Comparison of Sensitivity and Specificity of Tilt Protocols with and without Isoproterenol in Children with Unexplained Syncope

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ALEHAN, D., ET AL.: Comparison of Sensitivity and Specificity of Tilt Protocols with and without Isoproterenol in Children with Unexplained Syncope. Head-up tilt testing with or without isoproterenol is extensively used in the evaluation of patients with unexplained syncope. However, sensitivity and specificity of tilt protocols with and without isoproterenol have not been clarified in children, due to lack of age matched control subjects. This study was designed to assess and to compare the sensitivity and specificity of tilting alone and tilting in conjunction with isoproterenol. Thirty children with unexplained syncope (group I) and 15 age-matched control subjects (control group I) underwent successive 60° head-up tilts for 10 minutes during infusions of 0.02, 0.04, and 0.06 µg/kg/min of isoproterenol, after a baseline tilt to 60° for 25 minutes. Also, 35 children (group II) with unexplained syncope and 15 healthy control subjects (control group II) were evaluated by head-up tilt to 60° for 45 minutes without an infusion of isoproterenol. In response to tilt protocol with graded isoproterenol, 23 (76.6%) of the patients in group I and 2 of the 15 (13.3%) control subjects developed syncope. Accordingly, the sensitivity of tilt testing with isoproterenol was 76.6%, and its specificity was 86.7%. Tilt testing without isoproterenol was positive in 17 (48.5%) of the patients in group II but in only 1 of the 15 (6.6%) control subjects. Thus, sensitivity and specificity of tilt testing without isoproterenol were 48.5% and 93.4%, respectively. The mean heart rate and systolic blood pressure decreased significantly (P < 0.001) in all tilt positive patients during syncope. In conclusion, the head-up tilt test is a valuable diagnostic test in the evaluation of children with unexplained syncope, and isoproterenol is likely to increase the sensitivity of the test without decreasing its specificity. (PACE 1997; 20:1769-1776)

**Syncope, head-up tilt test, sensitivity, specificity, children**

**Introduction**

Syncope is one of the most common and challenging problems seen in the pediatric age group. Among all causes of syncope, vasovagal syncope (neurally-mediated syncope) is reported to be the most common etiology of fainting in children, accounting for approximately one third of all patients with syncope.\(^1\) Although a large number of diagnostic tests are available for the work up of syncope, until recently, neurally-mediated syncope was diagnosed primarily according to characteristic medical history with the exclusion of other etiologies. The head-up tilt test has gained wide acceptance as a useful provocative test in reproducing a hypotension-bradycardia syndrome, which is supposed to be equivalent to the spontaneous neurally-mediated syncope.\(^2,3\) However, relatively low sensitivity has been a significant limitation. Several authors have proposed isoproterenol infusion during tilting as a method of increasing the sensitivity of the test without decreasing the specificity.\(^4,5\) But the results of studies performed in adults are very controversial with respect to specificity, which varies in the range of 27–100%.\(^6,7\)

To our knowledge, the sensitivity and the specificity of tilt protocols with and without isoproterenol infusion have not been previously

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compared in children with homogenous age-matched control subjects. Therefore, this study was designed to investigate and compare the sensitivity and specificity of tilt protocols with and without isoproterenol in children with unexplained syncope.

**Patients and Methods**

Sixty-five patients admitted to Hacettepe Children’s Hospital for evaluation of unexplained syncope and 30 age-matched healthy control subjects without a history of syncope or presyncope were enrolled in the study between March 1993 and May 1995, after an informed written parental consent was obtained.

Patients were diagnosed as having unexplained syncope and included in the study if no cause could be identified despite the following investigations: complete history; thorough cardiac and neurological examinations; orthostatic blood pressure determinations; carotid sinus massage; complete blood cell count; urinalysis; measurement of blood electrolyte glucose and magnesium concentrations; chest X ray; standard 12-lead ECG; M mode Doppler; and two-dimensional echocardiogram; exercise stress test; and 24-hour ambulatory ECG monitoring.

