‘Front-loaded’ head-up tilt table testing: validation of a rapid first line nitrate-provoked tilt protocol for the diagnosis of vasovagal syncope

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Abstract

Head-up tilt testing is the investigation of choice in the diagnosis of vasovagal syncope. The test is time consuming and labour intensive, with conventional tilt testing taking up to 45 min. We compared a shortened ‘front-loaded’ 20-min glyceryl trinitrate-provoked head-up tilt (FLGTN-HUT) with the standard 40-min passive tilt (HUT) as first line investigations in patients with unexplained syncope and asymptomatic controls. In the study, 149 consecutive patients with unexplained syncope and 83 asymptomatic controls were enrolled. Subjects were randomly assigned to FLGTN-HUT (800 mcg, metered spray) or HUT, then the opposite tilt-test 1 week later. Seventeen (11.4%) patients had diagnostic haemodynamic changes and symptom reproduction during HUT and 54 (36.2%) during FLGTN-HUT. A total of 24.8% more patients had a positive test with FLGTN-HUT than with passive HUT (95% CI: 16.3%, 33.4%). Nine (10.8%) controls had significant haemodynamic changes during HUT and 23 (27.7%) during GTN provocation. Seven controls had haemodynamic changes on both HUT and FLGTN-HUT testing. The controls group had 16.8% more significant haemodynamic changes with FLGTN-HUT than with HUT (95% CI: 0.06, 27.4). The front-loaded GTN protocol provided a higher diagnostic rate than passive tilt testing, and provides a rapid alternative to conventional methods, though false positivity rates are higher.

Keywords: nitrates, head-up tilt testing, syncope, autonomic nervous system, vasovagal, elderly

Introduction

Head-up tilt table testing is well established as the investigation of choice in the laboratory investigation of vasovagal syncope [1–4]. The test is cheap and safe, with a good specificity [1, 2, 4–8], sensitivity [1, 2, 4, 8] and reproducibility [1, 2, 9–11] profile, and few reported serious adverse events worldwide [12, 13]. Many centres now use variations on the 35 min duration Italian protocol or ‘20/15’ tilt as the routine baseline tilt test [4, 5], while the prolonged passive tilt (HUT) of 40–45 min duration is still in common use [1, 2]. We hypothesised that a 20-min glyceryl trinitrate-provoked head-up tilt (FLGTN-HUT) is superior to prolonged, passive head-up tilt table testing as a first line diagnostic test for vasovagal syncope. Our objective was to determine the efficacy of HUT versus FLGTN-HUT as first line investigations in the diagnosis of vasovagal syncope in adults undergoing investigations for unexplained syncope and asymptomatic age- and sex-matched control subjects, through the medium of a prospective, randomised, controlled cross-over trial of the two procedures.
Methods

Inclusion criteria

Consecutive patients with unexplained syncope (two or more episodes, or one episode where driving or occupation required definitive diagnosis) or disabling pre-syncope (five or more episodes) referred to our tertiary referral falls and syncope facility and undergoing head-up tilt table testing as part of their investigation strategy were invited to participate in the study, along with a control group with no prior history of syncope, pre-syncope or dizziness and similar age and sex distribution. Hospital and university notice-board posters and local radio broadcasting recruited control subjects. Syncope and pre-syncope were investigated as per the European Society of Cardiology (ESC) guidelines [4], and were deemed unexplained if no diagnosis had been obtained following detailed history and examination, 12-lead electrocardiography (ECG), active stand to exclude orthostatic hypotension, 24-h ECG and in selected cases, carotid sinus massage (in those aged 40 years or more [4]), electrophysiology studies, electroencephalography, echocardiography and 24-h ambulatory blood pressure monitoring. Medications were continued during the test protocol, particularly, where these were potential aetiological culprits. Control subjects had no cardiovascular abnormalities on clinical examination or 12-lead ECG. Subjects were between 18 and 90 years of age and had to be able to give informed written consent. The study had the approval of the Local Research Ethics Committee.

