Poor Reproducibility of False-positive Tilt Testing
Results in Healthy Volunteers

Masataka Sumiyoshi, MD, Yoriaki Mineda, MD,
Satoshi Kojima, MD, Satoru Suwa, MD,
and Yasuto Nakata, MD

SUMMARY

Positive responses to head-up tilt testing occur in healthy subjects. However, the reproducibility of “false-positive” tilt testing results has not been clarified. To study the reproducibility of “false-positive” responses, we prospectively performed 2 tilt tests separated by 1 to 10 (mean 3.2) weeks in 20 healthy males aged 23 to 40 years (mean 30 years). The baseline tilt test (80° for 30 minutes) ended positive in 4 (20%) subjects on the initial test and 2 (10%) on the second test with only 1 (5%) who had consecutive positive responses. No additional positive responses were noted during the isoproterenol (0.01 μg/kg/min)-tilt test for 10 minutes.

We demonstrated that a false-positive response occurred in 5 (25%) of 20 young males who underwent 2 tilt tests, however, only 1 (5%) subject had consecutive positive responses. Poor reproducibility may be characteristic of false-positive responses in head-up tilt testing. (Jpn Heart J 1999; 40: 71–78)

Key words: Head-up tilt testing, Healthy subjects, False-positive response, Reproducibility

Although head-up tilt testing is known to be a useful tool for evaluating patients with neurally mediated syncope, tilt testing-induced neurally mediated syncope can occasionally be provoked in healthy individuals who have no history of syncope. This response is considered as a “false-positive” response. However, the reproducibility of false-positive tilt testing results has not been clarified. In order to confirm this issue, we prospectively performed head-up tilt testings on two occasions separated by several weeks in healthy volunteers.

METHODS

Study population: This study included 20 healthy men aged 23 to 40 years
(mean 30 years). None of the volunteers had a history of syncope or presyncope. They were not taking any medications. Thirteen of the volunteers were smokers. All of the volunteers had normal physical examinations. The 12-lead electrocardiogram was normal in all but 2 subjects. One had right axis deviation and another had incomplete right bundle branch block with right axis deviation. Both of these volunteers had normal echocardiographic findings.

**Tilt testing protocol:** Head-up tilt testing was performed in a quiet room after an overnight fast. Informed consent for the study was obtained from all volunteers before the initial test. To minimize variability, both the initial and second tests were performed at approximately the same time (between 9:00 a.m. and 12:00 noon). The volunteers were comfortably restrained on a tilt-table to prevent them from falling down if syncope occurred. A peripheral intravenous catheter was inserted 30 minutes before the tilt test and a saline solution of 4.3% glucose was started at a rate of 60 ml/hr. Electrocardiogram was monitored continuously during the test, and arterial blood pressure was monitored noninvasively by tonometry system (BP-508, Colin Electronics, Komatsu, Japan). Baseline measurements were obtained after 15 minutes of resting in the supine position. The subject was then positioned upright at an 80° angle for a maximum of 30 minutes on the tilt table equipped with a footboard for weight bearing (baseline tilt). The change from supine to 80° tilt occurred in 30 seconds. If the baseline tilt results was negative, the subject was returned to the supine position and intravenous isoproterenol was infused at 0.01 μg/kg body weight per min for 10 minutes. The tilt test was then repeated for a maximum of 10 minutes (isoproterenol tilt). If syncope or presyncope developed during the test, the table was rapidly lowered to the supine position and the study ended. A second tilt test was performed under identical conditions at approximately the same time of day using the same protocol 1 to 10 weeks (mean 3.2 weeks) following the initial study.

**Definitions:** A positive response was defined as the development of hypotension (systolic blood pressure < 90 mmHg) or bradycardia (heart rate < 50 beats/min), or both, with concomitant syncope or presyncope. Presyncope was defined as experiencing the premonitory signs and symptoms of imminent syncope (e.g., severe weakness or lightheadedness). Three types of responses were noted during testing: vasodepressor response, cardioinhibitory response, and mixed response.

**Statistical analysis:** All data are presented as the mean ± SD. Paired data were compared between the initial and second tests using the Student’s t test. A p value < 0.05 was considered statistically significant.
RESULTS

Response to initial tilt: During the initial baseline tilt testing, 4 (20%) volunteers had a positive response (Table I). They included 3 with a mixed response and 1 with a cardioinhibitory response. All positive responses occurred within 15 minutes (mean 10.9 minutes) after tilting. The 16 volunteers with a negative baseline result underwent an isoproterenol tilt test, however, no additional positive responses were elicited.

