Responses to the prolonged head-up tilt followed by sublingual nitrate provocation in asymptomatic older adults

N. Pradeep Kumar, Jane H. Youde¹, Charlotte E. Ruse¹, Martin D. Fotherby¹, Tahir Masud

Nottingham City Hospital NHS Trust, Hucknall Road, Nottingham NG5 1PB, UK
¹The Glenfield Hospital, Leicester, UK

Address correspondence to: T. Masud. Fax: (+44) 115 960 8409. Email: tm@nchhce.demon.co.uk

Abstract

Background: prolonged head-up tilt testing and sublingual nitrate provocation are increasingly used in the diagnosis of neurocardiogenic syncope. However there are few data regarding the results of these tests in asymptomatic older subjects.

Objective: to assess the responses to the prolonged head-up tilt test followed by sublingual glyceryl trinitrate provocation in asymptomatic subjects over the age of 60 years.

Design: observational study.

Methods: we recruited 64 asymptomatic subjects over the age of 60 (39 men, 25 women) from two general practice lists in Nottingham and Leicester. Exclusion criteria were: history of syncope, ischaemic heart disease, cerebrovascular disease, marked aortic stenosis, carotid artery disease and being unable to stand for the duration of the test. All subjects underwent a full clinical examination, a 12-lead electrocardiogram and a 30–40-min head-up tilt test, during which we monitored the heart rate and blood pressure continuously. We ended the test prematurely if the subjects developed syncope or symptoms of presyncope associated with hypotension with or without bradycardia. If they remained asymptomatic at the end of this period, they received 400 mg of sublingual glyceryl trinitrate and monitoring continued for another 15 min.

Settings: two teaching hospitals in Nottingham and Leicester.

Results: six (9%) of the subjects had a positive response (syncope or presyncope) to the prolonged head-up tilt test prior to glyceryl trinitrate provocation. After provocation, 30 (52%) of the remaining 58 subjects had a positive response.

Conclusion: the role of sublingual glyceryl trinitrate provocation following prolonged head-up tilt testing in the diagnosis of neurocardiogenic (vasovagal) syncope in older people is questionable, as many asymptomatic older subjects demonstrate syncopal or presyncopal symptoms.

Keywords: neurocardiogenic, nitrates, provocation, syncope, vasovagal

Introduction

Falls are common in old age and their consequences include injury, fracture, subdural haematoma, loss of confidence, institutionalization and death. Each year about 30% of people over 65 living at home fall, around half of them recurrently [1, 2]. An important cause of falls in older people is syncope [3], for which diagnostic work-up is often expensive and time-consuming. The aetiology of syncope may remain unexplained even after extensive investigations (including 24-h Holter monitoring and echocardiography). Neurocardiogenic (vasovagal or neurally mediated) syncope is an important cause of unexplained falls and blackouts. Typical vasomotor responses during orthostatic stress are increased heart rate and vasoconstriction (baroreceptor-mediated sympathetic stimulation) and prodromal symptoms such as nausea, sweating and palpitations, followed by hypotension and bradycardia, due to a sudden withdrawal of sympathetic tone and enhanced vagal outflow.

Head-up tilting has gained wide acceptance as a
diagnostic test for the evaluation of unexplained syncope [4-10]. There is, however, no consensus as to the exact protocol that should be used [4, 11, 12]. The use of the prolonged head-up tilt test has allowed many causes of unexplained falls and syncope to be diagnosed as neurocardiogenic syncope [3, 8, 10, 13-15].

The angle and duration of tilt and the practice of administering provocative agents such as isoprenaline or nitrates vary between different centres. Also, there are limited data on head-up tilt testing in well subjects with no history of syncope. Depending on the population studied and the protocol used, the test has provided diagnostic results in a proportion of patients ranging from 16 to 74% [6, 7, 10, 13-18].

