Seizure 2003; **12:** 295–299
doi:10.1016/S1059–1311(02)00294-7

Tilt table testing in patients referred from an epilepsy clinic

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***Objective*:** To assess the role of head up tilt testing (HUT) in diagnosing probable or possible vasovagal syncope (VVS) in patients referred from an epilepsy clinic.
***Methods*:** One hundred thirty two patients underwent HUT over 36 months. Complete data were available on 128 patients (52 male) aged 14–80 (mean 36.7) years. The main indication for HUT (head up tilt at 70° for 45 minutes) was recurrent undiagnosed blackouts, likely to be VVS. Patients were divided, prior to knowledge of the HUT results, into probable VVS, possible VVS, or probable/possible VVS associated with definite epilepsy.
***Results*:** HUT was positive in 72 patients (56%), and led to an alternative definite diagnosis in 31 (24%). Diagnostic change was more likely in those provisionally labelled either as possible VVS (15 of 34; 44%) or as a combination of epilepsy with possible or probable VVS (12 of 19; 63%) compared to those with probable VVS (4 of 75; 5%; $P < 0.01$).

Of the 45 patients previously treated with antiepileptic medications 27 did not have epilepsy.
***Conclusion*:** HUT has an important role in confirming or refuting the diagnosis of VVS in patients presenting with undiagnosed blackouts to an epilepsy clinic, and particularly so in patients with possible rather than probable VVS, and in those thought to have a combination of epilepsy and possible or probable VVS.

Key words: syncope; vasovagal; tilt table; epilepsy.

INTRODUCTION

Syncope accounts for about 3–5% of visits to emergency departments, and 1% of hospital admissions[1]. Vasovagal syncope (VVS) typically occurs in otherwise healthy individuals, whereas orthostatic and cardiac syncope usually accompany autonomic neuropathy or heart disease. The diagnosis of VVS rests principally upon the history; investigations other than electrocardiogram are often unnecessary. However, distinguishing VVS from seizures is occasionally difficult, especially without a clear witness account. Limb jerking is surprisingly common in VVS[2] and incontinence and injury may also occur. Clinical examination is rarely helpful in distinguishing the two; even lying and standing blood pressure (BP) is typically unchanged in patients with a history of VVS.

There is a clear need to improve syncope diagnosis and to optimise the application of available diagnostic techniques. Head up tilt table testing (HUT) is used increasingly to assist the evaluation of patients with VVS. Based upon an analysis of pooled data[3] Linzer *et al*.[4] recommended passive upright HUT for patients with recurrent unexplained syncope in whom cardiac causes, including arrhythmias, had been excluded. Most protocols involve passive upright tilt at 60–80° for 45 minutes. The response in normal individuals is a transient fall (5–15 mmHg) in systolic BP with a rise of diastolic BP of 5–10 mmHg; the heart rate (HR) may rise between 5 and 15 beats per minute. Patients with a history of VVS usually show more marked changes: a pure vasodepressor response (BP fall exceeding 20 mmHg), a cardio-inhibitory response (HR fall exceeding 10% of the baseline rate), or a mixed response.

We have evaluated the role of HUT in assisting the diagnosis of patients with recurrent blackouts referred from an epilepsy clinic.

METHODS

All patients referred for HUT from the University Hospital of Wales epilepsy clinic over 36 months (1998–2001) were included. Referral criteria were in line with published consensus guidelines for HUT[5] and therefore included patients with recurrent undiagnosed blackouts, likely to be VVS, in whom heart disease was either not suspected or had been excluded. Those in whom a diagnosis of VVS appeared obvious were not referred for HUT. Patients completed a proforma at the time of HUT giving details of associated symptoms including postural pre-syncope, incontinence, injury, tongue biting, and of antiepileptic medication.

One of us (S.S.M. Razvi), not involved in the clinical consultations and without knowledge of the HUT result, used the clinic notes and completed proformas to categorise each patient into one of three broad groups: 'probable VVS' (strong suspicion of syncope), 'possible VVS' (lesser suspicion of syncope), or 'epilepsy with probable or possible VVS'.

The HUT protocol followed standard guidelines involving 70° upright tilt for up to 45 minutes, with continuous BP and HR monitoring (Finapres). All HUTs were supervised by one of the authors (J. Pascual).

Table 1: Criteria for positive and negative HUT.

