Utility of a Single-Stage Isoproterenol Tilt Table Test in Adults
A Randomized Comparison With Passive Head-Up Tilt

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OBJECTIVES
This study was conducted to develop a time-efficient tilt table test.

BACKGROUND
Current protocols of tilt table testing are quite time-consuming. This study was designed to assess the diagnostic value, tolerance and procedural time of a single-stage isoproterenol tilt table protocol.

METHODS
A single-stage isoproterenol tilt table test was compared with the passive tilt table test. The study was prospectively designed in a randomized and crossover fashion.

RESULTS
The study population consisted of 111 patients with a history of syncope (mean age 55 ± 20 years). Of the total, 62 patients (56%; 95% confidence interval, 46% to 65%) had a positive vasovagal response during isoproterenol tilt table testing and 35 (32%; 23% to 41%) during passive tilt table testing (p = 0.002). The mean procedural times of the study population were 11.7 ± 3.6 min and 36.9 ± 13.3 min for isoproterenol and passive tilt table testing, respectively (p < 0.001). All patients tolerated single-stage isoproterenol testing. In the 23 control subjects (mean age 34 ± 11 years), the apparent specificities were 91% (72% to 99%) and 83% (61% to 99%) for passive and single-stage tilt table testing, respectively.

CONCLUSIONS
The single-stage isoproterenol tilt table test was more effective in inducing a positive vasovagal response in an adult population than the standard passive tilt table test, and it significantly reduced the procedural time. The increase in positive yield was associated with a moderate decrease in apparent specificity. These observations support the conclusion that single-stage tilt table testing could be a reasonable diagnostic option in patients undergoing syncope evaluation. (J Am Coll Cardiol 1999;33:985–90) © 1999 by the American College of Cardiology

Upright tilt table testing has been well-established as a provocative maneuver in patients with unexplained syncope (1–10). The sensitivity and specificity of tilt table testing in detecting vagally mediated syncope are difficult, if not impossible, to determine, because the true incidence of vasovagal syncope is unknown in most patient groups and diagnosis is usually based on a history of typical prodrome and the exclusion of other conditions. Despite the shortcomings of passive tilt table testing, data accumulated in the literature suggest that tilting at angles between 60° and 80° for at least 45 min provides acceptable test outcomes (4,11–13).

The addition of isoproterenol infusion to standard tilt table testing has been advocated as a means of increasing the sensitivity of the test (14–17). This is most likely accomplished at the expense of specificity. Several studies have reported that isoproterenol-induced vasovagal response during tilt table testing can be significantly less specific, especially in younger patients and with higher doses of isoproterenol (13,18–20). Recent studies suggest that infusion of lower doses of isoproterenol does not significantly compromise the specificity of the test (12,13). It has been reported that a single-stage isoproterenol tilt table test could be less time-consuming (16). Comparisons with the standard passive tilt and validations in normal controls have not been performed.

In this prospective study, a single-stage isoproterenol tilt table test was compared, in a randomized fashion, with the standard passive tilt table test for clinical usefulness. An intermediate dose and a shorter duration of the isoproterenol tilt table protocol were tested in adults with the final goals of reducing testing time and providing comparable positive yields without significantly compromising specificity of the test.
METHODS

Patient selection. Between January 1996 and June 1997, a total of 111 patients undergoing tilt table testing for evaluation of syncope were enrolled in the study. Each patient had at least one episode of syncope or presyncope. The cause remained uncertain despite comprehensive medical and neurologic evaluation when appropriate. Patients with orthostatic hypotension, significant anemia (hemoglobin value of <11 g/dl), and endocrinologic abnormalities, such as diabetes, hypoglycemia or thyroid dysfunction, were excluded from the study. Patients with abnormal findings during electrophysiologic testing (21) (defined as carotid sinus hypersensitivity, sinus node dysfunction, atrioventricular conduction system disease or sustained ventricular arrhythmias correlated with the patient’s clinical symptoms) were also excluded from the study. Twenty-three normal subjects with no history of syncope or presyncope underwent identical testing protocols and served as controls. The study was approved by the Mayo Clinic Institutional Review Board. Informed oral consent from all patients and written consent from all normal controls were obtained before tilt table testing.

