ORIGINAL ARTICLES

Long-Term Follow-Up of Patients with Syncope Evaluated by Head-Up Tilt Test

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Background: Clinicians may be tempted to consider a positive head-up tilt test (HUTT) an unfavorable prognostic indicator. We investigated whether results of routine HUTT predict long-term recurrence of syncope.

Methods: We analyzed syncope recurrence at long-term among 107 patients (mean age 51 ± 20 years) receiving HUTT for diagnostic evaluation of unexplained/suspected neurocardiogenic syncope in our Institute.

Results: HUTT was positive in 76 patients (vasodepressive response, $n = 58$; cardioinhibitory, $n = 5$; mixed, $n = 13$). During a median follow-up of 113 months (range, 7–161), 34 (32%) patients experienced recurrence (24 [32%] with positive HUTT during 110 months (7–159); 10 [32%] with negative HUTT during 120 [22–161] months). Actuarial freedom from recurrence at 10 years did not significantly differ for patients with positive/negative test results (after passive/active phases) or with different positive response patterns (vasodepressive, cardioinhibitory, mixed). By contrast, history of >4 syncopes in the 12 months preceding HUTT stratified risk of recurrence, irrespective of HUTT positivity/negativity. At Cox proportional hazards analysis, history of >4 syncopes in the 12 months preceding HUTT was the single independent risk factor for recurrence both in the overall study population (HR, 1.7; 95% CI, 1.07–2.69) and within the subset of patients who tested positive (HR, 1.83; 95% CI, 1.07–3.17).

Conclusions: This long-term follow-up study reinforces the concept that a positive HUTT should not be considered an unfavorable prognostic indicator; frequency of recent occurrences may be a more valid predictor.

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The head-up tilt test (HUTT) is a useful final diagnostic test for patients with unexplained or suspected neurocardiogenic syncope.^{1,2} Even though the prognosis of reflex syncope is generally favorable, the ability to predict recurrence is relevant in this clinical setting to help maintain patients' quality of life.^{3–6} In this context, the clinical history of syncope appears to be a predictor of recurrence. Although positive HUTT might be thought to be

another likely indicator, the few available studies do not support this hypothesis.^{7,8}

Nevertheless, studies with an extensive follow-up are currently lacking. The aim of this study was to assess the results of an initial HUTT performed for routine diagnostic evaluation of unexplained or suspected neurocardiogenic syncope as a predictor of long-term recurrence of syncope in clinical practice.

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PATIENTS AND METHODS

We retrospectively screened all patients submitted to HUTT in our Institute in the last 10 years to identify those tested to allow diagnostic evaluation of unexplained or suspected neurocardiogenic syncope. A sample of the whole population of patients evaluated by HUTT, that is, those with a follow-up in charge of our centre, for geographical and logistic reasons, were available for assessment of long-term outcome. These 107 patients (mean age 51 ± 20 years; M:F, 56:51) did not differ from the whole patient population evaluated by HUTT in the same period with regard to clinical and demographic variables, as well as with regard to HUTT results.

Broadly based on current guidelines,⁹ we classified patients as having unexplained/suspected neurocardiogenic syncope when the HUTT test record specified a history in the previous 12 months of either (1) suspected vasovagal syncope, or (2) syncope following situational factors such as various types of physical exertion or gastrointestinal stimulation, micturition, etc., or (3) unexplained syncope despite neurologic/cardiovascular tests. HUTT was performed due to unexplained syncope in 66 (62%) cases; suspected neurocardiogenic syncope in 28 (26%); coexistence of unexplained/suspected neurocardiogenic syncopes in 13 (12%).

During the previous 12 months, 64 patients had 1–2 syncopes; 18 had 3–4; 25 had >4 (median, 2; 75th percentile, 4). Twenty-eight (26%) patients had at least one traumatic episode. A total of 24 (22%) patients had structural heart disease; 18 (17%) had systemic hypertension. At the time of HUTT, 33 (31%) were receiving medical treatment for underlying disease (β -blockers, $n = 10$; α -agonists, $n = 1$; other antihypertensives, $n = 25$; selective serotonin reuptake inhibitors [SSRIs], $n = 3$).

