Contribution of Head-Up Tilt Testing and ATP Testing in Assessing the Mechanisms of Vasovagal Syndrome
Preliminary Results and Potential Therapeutic Implications

Daniel Flammang, MD; Mark Erickson, BS; Sally McCarville, MS; Timothy Church, PhD; Djamel Hamani, MD; Erwan Donal, MD

Background—In patients with vasovagal syndrome, head-up tilt testing may reproduce symptoms generally associated with vasodepression. Recent research suggests ATP testing identifies patients with abnormal vagal cardiac inhibition. This preliminary study examined the joint contribution of both tests in identifying underlying mechanisms in the general population with vasovagal syndrome.

Methods and Results—Both tests were performed in random order during 1 session and outside of predominant sympathetic periods in 72 patients hospitalized for syncope (n=56) or presyncope (n=16) for whom no cardiac or extracardiac cause was found. For passive and isoproterenol-provocative tilt testing by standard protocol, reproduction of symptoms defined a positive test. The ATP test consisted of injecting ATP 20 mg IV at bedside, continuously monitoring ECG and blood pressure; a vagal cardiac pause ≥10 seconds defined a positive test. For most patients (64%), ≥1 test was positive. Of the 41 patients (57%) with a positive tilt test (either passive or provoked by isoproterenol), 32% had cardiac disease; none had significant bradycardia (<50 bpm). Of the 8 patients (11%) with a positive ATP test, 62% had cardiac disease; the probability of a positive result increased with age (P=0.015). Both tests were positive in 3 patients and negative in 26 patients; the tilt and ATP test results were uncorrelated (P=0.28).

Conclusions—Results suggest tilt and ATP tests individually and jointly determine the mechanism of vasovagal symptoms in most patients and that vagal cardiac inhibition increases with age. (Circulation. 1999;99:2427-2433.)

Key Words: syncope ■ adenosine ■ vagus nerve ■ tests

Severity of vasovagal manifestations varies in daily life.1 In the same individual, symptom severity varies with intensity of the underlying mechanism along with situational factors. Whereas vagal afferent signals and their processing by the nervous system are complex, clinical manifestations usually stem from vasodepressive reactions, cardioinhibitory reflexes, or both mechanisms combined.2 Reproduction of spontaneous symptoms by head-up tilt test represents a useful and widely recognized option for diagnosis and selection of therapy.34 However, it may not always identify the mechanism of vasovagal syndrome, even though the symptoms produced during tilt testing are primarily associated with a significant drop of blood pressure due to predominant vasodepression.

The ATP test, a simple, quick, and safely performed test with immediate results, has recently been proposed for assessing the role of cardioinhibition in vasovagal syndrome.5 This test, which provokes a strong vagal response in response to injection of a 20-mg intravenous bolus of ATP, identifies vasovagal patients at high risk of severe cardioinhibitory response due to abnormal cardiac hypersensitivity to vagal stimulation by eliciting a cardiac pause longer than 10 seconds.5 Identification of the mechanism of vasovagal syndrome determines the therapeutic strategy: drugs for vasodepression, pacemakers for cardiac inhibition, or a combination. Thus, patients with a positive ATP test receive dual-chamber pacemakers, and patients with a positive tilt test receive β-blockers initially. The present study examines the frequency of cardiac inhibition and predominant vasodepression among vasovagal patients in response to administration of both tilt and ATP tests.

Population
Between January 1994 and June 1996, 115 consecutive patients were referred to our cardiology units with unidentified presyncope or syncope. Twenty-five patients were excluded from the study because their tilt-test protocol was nonstandard; 18 more were excluded after they refused the provocative tilt test after a negative passive test. This left 72 patients, 56 with syncope and 16 with presyncope only (Table 1). For 43 of these patients, the index episode was the first symptomatic episode. The remainder reported 108 total episodes (1

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From Angoulême General Hospital (D.F., D.H., E.D.), Saint Michel, France; Medtronic Inc (M.E., S.M.), Minneapolis, Minn; and Environmental and Occupational Health (T.C.), University of Minnesota, Minneapolis, Minn.
Reprint requests to Daniel Flammang, MD, Department of Cardiology, Angoulême General Hospital, 16470 Saint Michel, France.
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2427
to 8 per patient) before the index episode; these previous episodes occurred an average of 4.3 months apart (range, 1 day to 60 months).

After informed consent was obtained from each patient, tilt and ATP tests were performed in random order. For patients taking antiarrhythmics, testing was delayed 5 half-lives. Both tests were performed the same day between 15 and 60 minutes apart without removal of the patient from the table.

### Test Procedure

#### Tilt Test

We used the widely accepted Westminster tilt-table protocol 6–9 followed by a provocative test after a negative test; testing was performed between 4 and 6 PM in a quiet room maintained at 20°C and equipped for resuscitation. While the patient lay on the tilt table for 30 minutes to become familiar with the environment, a brachial intravenous line with 5% dextrose was inserted; 6-lead ECG and external blood pressure recorders were attached and regularly activated to familiarize the patient with their operation; and the footboard support and chest and knee belts were adjusted and secured. For 15 minutes before tilting, ECG and blood pressure were recorded every minute. Then the table was smoothly tilted to 60° for 45 minutes. ECG and external blood pressure were continuously monitored. The table was quickly reset to the supine position when symptoms occurred or the test ended. The test was considered positive when it reproduced spontaneous symptoms, usually with severe hypotension and occasionally some bradycardia (Figure 1).