Exclusion criteria

Exclusion criteria included relative contraindications to tilt table testing (clinically severe left ventricular outflow obstruction, critical mitral stenosis, proximal coronary artery stenoses, and known severe cerebrovascular stenosis [1, 2]), previous adverse reaction to nitrates, or inability to attend the second tilt test because of other commitments.

Head-up tilt protocols

1. Passive head-up tilt. Subjects rested supine for 10 min and were then tilted to the 70° position for 40 min, or until positivity criteria were reached (see below).

2. Front-loaded GTN head-up tilt. As validated in previous reports [14, 15], subjects rested supine for 10 min after which 800 mcg sublingual GTN was administered in the spray form. They were then tilted to the 70° position for 20 min, or again until positivity criteria were reached.

In both cases, surface electrocardiograph at 25 mm/s was continuously monitored as was beat-to-beat blood pressure using digital photoplethysmography (Finapres, Ohmeda, Wisconsin).

Positivity criteria

The FLGTN-HUT or HUT positivity was defined as hypotension [fall in systolic blood pressure (SBP) to ≤80 mmHg, or by >50% from baseline] and/or bradycardia/asystole with symptom reproduction (i.e. syncope or pre-syncope) in patients, or de novo in controls. A false positive tilt was defined as a haemodynamic change without symptom reproduction in patients. A false positive tilt could not be described in controls, as defining symptoms had never before been experienced. Tilt tests were also terminated if requested by subjects, or if significant arrhythmia or other adverse events developed.

Randomisation procedure

All subjects eligible for inclusion in the study were randomised via table of random numbers and allocated with sealed envelopes to either initial HUT or GTN-HUT, and 1 week later, crossed over to the opposite procedure at the same time of the day.

Power calculation

Sample size calculations are based on previous work from our unit using a similar population undergoing passive tilt, GTN tilt and isoproterenol tilt [14]. Thirty one of 88 (35%) patients had a positive 40 min HUT. These 31 patients did not go on to have provoked testing. In all 26 of 55 (47%) patients had a positive GTN-provoked HUT. Thus approximately 65% of patients were positive on either unprovoked or provoked HUT test [14]. We assumed that the majority of patients who were positive on unprovoked tilt would have been positive on provoked tilt and that 65% of patients overall would have concordant results. We calculated that 140 patients would provide an estimate of the treatment difference with a standard error of 2.5%.

Statistical analysis

The effect of order on each of the tests was tested using Fisher’s exact test. The estimate of the difference in proportions of positive test results was estimated using the paired data and the estimate of standard error was calculated using STATA v7 Epitab command. The P-values for the treatment comparisons were calculated using McNemar’s test. Sensitivity and specificity calculations (though used widely in the tilt testing literature) are potentially misleading because of the lack of a gold standard comparator to head-up tilt testing and the reliance on symptom reproduction to establish tilt positivity, and are deliberately avoided here.

Results

Subjects

One hundred and fifty-nine patients with unexplained syncope, undergoing tilt testing as part of their investigations and seen at our syncope facility between March 1999 and September 2000, were invited to participate in the study, of whom 150 were enrolled. Nine were unable to attend the second tilt test, and hence were excluded. All but one (i.e. 149 patients) completed both tilt protocols. Eighty-five control subjects were recruited to the study, of whom two
refused the second tilt. Clinical characteristics of patients and controls are shown in Table 1. Patients and controls were of similar age and sex distribution, though patients suffered more cardiovascular co-morbidity and were taking more cardiovascular medications.

**Head-up tilt test results**

Seventeen (11.4%) patients (Table 2) had diagnostic haemodynamic changes and symptom reproduction during HUT and 54 (36.2%) during FLGTN-HUT (true positives). A total of 24.8% more patients had a positive test with FLGTN-HUT than with passive HUT (95% CI: 16.3%, 33.4%). One patient had a false positive HUT result, while eight had a false positive FLGTN-HUT result (classified as HUT- and FLGTN-HUT negative. See Appendix 1 in the supplementary data on the journal’s website http://www.ageing.oxfordjournals.org). None of the patients had a false positive result for both tests. Nine (10.8%) control subjects had significant haemodynamic changes during HUT and 23 (27.7%) during GTN provocation (Table 3). Seven controls had haemodynamic changes on both HUT and FLGTN-HUT testing. In this study, 16.8% more controls had significant haemodynamic changes with FLGTN-HUT than with HUT (95% CI 0.06, 27.4).