Follow-up was closed in July–September 2007 (to provide a minimum period of 6 months), when one of the investigators (G.D.) interviewed by phone the eligible patients regarding recurrence(s), year of the first recurrence, therapy (type/duration), compliance to behavioral advice (patients who both recalled the advice and claimed to have followed it were categorized as having complied). Patients who provided all this information were included in the main analysis. The main outcome measure was any recurrence of syncope.

All patients provided informed consent for anonymous use of their data for scientific research purposes. Application for official ethical approval would not have been considered institutionally appropriate for this retrospective analysis data involving routine use of noninvasive procedures study (however, the objectives and design of the study were informally approved during internal board meetings).

HUTT PROTOCOL

HUTT were performed following a standardized institutional protocol.¹⁰ Either isoproterenol or isosorbide dinitrate was used in the active phase. Positive test results were classified as (1) cardioinhibitory (syncope with heart rate <40 bpm for over 10 seconds or an asystolic pause ≥ 3 seconds); (2) mixed (syncope with $\geq 50\%$ reduction in heart rate plus a >50 mmHg drop in systolic blood pressure); (3) vasodepressive (syncope with a >50 mmHg drop in systolic blood pressure followed by a <50% decrease in heart rate). In routine practice, we consider HUTT to be negative in the absence of syncope (even when, for clinical reasons, the active phase is not attempted/completed). Pharmacological prophylaxis was at clinicians' discretion. Periodic check-ups were planned in our Institute or elsewhere.

DATA ANALYSIS

Continuous variables were expressed as mean $\pm$ SD or as median (range); categorical variables as numbers (percentages). We used Student's *t*-test for comparisons of normally distributed variables; Mann-Whitney for nonnormally distributed variables; and the chi-square test for categorical variables. We constructed Kaplan-Meier curves describing freedom from syncope in patients who tested positive/negative at HUTT and in predefined subgroups, including all HUTT results after the passive phase; those who completed the active phase; types of HUTT positivity (vasodepressive, cardioinhibitory, mixed); numbers of syncopes in the 12 months before HUTT; older age; pharmacological prophylaxis; the log rank test was used for comparisons. To identify predictors of recurrence, variables that reached $P < 0.05$ when examined at univariate analysis were entered in Cox proportional hazards model. All analyses were

Table 1. Patients' Baseline Characteristics According to Their Eventual HUTT Result

	Patients Who Tested Positive (n = 76)	Patients Who Tested Negative (n = 31)	P Value
Age, years, mean $\pm$ SD	50 $\pm$ 21	56 $\pm$ 18	0.2
Men, n (%)	40 (53)	16 (52)	0.9
Hypertension, n (%)	13 (17)	5 (16)	0.9
Structural heart disease, n (%)	14 (18)	10 (32)	0.2
β -blockers (for underlying disease), n (%)	8 (11)	2 (6)	0.8
Syncopes in the 12 months preceding HUTT, median [range]	2 [1–21]	2 [1–20]	0.5
Patients with traumatic episodes in the 12 months preceding HUTT, n (%)	24 (32)	4 (13)	0.08
Diagnosis before HUTT			
Suspected vasovagal syncope, n (%)	5 (7)	6 (19)	0.8
Suspected situational syncope, n (%)	13 (17)	4 (13)	0.8
Unexplained syncope, n (%)	47 (62)	19 (61)	0.9
Coexistence of unexplained/suspected neurocardiogenic syncope, n (%)	11 (15)	2 (7)	0.4

HUTT = head-up tilt test; SSRIs = selective serotonin reuptake inhibitors.

run on Stata 9.0 (StataCorp LP, College Station, TX, USA); $P < 0.05$ was considered statistically significant.

