The influence of sex and age on response to head-up tilt-table testing in patients with recurrent syncope

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Abstract

Background: syncope is a common problem, accounting for 6% of hospital admissions. Often a diagnosis is not established. Head-up tilt testing is a diagnostic test for neuro-cardiogenic syncope, a condition which is often thought to affect younger women and be relatively rare in older people. We examined the effect of sex and age on response to head-up tilt testing in patients with unexplained syncope.

Methods: we performed a retrospective analysis on consecutive tilt tests performed using the Westminster drug-free protocol from January 1992 to June 1998. Patients were divided into four groups on the basis of sex and age (≤ or > 65 years). Responses were classified according to the Vasovagal International Study Investigators’ criteria.

Results: we performed 665 tests in 590 patients. Mean age was 50 years ± 17.6 (range 12–83). One hundred and fifty-three patients (23%) were > 65 years. There was an almost equal sex distribution. Two hundred and eight tests (31%) were positive, with 113 (54%) showing a mixed response (type 1), 65 (32%) a cardio-inhibitory response (type 2) and 30 (14%) a vasodepressor response (type 3). Age and sex had no effect on rates of positive tests or time to positive result. There was no gender influence with respect to response type. However, subjects aged > 65 years had a higher incidence of vasodepressor response (type 3)—29% versus 9% (P<0.001).

Conclusions: head-up tilt testing is a useful tool in the investigation of all patients with suspected neuro-cardiogenic syncope. Age and sex do not influence the likelihood of a positive response, but older patients have an increased frequency of pure vasodepressor responses. This may have implications with respect to treatment strategies.

Keywords: neuro-cardiogenic syncope, tilt table, vasovagal syncope

Introduction

Recurrent syncope accounts for up to 6% of all admissions to hospital and 3% of visits to the emergency room in the US [1, 2]. Despite extensive and often costly investigations, the aetiology remains unclear in up to 50% of patients [3]. Head-up tilt-table testing is useful in the evaluation of patients with unexplained syncope and is increasingly recognized as an effective diagnostic test for neuro-cardiogenic syncope [4, 5].

Although syncopal episodes are commonest in older patients, a neurally mediated aetiology may be more common in young people, particularly women, and be relatively rare in older people, in whom it is often said to have a multifactorial aetiology [1]. Recently, however, Bloomfield et al. reported a higher than expected incidence of neuro-cardiogenic syncope in older patients, with no sex preponderance [6].

In this study, we examined the effect of gender and age on response to head-up tilt testing in patients with recurrent syncope.

Methods

Study subjects

Between January 1992 and June 1998 we carried out 665 consecutive tilt tests at a regional centre for cardiac electrophysiology. All tilt-table tests performed at this institution are recorded on a database using a proforma and we performed a retrospective analysis of the results. For the purposes of analysis, patients were divided into four groups on the basis of sex and age (≤ or > 65 years).
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Head-up tilt testing

We performed all tests in the morning on patients who had fasted. All patients had an intravenous cannula inserted before the test. We made baseline recordings of heart rate and blood pressure after 10 min stabilization in the supine position. Patients were tilted head upwards to 60° using a motorized tilt table for up to 45 min in accordance with the drug-free Westminster protocol [7]. Heart rate and rhythm were recorded continuously by 12-lead electrocardiography, and heart rate determined by a series of RR intervals. We measured blood pressure non-invasively every 3 min by automatic sphygmomanometry. Testing was aborted, with a rapid return to the supine position, if syncope, or presyncope with limiting symptoms, occurred in association with hypotension and/or bradycardia. No pharmacological provocation was used.

Definitions

A positive test was defined as symptoms of presyncope or syncope with associated hypotension and/or bradycardia. We classified positive responses as recommended by the Vasovagal International Study Investigators [8]:

1. Mixed—heart rate decreases but remains > 40 beats/min or < 40 beats/min for < 10 s and without asystole for > 3 s. Blood pressure falls before heart rate decreases.
2. Cardio-inhibitory—heart rate decreases < 40 beats/min for > 10 s or asystole > 3 s. Blood pressure falls before or after heart rate falls.
3. Vasodepressor—heart rate does not decrease more than 10% from peak value at time of syncope. Fall in blood pressure alone accounts for syncope.

For the purposes of this study, hypotension was defined as a fall in systolic pressure of > 50 mmHg.