Study protocol. Electrocardiographic (ECG) limb leads I, II, III, aVF, V₁ and V₆ were continuously monitored. Arterial pressure was monitored by an intra-arterial catheter. Recordings were saved to computer (EP Lab and BioMed Medical Manufacturing, Irvine, California).

All studies were performed with the subject in the fasting state for 6 to 10 h. The study protocol (Fig. 1) consisted of a standard passive tilt table test for 45 min at an angle of 70° and a single-stage isoproterenol tilt table test with a constant infusion of isoproterenol at 0.05 μg/kg/min (not exceeding the highest dose at 5 μg/min) for 5 min in the supine position and then 10 min in the tilted position at a 70° angle. Each patient and control subject underwent both tilt table testing protocols. The sequence of the passive tilt table test and isoproterenol tilt table test was randomized. A minimum interval of 10 min in the supine position to achieve steady-state hemodynamics was interspersed between the two tilt table tests. The second test in sequence began when blood pressure and heart rate returned to within 10% of baseline values. If a vasovagal response was induced during any stage of the test protocol, the subject was immediately returned to the supine position. Regardless of the response of the subject during the first sequence of the test protocol, the second sequence of tilt table testing proceeded after complete recovery of the subject.

A positive response was defined as provocation of a vasovagal reaction during either or both of the testing protocols. A vasovagal response was defined as the development of syncope or presyncope in association with relative bradycardia (a decrease in heart rate of at least 20% from the steady-state rate immediately preceding the development of symptoms) or hypotension (a minimum decrease in systolic pressure of 30 mm Hg), or both. Because of the sequential design of the study, preparation times for the two tests could not be separated from each other. The procedural time for the passive tilt table test was defined as the period from the beginning of tilt to the resumption of the supine position. The procedural time for the single-stage isoproterenol test was defined as the interval from the time the isoproterenol infusion was begun in the supine position to the time the patient was returned to the supine position from tilting.

Statistics. To determine whether the results of the single-stage isoproterenol tilt table test were significantly different from those of the passive tilt table test, a McNemar’s test was completed. A paired t test was used to compare variables between the isoproterenol test and passive tilt. Differences between groups were compared for categorical variables by use of the chi-square test for independence. For continuous variables, differences between groups were compared by use of the two-sample t test. A p value of <0.05 was considered significant.
RESULTS

Demographics. The clinical characteristics of the patients are summarized in Table 1. The mean age (± SD) of the 111 patients was 55 ± 20 years (median 60 years; range 17 to 85 years). There were 56 male and 55 female patients. All patients had a history of syncope (98 patients) or recurrent presyncope (13 patients). The mean number of episodes of syncope in the 1 year before tilt table testing was 3 ± 5 (range 1–28), documented in 98 patients. None of the patients had organic heart disease. The mean left ventricular ejection fraction was 0.61 ± 0.06 in the 70 patients in whom it was measured.

Test outcome. Of the study patients, 62 (56%; 95% confidence interval [CI], 46% to 65%) had a positive vasovagal response during isoproterenol tilt table testing, 35 (32%; 23% to 41%) had a positive response during passive tilt table testing, and 70 (63%; 53% to 72%) had a positive response during either of the two tests (Table 2). Of the 62 patients with at least one positive response, 62 (89%; 79% to 95%) had the response during isoproterenol tilt table testing, 35 (50%; 38% to 62%) during passive tilt table testing, and 27 (39%; 27% to 51%) during both tests.

Outcomes were significantly different (p = 0.002) between the two tests. The positive response rate was significantly higher during isoproterenol tilt table testing than during passive tilt table testing. Of the 35 patients with a positive response during passive tilt table testing, 27 (77%; 60% to 90%) had the same response during isoproterenol tilt table testing. Of the 62 patients with a positive response during isoproterenol tilt table testing, 27 (44%; 31% to 57%) had the same response during passive tilt table testing.