Positive test
Typical symptoms accompanying one of the following
BP fall by >20 mmHg.
BP fall by >20 mmHg with HR fall >10% of baseline.
Postural tachycardia (HR increase by ≥30 BPM or maximum of 120 BPM in the first 10 minutes of HUT accompanied by symptoms).
BP fall by >20 mmHg induced by cough, carotid massage, isoprenaline, or glyceryl trinitrate.
Negative test
One of the following
BP fall <20 mmHg or HR fall >10% of baseline alone (vasovagal tendency).
BP fall by >20 mmHg without typical symptoms.
Typical symptoms without haemodynamic changes (true negative).

The haemodynamic responses to cough and to carotid massage were assessed where clinically relevant, and isoprenaline or glyceryl trinitrate sublingual spray was administered following an initial negative test if there was still strong clinical suspicion of VVS. Lying and standing BP were recorded in all patients. The criteria for positive and negative HUT are shown in Table 1.

The Statistical Package for Social Sciences (SPSS) version 9.0 was used for statistical analysis, utilising Fisher's exact test (two-tailed).

RESULTS

One hundred thirty two patients were referred for HUT over 36 months. Complete clinical and laboratory data before testing were available on 128 patients (52 male), aged 14–80 (mean 36.7 ± 5.5 [SD]) years, and the analysis was based upon these. HUT was positive in 72 of the 128 (56%) patients. A change to an alternative definite diagnosis followed HUT in 31 cases (24%; Table 2).

Changes in diagnosis

All patients followed up after a positive HUT were given a final diagnosis of VVS, with or without accompanying epilepsy. The HUT results and changes in diagnosis with respect to the provisional diagnostic groupings were as follows.

- Probable VVS: HUT was positive in 49 of the 75 (65%) with this provisional diagnosis; 22 of the remainder (29%) were considered still to have VVS, even after a negative test. The diagnosis was changed to an alternative definite diagnosis in only 4 of the 75 (5%), 1 to epilepsy, and 3 to other disorders.
- Possible VVS: HUT was positive in 16 of the 34 (47%) with this provisional diagnosis; 16 had a final diagnosis of syncope (14 HUT positive) and 3 had a combination of epilepsy with syncope (2 HUT positive). The diagnosis was subsequently changed to an alternative definite diagnosis in 15

Table 2: Provisional diagnoses before HUT (horizontal), re-classified following completion of investigation (vertical).

	Probable VVS ($n = 75$)	Possible VVS ($n = 34$)	Epilepsy with probable or possible VVS ($n = 19$)	Total (post-HUT)
VVS	64	16	2	82
Epilepsy with VVS	0	3	5	8
Epilepsy	1	6	9	16
Other diagnosis	3	6	1	10
Uncertain	7	3	2	12
Total (pre-HUT)	75	34	19	128

(44%), 6 to epilepsy, 3 to epilepsy with VVS, and 6 to other disorders.

- Epilepsy with probable/possible VVS: HUT was positive in 6 of the 19 (32%) with this provisional diagnosis. This was the final diagnosis in only 5 of this group, 4 of whom had a positive HUT. The diagnosis was changed to an alternative definite diagnosis in 11 (58%), with epilepsy excluded in 2, and VVS considered excluded in 9.

A change in diagnosis was therefore significantly more likely (Fisher's exact test) in the groups categorised prior to HUT as either possible VVS or as epilepsy with probable or possible VVS, compared to the probable VVS group ($P < 0.01$).

HUT result details

The HUT results with respect to the final diagnostic groupings were as follows.

- VVS group: of the patients with a final diagnosis of VVS ($n = 82$), HUT was positive in 65 (79%); 38 with BP fall alone, 20 with BP and HR fall, 1 with postural tachycardia, 3 with haemodynamic changes following carotid massage, 2 following cough, and 1 with haemodynamic changes only following isoprenaline infusion.
- VVS with epilepsy: of those with a final diagnosis of VVS and epilepsy ($n = 8$), HUT was positive in six (75%); two with BP fall alone, three with BP and HR fall, and one with haemodynamic changes only during carotid massage.
- Epilepsy alone: of those with a final diagnosis of epilepsy alone ($n = 16$), HUT was negative in all; this included four with significant BP fall without accompanying symptoms and one with a vasovagal tendency only.
- Other disorders: HUT was negative in all 10 patients in this group, including 1 showing a vasovagal tendency only.
- Uncertain: of those in whom no certain final diagnosis was made, one had a positive HUT (BP fall with symptoms) but was subsequently lost to follow up and no definite diagnosis established, and one showed vasovagal tendency only.