Statistical analysis

We used $\chi^2$ testing to assess differences between the defined subgroups with respect to response types. Continuous variables were expressed as mean ± SD and were compared using unpaired student's $t$-tests. A $P$ value of < 0.05 was considered significant.

**Table 1. Effect of age and sex on positive results**

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>% of tests</th>
<th>Mean time taken, min (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>208</td>
<td>31.4</td>
<td>19.9 (12.0)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>110</td>
<td>32.4</td>
<td>20.1 (11.7)</td>
</tr>
<tr>
<td>Female</td>
<td>98</td>
<td>30.1</td>
<td>19.6 (11.7)</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 65</td>
<td>48</td>
<td>31.4</td>
<td>21.7 (12.9)</td>
</tr>
<tr>
<td>≤ 65</td>
<td>160</td>
<td>31.3</td>
<td>19.6 (11.7)</td>
</tr>
</tbody>
</table>

**Results**

Study population

We performed 665 tests in 590 patients. Demographics at referral are illustrated in Figure 1. Mean age at referral was 50 ± 17.6 years, with a wide range (12–83 years). One hundred and fifty-three tests (23%) were performed on patients aged > 65 years. There was no sex preponderance (339 men versus 326 women) and no difference in mean age between the sexes.

Positive results

We considered 208 tests (31%) to be positive. Patients with a positive tilt test had a mean age of 52 years, while those with a negative test had a mean age of 49 years (difference not significant). Of positive results, 113 (54%) were classified as type 1 (mixed response), 65 (32%) as type 2 (cardio-inhibitory) and 30 (14%) as type 3 (vasodepressor). Asystole > 3s occurred in 34 patients, accounting for 5.1% of all tests but 16% of positive tests.

Effect of gender and age on results

Both sexes and age groups had similar overall rates of positive tests. Neither age nor sex had any influence on time to positive result (Table 1). However, age influenced type of positive response. In the > 65-year group, there was a significantly higher incidence of pure vasodepressor (type 3) response to tilt testing (29% versus 9%) with a reduction in mixed (type 1) response (38% versus 61%; $P<0.001$). There was no gender influence with respect to response type. Subgroup classification of positive test results is shown in Figure 2.

Prosyncopal therapy

A total of 123 tests were performed on patients taking potentially prosyncopal therapy. Twenty-five percent of patients aged > 65 years ($n=39$) were taking prosyncopal therapy compared with 16% in the younger group.

**Figure 1. Patient characteristics at referral. □, men; ■, women.**
Tilt-table responses by age and sex

Figure 2. Type of positive response by age and sex. □ type 3 (vasodepressor); □ type 2 (cardio-inhibitory); ■ type 1 (mixed).

Table 2. Effect of concurrent therapy with potentially pro-syncopal drugs on positive results

<table>
<thead>
<tr>
<th>Prosyncopal drug treatment</th>
<th>% of tests</th>
<th>Mean time taken (min (SD))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>33.6</td>
<td>18.2 (11.9)</td>
</tr>
<tr>
<td>No</td>
<td>30.8</td>
<td>20.4 (11.1)</td>
</tr>
</tbody>
</table>

Table 3. Pro-syncopal therapy

<table>
<thead>
<tr>
<th>Class of drug</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretic</td>
<td>33</td>
</tr>
<tr>
<td>β-blocker</td>
<td>70</td>
</tr>
<tr>
<td>Calcium antagonist</td>
<td>57</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitor</td>
<td>31</td>
</tr>
<tr>
<td>Nitrate</td>
<td>51</td>
</tr>
</tbody>
</table>

(n=84; P=0.011). However, the use of these drugs had no effect on the rate of positive tests or time to positive result (Table 2). Table 3 demonstrates number of patients taking each class of drug.

Discussion

Traditionally, neurally mediated syncope is considered primarily to be a condition of young people, especially women [1]. One study has, however, suggested it might be more common in men [9]. On clinical grounds alone, the incidence of a neurally mediated aetiology as an explanation for recurrent syncpe in one study was estimated at only 1.4% in older patients (>65 years) compared with 15.3% in their younger counterparts [10]. However, the advent of tilt-table testing in the mid-1980s [4] allowed investigators to gain direct diagnostic evidence of an individual’s susceptibility to neuro-cardiogenic syncpe, and subsequent studies have suggested that this may be a considerable underestimate of its incidence [6, 11, 12].