Factors influencing tilt table response. The effects of testing sequence, age and gender on the tilt table response were examined. Sequence of the testing protocol had no significant effect on the response to isoproterenol tilt table testing (p = 0.4). For passive tilt table testing, a trend was noted toward a higher positive response rate when passive tilt was second in the sequence, but it was not statistically significant (p = 0.06). Age did not affect the testing outcomes. The mean age was 54 ± 20 years for the 62 patients who had a response to isoproterenol and 56 ± 20 years for the 49 who did not have a response (p = 0.7). The mean ages were 53 ± 20 years for the 35 patients with a response to passive tilt and 56 ± 19 years for the 76 without a response (p = 0.4).

Patterns of response according to gender were assessed. During isoproterenol tilt table testing, 29 male patients (52%; 38% to 65%) and 33 female patients (60%; 46% to 73%) had a positive response (p = 0.4). During passive tilt table testing, 14 male patients (25%; 14% to 38%) and 21 female patients (38%; 25% to 52%) had a positive response (p = 0.1). Among the subjects with positive responses, 20 male (69%; 49% to 85%) and 15 female (45%; 28% to 64%) patients required isoproterenol to elicit a positive response (p = 0.06).

Time associated with tilt table testing. For the total study population, the mean procedural time was 11.7 ± 3.6 min (all procedural times reported for the isoproterenol test included 5 min in the supine position during initiation of isoproterenol infusion) for isoproterenol and 36.9 ± 13.3 min for passive tilt table testing (p < 0.001). Among the responders, the mean time to a positive response after tilting was 4.0 ± 2.8 min during isoproterenol and 19.3 ± 10.5 min during passive tilt table testing (p < 0.001). For the 27 patients with a positive response during both tests, time to the response was significantly shorter (p < 0.001) during isoproterenol (3.4 ± 2.8 min) than during passive (18.4 ± 10.4 min) tilt table testing.

Hemodynamic response during tilt table testing. Hemodynamic responses during the two test protocols are summarized in Table 3. Among the 27 patients with a positive response during both tests, heart rate was significantly higher (p < 0.001) during isoproterenol (102 ± 19 beats/min) than during passive (72 ± 13 beats/min) tilt table testing in the supine position. Although systolic blood pressure was not significantly different (p = 0.8), diastolic pressure was significantly lower (p = 0.02) during isoproterenol than during passive tilt table testing in the supine position before any symptoms developed. At the time of syncope, heart rate, systolic blood pressure, and diastolic blood pressure were significantly lower during passive tilt table testing than during isoproterenol tilt table testing.

Results in normal control subjects. A total of 23 normal subjects were enrolled in the current study. The mean age was 34 ± 11 years. There were 13 male and 10 female patients. A positive response was elicited in four subjects (17%; 5% to 39%; three male and one female) during
isoproterenol and two subjects (9%; 1% to 28%; both male) during passive tilt table testing.

**DISCUSSION**

**Major findings.** In this prospective, randomized study, a single-stage isoproterenol tilt table test and the standard passive tilt table test were compared for clinical utility. In the patient population, inducibility of a vasovagal response was significantly higher during isoproterenol than during passive tilt table testing (56% [46% to 65%] vs. 32% [23% to 41%], p = 0.002). Among those with a positive response during passive tilt table testing, 77% (60% to 90%) had syncope reproduced by isoproterenol tilt table testing. Among those with a positive response during isoproterenol tilt table testing, 44% (31% to 52%) had syncope reproduced by passive tilt table testing.

In the normal controls, a vasovagal response was induced in 17% (5% to 39%) during isoproterenol and 9% (1% to 28%) during passive tilt table testing. Procedural time was significantly shorter during the single-stage isoproterenol tilt table test. All patients and control subjects were able to tolerate the unit dose of isoproterenol infused (0.05 μg/kg/min). These results suggest that the single-stage isoproterenol tilt table test can be effective in inducing a vasovagal response in susceptible patients and can do so in significantly less time than the passive tilt table test. The single-stage isoproterenol tilt table test is a reasonable diagnostic option in patients undergoing syncope evaluation.