Postural pre-syncope symptoms during attacks were reported by 47 of 128 (37%) patients, but a postural fall in BP was documented before HUT in only 4.5%. However, postural pre-syncope was significantly more likely in patients whose final diagnosis was VVS (37 of 81 patients; 46%), rather than those diagnosed as epilepsy (2 of 16 patients; 12.5%; $P < 0.05$). Fifty one patients (40%) reported physical injury (excluding tongue biting) during blackouts, and this was significantly more likely in those diagnosed as epilepsy (10 of 16; 63%) than in those diagnosed as VVS (28 of 82; 34%; $P < 0.05$). Tongue biting during episodes occurred in 15 of the 128 patients (12%), but was no more likely among those subsequently diagnosed as epilepsy (4 of 15; 27%) than among those with a final diagnosis of VVS (7 of 82; 9%; $P = 0.064$, NS). Urinary incontinence accompanied attacks in 29 patients (23%), including 5 of 15 (33%) subsequently diagnosed as epilepsy alone, and 20 (24%) diagnosed as VVS (NS).

Antiepileptic medications were currently or previously prescribed in 45 (35%) patients, yet epilepsy was not the diagnosis in 27 (60%) of these. Indeed, antiepileptic medications had been prescribed to 21 of the 82 patients (25%) diagnosed as VVS alone and to 4 of the 10 patients (40%) with either psychogenic non-epileptic attack disorder or other non-epilepsy diagnoses.

DISCUSSION

We have shown that head up tilt table testing (HUT) has an important role in confirming or refuting the diagnosis of VVS in patients with undiagnosed blackouts presenting to an epilepsy clinic, aiding a change in diagnosis in about a quarter of such patients.

Our patients do not represent a population with either syncope or unspecified blackouts, for two reasons. Firstly, cases were ascertained from a specialist epilepsy clinic, possibly over-representing epilepsy compared to a community-ascertained group, and secondly, those in whom VVS was either obvious or unlikely were not included. Nevertheless, our sample does represent those patients most likely to be referred for HUT, i.e. recurrent undiagnosed blackouts, with VVS considered a possible or probable diagnosis, and where heart disease is either not suspected or has been excluded.

This study was retrospective, with the pre-test and final diagnoses derived from available case notes. Also, being a study of usual clinical practice, the HUT was not the sole determinant of the final diagnosis. Prior knowledge of the clinical history at the time of HUT may have evoked observer bias in its interpretation, though consistency was maximised by all tilt tests being supervised and evaluated by one clinician, using previously agreed criteria. The pre-test categorisation into probable and possible VVS was also liable to observer bias, though again minimised by the classifying clinician being independent of the original consultations and having no prior knowledge of the HUT results.

VVS episodes, particularly when accompanied by convulsive features, are commonly mistaken for seizures[6]. Lempert *et al.*[2] demonstrated that myoclonus, usually multifocal, accompanies 90% of syncope induced in healthy volunteers and that additional features such as head turning, oral movement or attempts to sit up occur in 80%. It is perhaps not surprising, therefore, that VVS is frequently identified among patients labelled and treated as epilepsy[7] perhaps accounting for 26% of patients with a diagnosis of refractory epilepsy[8]. The costs of misdiagnosing patients as having drug resistant epilepsy are considerable[9] aside from the inconvenience and risk of unnecessary antiepileptic drug exposure, e.g. during pregnancy. These data highlight the potential value of HUT in seeking alternative diagnoses in cases of resistant 'known epilepsy'. There is a clear need to improve awareness and availability of techniques for diagnosing VVS.

The evaluation of diagnostic techniques almost invariably lags behind that of treatments[10]. A particular problem in considering the accuracy and clinical usefulness of many diagnostic tests is the absence of a suitable reference standard or 'gold standard' for diagnosis. VVS is a good example of there being a spectrum of susceptibility within the healthy population with no clear cut divide between 'normal' and 'abnormal'. Furthermore, the diagnosis of recurrent blackouts relies principally upon the clinical history, which is often incomplete from the patient, or lacking a witness account. The clinical diagnosis can be assisted by investigations, but the diagnosis of recurrent blackouts only rarely rests upon a single laboratory result.

The sensitivity of HUT for VVS (probability of a positive test in people with VVS) has been previously estimated at between 67 and 85%[11,12]. The specificity for VVS (probability of negative test in people without VVS) is around 90%[13], although far less if high dose isoproterenol is used. Our study excluded patients with definite VVS and so we cannot derive an estimate of sensitivity of HUT for VVS from our data. Among the population studied, however, the sensitivity of HUT was 71 out of 90 (79%). It would be realistic to say that the false positive rate in epilepsy can be determined only by further studies in this specific group.