Order effects were not seen (Fisher’s exact test $P = 0.7$), and neither subjects nor controls had evidence of orthostatic hypotension (20 mmHg fall in systolic, or 10 mmHg fall in diastolic blood pressure with the assumption of the upright posture), either from morning orthostatic measurements (active stand) or during the first 3 min of tilt testing [1]. Side effects were minimal, with seven (4.6%) patients and six (7.2%) controls suffering headache following GTN administration. There were no arrhythmic side effects. Appendix 1 shows the ‘New VASIS’ classification [4] of the type of vasovagal syncope according to the haemodynamic results of head-up tilt testing in adults, while Appendix 2 applies the classification to the positive tilt test results in patients and control subjects. Appendix 1 and 2 are available as supplementary data on the journal’s website http://www.ageing.oxfordjournals.org. Again there is an overlap between the results for each of the tests due to the paired nature of the design. The majority of both patients and controls had Type 3 (pure vasodepressor) responses to both FLGTN-HUT and HUT, with a significant minority in both groups having Type 1 (mixed, without significant cardioinhibition) responses (see Appendix 2 in the supplementary data on the journal’s website http://www.ageing.oxfordjournals.org). Few patients had significant bradycardia or asystole, which occurred exclusively in the FLGTN-HUT positive patients (6 [11.1%] Type 2A, 2 [3.7%] Type 2B; see Appendix 2 in the supplementary data on the journal’s website http://www.ageing.oxfordjournals.org). Only two control subjects had significant bradycardia (without asystole: Type 2A), one during HUT and one during FLGTN-HUT.

**Discussion**

The front-loaded GTN head-up tilt test takes half the time to perform compared to its conventional equivalent, with a higher diagnostic rate and no significant side effects. Though a formal economic analysis was not part of our study design, the front-loaded GTN-HUT must be more efficient than its prolonged predecessor in both clinical and resource utilisation terms. Our study is also unique in the tilt testing literature in being demonstrably adequately powered to draw our conclusions. FLGTN-HUT provides a sensitive alternative to more prolonged tilt protocols as the first line investigation in the diagnosis of vasovagal syncope. The test was well tolerated in all (adult) age groups, from young adulthood to extreme old age, with no significant adverse effects. Previous studies tended to focus on younger individuals with a much narrower age range [5, 6, 16–18].

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**Table 1. Clinical characteristics of patients and control subjects**

<table>
<thead>
<tr>
<th></th>
<th>Patients $n=149$</th>
<th>Controls $n=83$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age in years (SD)</td>
<td>58.0 (19.3)</td>
<td>54.5 (19.4)</td>
</tr>
<tr>
<td>Range</td>
<td>18–89</td>
<td>18–90</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>Female</td>
</tr>
<tr>
<td></td>
<td>90 (60%)</td>
<td>45 (54%)</td>
</tr>
<tr>
<td>Co-morbidity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina</td>
<td>28 (23%)</td>
<td>4 (5%)</td>
</tr>
<tr>
<td>MI</td>
<td>16 (11%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>50 (29%)</td>
<td>10 (12%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3 (2%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Cardiovascular drugs</td>
<td>59 (35%)</td>
<td>16 (19%)</td>
</tr>
</tbody>
</table>

**Table 2. Head-up tilt test results in patients**

<table>
<thead>
<tr>
<th>FLGTN-HUT positive</th>
<th>No</th>
<th>Yes</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>HUT positive</td>
<td>91</td>
<td>41</td>
<td>132</td>
</tr>
<tr>
<td>Yes</td>
<td>4</td>
<td>13</td>
<td>17</td>
</tr>
<tr>
<td>Total</td>
<td>95</td>
<td>54</td>
<td>149</td>
</tr>
</tbody>
</table>