**Definitions**

Syncope was defined as a transient state of unconsciousness and loss of postural tone characterized by spontaneous recovery. Presyncope was defined as a state of lightheadness usually associated with one or more symptoms of decreased vision, the sensation of hearing voices distinctly, slow response times to verbal stimuli, nausea, vomiting, and partial loss of postural tone, which substantially reproduced the patients' clinical presyncope. Positive response to head-up tilt was defined as the development of syncope or presyncope associated with hypotension, bradycardia or both, and a negative test was defined as one that ended without symptoms.9

The vasodepressor response, observed during tilt testing, was associated with a marked decrease in systolic blood pressure (> 60%) without a significant heart rate decrease during symptoms. The cardioinhibitory response was defined as an abrupt decrease in heart rate (> 50%) without any antecedent decrease in systolic blood pressure. A mixed pattern of response was characterized by both blood pressure and heart rate decrease compared with averages before onset of symptoms.

The exact sensitivity and specificity of tilt table testing are difficult to assess, as the true cause for syncope is unknown, and there is presently no reference standard test for the diagnosis of neurocardiogenic syncope. Therefore, in this study, as in others, “sensitivity” was defined as the proportion of patients with unexplained syncope who had a positive test result, and “specificity” was defined as the proportion of patients in the control group with a negative test result.9,10

Of the 65 patients with unexplained syncope, 30 formed group I and underwent tilt testing with isoproterenol infusion, and the remaining 35 patients formed group II and underwent a tilt protocol without isoproterenol infusion. Control group I consisted of 15 control subjects who underwent a tilt testing with isoproterenol infusion, and control group II consisted of 15 control subjects who underwent tilt testing without isoproterenol infusion.

**Head-Up Tilt Protocol**

A previously described tilt protocol11 with isoproterenol infusion was modified and performed in 30 patients (group I) and 15 control subjects (control group I). To minimize the impact of other uncontrollable variables, the test was performed after a light meal, at approximately the same time of day. Patients were connected to a standard three lead cardiac monitor for continuous recording of heart rate and rhythm throughout the test. A manual sphygmomanometer was used for blood pressure measurement every 2 minutes. Whenever symptoms or alterations in blood pressure or heart rate were observed, blood pressure was recorded as frequently as possible (every 30 s). An intravenous catheter was placed for fluid and drug administration (isoproterenol infusion). First, patients were allowed to rest for 15 minutes while lying supine on a foot support type tilt table in order to stabilize their blood pressure and heart rate, and then were positioned at an angle of 60 from the horizontal plane, for 25 minutes. As soon as symptoms (syncope or presyncope) developed during head-up tilt, the tilt table was lowered to the supine position and the test was terminated. If
no symptoms occurred during the initial tilt, the patient was returned to the supine position at the end of the 25-minute period. Intravenous low dose isoproterenol infusion was initiated (0.02–0.04 μg/kg/min) while the patient was lying supine, and after a resting period of 5 minutes to achieve a stable isoproterenol blood level, the patient was tilted to 60° for 10 minutes or until symptoms occurred. If the tilt test was negative during low dose isoproterenol infusion, the same protocol was repeated first with medium dose (0.04–0.06 μg/kg/min) and then with high dose (0.06–0.08 μg/kg/min) isoproterenol infusion. Equilibration periods of 5 minutes were introduced between each successive dose increase. The test was terminated either when a positive response was observed or after maximal isoproterenol dose was administered.

Thirty-five patients (group II) and 15 control subjects (control group II) underwent tilt testing without receiving isoproterenol. After the same initial procedures and 15 minutes for resting, the table was tilted to 60° and the patients remained in this position for a maximum period of 45 minutes or until syncope or presyncope was produced.

Statistical Methods

Results are expressed as mean values ± standard deviation. ANOVA was used to compare differences between multiple groups. Student’s t-tests (paired or unpaired) were used to compare differences between pairs of groups. Categoric variables were compared by the Chi-square test or Fisher’s exact test. A P value < 0.05 was considered statistically significant.

Results

There was no statistical difference among the four groups with respect to age, gender, baseline heart rate or blood pressure. The number of syncopal episodes was also similar for group I and group II (Table I).

In response to upright tilt testing with isoproterenol infusion, 23 of the 30 patients in group I (76.6%) had a positive response. In five patients, symptoms occurred in the baseline tilt; in four patients during low dose isoproterenol infusion; in eight patients during medium dose; and in 6 patients during high dose isoproterenol infusion (Fig. 1). The average time for the onset of symptoms was 22 minutes (range 5–25 minutes) during baseline tilt, and 7.3 minutes (range 3–10) during isoproterenol infusion. Only two of the 15 (13.3%) control subjects in control group I had a positive response to tilting during the medium dose isoproterenol infusion. Accordingly, the sensitivity and the specificity of tilt protocol with isoproterenol infusion were calculated as 76.6% and 86.7%, respectively.

