Review

Tilt table testing in the diagnosis of unexplained syncope

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**Introduction**

While the investigation of the physiological and pathophysiological effects of orthostatic stress induced by head-up tilt table testing in humans began more than 50 years ago, it was not until 1986 that the utility of tilt testing in the diagnosis of unexplained syncope was demonstrated. In the absence of a ‘gold-standard’ diagnostic test for vasovagal syncope, an appropriate clinical history in association with a positive head-up tilt test currently provides the cornerstone for the diagnosis of vasovagal syncope. This article will provide an overview of the rationale for the head-up tilt test in relation to its main diagnostic use, vasovagal syncope, a discussion of the methodological issues surrounding the test and the uses of tilt table testing in the further differential diagnosis of unexplained syncope.

**Vasovagal syncope and the pathophysiological rationale for head-up tilt testing**

More than 60 years after the introduction of the term ‘vasovagal syncope’ by Lewis, the exact mechanisms responsible for loss of consciousness associated with profound hypotension and/or bradycardia, and mediated by vagal excess and sympathetic withdrawal, remain uncertain. The main trigger factors for the vasovagal cascade can be divided into central and peripheral provocateurs, with the latter providing the substrate for the diagnostic use of the tilt table. Head-up tilt table testing provides a powerful, controlled orthostatic stimulus simulating under laboratory conditions the peripheral provocation of vasovagal syncope. The pathophysiology of the vasovagal response is thus central to an understanding of the role of tilting in its diagnosis.

Although central, higher cortical provocation of vasovagal syncope through emotional stress and pain is a clinical commonplace, the neuronal connections mediating the response are far from certain. Animal models implicate the limbic system as the relay region for stress-related neuronal activity, with the ultimate control mechanisms residing in hypothalamic and brain-stem autonomic nuclei. Human vasovagal syncope tends to present more prosaically, with many episodes following periods of prolonged standing, for example in church or in shopping queues. This observation led to the hypothesis that defective neurocardiovascular compensatory mechanisms during orthostatic stress were responsible for the initiation of the vasovagal cascade through an inappropriate Bezold-Jarisch-type reflex. Exaggerated venous pooling in capacitance vessels in the lower part of the body is thought to provoke relative central hypovolaemia with compensatory vigorous left ventricular contraction and sympathetic stimulation, resulting in inappropriate mechanoreceptor activation. The resultant afferent traffic is then relayed via unmyelinated vagal C-fibres to the nucleus tractus solitarius of the medulla which orchestrates the efferent limb of the vasovagal response by undetermined mechanisms. Further support for this hypothesis is derived from the echocardiographic demonstration of vigorous left ventricular contractions and relatively low ventricular volumes in patients with tilt-induced syncope, but the demonstration of classic vasovagal...
syncope in orthotopic heart transplant recipients without evidence of vagal reinnervation provides a cautionary note, suggesting that the exact mechanisms responsible for the vasovagal neurocardiovascular cascade have yet to be fully elucidated.

The head-up tilt table test therefore mimics the orthostatic stress, resulting in maximal venous pooling, central hypovolaemia and peripheral provocation of vasovagal syncpe. While the initial response to the assumption of the upright posture is similar in healthy subjects and syncopal patients, namely maintenance of arterial normotension through increasing cardiac inotropy and chronotropy and vasoconstriction of splanchnic and skeletal vascular beds, patients eventually exhibit the hallmark clinical and neurocardiovascular features of the vasovagal event. The fact that the tilt-induced syncopal episode is analogous to spontaneous attacks is evidenced by the similarity of symptoms leading up the event and the identical sequence of haemodynamic and neuroendocrine changes, in particular the dramatic arterial hypotension (with or without bradycardia/asystole) and catecholamine surge just before syncope.

Indications and contraindications

Head-up tilt table testing is indicated in the diagnosis of recurrent syncope where initial history, clinical examination and appropriate neurological and cardiovascular investigations have been non-diagnostic. Tilt-table testing may also be appropriate in patients with single syncopal episodes who have sustained injuries during attacks or who have experienced syncope while driving. Tilt testing may also be useful in the assessment of older patients with unexplained falls. Relative contraindications include proximal coronary artery stenosis, critical mitral stenosis, clinically severe left ventricular outflow obstruction and known severe cerebrovascular stenosis.

Methodology of the head-up tilt table test

Equipment, monitoring and environment

The tilt table should be of the foot-plate support type, and whether mechanically or electrically powered, should be able to achieve the upright posture within 15 s and allow calibrated tilt angles of between 60° and 80° (Figure 1).