RESULTS

Among the 107 patients evaluated at long-term, 76 (71%) had a positive HUTT (vasodepressive, $n = 58$; cardioinhibitory, $n = 5$; mixed, $n = 13$). The 31 negative tests regarded 14 patients who completed the entire HUTT protocol including the active phase and 17 who completed only the passive phase. In the active phase, 55 patients received isoproterenol, while the remaining 20 patients who reached this phase were given isosorbide dinitrate. Table 1 summarizes patients' main baseline characteristics according to their eventual HUTT result. After HUTT, medical therapy was given to 34 (45%) patients who tested positive (β -blockers only, $n = 25$; SSRIs, $n = 5$; α -agonists, $n = 2$; β -blockers plus SSRIs, $n = 2$), as compared with 4 (13%) who tested negative (all β -blockers) ($P = 0.004$ overall). During a median follow-up of 113 months (range, 7–161), 34 (32%) patients experienced a recurrence [24 (32%) with positive HUTT during 110 months (7–159); 10 (32%) with negative HUTT during 120 (22–161) months]. Of note, during follow-up pacemaker devices were implanted in five patients with negative HUTT (two recurrences) and four with positive vasodepressive HUTT (one recurrence). Kaplan-Meier curves for freedom from recurrence are shown in Figure 1. No statistically significant

difference emerged between patients with positive and negative HUTT (Fig. 1A); patients with different positive responses (Fig. 1B); patients who were positive/negative after just the passive phase of HUTT (Fig. 1C). On the other hand, patients who reported >4 episodes in the 12 months before HUTT did show worse freedom from recurrence, irrespective of HUTT positivity (Fig. 1D). Table 2 reports the results of Cox proportional hazards analysis. At multivariate analysis, the only predictor of relapse was history of >4 syncope in the previous 12 months (~ 1.7 -fold excess risk; cut-off based on 75th percentile). Remarkably, this variable was also the only significant predictor of relapse in a supplementary analysis of the subset of patients who eventually tested positive at HUTT (HR, 1.83; 95% CI, 1.07–3.17).

DISCUSSION

Contrary to the general opinion established during the 1990s in the wake of the introduction of HUTT, the present study indicates that HUTT results do not predict recurrence of syncope at long-term follow-up. Whereas the number of syncope in the 12 months preceding HUTT was a significant predictor of long-term recurrence, we could not identify any HUTT-related predictors. These findings reinforce the concept that, on clinical grounds, patients with unexplained syncope may be considered as a single population regardless of HUTT results.⁸

Figure 1. Kaplan-Meier curves depicting freedom from syncope: in patients with positive and negative HUTT (panel A); in patients with different positive responses (panel B); in patients who tested negative/positive after just the passive phase of HUTT (panel C); in patients who tested negative/positive and with ≤ 4 or > 4 syncopes in the 12 months before HUTT (panel D).

In line with previously reported studies,^{7,8} only a minority (about one-third at 10 years) of patients reported recurrence. Actuarial probabilities of freedom from recurrence at 10 years among patients submitted to HUTT did not significantly differ for patients with positive/negative test results (whether after the passive or active phase) or with different positive response patterns (vasodepressive, cardioinhibitory, mixed) (Figs. 1A–C); of note, our decision to consider various categories of HUTT positivity after the passive/active phase was based on the consideration that not all patients completed the active phase, together with concerns about the real predictive accuracy (diagnostic rele-

vance) of this phase.⁹ By contrast, a history of frequent (more than 4) syncopes in the 12 months preceding HUTT stratified risk of recurrence, irrespective of HUTT test positivity/negativity (Fig. 1D). At Cox proportional hazards analysis, this readily available anamnestic variable turned out to be the single independent predictor of recurrence both in the overall study population and within the subset of patients who tested positive at HUTT (Table 2). The findings regarding the prognostic significance of frequent recent history of syncope have clinical implications, providing additional tools for physicians' predictions, beyond previously reported associations between numbers of previous episodes

Table 2. Risk Factors for Recurrence of Syncope at Cox Proportional Hazards Analysis in the Overall Study Population and within the Subset of Patients Who Tested Positive at HUTT