**Table 3. Head-up tilt test results in control subjects**

<table>
<thead>
<tr>
<th>FLGTN-HUT positive</th>
<th>No</th>
<th>Yes</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>HUT positive</td>
<td>58</td>
<td>16</td>
<td>74</td>
</tr>
<tr>
<td>Yes</td>
<td>2</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
<td>23</td>
<td>83</td>
</tr>
</tbody>
</table>

*MRI, myocardial infarction; SD, standard deviation.*
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FLGTN-HUT provided not only a higher true positivity rate but also a much shorter time to achieve a positive diagnosis. Mean time to symptom reproduction in patients was 11.3 min during GTN-HUT versus 23.3 min with HUT, significantly reducing testing time compared not only to conventional tilt testing but also to the Italian protocol [5].

The high positivity rate (23 [27.7%]) of FLGTN-HUT in previously asymptomatic control subjects is clearly of importance, and has recently been described by others [19]. The higher dose of GTN (800 mcg) used in our study may have contributed, but was used to overcome the large inter-subject variability in absorption and elimination of glyceryl trinitrate and its metabolites [20]. Furthermore, Bartoletti et al. found a lower positivity rate during nitrate-provoked tilt using 400 mcg of sublingual GTN [21]. The higher dose has been previously validated [14, 15], and has similar sensitivity and specificity to isoproterenol tilt testing and with fewer side effects [14].

The diagnostic criteria applied during tilt testing are important in assessing the relevance of the high positivity rate in controls during FLGTN-HUT. The head-up tilt test is acknowledged as an inexact tool, which relies on symptom reproduction during characteristic haemodynamic changes to establish its positivity; by definition, asymptomatic controls cannot experience a positive head-up tilt test. Some of these controls may go on to experience syncope at a later date, but there is no published evidence to support this. In the absence of a ‘gold standard’ diagnostic test in vasovagal syncope, it is difficult to assess the import of this high positivity rate in control subjects. As long as the criteria of symptom reproduction with arterial hypotension, with or without bradycardia/asystole, are rigidly adhered to, the potential for false positive results in patients should be minimal.

Positivity rates as low as 32% have been recorded for passive tilt testing [22], but the even lower diagnostic rate with both passive and FLGTN-HUT in our study merits comment. As in previous studies, all patients underwent an extensive diagnostic work-up prior to study inclusion, so alternative causes of syncope were effectively ruled out. However, in accordance with our practice [1, 3] and the recommendations of others [23], those with a history strongly suggestive of vasovagal syncope who did not require tilt testing to confirm the diagnosis were not included, effectively (but clinically appropriately) reducing the pool of potential positive responses.

The pattern of haemodynamic responses to GTN-HUT testing was similar to that previously described for passive tilt testing, with a predominance of VASIS Type 1 and 3 responses in both patients and controls. Contrary to findings in smaller studies [24], there was no excess incidence of severe cardioinhibition in either patients or controls.

In conclusion, the 20 min GTN-provoked head-up tilt table test provided a diagnosis more frequently than the prolonged passive tilt, was well tolerated in all age groups, and had minimal side effects. The front-loaded GTN tilt can provide a valuable time and resource-saving alternative to more prolonged tilt testing in adults undergoing investigation for unexplained syncope.

Key points

- Head-up tilt testing may be useful in the diagnosis of vasovagal syncope.
- Prolonged tilt testing is time consuming and labour intensive.
- We describe here a randomised cross-over comparison of a shortened GTN-provoked tilt test versus conventional tilting.
- The shortened test had superior positivity to conventional tilt, though with a higher false positive rate.

Acknowledgement

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Sources of support

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Supplementary data

Supplementary data for this article are available online at http://ageing.oxfordjournals.org.

References

Front-loaded nitrate-provoked tilt testing


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