.33
Male gender, n (%)	31 (50)	51 (47)	0.75
Syncopal episodes, (mean ± SD)	2.5 ± 2.2	2.8 ± 3.6	0.49
Presyncopal episodes, (mean ± SD)	1.4 ± 2.4	2.4 ± 4.6	0.09
Traumatic syncope, n (%)	31 (50)	56 (51)	0.87
Major trauma, n (%)	18 (29)	13 (12)	0.01
Fractures, n (%)	11 (18)	13 (12)	0.29
Prodromal symptoms, n (%)	20 (32)	43 (39)	0.43
Time interval between the last syncopal episode and HUT, days (mean ± SD)	36 ± 38	165 ± 916	0.27
Age at first syncope, yrs (mean ± SD)	60 ± 20	57 ± 21	0.20
Other diseases, n (%)			
Hypertension	22 (35)	45 (41)	0.55
Diabetes	5 (8)	13 (12)	0.33
Neurological disorders	3 (5)	9 (8)	0.28
Other	5 (8)	4 (4)	0.79
Therapy, n (%)			
Antihypertensive drugs	26 (42)	38 (35)	0.96
Psychiatric drugs	4 (6)	10 (9)	0.12
Other	20 (33)	22 (20)	0.52

VVS, vasovagal syncope; HUT, head-up tilt test.

Table 4. Univariate and multivariate predictors of a positive response to head-up tilt test

	Wald $\chi 2$	p Value	Exp (β)	95% CI
Univariate predictors				
Typical VVS	18.999	0.0001		
Time interval between the last syncope – HUT (≤ 28 days)	10.535	0.001		
Prodromal symptoms	7.427	0.006		
Nausea/vomiting	7.070	0.008		
Sweating preceding syncope	6.604	0.008		
Pallor	6.432	0.008		
Previous syncopal episodes ≥ 3	4.909	0.02		
Baseline systolic pressure (≤130 mmHg)	4.853	0.03		
Age ≤ 60 years at first evaluation	4.641	0.03		
Age ≤ 57 years at first syncope	4.213	0.04		
Presence of co-morbidities	3.331	0.07		
Epigastric discomfort	2.734	0.09		
Multivariate predictors				
Typical VVS	20.768	0.0001	2.855	1.81-4.41
Time interval between the last syncopal episode and HUT (≤28 days)	11.318	0.001	2.112	1.34-3.32

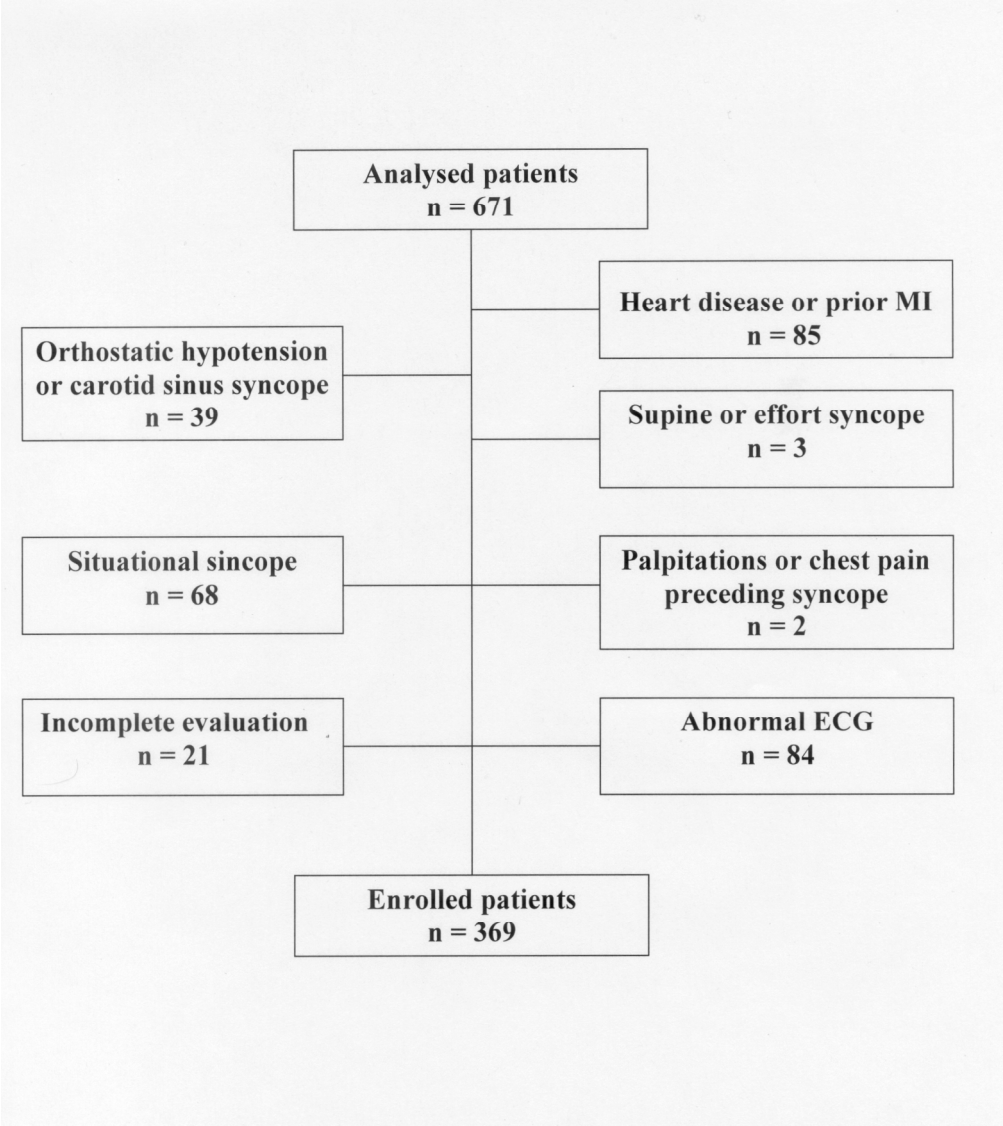
HUT, head-up tilt test; VVS, vasovagal syncope.