Another point to ponder is the issue of potential adverse outcomes. HUT is contraindicated in patients with significant ischaemic heart disease and in pregnant women. Several centres in the United States perform a stress test prior to HUT in high-risk individuals. However, the relative incidence of adverse effects is minimal. Problems usually encountered are secondary to haemodynamic changes and include hypotension, tachycardia and bradycardia associated with orthostatic intolerance, pre-syncope and syncope. Occasionally chest pain, coronary vasospasm and tachyarrhythmia may occur, especially after provocative testing with a pharmaceutical agent[3]. Dhala *et al.*[14] reported a 9% incidence of asystolic reactions on HUT among 209 patients tested for neurocardiogenic syncope. These events however, were transient and did not affect long-term outcome measures. They compared with a 3% incidence among 75 healthy volunteers. This figure probably represents the expected incidence of adverse effects of HUT in patients with epilepsy.

Our results highlight the value of HUT in assisting the diagnosis of recurrent blackouts but we cannot quantify its contribution precisely from retrospective data. We are currently planning to evaluate HUT prospectively in patients with undiagnosed blackouts. A randomised controlled trial would be necessary to study its true impact on diagnosis and clinical decision-making, but devising a HUT placebo presents a practical challenge. One solution, if ethically permissible, might be to apply the HUT to all, but to randomise disclosure of its results to the clinicians involved. Wider availability of HUT may allow its selective use to support clinical management by increasing the certainty of a diagnosis of VVS in patients presenting with undiagnosed blackouts.

ACKNOWLEDGEMENT

We thank the staff of the syncope clinic, University Hospital of Wales for their help in obtaining the data for this study.

REFERENCES

1. Kapoor, W. N., Karpf, M., Maher, Y., Miller, R. A. and Levey, G. S. Syncope of unknown origin: the need for a more cost effective approach to its diagnostic evaluation. *JAMA: The Journal of American Medical Association* 1982; **247**: 2687–2691.
2. Lempert, T., Bauer, M. and Schmidt, D. Syncope: a videometric analysis of 56 episodes of transient cerebral hypoxia. *Annals of Neurology* 1994; **36**: 233–237.
3. Kapoor, W. N., Smith, M. A. and Miller, N. L. Upright tilt testing in evaluating syncope: a comprehensive literature review. *American Journal of Medicine* 1994; **97**: 78–88.
4. Linzer, M., Yang, E. H., Estes, M. *et al.* Clinical guideline for diagnosing syncope (American College of Cardiologists). *Annals of Internal Medicine* 1997; **126**: 989–996.
5. Brignole, M., Alboni, P., Benditt, D. *et al.* Guidelines on management (diagnosis and treatment) of syncope. Task Force on syncope, European Society of Cardiology. *European Heart Journal* 2001; **22**: 1256–1306.
6. Chadwick, D. W. and Smith, D. The misdiagnosis of epilepsy. *BMJ* 2002; **324**: 495–496.
7. Smith, D., Defalla, B. A. and Chadwick, D. W. The misdiagnosis of epilepsy and the management of refractory epilepsy in a specialist clinic. *QJM: Monthly Journal of The Association of Physicians* 1999; **92**: 15–23.

8. Zaidi, A., Clough, P., Cooper, P., Scheepers, B. and Fitzpatrick, A. P. Misdiagnosis of epilepsy: many seizure-like attacks have a cardiovascular cause. *Journal of American College of Cardiology* 2000; **36**: 181–184.
9. Cockerell, O. C., Hart, Y. M., Sander, J. W. A. S. and Shorvon, S. D. The cost of epilepsy in the United Kingdom: an estimation based on the results of two population-based studies. *Epilepsy Research* 1994; **18**: 249–260.
10. Knottnerus, J. A., van Weel, C. and Muris, J. W. M. Evaluation of diagnostic procedures. *BMJ* 2002; **324**: 477–480.
11. Calkins, H., Kadish, A., Sousa, J. *et al*. Comparison of responses to isoproterenol and epinephrine during head-up tilt in suspected vasodepressor syncope. *American Journal of Cardiology* 1991; **67**: 207–209.
12. Waxman, M. B., Yao, L., Cameron, D. A. *et al*. Isoproterenol induction of vasodepressor-type reaction in vasodepressor-prone persons. *American Journal of Cardiology* 1989; **63**: 58–65.
13. Schnipper, J. L. and Kapoor, W. N. Diagnostic evaluation and management of patients with syncope. *The Medical Clinics of North America* 2001; **85**: 423–456.
14. Dhala, A., Natale, A., Sra, J., Deshpande, S., Blanck, Z., Jazayeri, M. R. *et al*. Relevance of asystole during head-up tilt testing. *American Journal of Cardiology* 1995; **75**: 251–254.