Table I.

Clinical Characteristics and Baseline Hemodynamic Data of Patients with Unexplained Syncope and the Control Group

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>Control Group I</th>
<th>Control Group II</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>30</td>
<td>35</td>
<td>15</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>12.8 ± 2.6</td>
<td>11.9 ± 2.8</td>
<td>11.4 ± 1.7</td>
<td>12.5 ± 1.9</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>11/19</td>
<td>12/23</td>
<td>5/10</td>
<td>6/9</td>
<td>NS</td>
</tr>
<tr>
<td>Mean number of syncopal episodes</td>
<td>2.8 ± 1.3</td>
<td>2.3 ± 1.4</td>
<td>none</td>
<td>none</td>
<td>NS</td>
</tr>
<tr>
<td>Mean systolic blood pressure (mmHg)</td>
<td>112 ± 8.4</td>
<td>105 ± 11</td>
<td>107 ± 9</td>
<td>98 ± 5.4</td>
<td>NS</td>
</tr>
<tr>
<td>Mean diastolic blood pressure (mmHg)</td>
<td>81 ± 8.3</td>
<td>76 ± 5.4</td>
<td>77 ± 7.5</td>
<td>79 ± 6.2</td>
<td>NS</td>
</tr>
<tr>
<td>Mean heart rate (beats/min)</td>
<td>83 ± 7.6</td>
<td>87 ± 13</td>
<td>91 ± 14</td>
<td>81 ± 7.5</td>
<td>NS</td>
</tr>
<tr>
<td>Mean respiratory rate (breaths/min)</td>
<td>16 ± 2.5</td>
<td>18.4 ± 4.5</td>
<td>15 ± 3.5</td>
<td>14.8 ± 1.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

a = comparison of Group I and Group II; Group I = patients underwent tilt testing with isoproterenol administration; Group II = patients underwent tilt testing without isoproterenol; Control Group I = control subjects underwent tilt testing with isoproterenol; control Group II = control subjects underwent tilt testing without isoproterenol; NS = not significant.
Head-up tilt testing without isoproterenol infusion was positive in 17 of the group II patients (48.5%), but in only one of the 15 (6.6%) control subjects (control group II). Hence, sensitivity of the tilt test without isoproterenol infusion was 48.5%, and the specificity 93.4%. The mean time to syncope was 23.7 ± 14 minutes for the patients, and 16 minutes for the tilt positive control subject.

The patients with positive test results showed three patterns of response to tilting. In group I, 12 patients (52.2%) had a predominantly vasodepressor response; two patients (8.7%) had a cardioinhibitory response; and nine (39.1) had a mixed response. In group II, 12 patients (70.6%) had a mixed response; three (17.6%) had vasodepressor; and two (11.8%) had cardioinhibitory response.

Heart Rate and Blood Pressure Responses

Group I

Tilt positive patients initially responded to tilting and isoproterenol infusion by increasing their peak heart rate from 89 ± 13 beats/min to 146 ± 26 beats/min (P < 0.001), and their maximal systolic blood pressure from 114 ± 5 mmHg to 134 ± 15 mmHg (P < 0.001). However, hemodynamic parameters were not stable throughout tilting, and during symptoms significant decreases were observed both in mean heart rate and in mean systolic blood pressure (from 146 ± 26 to 82 ± 35 beats/min, and from 134 ± 15 to 60 ± 33 mmHg respectively, P < 0.001). The response of tilt negative patients to isoproterenol was similar and consisted of an increase in mean heart rate from 84 ± 6 beats/min to 141 ± 12 beats/min (P < 0.001) and an increase in mean systolic blood pressure from 108 ± 12 mmHg to 144 ± 17 mmHg (P < 0.001). However, unlike tilt positive patients, these patients had no symptoms during tilting and hemodynamic parameters remained stable throughout tilt testing (Table II) (Fig. 2).