**Passive tilt table testing.** It has been proposed that upright tilting from a supine position precipitates a vasovagal response in a predisposed patient. Normal physiologic response includes the proper hemodynamic adjustment to venous pooling associated with gravitational stress; blood pressure is stabilized by an increase in heart rate and contractility as well as by peripheral vasoconstriction (22,23). In predisposed persons, this stimulus presumably results in an abrupt withdrawal of various degrees of peripheral sympathetic tone, causing hypotension or a sudden surge of vagal discharge resulting in bradycardia, or both.

It has been well-recognized that the “sensitivity” of tilt table testing for the diagnosis of vasovagal syncope cannot be determined, because the clinical diagnosis is usually presumptive and the cause of syncope in patients undergoing tilt table testing is usually unknown. Depending on the selected patient population and tilt table protocol, it has been estimated that during passive tilt table testing, a vasovagal response develops in 25% to 75% of patients with unexplained syncope (3,6,8,10,24,25). A study by Fitzpatrick et al. (4) reported that the mean time to syncope was 24 ± 10 min when the tilt was at 60°. From this observation, it was suggested that the minimum duration of a tilt table test should be 45 min (mean time to syncope ± 2 SDs).

The specificity of tilt table testing is defined by the portion of the subjects who have never fainted and have had a negative test result. Most passive tilt studies have been conducted at a 60° angle (3,8,10,24), and specificity has ranged from 90% to 100%. Natale et al. (13) reported decreased specificity during tilt table testing at 80° compared with that at 60° and 70° angles.

From the data reviewed above, the “standard” passive tilt table test used in our laboratory since January 1996 and for the current study has been at a 70° angle for 45 min. Results from the current study are comparable with those in previous reports. A vasovagal response was induced in 33% of adult patients with syncope that remained unexplained after comprehensive medical evaluation. A vasovagal response was induced in 9% (1% to 28%) of controls, resulting in an apparent specificity of 91% (72% to 99%). The study was time-consuming. The mean time to a positive response was 19.3 ± 10.5 min. Of the total patients, 68% (59% to 77%) with a negative response underwent the entire 45-min testing protocol.

**Isoproterenol tilt table testing.** Results of several studies have reported increased positive response when isoproterenol is used in combination with tilt table testing (5,14,15,17). Positive yield has been estimated to be in the 60% to 85% range, primarily from various multistage, incremental isoproterenol tilt table protocols. Although most studies have suggested acceptable specificity of 80% to 90%, Kapoor and Brant (19) reported that specificity was as low as 35% in 20 younger control subjects during multistage isoproterenol tilt table testing, and they recommended caution in the interpretation of results from isoproterenol tilt table testing in younger persons. Natale et al. (13) examined the dose-dependent effect of isoproterenol testing and reported a decrease in specificity during higher doses of isoproterenol infusion (3 μg/min and 5 μg/min) from that with a lower dose (1.5 ± 0.5 μg/min). The apparent specificity of a lower isoproterenol tilt table testing was adequate when the tilt duration was limited to 10 min, as implemented in our current study. The mean age of the

**Table 3. Comparison of Hemodynamics in Patients With a Vasovagal Response During Both Tests**

<table>
<thead>
<tr>
<th></th>
<th>Heart Rate (beats/min)</th>
<th>Blood Pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Systolic</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Passive tilt</td>
<td>72 ± 13</td>
<td>139 ± 22</td>
</tr>
<tr>
<td>Isoproterenol tilt</td>
<td>102 ± 19</td>
<td>137 ± 26</td>
</tr>
<tr>
<td>Mean difference</td>
<td>29 ± 19*</td>
<td>2 ± 29</td>
</tr>
<tr>
<td>Vasovagal response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Passive tilt</td>
<td>56 ± 19</td>
<td>60 ± 13</td>
</tr>
<tr>
<td>Isoproterenol tilt</td>
<td>79 ± 28</td>
<td>68 ± 16</td>
</tr>
<tr>
<td>Mean difference</td>
<td>23 ± 29†</td>
<td>9 ± 14†</td>
</tr>
</tbody>
</table>

Heart rate and blood pressures during a vasovagal response in a given patient were calculated as the mean from a 20+ continuous, beat-to-beat recording before return to the supine position.  
* p < 0.001. † p < 0.05.
control population was 41 ± 15 years, and the test duration was 20 min.