Electrocardiographic monitoring should occur continuously during symptoms or haemodynamic changes and every 5 min otherwise. Blood pressure monitoring should ideally be of the continuous, non-invasive variety (e.g. digital photoplethysmography, Finapres) though sphygmomanometric measures are widely used. Blood pressure should similarly be recorded continuously (or as frequently as is practicable) during symptoms and at 1-min intervals otherwise. In order to minimize stimuli affecting autonomic nervous function, the test should occur in a quiet, dimly lit room at a comfortable temperature. Resuscitation equipment should be immediately available, and to the standard required in exercise tolerance testing facilities. The test should be continuously supervised by a physician, nurse or technician experienced in the management of the test and its potential complications.

Patient preparation

Patients should be fasted for 2 or more hours prior to the procedure (in order to minimize the confounding effects of post-prandial orthostatic hypotension) and then rested supine for 20 to 45 min, with longer periods necessary if intravascular instrumentation (which increases the risk of false positive results) is used. The procedure should be explained to the patient, who should be securely strapped to the tilt table prior to the assumption of the upright position to prevent collapse and injury during syncope. Drugs affecting cardiovascular or autonomic function should be discontinued for a minimum of five half-lives pre-test, unless they are aetiologically implicated. During the test the patient should be instructed to avoid movements of the lower extremities to maximize venous pooling.

Tilt angle and duration of the head-up tilt test

The angle and duration of the test are the most powerful determinants of its diagnostic utility. The evidence available to date suggests that tilt angles between 60° and 80° are optimal in creating sufficient orthostatic stress without increasing the number of false positive or negative results. The duration of the test also varies between centres, but the available evidence suggests that prolonged tilt for 30–45 min is optimal with longer periods engendering unacceptably high proportions of false positive results. Our own practice uses a 70° tilt angle for 40 min.

Sensitivity and specificity of the head-up tilt table test

These issues were touched upon in the previous section, but deserve closer attention. The absence of a ‘gold-standard’ diagnostic test for vasovagal syncope makes the calculation of the exact specificity
and sensitivity of the tilt test difficult, particularly in view of the variable methodologies used by different groups reporting results. The ability of the test to differentiate patients from healthy controls is nonetheless well established, with specificity generally up to 90% at tilt angles between 60° and 70°, and sensitivity ranging between 32% and 85%, with the median closer to the upper number. These figures compare well with standard cardiological diagnostic tests, including the 12-lead ECG and exercise testing.3,28,32–34

**Reproducibility of the head-up tilt table test**
Reproducibility studies on the responses to head-up tilt table testing have produced some contradictory results. Long-term reproducibility, from periods of 1 day35 to 4 years36 have generally shown reproducible responses in 62% to 85% of subjects,35–38 although one report found 1-day reproducibility to be as low as 35%.39 Repeated testing within 30 min shows consistently concordant responses in 67% to 87%.40 of the patients studied, though several studies report marked intra-individual variability in the degrees of cardioinhibition and vasodepressor components to the vasovagal responses elicited.41–43

**Positivity of the head-up tilt table test**
The head-up tilt table test should only be judged positive if symptoms reproducing entirely the patients original pre-syncope or syncopal symptoms are accompanied by arterial hypotension, bradycardia or both.3,28,44 Haemodynamic changes in isolation should not prompt a diagnosis of vasovagal syncope.

**Pharmacological provocative agents in head-up tilt table testing**
Provocative agents to both shorten the duration and increase the specificity of the head-up tilt test have a well-established role in the diagnosis of vasovagal syncope. If the initial prolonged, drug-free tilt test is non-diagnostic, pharmacological provocateurs should be considered.

**Isoproterenol**
The observation of a catecholaminergic surge immediately prior to tilt-induced syncope in susceptible individuals22 prompted the administration of exogenous catecholamines to precipitate syncope in patients suspected of suffering from vasovagal syncope.
Following the initial report by Almquist et al., many centres have now reported improved sensitivity in the diagnosis of vasovagal syncope, though at the expense of a fall in specificity using high-dose regimens. Isoproterenol tilt is safe, with few adverse events reported, though recent data from our group has shown that the procedure is poorly tolerated in older subjects. Contraindications to isoproterenol include coronary artery disease, uncontrolled hypertension, significant aortic stenosis and left ventricular outflow obstruction, and the drug should be used with caution in subjects with known supraventricular or ventricular arrhythmias.

