Syncope recurrence can better be predicted by history than by head-up tilt testing in untreated patients with suspected neurally mediated syncope

W. Grimm, M. Degenhardt, J. Hoffmann, V. Menz, A. Wirths and B. Maisch

Clinical Electrophysiology Laboratory, Cardiology Division, Department of Medicine, Hospital of the Philipps-University of Marburg, Marburg, Germany

Background

Head-up tilt testing is widely used in the evaluation of patients with suspected neurally mediated syncope. Although it remains unclear which patients require medical therapy to prevent recurrent syncope, most centres initiate empiric medical therapy in all patients in whom neurally mediated syncope has been diagnosed. To determine the natural history of this condition, we followed 80 untreated patients.

Methods

All 80 study patients fulfilled the following inclusion criteria: (1) ≥1 syncope in the upright position, (2) absence of structural heart disease, (3) unremarkable work-up for other known causes of syncope. Thirty-nine patients had a history of one episode of syncope (group A) and 41 ≥2 episodes of syncope (group B). Head-up tilting was performed in all patients at 60° for a maximum of 45 min without medical provocation ('Westminster Protocol').

Results

Suspected neurally mediated syncope could be reproduced by tilt testing in four of 39 patients from group A vs 10 of 41 patients from group B (10% vs 24%, P=0.02). Independent of the result of head-up tilt testing, all patients were prospectively followed without medical therapy. During 23 ± 8 months follow-up, syncope recurred in four of 39 group A patients vs 22 of 41 group B patients (10% vs 54%, P<0.05). The incidence of syncope during follow-up was not significantly different between patients with and without positive baseline tilt test (43% vs 30%, P=ns).

Conclusions

(1) 90% of patients with a single episode of syncope remain free of recurrent syncope without medical therapy irrespective of the result of tilt testing. (2) About half of patients with a history of ≥2 syncopal episodes have recurrent syncope and, thus, may be appropriate candidates for prophylactic medical therapy. (3) Although head-up tilt testing at 60° for up to 45 min does not appear to be useful to predict recurrent syncope in untreated patients, it is still a useful test in its evaluation.

Key Words: Neurally mediated syncope, head-up tilt table testing.
Table 1 Clinical characteristics of 80 study patients

<table>
<thead>
<tr>
<th></th>
<th>Number of patients</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Underlying heart disease</th>
<th>Syncope within the last 24 months</th>
<th>Pre-syncope within the last 24 months</th>
<th>Result of baseline tilt testing</th>
<th>Electrocardiographic leads I, II, III, aVR, aVL and aVF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>80 (100%)</td>
<td>40 ± 16</td>
<td>39 (49%)</td>
<td>41 (51%)</td>
<td>0</td>
<td>4 ± 2</td>
<td>14 (18%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range 16-69</td>
<td></td>
<td></td>
<td>Range 1-7</td>
<td>Range 2-12</td>
<td>Positive tilt test</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Patients with 1 syncope (n)</td>
<td>Patients with ≥ 2 syncope (n)</td>
<td>Negative tilt test</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>39 (49%)</td>
<td>41 (51%)</td>
<td>66 (82%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Range 4 ± 2</td>
<td>Range 2-12</td>
<td>Time to syncope during tilt (min; n=14)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20 ± 18</td>
<td></td>
</tr>
</tbody>
</table>

cardiology outpatient department. All study patients with suspected neurally mediated syncope fulfilled the following inclusion criteria:

1. history of ≥ 1 episode of syncope and ≥ 2 episodes of pre-syncope in the upright position,
2. no evidence of structural heart disease by history, physical examination or non-invasive cardiovascular evaluation, and
3. unremarkable work-up for other known causes of syncope including laboratory tests, neurological examination and 24 h Holter in all patients.

Patients with any known condition predisposing to syncope such as sick sinus syndrome, atrioventricular conduction disturbances, epilepsy, or drug-induced hypotension were excluded from this study. In addition, study participation was limited to patients with an age ≥ 16 years and ≤ 70 years.

Thirty-nine of 80 study patients had a history of one episode of syncope and at least two episodes of pre-syncope within 24 months before study entry (group A). Forty-one patients had ≥ 2 episodes of syncope and at least one episode of pre-syncope within 24 months before study entry (group B). The clinical characteristics of the study patients are summarized in Table 1.

Head-up tilt table testing

After informed consent was obtained, all study patients underwent head-up tilt table testing in a fasting, non-sedated state between 0900 and 1200 h on a motorized tilt table to 60°, having rested in the supine position for 15 min prior to recording baseline measurements. The travel time of the tilt table between 0° and 60° was 15 s. During tilt, patients rested on a footplate support and the period of tilt was 45 min unless aborted by pre-syncope or syncope ('Westminster Tilt Protocol').