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**Table II.** Comparison of Hemodynamic Variables of Patients with Unexplained Syncope and the Control Group During Head-Up Tilt

<table>
<thead>
<tr>
<th></th>
<th>Heart Rate (beats/min)</th>
<th>Systolic Blood Pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Maximal Value</td>
</tr>
<tr>
<td>Group I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tilt positive</td>
<td>89 ± 13</td>
<td>146 ± 26</td>
</tr>
<tr>
<td>Tilt negative</td>
<td>84 ± 6</td>
<td>141 ± 12</td>
</tr>
<tr>
<td>Group II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tilt positive</td>
<td>91 ± 8</td>
<td>97 ± 8</td>
</tr>
<tr>
<td>Tilt negative</td>
<td>95 ± 14</td>
<td>106 ± 9</td>
</tr>
<tr>
<td>Control Group I*</td>
<td>78 ± 9</td>
<td>139 ± 18</td>
</tr>
<tr>
<td>Control Group II*</td>
<td>82 ± 9</td>
<td>92 ± 12</td>
</tr>
</tbody>
</table>

* = for tilt positive patients maximal value before syncope; ‡ = for tilt positive patients minimal value during syncope; § = comparison of baseline and the maximal value; ¶ = comparison of maximal and minimal values; * = results of tilt negative subjects are given. Other abbreviations as in Table I.
Control Group I

The changes in heart rate and blood pressure of the control group who underwent tilt testing with isoproterenol infusion, were similar to changes observed in tilt negative patients of Group I. Isoproterenol caused an increase in both mean heart rate and mean systolic blood pressure of the control subjects. Mean heart rate increased from 78 ± 9 to 139 ± 18 beats/min, and blood pressure from 115 ± 12 to 149 ± 16 mmHg (P < 0.001). There were no significant decreases in systolic blood pressure and mean heart rate during tilting except in two subjects, who had syncope and concomitant blood pressure decrease.

Group II

In positive responders, although heart rate and blood pressure were stable at the initial stages of tilting, syncope was associated with a marked decrease in systolic blood pressure from 102 ± 14 to 41 ± 17 mmHg (P < 0.001), and mean heart rate from 97 ± 8 to 40 ± 17 beats/min (P < 0.001). In negative responders, significant change was not observed either in mean heart rate, or in systolic blood pressure during tilting (Fig. 3).

Control Group II

Heart rate and blood pressure were stable throughout tilt testing in all but one control subject, who experienced syncope during tilting.

Discussion

The head-up tilt test has become an important tool for evaluation of children with unexplained syncope. Tilt table testing is not only useful as a method of provoking episodes of neurocardiogenic syncope in susceptible individuals, but is also used as a method of assessing the efficacy of various therapies used to prevent further syncopal episodes in pediatric patients. However, the pathophysiological mechanism that leads to the development of tilt induced or spontaneous neurally-mediated syncope is incompletely understood. The generally accepted model suggests involvement of a vagally mediated reflex initiated
by cardiac mechanoreceptors. This reflex is triggered by reduction in left ventricular filling, secondary to pooling of blood in the lower parts of the body during tilting. Reduction in left ventricular volume results in vigorous myocardial contraction, which in turn activates myocardial mechanoreceptors. This activation produces sympathoinhibition and parasympathetic discharge, which results in the reflex bradycardia and hypotension that are known as Bezold-Jarisch reflex. Two recent studies are also in agreement with the hypothesis that the autonomic nervous system may be central to the development of vasodepressor syncope. However, induction of syncope in patients after cardiac transplantation suggests that the cardiac mechanoreceptor theory is not the sole mechanism mediating these responses, as the transplanted heart is denervated.

The sensitivity of head-up tilt without isoproterenol infusion varies from 24–74%; and on the whole, a positive response has been observed in approximately 50% of adult patients with unexplained syncope but in only 10% of asymptomatic control subjects.

In pediatric studies using tilt testing without isoproterenol administration, the results are similar and the sensitivity is reported to be low. In one study, Lerman-Sagie et al. reproduced syncope in six of 15 children (43%) with unexplained syncope. None of the children in the control group (10 subjects) had syncope during tilting. Ross et al. have applied a similar test, orthostatic testing, in the evaluation of 104 young patients with syncope and observed syncope in 47 (44%). Of 12 control subjects, none became symptomatic with orthostatic testing. Fouad et al. provoked syncope in 25 of 45 patients (57%) and in three of 16 control subjects (17%). In the current study, 17 of the 35 patients, and only one of the 15 control subjects developed a vasovagal response yielding a sensitivity of 48.5% and a specificity of 93%. Thus, despite the high specificity of tilt testing without isoproterenol infusion, the overall sensitivity of tilting, which is approximately 50%, is relatively low.