When conventional prolonged head-up tilt testing is negative, provocative agents such as isoprenaline or glyceryl trinitrate infusion have been proposed as adjunct measures to induce neurocardiogenic syncope in susceptible patients [4, 8, 12, 18, 19]. Isoprenaline, however, causes catecholamine-associated complications, such as ventricular arrhythmia and angina pectoris in patients with coronary heart disease, making it less desirable for an unselected population. Intravenous glyceryl trinitrate is an alternative for pharmacological stimulation during tilt testing [8]. However, this procedure is cumbersome and time-consuming, and venepuncture can also precipitate vasovagal syncope and influence the sensitivity and specificity of the tilt tests [20-22]. Alternatively, sublingual administration of glyceryl trinitrate following head-up tilt test is used in some centres to facilitate the diagnosis of neurocardiogenic syncope [23, 24]. There are few data on the use of sublingual glyceryl trinitrate during head-up tilt testing in older patients. In a younger age group (mean age 43 ± 21 years), a study of 32 patients with a history of vasovagal syncope showed that sublingual glyceryl trinitrate increased the accuracy of the prolonged head-up tilt test [23]. The aim of the present study was to assess the responses to the prolonged head-up tilt test followed by provocative administration of sublingual glyceryl trinitrate in asymptomatic older subjects.

Methods

The study group was 64 asymptomatic subjects (39 men, 25 women) randomly selected from the registers of two general practices in Nottingham and Leicester. We enrolled subjects over 60 with no history of syncope or presyncope. Syncope was defined as transient loss of consciousness with inability to maintain postural tone and presyncope was defined as the complex of premonitory signs and symptoms of imminent syncope (severe light-headedness, severe weakness, transient greying of vision with difficulty in maintaining postural tone), both being associated with hypotension with or without bradycardia [8]. We excluded those with a history of ischaemic heart disease, clinically diagnosed aortic stenosis or carotid bruit and those unable to stand for the duration of the test.

We obtained informed consent from the subjects, and the study was approved by the Nottingham City Hospital and Leicester research ethics committees. We performed the test between 0900 h and 1200 h. All subjects had a light breakfast and their usual medication. We performed a detailed clinical examination and a 12-lead electrocardiogram before the prolonged head-up tilt test.

We performed tilt tests using a standardized tilt table, digital plethysmography—which measured beat to beat blood pressure (Finapress-Ohmeda)—and continuous electrocardiogram monitoring (Hewlett-Packard Codemaster). After 10 min in the supine position, the table was tilted to 70°. After 40 min (Nottingham) and 30 min (Leicester), in the absence of syncope or presyncope, we administered a single metered dose (400 μg) of glyceryl trinitrate sublingually and continued monitoring for a further 15 min. The test was prematurely ended if subjects developed symptoms of syncope or presyncope (a positive tilt response), whereupon the table was immediately lowered to the supine position.

Results

We recruited 64 subjects (44 from Nottingham and 20 from Leicester). Their mean age was 70 years (range 61-84). Subject characteristics of the groups are in Table 1. Positive responses (presyncope or syncope) to the prolonged head-up tilt tests, pre- and post-glyceryl trinitrate administration, are shown in Table 2. In total, 36 (56%) had a positive prolonged head-up tilt test. Only six (9%) showed a positive response to the prolonged head-up tilt test before nitrate provocation. Of the remaining 58 subjects in whom sublingual glyceryl trinitrate was administered, a further 30 (52%) developed a positive response. Test details in subjects with positive responses before glyceryl trinitrate provocation are shown in Table 3. Two of the five subjects in Nottingham who had syncope or presyncope pre-nitrate provocation showed a positive response between 30 and 40 min, and therefore would have been classified as negative if the test had been performed using the Leicester protocol.

None of the six patients with a positive test in the pre-provocative stage and four of the 30 subjects who had a positive after nitrate provocation were taking β-blockers.

Prior to nitrate provocation, in the positive subjects, the mean time to symptoms was 28.7 ± 9.6 min. After nitrate provocation, the mean time to symptoms was 4.5 ± 2.1 min in the Nottingham
group (total tilt time 44.5 ± 2.1 min) and 5.3 ± 2.8 min in the Leicester group (total tilt time 35.3 ± 2.8 min).

Discussion

More than half of older subjects with no history of syncope or presyncope had a positive prolonged head-up tilt test when sublingual glyceryl trinitrate was used as a provocative agent. In tilt testing the use of pharmacological provocation, the agent used, route and timing of administration are variable. Normal healthy younger subjects have a low rate of syncope with upright tilt testing [23, 24]. Sutton et al. noted a 13% positive tilt test rate (60° for 60 min) in control subjects [25]. In another study of older subjects, Fitzpatrick et al. showed that tilt testing (60° for 60 min) caused syncope in only 7% of controls (mean age 69 years) without a history of syncope [15]. Kapoor and Brant reported that the use of isoprenaline decreased the specificity of tilt testing in young adults, with 45–65% of asymptomatic controls having positive results following its administration [26]. Another study investigated the influence of various tilt angles and different doses of isoprenaline in a group of 150 control subjects (mean age 41 ± 21 years) without a history of syncope and showed that tilt testing at 60, 70 and 80° demonstrated specificities of 88, 88 and 60% respectively in the presence of low-dose isoprenaline provocation, although the baseline tilt was performed for only 20 min, which may have underestimated positive responses compared to longer protocols [27].