Response to second tilt: During the second baseline tilt testing, 2 (10%) volunteers had a positive response including a mixed response and a vasodepressor response (Table I). The time to a positive response was 23.5 and 26 minutes, respectively. Only 1 of the 4 subjects who had a positive response on the initial test had a positive result on the second test. In this person, the time to the onset of symptoms was prolonged from 15 to 26 minutes, and the type of response changed from mixed to vasodepressor response. The remaining 3 subjects with a positive result on the initial test had negative responses during the second baseline and isoproterenol tilt tests. Another subject whose initial test ended negative had a positive response on the second test. Eighteen subjects with a

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr)</th>
<th>Resting ECG</th>
<th>Response to tilt test</th>
<th>Type of response (tilting time)</th>
<th>Interval between 2 tests (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Initial</td>
<td>Second</td>
<td>Initial</td>
</tr>
<tr>
<td>1</td>
<td>39</td>
<td>N</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>34</td>
<td>N</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>N</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>28</td>
<td>N</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>N</td>
<td>+</td>
<td>+</td>
<td>M (15 min)</td>
</tr>
<tr>
<td>6</td>
<td>29</td>
<td>N</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>27</td>
<td>N</td>
<td>+</td>
<td>-</td>
<td>M (7.5 min)</td>
</tr>
<tr>
<td>8</td>
<td>33</td>
<td>N</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>31</td>
<td>N</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>35</td>
<td>N</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>39</td>
<td>N</td>
<td>+</td>
<td>-</td>
<td>M (10 min)</td>
</tr>
<tr>
<td>12</td>
<td>31</td>
<td>N</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>34</td>
<td>N</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>14</td>
<td>25</td>
<td>RAD</td>
<td>+</td>
<td>-</td>
<td>C (11 min)</td>
</tr>
<tr>
<td>15</td>
<td>23</td>
<td>N</td>
<td>-</td>
<td>+</td>
<td>M (23.5 min)</td>
</tr>
<tr>
<td>16</td>
<td>31</td>
<td>N</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>17</td>
<td>29</td>
<td>N</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>18</td>
<td>29</td>
<td>RAD, IRBBB</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>19</td>
<td>37</td>
<td>N</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>20</td>
<td>28</td>
<td>N</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

ECG = electrocardiogram; N = normal; RAD = right axis deviation; IRBBB = incomplete right bundle branch block; + = positive response; - = negative response; M = mixed response; C = cardioinhibitory response; V = vasodepressor response; ( ) = time to positive response.
negative response during the second baseline tilt were retilted after isoproterenol infusion. No additional positive responses were elicited.

**Comparison of hemodynamic variables:** Hemodynamic variables including heart rate and mean blood pressure were compared between the initial and second tilt tests. Heart rate before and during the tilt test tended to be higher on the initial test than on the second test. However, the difference was not statistically significant (Table II). Mean blood pressure in the supine position immediately before tilting was significantly higher on the initial test than on the second test (81.7 ± 5.3 vs. 78.6 ± 7.0 mmHg, p = 0.043). Mean blood pressure was higher during the initial test than during the second test. Specifically, the differences at 20 min baseline tilting and at 10 min tilting with isoproterenol were statistically significant (p = 0.0034 and p = 0.011, respectively) (Table II).

**Reproducibility of test outcomes:** A positive result was reproducible in only 1 (25%) of the 4 volunteers on the second test. Conversely, a negative result was reproducible in 15 (94%) of the 16 subjects on the second test. The overall test results were reproducible in 16 of the 20 subjects (80%). In addition, only 1 (5%) subject had consecutive positive responses on the 2 tilt tests. The mean age of those with discordant results was slightly younger than that of the concordant subjects (28.5 vs. 31.8 years), but the difference was not significant. The time interval between the 2 tests did not differ between the discordant and the concordant groups (3.0 vs. 3.2 weeks).

**Discussion**

The main finding of this study was that a false-positive response in young, healthy males was noted in 5 (25%) of 20 subjects on the 2 tilt tests, however, only 1 (5%) subject had consecutive positive responses. Poor reproducibility may be characteristic of false-positive responses in head-up tilt testing.