Several small studies have demonstrated a 31–36% positive response to head-up tilt-table testing in patients aged ≥65 years [11, 12], increasing to >60% if pharmacological provocation is used [11, 13]. Although the numbers involved in these studies were small (ranging from 18 to 59 patients), their findings have recently been supported in a larger study by Bloomfield and colleagues [6], who examined the results of 352 tilt tests, 133 of which were performed on patients over 65. They found that positive head-up tilt-table testing occurred more frequently in younger patients, with >50% of tests being positive in those aged ≤65 compared with only 37% in the >65-year group. However, our large study of 665 tests in 590 patients did not find such an age-related decline in positive results.

The positive yield to head-up tilt testing in our study was 32.2% in the >65-year group, which was similar to that seen in those aged ≤65 years (31.4%). Nor was there any difference in mean age between those with positive and negative results. A total of 153 tests were performed on those aged >65 years and, unlike previous studies, ours did not find age to be predictive of a positive response to tilt testing; nor did it influence time to positive result. Equally, the frequency of positive responses and time to a positive response were unaffected by sex.

Although age and sex did not predict a positive response to head-up tilt testing or time to positive test, age significantly influenced response type. The recent North American Vasovagal Pacemaker Study demonstrated the efficacy of rate-drop-responsive dual-chamber pacing in the treatment of neuro-cardiogenic syncpe in patients with a relative bradycardic response to head-up tilt testing, i.e. a type 1 or 2 response [14]. An increased rate of bradycardic responses to head-up tilt testing in older people might be expected, given the increased likelihood of conduction system disease in this age group. However, our study demonstrated a significantly higher incidence of pure vasodepressor (type 3) responses to tilt testing in those aged >65 years, and fewer cardio-inhibitory or mixed responses. This may have implications for treatment strategies. The main entry criterion for The North American Vasovagal Pacemaker Study was the presence of a relative bradycardia during head-up tilt-table testing [14]. The proportion of patients in our study who would meet this criterion is lower among those aged over 65 than in the younger age group. Nonetheless, head-up tilt-table testing could be used to identify the small subgroup of older patients who might benefit from pacemaker implantation.

There is evidence that midodrine is a successful agent in treating some patients with a primary vasodepressor response and may be the drug of choice in patients in this group [15, 16]. Other α-agonists may also be beneficial [17]. However, these drugs may be difficult to initiate, or be contra-indicated, because of concomitant conditions such as hypertension, prostatism and valvular or coronary heart disease.

Even accepting the use of β-blockers and angiotensin-converting enzyme inhibitors as potential
treatments for neurally-mediated syncope [18, 19], we were surprised by the high use of potentially pro syncopal therapy in patients referred for tilt testing. Although there was no demonstrable relationship between pro syncopal therapy and test result in this study, the physician should be aware that the use of pro syncopal therapy might still be an aetiologic factor or at least contribute to symptoms.

**Study limitations**

There are several limitations to this study. Because of its retrospective nature, it is possible that referral bias resulted in fewer type 1 or 2 responses in the >65-year group. Subjects with type 1 or 2 syncope might have been identified at referring institutions (for example by conduction defects on 24-h tapes) and therefore not referred for tilt-table testing. It is also possible that only more severe cases were referred to our institution. However, this potential error should be diluted on account of the large study population and the fact that nearly one-quarter of referrals were of patients aged 65 or older.

The protocol for head-up tilt-table testing at our institution does not allow for invasive intra-arterial monitoring for beat–beat blood pressure recording. It is therefore possible that the use of non-invasive blood pressure monitoring at 3-min intervals may have resulted in some inaccuracies in identifying types of response. However, all tests were supervised by medical staff experienced in tilt testing who would take immediate blood pressure measurements if any signs or symptoms presented.

In summary, we believe that head-up tilt testing is a useful investigation in the assessment of unexplained syncope in all age groups, regardless of sex.

**Key points**

- Head-up tilt-table testing is a useful tool for the investigation of unexplained syncope.
- The response to head-up tilt-table testing is not influenced by sex.
- Although older people were as likely to have a positive test as their younger counterparts, the type of response differed according to age: older people were more likely to have a pure vasodepressor response without a relative bradycardia.

**References**


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