Regarding sublingual provocation, Ammirati et al. showed that 19% of patients with unexplained syncope (mean age 40 ± 22 years) had a positive tilt test (30 min at 60°) and by giving the remainder 1.25 mg isosorbide dinitrate sublingually at 30 min and continuing monitoring for another 15 min, the positive rate increased to 58%, whereas no subject in the control group was positive before or after provocation [28]. Del Rosso et al. gave sublingual glyceryl trinitrate (400 mg) at 20 min during a 45-min tilt test (60°) to syncopal patients (mean age 49 ± 19 years) and controls (mean age 45 ± 17 years) [29].

During the unmedicated phase, 11% of patients and 1% of controls were positive and after nitrate provocation a further 59% of patients and 1% of controls became

Table 1. Subject characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nottingham (n = 44)</th>
<th>Leicester (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>70.2</td>
<td>69.5</td>
</tr>
<tr>
<td>Median (range)</td>
<td>70.5 (65–84)</td>
<td>68 (61–78)</td>
</tr>
<tr>
<td>No. (and %) male</td>
<td>28 (64%)</td>
<td>11 (55%)</td>
</tr>
<tr>
<td>Tilt time pre-glyceryl trinitrate, min</td>
<td>40</td>
<td>30</td>
</tr>
<tr>
<td>Hypertension, no. (and %) of subjects</td>
<td>10 (23%)</td>
<td>7 (35%)</td>
</tr>
<tr>
<td>Medication, no. (and %) of subjects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>5 (11%)</td>
<td>5 (25%)</td>
</tr>
<tr>
<td>β-blockers</td>
<td>5 (11%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Calcium channel antagonists</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>1 (2%)</td>
<td>0</td>
</tr>
</tbody>
</table>

CI, confidence interval.

Table 2. Positive responses to the prolonged head-up tilt test pre- and post-glyceryl trinitrate provocation

<table>
<thead>
<tr>
<th>Centre</th>
<th>Pre-provocation</th>
<th>Post-provocation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nottingham</td>
<td>5/44 (11.4%; 95% CI = 2.0–22.7%)</td>
<td>22/39 (56.4%; 95% CI = 40.8–72.0%)</td>
</tr>
<tr>
<td>Leicester</td>
<td>1/20 (5%; 95% CI = 0–14.6%)</td>
<td>8/19 (42.1%; 95% CI = 19.9–64.3%)</td>
</tr>
<tr>
<td>Combined</td>
<td>6/64 (9.4%; 95% CI = 2.3–16.5%)</td>
<td>30/58 (51.7%; 95% CI = 38.87–64.6%)</td>
</tr>
</tbody>
</table>
positive. McIntosh et al. showed that in 14 healthy controls (mean age 69 ± 7 years) no subject had a positive response to tilt alone (30 min) but those given 400 μg of glyceryl trinitrate before the tilt showed a 14% positive rate [30]. Patients with unexplained syncope (mean age 70 ± 6 years) showed a 24% positive rate without provocation and a 67% positive rate with nitrate provocation before tilting. In a study comparing isoprenaline to sublingual glyceryl trinitrate in subjects over 60 years, Natale et al. showed that their nitrate-provocation protocol (unmedicated tilt at 70° for 20 min, and if no response return subjects to supine and administer 400 μg of glyceryl nitrate sublingually and, after 5 min, re-tilt for another 15 min) maintained an adequate specificity and provided a better sensitivity than isoprenaline [31]. Raviele et al. noted no positive responses following prolonged head-up tilt testing (45 min at 60°) and a 6% positive response following glyceryl trinitrate administration in healthy controls (mean age 52 ± 20 years) [24]. Sublingual glyceryl trinitrate following prolonged head-up tilt testing (40 min at 70°) increased the diagnostic yield of the test in syncopal patients (mean age 43 ± 21 years) [23]. Before nitrate provocation, 13% of patients developed syncope, whereas after provocation the positive rate increased to 87%. In the control group of the same study, (mean age 27 ± 4 years) no subjects had a positive response before provocation, whereas 50% were positive after nitrate administration.