Considering the demonstration of enhanced sympathetic activity and excess increase in catecholamines before episodes of vasodepressor syncope, isoproterenol is advocated for use in conjunction with head-up tilting to increase the sensitivity of the test. Isoproterenol, which is an exogenous catecholamine, is well known for its adrenergic stimulation resulting in increased myocardial contractility. It reduces left ventricular volume and dimensions, which are exaggerated during a passive tilt. Additionally, isoproterenol produces venodilatation by means of β2 adrenergic stimulation, and thus may lead to further pooling of blood in the lower limbs during upright tilting. These effects, by activating mechanoreceptors, may induce syncope in susceptible subjects. Although it is generally agreed that isoproterenol administration increases sensitivity in patients with neurally-mediated syncope, its effects on the specificity of the test have not been clarified either in adults or children. In previously published studies, performed in adults, the results were controversial, with the specificity of tilt protocols with isoproterenol infusion varying from 27% to 100%.

Despite several investigations assessing the utility of tilt testing in children, only a few had control subjects in these studies, and we are unaware of any previous report comparing the sensitivity and specificity of tilt protocols with and without isoproterenol administration in pediatric patients.

Pongiglione et al. reported that symptoms were elicited in 80% of 20 patients who underwent head-up tilting with isoproterenol infusion. Similarly Thilenius et al., also using a graded isoproterenol infusion, provoked syncope in 26 of 35 pediatric patients (74%). In the study of Grubb et al., syncope was reproduced in 21 of 30 children (70%) with unexplained syncope. Although these studies have demonstrated a high sensitivity of tilt testing with isoproterenol administration in pediatric patients, specificity of the test could not be estimated due to the absence of control subjects. In the present study, the tilt test with isoproterenol infusion was positive in 77% of children with unexplained syncope, but only in 13% of the control subjects. Accordingly the sensitivity of tilt testing with graded isoproterenol infusion was 77% and the specificity 87%. Thus, our study demonstrates that isoproterenol administration in
Sensitivity and Specificity of Tilt Protocols

Pediatric patients increases the sensitivity of tilt testing significantly, without decreasing the specificity.

Several factors including age, angle of tilt, support technique, intravenous cannulation, and time of the day when tilting is performed are known to influence the results of tilt testing. Taking into account the results of previous studies, documenting higher rates of false-positive tests with angles greater than 60° and a decreased sensitivity with tilt angles less than 60°, we used a 60° tilt. In our study there were no differences in terms of age, gender, and baseline hemodynamic data of the patients and the control group. Tilt tests were conducted under similar (if not identical) conditions and at approximately the same time of day in order to minimize the impact of variables that could alter the autonomic state and test outcomes. Therefore, we consider that our finding of a higher sensitivity without reducing the specificity in tilt testing with graded isoproterenol infusion is due to the effects of isoproterenol rather than the influence of an uncontrolled variable.

The majority of tilt positive patients in group I (with isoproterenol infusion) had a predominantly vasodepressor response, whereas two thirds of tilt positive patients in group II (without isoproterenol infusion) showed a mixed pattern of response during symptoms. These varied responses may illustrate the complexity of the mechanisms that are responsible for the reflex bradycardia-hypotension syndrome and suggest that further evaluations are needed to determine whether such divisions have prognostic significance.

Limitations

It is difficult to assess the exact sensitivity of tilt table testing, as there is no "gold standard" against which the test can be compared. Also we have not examined the reproducibility of tilt protocols with or without isoproterenol infusion in our patients. However, several studies have demonstrated an 80–90% reproducibility of tilt testing in patients with unexplained syncope, when tests are performed either on the same day or on different days.

We conclude that the head-up tilt test is a safe, useful, sensitive, and specific diagnostic method for the work-up of children with unexplained syncope, and should be considered during the first step in evaluating such patients. Isoproterenol is likely to increase the sensitivity of the test without decreasing its specificity significantly. However, further well-designed controlled studies may be needed to define the optimal tilt protocol in pediatric patients.

References

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