Significant bradycardia was considered a sinus rhythm, 50 bpm.

Figure 1. Positive response to tilt testing. Syncope, developing 23 minutes after tilting, was associated with marked decreases in systolic and diastolic blood pressure followed by a small decrease in heart rate.

### Table 1. Patient Characteristics at Inclusion

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total Before Grouping (n=72)</th>
<th>Grouping by ATP Test Results</th>
<th>Grouping by Tilt-Test Results</th>
<th>Grouping by Results of Both Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive (pause &gt;10 s) (n=8)</td>
<td>Negative (pause &lt;10 s) (n=64)</td>
<td>Positive (n=41)</td>
<td>Negative (n=31)</td>
</tr>
<tr>
<td>Mean age, y (SEM)</td>
<td>65.0 (1.9)</td>
<td>77.6 (3.2)</td>
<td>63.4 (2.0)</td>
<td>63.3 (2.4)</td>
</tr>
<tr>
<td>Weight, kg (SEM)</td>
<td>68.8 (1.7)</td>
<td>61.9 (4.0)</td>
<td>69.7 (1.8)</td>
<td>67.1 (1.8)</td>
</tr>
<tr>
<td>CT ratio, % (SEM)</td>
<td>52.3 (0.7)</td>
<td>53.1 (2.6)</td>
<td>52.2 (0.8)</td>
<td>53.1 (0.9)</td>
</tr>
<tr>
<td>Resting HR, bpm (SEM)</td>
<td>69.3 (1.4)</td>
<td>69.9 (5.4)</td>
<td>69.2 (1.5)</td>
<td>72.0 (2.0)</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>43/29</td>
<td>3/5</td>
<td>40/24</td>
<td>22/19</td>
</tr>
<tr>
<td>Absence of cardiopathy, n</td>
<td>47</td>
<td>3</td>
<td>44</td>
<td>28</td>
</tr>
<tr>
<td>Absence of risk factors, n</td>
<td>26</td>
<td>2</td>
<td>24</td>
<td>17</td>
</tr>
<tr>
<td>Most severe symptoms, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presyncope</td>
<td>16 (22)</td>
<td>0</td>
<td>16 (25)</td>
<td>11 (27)</td>
</tr>
<tr>
<td>Syncope</td>
<td>56 (78)</td>
<td>8 (100)</td>
<td>48 (75)</td>
<td>30 (73)</td>
</tr>
<tr>
<td>Vagal circumstances</td>
<td>36 (50)</td>
<td>5 (62)</td>
<td>31 (48)</td>
<td>22 (54)</td>
</tr>
</tbody>
</table>

CT ratio indicates cardiothoracic ratio; HR, heart rate.

General characteristics of all patients (Total) and by ATP and tilt-test results (positive vs negative) as well as by selected combined results (both positive vs both negative). Cardiopathy was a dichotomous variable (yes vs no), as was risk factors.
for 5 minutes. Then, while the dosage was maintained, the table was tilted until symptoms were reproduced (positive test) or for 15 minutes (negative test). The trend of blood pressure was also recorded.

**ATP Test**

At a dose of 0.3 mg/kg, ATP, an endogenous purine nucleotide, first produces abrupt negative chronotropic and dromotropic vagal effects in <30 seconds and then produces peripheral vasodilation. Preparation for ATP testing was the same as for the tilt test. Before the test, all patients were in sinus rhythm (mean heart rate, 69.3 ± 1.4 bpm). In the ATP test, an intravenous bolus injection of 20 mg of ATP (Striadyne, Wyeth Laboratories; 20 mg/2 mL vial) was followed by a 20-mL flush of 5% dextrose while the ECG was continuously recorded at 25 mm/s. To prevent reflex sympathetic reaction, the patient was kept unaware of the potential transitory effects of ATP until the time of the injection.

The ECG response consists of 5 phases, summarized as follows: phase I, progressive slowing of sinus rhythm; phase II, first- or second-degree AV block; phase III, cardiac pause of variable duration due to complete AV or SA block (this phase may not occur); phase IV, return to pretest sinus rhythm via a second- or first-degree AV block; and phase V, reflex sympathetic sinus tachycardia (Figure 2). The clinical response to ATP varies from a simple vasodilating flush to presyncope to syncope. After testing, the patient is asked to compare spontaneous symptoms with provoked symptoms.

The test result is defined by the presence and duration of phase III. The test is positive when the phase III cardiac pause is >10 seconds and negative when there is no phase III pause (eg, simple bradycardia of any type) or the pause is ≤10 seconds. A positive ATP test signals an abnormal hypersensitivity of the heart to vagal stimulation associated with a cardioinhibitory reflex.