**Specificity of head-up tilt testing:** The rate of false-positive responses during
tilt testing depends on age of the patients, angle and duration of tilting, provocation with isoproterenol, and dose of isoproterenol. Younger people tend to experience a vasovagal response.12-14 Particularly in adolescents, false-positive tilt testing results have been reported to be high.13,15 Newman, et al.18 have compared the tilt testing results of healthy subjects in 3 different aged groups: young (average: 28 years), middle (51 years), and elderly (81 years). They have reported that syncope occurred only in 2 of the young subjects during the passive tilt testing. In addition, a steeper angle has been reported to reduce the specificity of the test.9,15 Although Grubb, et al.17 have reported a good specificity of 91% using an 80° tilt for 45 minutes, Natale, et al.9 and Lewis, et al.18 have shown more false-positive responses in 80° tilt compared to 60° or 70° tilt. Our study population consisted of young subjects (average: 30 years) and we used a steep angle of 80°. These factors may contribute to a relatively high false-positive rate in our tilt protocol.

Our results demonstrated that the specificity of an 80° tilt test was the same as that of Natale, et al.9 (80%) on the initial test. However, if only the results of the second tilt test are utilized, the specificity increases to 90%, which was similar to that of Grubb, et al.17 In addition, heart rate and mean blood pressure were higher on the initial test. Anxiety, in the setting of an unfamiliar test, may increase the sympathetic drive which would increase the likelihood of a false-positive vagal response on the initial tilt test. As a result, a conditioning effect may improve the specificity on the second tilt test.

The use and dose of isoproterenol is another major factor that affects the tilt test. Although the use of isoproterenol improves the sensitivity and shortens the procedure time for the tilt test,6,10,19 Kapoor, et al.19 have questioned whether this increase in sensitivity may result in a decrease in specificity. In the present study, we demonstrated that the use of a very low dose of isoproterenol (0.01 µg/kg per min) does not reduce the specificity of the tilt test.

Reproducibility of test outcomes: The usefulness of any test is dependent on the reproducibility of its results. Although patient selection, the tilt protocol (tilt angle, duration, and use of isoproterenol), and the time interval between tests have varied in previous studies, the overall reproducibility of head-up tilt testing results in patients with syncope ranges from 77% to 98% immediately,20-23 day-to-day reproducibility ranged from 65% to 90%.24-26 However, the reproducibility of test results is not identical between patients with initially positive and initially negative responses. Irrespective of the time interval between tests, the reproducibility of an initially negative result is reported to be good, ranges from 83% to 100%.20,21,25,26 In contrast, the reproducibility of an initially positive result was relatively lower, 67% to 92% immediately,20-23,27 day-to-day reproducibility ranges from 37% to 93%.24-26,28-30 In healthy subjects, Kochiadakis, et al.30 have reported an excellent reproducibility (100%) of negative results on retesting 7
days after the initial test. Hohnloser, et al.\textsuperscript{31} also have noted a good day-to-day reproducibility (91\%) of tilt testing results. However, these 2 studies included only one subject with positive response. In the present study of healthy young males, the overall reproducibility of the test outcomes was satisfactory (80\%). While we demonstrated an excellent reproducibility for negative responses (94\%), there was a poor reproducibility for positive responses (25\%) in a small number of our subjects. This result may be a characteristic in healthy subjects.

**Hemodynamic variables during tilt tests:** Several investigators have compared heart rate and blood pressure changes between the initial and second tilt tests. Brooks, et al.\textsuperscript{26} and Sheldon, et al.\textsuperscript{26} have found no differences in either heart rate or blood pressure prior to or during the tilt tests. However, Chen, et al.\textsuperscript{20} have demonstrated that the heart rate in the supine position was significantly greater prior to the initial test than before the second test in patients with positive responses. A similar tendency was also noted in patients with negative responses. While we continuously monitored heart rate and blood pressure throughout the tilt test, previous investigators have assessed these parameters at only one or two points prior to or during the tests.\textsuperscript{20,24,26} In the present study, the heart rate and mean blood pressure tended to be higher during the initial test. As mentioned above, these results may suggest a predominance of sympathetic tone during the initial test, which would increase the likelihood of false-positive responses.

**Study limitations:** There are several limitations to the present study. First, the interval between the 2 tilt tests was different for each person because of their availability. However, the interval between the tests was almost identical between the concordant (3.2 weeks) and discordant (3.0 weeks) groups. We therefore believe that this issue does not influence our conclusions. Second, our study population was made up of only young males. The response to the tilt test is known to vary with age.\textsuperscript{12-14} In addition, sex differences for the tilt test have not been studied. Therefore, we studied a uniform cohort to avoid age-related or sex-related differences. In this study, we tested a small number of subjects including only 5 men with positive response. Prospective studies of larger populations will be required to establish more precisely the reproducibility of false-positive tilt testing results separated by days, weeks, or months.

**Acknowledgement**

We wish to thank Ms Midori Yata for her assistance in performing the tilt tests.
REFERENCES