Systolic and diastolic blood pressure were recorded at 2-min intervals by Dinamap (Critikon) and at 1-min intervals manually with the development of symptoms. Electrocardiographic leads I, II, III, aVR, aVL and aVF were recorded at 2-min intervals in symptom-free patients and continuously with the development of symptoms by Mingograph (Siemens Elema).

Interventions

After tilt table testing and a brief resting period, all patients underwent counselling with regard to the diagnosis of suspected neurally mediated syncope, probable pathophysiology, lack of mortality and lack of standardized medical therapy proven to be uniformly effective for prevention of recurrent syncope. All patients were reassured, counselled on recognizing their pre-syncope prodromal symptoms, and urged to take specific appropriate postural manoeuvres as soon as possible when pre-syncope. In addition, the recommendation was made to all patients to avoid salt depletion and hypovolaemia without additional medical therapy until spontaneous syncope occurred. All patients were asked to notify our cardiology outpatient clinic of their first recurrence of syncope.

Follow-up

All patients were prospectively followed and contacted every 6 months by telephone beginning at the time of tilt table testing until the end of follow-up in September 1996. Follow-up could be completed in all 80 study patients.

Definitions

Syncope was defined as transient loss of consciousness and muscle tone that by history was not suggestive of other altered states of consciousness. Near syncope (pre-syncope) was defined as premonitory signs and symptoms of imminent syncope, i.e. severe lightheadedness, severe weakness, transient hearing loss or graying vision. A positive response to tilt testing was defined as either pre-syncope or syncope associated with a cardioinhibitory response, a vasodepressor response, or both. A cardioinhibitory response was defined as marked decrease in heart rate to <50 beats . min⁻¹ or asystole at the onset of symptoms. A vasodepressor response was diagnosed when systolic blood pressure decreased to ≤ 85 mmHg.

Statistical analysis

Results are expressed as mean ± standard deviation unless stated otherwise. Chi-square tests and Student's t-test for paired and unpaired comparisons were performed where appropriate. A P-value < 0.05 was considered to be significant.
Neurally mediated syncope

Study patients

Group A: 39 patients (history of 1 syncope)
Group B: 41 patients (history of >2 syncope)

Tilt negative
n = 35 (90%)
Tilt positive
n = 4 (10%)

Recurrences
n = 3 (9%)

Tilt negative
n = 31 (75%)
Recurrences
n = 1 (25%)
Tilt positive
n = 10 (25%)
Recurrences
n = 17 (55%)
Recurrences
n = 5 (50%)

Figure 1 Recurrences of syncope in 80 study patients.

Results

Response to head-up tilt testing

During baseline tilt testing, syncope or pre-syncope occurred in 14 of 80 study patients (Table 1). Suspected neurally mediated syncope could be reproduced by head-up tilt testing in four of 39 patients of group A and in 10 of 41 patients of group B (10% vs 24%, P<0-05). Other clinical variables including age and gender were also not predictive for syncope recurrences (Table 2).

Recurrences of syncope during prospective follow-up

During 23±8 months prospective follow-up after baseline tilt testing, 26 of 80 patients (33%) had another episode of syncope (Fig. 1). Syncope recurred in four of 39 patients of group A and in 22 of 41 patients of group B (10% vs 54%, P<0-05). Of note, the incidence of syncope recurrences was not different between patients with a positive baseline tilt test compared to patients with a negative baseline tilt test (43% vs 30%, P=ns).

Table 2 Relationship between clinical variables, result of baseline head-up tilt testing and recurrent syncope during 23±8 months prospective follow-up

<table>
<thead>
<tr>
<th>Study population</th>
<th>Recurrence of syncope</th>
<th>No recurrence of syncope</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>80</td>
<td>26 (33%)</td>
<td>54 (67%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>40±16</td>
<td>39±15</td>
<td>41±16</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>39</td>
<td>10 (26%)</td>
<td>29 (74%)</td>
</tr>
<tr>
<td>Women</td>
<td>41</td>
<td>16 (39%)</td>
<td>25 (61%)</td>
</tr>
<tr>
<td>History of syncopal episodes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Syncope (n)</td>
<td>39</td>
<td>4 (10%)</td>
<td>35 (90%)</td>
</tr>
<tr>
<td>≥2 Syncope (n)</td>
<td>41</td>
<td>22 (54%)</td>
<td>19 (46%)</td>
</tr>
<tr>
<td>Baseline tilt testing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive tilt test</td>
<td>14</td>
<td>6 (43%)</td>
<td>8 (57%)</td>
</tr>
<tr>
<td>Negative tilt test</td>
<td>66</td>
<td>20 (30%)</td>
<td>46 (70%)</td>
</tr>
</tbody>
</table>