Table 5. Clinical features of patients undergoing a major diagnostic and/or therapeutic procedure at follow-up

Patient	Type of major procedure	Condition requiring a major procedure	Type of syncope	Gender	Age	HUT results	Syncope recurrence*
1	EPS, ILR †	Syncope recurrence	Established VVS	F	46	VASIS 1	+
2	CP	Syncope recurrence	Likely VVS	M	74	VASIS 2B	+
3	RFA	PSVT	Likely VVS	F	34	Negative	0
4	CP	Syncope recurrence	Likely VVS	M	72	VASIS 2A	0
5	CP	Syncope recurrence	Likely VVS	F	79	VASIS 2A	+
6	EPS‡, CP	Syncope recurrence	Likely VVS	M	83	Negative	0
7	EPS, ILR	Syncope recurrence	Likely VVS	M	68	Negative	0
8	ILR§, CP	Syncope recurrence	Likely VVS	F	79	VASIS 1	+

CP, permanent cardiac pacing; EPS, electrophysiologic study; ILR, implantable loop recorder; PSVT, paroxysmal supraventricular tachycardia; RFA, radiofrequency ablation; VVS, vasovagal syncope.

*syncope recurrence after a major procedure; †normal sinus rhythm during syncope; ‡HV interval of 110 ms after ajmaline administration; §asystole during syncope



Flow diagram of the study patients undergoing head-up tilt testing potentiated with sublingual nitroglycerin. Of the 671 eligible patients (pts), 302 were excluded from the analysis on the basis of well established criteria. The remaining 369 patients formed the population of the present study
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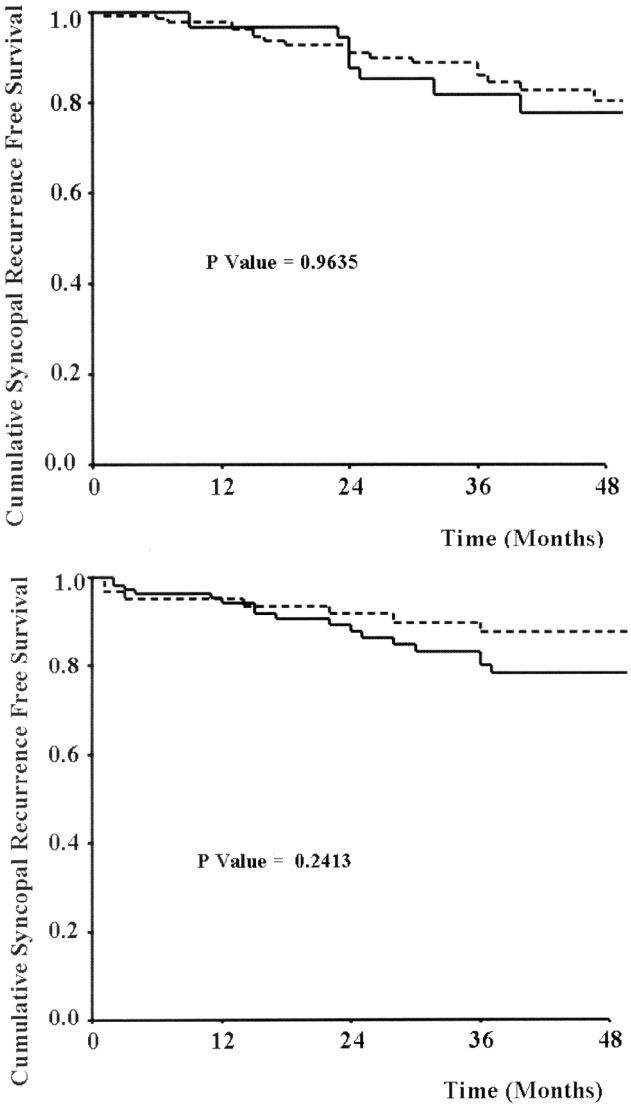