In our study of healthy older subjects, we used similar tilt test and sublingual nitrate provocation methodology to those in the latter study. With the unprovoked prolonged head-up tilt test for 30–40 min at 70°, only 9% of subjects had a positive response, but after nitrate provocation over half of the remaining subjects had a positive response. The use of sublingual glyceryl trinitrate provocation at the end of the tilt test (at 70° for 30–40 min) to diagnose neurocardiogenic syncope is thus questionable in older people, as even in normal asymptomatic older subjects there is a high positive response rate. These data contrast with the other studies in older age groups, which show that sublingual nitrate administration increases the yield of the tilt test whilst maintaining an acceptable specificity, although the timing of provocation and duration of tilting were different [30, 31].

The higher positive rates pre- and post-nitrate provocation in the Nottingham group compared with the Leicester group may be explained by the differences in time of the tilt test before provocation (40 and 30 min respectively). The proportion of healthy subjects experiencing hypotension with or without bradycardia during tilt testing rises dramatically with increases in tilt time beyond 45 min. Consensus seems to be emerging that tilt tests should be performed for no more than 45 min [32]. As nitrate was administered while the patients were still upright, it is possible that the higher number of positive tilts was simply a function of prolongation of the tilt test to 55 min (Nottingham) or 45 min (Leicester).

The main limitation of this study is that we did not repeat the test for 55 and 45 min respectively without nitrate provocation or have a matched control group undergoing unprovoked 55- and 45-min tilt testing respectively. Nevertheless, the data show that both the Nottingham and Leicester protocols show an acceptably high positive rate with nitrate provocation. The study included a number of people with hypertension and some who were taking vasoactive medication. Although the study results may not be directly applicable to entirely healthy older people, many older subjects who attend syncope clinics have a background of cardiovascular disease and often use a number of drugs. The study is therefore relevant to clinical practice.

In conclusion, this study suggests that in asymptomatic older subjects, the unprovoked prolonged head-up tilt test for 30–40 min at 70° has an acceptable low positive rate. However, the increasingly widespread use of sublingual glyceryl trinitrate at the end of the test as a provocative agent in an attempt to increase the diagnostic yield in syncopal patients needs to be questioned, as there is an unacceptably high positive rate in asymptomatic older subjects. This is likely to lead to a high false-positive rate when investigating

### Table 3. Subjects with positive response to the prolonged head-up tilt test pre-glyceryl trinitrate

<table>
<thead>
<tr>
<th>Centre</th>
<th>Age/sex</th>
<th>Time to symptoms (min)</th>
<th>Type of response</th>
<th>Blood pressure</th>
<th>Heart rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Baseline</td>
<td>Lowest</td>
</tr>
<tr>
<td>Nottingham</td>
<td>72/F</td>
<td>40</td>
<td>Presyncope</td>
<td>126/66</td>
<td>66/47</td>
</tr>
<tr>
<td>Nottingham</td>
<td>72/F</td>
<td>30</td>
<td>Presyncope</td>
<td>161/91</td>
<td>80/60</td>
</tr>
<tr>
<td>Nottingham</td>
<td>67/F</td>
<td>35</td>
<td>Presyncope</td>
<td>160/76</td>
<td>59/43</td>
</tr>
<tr>
<td>Nottingham</td>
<td>72/F</td>
<td>30</td>
<td>Presyncope</td>
<td>167/85</td>
<td>57/41</td>
</tr>
<tr>
<td>Nottingham</td>
<td>68/M</td>
<td>25</td>
<td>Presyncope</td>
<td>152/89</td>
<td>39/31</td>
</tr>
<tr>
<td>Leicester</td>
<td>66/F</td>
<td>12</td>
<td>Presyncope</td>
<td>139/64</td>
<td>69/41</td>
</tr>
</tbody>
</table>
patients with syncope and calls into question the specificity of head-up tilt testing using nitrate provocation. Further work is required to assess the usefulness of different types of agents in provoking the response and the timing of their use in tilt testing.

**Key points**
- Syncope is a common cause of morbidity and mortality in elderly people.
- Neurocardiogenic syncope is a common cause of syncope in older adults.
- The prolonged head-up tilt test is a useful way of diagnosing neurocardiogenic syncope.
- The addition of sublingual glyceryl trinitrate as a provocative agent following the prolonged head-up tilt test is questionable in older people because there is a high positive rate, even in asymptomatic subjects.

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**References**


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