Discussion

This study prospectively determined the incidence of syncope recurrence in medically untreated patients with suspected neurally mediated syncope, i.e. syncope in an upright position in the absence of other known causes of syncope in patients without structural heart disease. This study demonstrated that during mean follow-up of 2 years (1) 90% of patients with a single episode of syncope remain free of recurrent syncope without medical therapy irrespective of the result of tilt testing, (2) about half of patients with a history of ≥2 syncopal episodes have recurrent syncope and, thus, may be appropriate candidates for prophylactic medical therapy, and (3) although head-up tilt testing at 60° for up to 45 min without medical provocation does not appear to be useful to predict recurrent syncope in untreated patients, it is still a useful test in the evaluation of syncope.

Comparison to previous studies in patients with neurally mediated syncope

To the best of our knowledge, there is only one other study besides ours, published by Sheldon et al.[6], which analysed risk factors for recurrent syncope in 101 medically untreated patients with suspected neurally mediated syncope. Overall, only 33% of patients in our study and 28% of patients in the study of Sheldon et al.[6] had recurrent syncope during follow-up despite the lack of...
prophylactic medical therapy in both studies. This means that three out of four patients with suspected neurally mediated syncope in both studies would not have had any benefit from prophylactic medical therapy. Furthermore, the low recurrence rate of syncope after baseline tilt testing without medical therapy in the study of Sheldon et al.[6] as well as our study emphasizes the need for randomized untreated control groups in any future study designed to evaluate the efficacy of medical therapy for neurally mediated syncope.

Similar to the findings of our study, Sheldon et al.[6] demonstrated that in patients with neurally mediated syncope the risk of recurrence of syncope after baseline tilt testing could be predicted by the number of preceding syncopal spells. In contrast to our study, in which prolonged tilt table testing was performed without medical provocation, Sheldon et al.[6] routinely used isoproterenol-head-up tilt testing to evaluate suspected neurally mediated syncope. With isoproterenol-head-up tilting, Sheldon et al.[6] observed a positive tilt test in 58% of patients with syncope of unknown origin compared to only 18% positive tilt tests in our study, in which conventional tilting without isoproterenol provocation was used. Since there is no ‘gold standard’ for the diagnosis of neurally mediated syncope it remains undetermined whether the difference in tilt-positive patients between both studies is due more to false-positive tilt results in the study of Sheldon et al.[6] or to false-negative results in our study. In contrast to the number of preceding syncopal spells, the result of tilt table testing was not useful in the prediction of recurrent syncope in the present study. Since patients with a negative tilt test were excluded from further follow-up in the study of Sheldon et al.[6] the predictive value of tilt testing for recurrent syncope cannot be assessed in this study.

In contrast to previous studies[4,5,8,11,12], participation in our study was restricted to patients ≤70 years. This resulted in a fairly young patient population in our study with a mean age of 40 ± 16 years, which is comparable to the patient age in the study of Sheldon et al.[6] with 36 ± 19 years, but significantly less than the mean patient age in the study of Fitzpatrick et al.[5] with 69 ± 10 years. This age difference between our study and the study of Fitzpatrick et al.[5] may, in part, explain the difference of positive tilt tests despite the use of the same protocol in both studies. Prolonged head-up 60° tilt testing without medical provocation resulted in presyncope or syncope in 75% of elderly patients in the study of Fitzpatrick et al.[5] compared to only 18% of younger patients in our study. Different pathophysiological mechanisms are likely to be responsible for neurally mediated syncope at different age levels, with vasovagal syncope predominating in young patients[2,3,6,7,9,14]. Therefore, the follow-up results of untreated patients in our study cannot be extrapolated to older patient cohorts with suspected neurally mediated syncope. In addition, patients with other causes of syncope including various forms of autonomic failure or drug-induced hypotension were excluded in our study. In contrast to the patient population described in our study, however, tilt table testing may be beneficial to guide therapy in other patient groups.

Clinical implications

The findings of the present study as well as the results of Sheldon et al.[6] suggest that the treatment of choice for the majority of young patients with suspected neurally mediated syncope should consist of patient reassurance and counselling on diagnosis, on benign prognosis and on recognizing their pre-syncopal prodromal symptoms in order to take appropriate postural manoeuvres when pre-syncopal. Since the majority of patients will remain free of recurrent syncope without medical therapy, prophylactic drug treatment should be restricted to patients with a longstanding history of frequent syncope and patients with recurrent syncope after baseline tilt testing. Although head-up tilt testing may not predict recurrent syncope in young patients with suspected neurally mediated syncope, it is still a useful test in the evaluation of syncope.

References