Although more positive responses occur during isoproterenol testing, the multistage protocol continues to be time-consuming. In an attempt to reduce testing time, Sheldon (16) compared single-stage (5 μg/min) with multistage isoproterenol tilt table testing. Positive response rates were comparable between the single-stage and the multistage isoproterenol tilt table tests, and the single-stage test was associated with significant time savings. Specificity from normal controls was not examined in this study. More recently, Blanc et al. (26) reported that single-dose isoproterenol (5 μg/min) tilt table testing reproduced 95% of passive tilt responses and saved more time.

For the reasons provided earlier in this article, an intermediate unit dose of isoproterenol at 0.05 μg/kg/min was selected in our current protocol in this adult patient population. A unit dose per kilogram of body weight provides a more uniform physiologic response and minimizes variations as a function of body weight. Single-stage isoproterenol testing was compared with “standard” tilt table testing. The positive response rate, 56% (46% to 65%), observed in our study was in general agreement with the data reported in the literature. A single-stage isoproterenol tilt table test was tolerated by all patients and reproduced 77% (60% to 90%) of the passive tilt table responses. The apparent specificity in normal subjects (a younger age group) was 83% (61% to 95%). Procedural time was significantly reduced. In the entire study population, the mean procedural time, including 5 min of infusion in the supine position, was 11.7 ± 3.6 min.

Isoproterenol versus passive tilt table testing. Differences exist between single-stage isoproterenol and passive tilt table testing. Heart rate and blood pressure responses are significantly different between the two tests both before and during the development of vasovagal symptoms. The differences in hemodynamics before the onset of symptoms are consistent with findings in our recent report on the different triggering mechanisms for vasovagal syncope (27). Differences in hemodynamics during the vasovagal responses raise caution in the interpretation of laboratory observations and stress the importance of correlating laboratory observations to spontaneous clinical presentation.

Gender-related differences in the tilt table responses could be present. The additional effect of isoproterenol in eliciting a positive response in more male than female patients showed a trend toward statistical significance (p = 0.06). The different responses to orthostatic stress and isoproterenol between male and female patients may suggest a gender-dependent mechanism for vasovagal syncope. Gender-related issues in tilt table testing have not been explored at this time.

Study limitations. Intrinsic limitations of tilt table testing have been well outlined in the discussion. Although the variable observations on the reproducibility of tilt table testing are well recognized (28–33), a randomized, crossover study design such as in our study should minimize type II errors. The trend toward a higher positive response when passive tilt was second in sequence could be a result of the length of the study protocol. Other potential contributing factors are residual isoproterenol effect, volume shifts provoked by tilt and vasodilation. Age differences between the patient population and controls may have affected the apparent specificity observed in our study. However, the younger controls should provide only the “worst” model for tilt table specificity on the basis of information available in the current literature. Intra-arterial blood pressure monitoring may affect the net specificity of the study protocols. A significant differential effect on each test individually is not expected, because of the randomized, sequential nature of the study design.

Clinical implications and conclusions. Results from our study support the conclusion that single-stage isoproterenol tilt table testing at 0.05 μg/kg/min and a 70° angle for 10 min was more effective in inducing a vasovagal response than “standard” tilt table testing in adult patients. This increased positive response was achieved at a moderate reduction in the apparent specificity, from 91% (72% to 99%) to 83% (61% to 99%). The single-stage isoproterenol tilt table test significantly reduced procedural time and could be a reasonable alternative diagnostic test in patients undergoing syncope evaluation. Differences in hemodynamic responses between tests stress the importance of correlating patient’s clinical presentations to laboratory findings.

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