Cumulative syncopal recurrence free-survival in patients with established VVS and likely VVS in relation to HUT results. Comparison of 4-year syncopal recurrence free- survival curves of patients with established (top panel) and likely VVS (bottom panel) in relation to HUT results. Solid lines represent HUT-positive patients and dotted lines represent HUT-negative patients. Note that no significant differences in syncope recurrence in relation to HUT results were found between groups.
HUT, head-up tilt test; VVS, vasovagal syncope.

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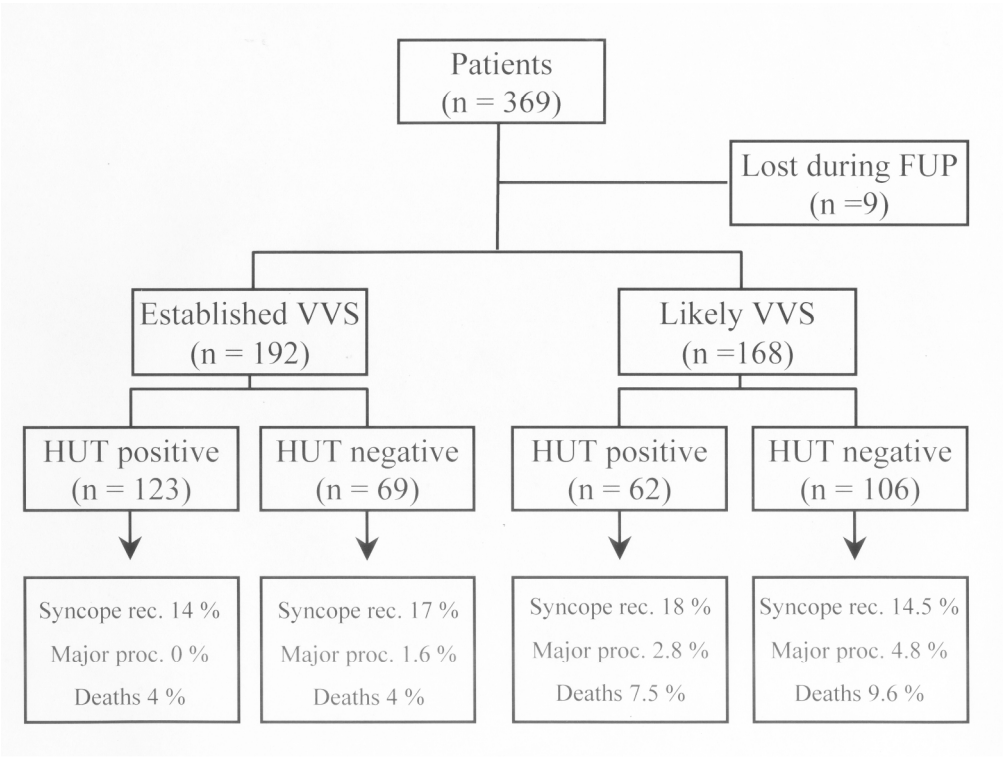

Rate of major clinical events in relation to the clinical presentation of syncope and HUT results. Comparison of the rate of major clinical events between patients with established and likely VVS in relation to HUT results.
Syncope rec. = syncope recurrence rate; Major proc. = Major diagnostic and/or therapeutic procedure.
HUT, head-up tilt test; VVS, vasovagal syncope.

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