	Overall Study Population		Patients Who Tested Positive	
	Univariate HR (95% CI)	Multivariate HR (95% CI)	Univariate HR (95% CI)	Multivariate HR (95% CI)
Age, per year	0.98 (0.97–1.00)		0.98 (0.97–1.00)	
Male gender	0.68 (0.34–1.34)		0.73 (0.33–1.64)	
Structural heart disease	1.23 (0.57–2.63)		1.24 (0.46–3.32)	
Hypertension	0.55 (0.17–1.79)		0.20 (0.03–1.48)	
β -blockers for underlying disease	1.75 (0.68–4.54)		2.65 (0.98–7.15)	
Antihypertensive therapy	1.16 (0.52–2.56)		1.40 (0.52–3.76)	
>4 syncopes in the 12 months preceding HUTT	3.35 (1.69–6.63)	1.70 (1.07–2.69)	3.42 (1.52–7.70)	1.83 (1.07–3.17)
Traumatic episode(s) in the 12 months preceding HUTT	1.61 (0.78–3.30)		1.22 (0.52–2.86)	
Suspected vasovagal syncope	0.33 (0.10–1.09)		0.39 (0.09–1.65)	
Suspected situational syncope	0.50 (0.19–1.29)		0.51 (0.17–1.50)	
Unexplained syncope	2.43 (1.00–5.88)		2.14 (0.73–6.27)	
Positive at passive phase of HUTT (vs negative HUTT)	1.48 (0.61–3.57)		N.A.	
Positive at active phase of HUTT (vs negative HUTT)	0.85 (0.37–1.91)		N.A.	
Vasodepressive response	1.01 (0.47–2.19)		0.62 (0.24–1.58)	
Cardioinhibitory response	1.46 (0.32–6.71)		0.78 (0.38–1.55)	
Mixed response	0.98 (0.31–3.12)		0.73 (0.39–1.36)	
β -blockers after HUTT	1.85 (0.93–3.66)		2.93 (1.30–6.61)	
SSRIs after HUTT	2.06 (0.63–6.77)		1.98 (0.59–6.67)	
α -agonists after HUTT	1.76 (0.24–13.03)		1.85 (0.25–13.92)	
Duration of pharmacological therapy	0.99 (0.99–1.00)		0.99 (0.99–1.00)	
Behavioral compliance	2.30 (1.17–4.54)		2.59 (1.14–5.86)	

HUTT = head-up tilt test; SSRIs = selective serotonin reuptake inhibitors; N.A. = not applicable.

of syncope and risk of relapse after a positive HUTT^{11–15} (and in one analysis also in patients with negative HUTT).¹³

The retrospective study design obviously represents a limitation, especially with regard to influence of pharmacological prophylaxis on recurrence. In this study, treatment with β -blockers appeared ineffective in preventing recurrences of syncope, since no protective effect emerged at the multivariate analysis of factors predicting recurrence of syncope. The lack of efficacy of β -blockers has been previously demonstrated in mid-term prospective studies.^{16,17} It is noteworthy that in our study treatment with beta-blockers resulted to carry some implications for prediction of syncopal recurrences at univariate analysis (more evident in patients with a positive HUTT), probably reflecting the facilitation of asystolic responses that may be found in some patients, as reported in anecdotal cases.^{18,19} Anyway, at multivariate analysis

such predictive value of β -blockers treatment was lost. Further evaluation on β -blockers would require a prospective study, with an extended follow-up period, but this seems an unlikely undertaking in this context.

CONCLUSIONS

Even though clinicians may be tempted to consider a positive HUTT an unfavorable prognostic indicator (in terms of risk of recurrence of syncope), there is no evidence to support this supposition. The present study, characterized by a long-term follow-up, reinforces the concept that frequency of recent occurrences of syncope may be a more valid indicator of risk of long-term recurrence, irrespective of HUTT results. Despite the lack of ability to predict syncopal recurrences, HUTT remains the main validated diagnostic tool to make the diagnosis of reflex syncope in

unexplained syncope. These concepts are relevant to clinical practice for management of patients with syncope.