**Nitropenic agents**

Nitropenic agents have been used as provocative agents in the tilt-table aided diagnosis of vasovagal syncope for several years. Their venodilatory properties are thought to promote the syncopal cascade through the peripheral route. Glyceryl trinitrate in both intravenous and sublingual preparations has been used for 20–30 min following an initial drug-free passive tilt. Sensitivity ranges from 51 to 81%, and specificity from 85% to 94%. Our own recent data shows comparable specificity and sensitivity with both passive and isoproterenol tilts, with the added benefits of ease of administration, relative lack of side-effects and the avoidance of intra-vascular instrumentation, which is known to affect specificity adversely.

**Other pharmacological provocative agents**

The endogenous nucleoside adenosine, which enhances sympathetic nervous activity and promotes vasodilatation, has been used to shorten the duration of tilt testing with some success in several small studies. Edrophonium and clomipramine have also been used to accelerate the tilt table test with some success, though the methods need further assessment before their widespread adoption.

**Classification of vasovagal syncope**

Positive responses to tilt testing can be divided into four subgroups based on specific patterns of heart rate and blood pressure changes during syncope and these are described in Table 1. This classification is useful in both the research arena and in the choice of permanent pacing versus pharmacological therapy for vasovagal syncope.

**Head-up tilt table testing at the extremes of age**

Tilt table testing has been reported at all ages at which prolonged standing is practicable, with subjects as young as 3 years being described. Indications, contraindications and methodology are essentially the same in paediatric and elderly subjects, with the proviso that isoproterenol dosage should not exceed 0.03 mg/kg in children. Elderly patients often have sudden onset syncope with little or no prodrome, so positivity criteria need to be viewed with this in mind. Isoprenaline is more often contraindicated in this age-group because of associated co-morbidity and more pronounced side-effects. Recent data from our group shows GTN tilt to be well-tolerated in older subjects undergoing provoked tilt, with no effects on sensitivity and specificity.

**Further differential diagnosis of unexplained syncope using tilt table testing**

A summary of the alternative differential diagnoses achievable with tilt-testing is given in Table 2. Head-up tilt test is a useful adjunct in the diagnosis of psychogenic syncope, i.e. syncope during tilt testing in the absence of haemodynamic, electroencephalographic or transcranial doppler abnormalities. Such patients tend to exhibit features rarely seen during vasovagal syncope, namely sudden, dramatic syn-
cope, post-event disorientation and a prolonged period of recovery.64 Hyperventilation syncope can similarly be diagnosed during tilt testing through the demonstration of hypocapnia (which is thought to stimulate cerebral arterial vasoconstriction) and alkalosis during syncope through arterial blood gas analysis,49 though a recent report has accomplished the diagnosis using end-tidal PCO$_2$ as the marker of hyperventilation.65 The postural orthostatic tachycardia syndrome (POTS),66 a mild form of dysautonomia, can be diagnosed during head-up tilt table testing through the demonstration of a rise in heart rate of more than 30 beats per minute (bpm) (or a maximum heart rate of 120 bpm) in the absence of hypotension but in association with characteristic symptoms including light-headedness, fatigue, pre-syncope and dizziness.66 Recent guidelines from the American Autonomic Society and the American Academy of Neurology on the diagnosis of orthostatic hypotension have expanded the definition to include a fall in systolic blood pressure of >20 mmHg or diastolic blood pressure of >10 mmHg within 3 min of the assumption of the 60° head-up tilt position.67 Tilt table testing may also be useful in the differential diagnosis of convulsive syncope from epilepsy. Short lived tonic-clonic movements are a not infrequent accompaniment of vasovagal syncope, particularly during prolonged asystole,21 and their presence may prompt a misdiagnosis of epilepsy,21,68 often labelled as refractory.69 Speed of recovery, the short duration of ictus and the absence of post-ictal signs and symptoms are pointers towards the true diagnosis, which can only be made with a high index of suspicion and appropriate tilt testing, particularly with concurrent electroencephalography.21,68,69 Finally, carotid sinus massage immediately following the assumption of the head-up tilt posture may provide a positive diagnosis of carotid sinus hypersensitivity (CSH) where initial supine massage is non-diagnostic.70–73 While afferent pathways are clearly distinct in CSH and vasovagal syncope, a common central modulatory mechanism may underlie both disorders. Indeed recent data from our group showed that 31% of patients presenting with unexplained falls and syncope with CSH had a positive response only in the 70° head-up tilt position.73 Where history is suggestive and massage is negative in the supine position, repeat carotid sinus massage in the head-up tilt position is advisable.

References