REFERENCES

1. Grubb BP. Neurocardiogenic syncope. *N Engl J Med* 2005;352:1004–1010.
2. Parry SW, Kenny RA. Tilt table testing in the diagnosis of unexplained syncope. *Q J Med* 1999;92:623–629.
3. Sarasin FP, Louis-Simonet M, Carballo D, et al. Prospective evaluation of patients with syncope: A population-based study. *Am J Med* 2001;111:177–184.
4. Blanc JJ, L'Her C, Touiza A, et al. Prospective evaluation and outcome of patients admitted for syncope over a 1 year period. *Eur Heart J* 2002;23:815–820.
5. Graf D, Schlaepfer J, Gollut E, et al. Predictive models of syncope causes in an outpatient clinic. *Int J Cardiol* 2008;123:249–256.
6. Gielerak G, Makowski K, Cholewa M. Prognostic value of head-up tilt test with intravenous beta-blocker administration in assessing the efficacy of therapy in patients with vasovagal syncope. *Ann Noninvasive Electrocardiol* 2005;10:65–72.
7. Gatzoulis K, Sideris S, Theopistou A, et al. Long-term outcome of patients with recurrent syncope of unknown cause in the absence of organic heart disease and relation to results of baseline tilt table testing. *Am J Cardiol* 2003;92:876–879.
8. Sheldon R, Rose S, Koshman ML. Comparison of patients with syncope of unknown cause having negative or positive tilt-table tests. *Am J Cardiol* 1997;80:581–585.
9. Brignole M, Alboni P, Benditt DG, et al. Guidelines on management (diagnosis and treatment) of syncope – Update 2004. *Eur Heart J* 2004;25:2054–2072.
10. Biffi M, Boriani G, Bronzetti G, et al. Neurocardiogenic syncope in selected pediatric patients—Natural history during long-term follow-up and effect of prophylactic pharmacological therapy. *Cardiovasc Drug Ther* 2001;15:161–167.
11. Sheldon R, Rose S, Flanagan P, et al. Risk factors for syncope recurrence after a positive tilt-table test in patients with syncope. *Circulation* 1996;93:973–981.
12. Natale A, Geiger MJ, Maglio C, et al. Recurrence of neurocardiogenic syncope without pharmacologic intervention. *Am J Cardiol* 1996;77:1001–1003.
13. Grimm W, Degenhardt M, Hoffmann J, et al. Syncope recurrence can better be predicted by history than by head-up tilt testing in untreated patients with suspected neurally mediated syncope. *Eur Heart J* 1997;18:1465–1469.
14. Kouakam C, Vaksman G, Pachy E, et al. Long-term follow-up of children and adolescents with syncope. *Eur Heart J* 2001;22:1618–1625.
15. Barón-Esquivias G, Errázquin F, Pedrote A, et al. Long-term outcome of patients with vasovagal syncope. *Am Heart J* 2004;147:883–889.
16. Madrid AH, Ortega J, Rebollo JG, et al. Lack of efficacy of atenolol for the prevention of neurally mediated syncope in a highly symptomatic population: A prospective, double-blind, randomized and placebo-controlled study. *J Am Coll Cardiol* 2001;37:554–559.
17. Sheldon R, Connolly S, Rose S, et al.; POST Investigators. Prevention of Syncope Trial (POST): A randomized, placebo-controlled study of metoprolol in the prevention of vasovagal syncope. *Circulation* 2006;113:1164–1170.
18. Gardini A, Benedini G, Proto C. Worsening of head-up tilt test response during chronic beta-blocker therapy in patients treated for neurally mediated syncope. *G Ital Cardiol* 1998;28:899–903.
19. Freitas J, Puig J, Campos J, et al. Malignant vasovagal syncope: A case of prolonged asystole induced by the “tilt” test and aggravated by therapy with a beta blocker (a clinical case and diagnostic, physiopathologic and therapeutic review). *Rev Port Cardiol* 1993;12:745–751, 702.