**Statistical Methods**

Age, weight, cardiothoracic ratio, resting heart rate, time interval before symptom reproduction during tilt test, and ATP test-phase duration are reported as mean ± SEM. Continuous variables were compared by Wilcoxon rank sum test with StatXact software. Sex, structural cardiac disease, risk factors, and presenting spontaneous symptoms are described by frequency and percent relative frequency by respective groups. Frequency data were compared by Fisher’s exact test with SYSTAT 5.0 software. Tests of the relationship of age to the probability of a positive test were made by 2-sided, 5%-level Wald statistics from generalized linear models computed in S-Plus 4 for Windows. The association between results of the 2 diagnostic tests was estimated by the cross-product ratio, a measure of association, and independence was tested by Fisher’s exact test.

**Results**

**Patient Characteristics**

Table 1 gives the baseline characteristics of all 72 patients and of subgroups by tilt and ATP test results. The patients (predominantly male [60%], as is typical in vasovagal syndrome; aged 65 years on average; 35% with cardiac disease) were similar to other studied populations, and the prevalence of syncope was consistent with the large number of episodes usually reported. Both tilt-test subgroups had similar baseline characteristics except for a higher pretest heart rate in patients with a positive tilt test. Both ATP test subgroups had similar baseline characteristics except that patients with a positive ATP test were older and had more peripheral vascular disease and slightly more cardiac disease. Presenting symptoms occurred during typical vagal circumstances in only 36 (50%) of the 72 patients.

**Results of Tilt Test**

Passive testing was positive in 16 (22%) of the 72 patients, producing symptoms after 13.9 ± 1.9 minutes of tilting (Table
Provocative testing was positive in 25 patients (45% of the 56 patients who were negative on the passive test), producing symptoms after 6.2 ± 0.9 minutes, approximately half the amount of time observed during the passive test. Combined, the tilt test was positive in 41 patients (57%), with a mean drop of blood pressure of 46%.

Four (10%) of these 41 positive patients had neither a 25% drop in systolic blood pressure nor bradycardia (heart rate < 50 bpm); however, the small changes all 4 did have violated the usual criteria for psychogenic syncope. Four of the 31 negative patients had a significant drop in systolic blood pressure (mean, 36%; range, 29% to 40%).

### Results of ATP Test

#### ECG Response

In the 8 patients (11%) who tested positive on the ATP test, the mean cardiac pause (phase III) was 17.2 ± 1.8 seconds. In the 64 patients with a negative ATP test, a short cardiac pause was observed in 27 patients (mean, 5.6 ± 0.4 seconds), and no cardiac pause was seen in 37 patients (Table 3). The mean duration of phases I, II, IV, and V (reflex tachycardia) and percentage change in heart rate were similar in both positive and negative test subgroups (Table 3).

#### Clinical Response

As previously observed and confirmed by the present study, symptoms provoked by ATP are related to phase III cardiac pause duration and uncorrelated with spontaneous symptoms (Tables 1 and 4).

### Association of ATP and Tilt Test Results

At least 1 of the tests was positive in 46 (64%) of the vasovagal patients: tilt test alone was positive in 38 patients, ATP test alone in 5, and both tests in 3 (Table 5). In the remaining 26 patients, both tests were negative. The results of the 2 tests were uncorrelated. The cross-product ratio was 2.4, which was not significantly different from 1 (P = 0.2776).

### Age and Probability of Positive Tests

Age was not significantly related to the probability of a positive tilt test. However, the ATP test was more likely to be positive as age increased (P = 0.0153), with a probability of < 4.5% at age 60, increasing ≈ 9% of this rate each year (eg, ≈ 0.4% from age 60 to age 61).

### Discussion

#### Contribution of ATP and Tilt Tests in Diagnosis of Vasovagal Syndrome

This study examined the joint use of the 2 tests to determine the relative strength of the mechanisms (vasodilation, cardioinhibitory reflex, or both) responsible for vasovagal symptoms and to provide preliminary information for therapeutic

### Table 2. Tilt-Test Results

<table>
<thead>
<tr>
<th></th>
<th>Passive Positive</th>
<th>Passive Negative</th>
<th>ISO Positive</th>
<th>ISO Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tilt (n = 25)</td>
<td>Tilt (n = 31)</td>
<td>Tilt (n = 41)</td>
<td>Tilt (n = 46)</td>
</tr>
<tr>
<td>Baseline HR, bpm</td>
<td>Mean ± SEM</td>
<td>Mean ± SEM</td>
<td>Mean ± SEM</td>
<td>Mean ± SEM</td>
</tr>
<tr>
<td>Tilt HR, bpm</td>
<td>76 ± 5.0</td>
<td>78 ± 1.9</td>
<td>84 ± 4.8</td>
<td>97 ± 2.9</td>
</tr>
<tr>
<td>Baseline BP, mm Hg</td>
<td>128/71 ± 3.4/2.0</td>
<td>142/78 ± 2.7/1.5</td>
<td>132/64 ± 4.9/3.0</td>
<td>146/76 ± 3.7/2.1</td>
</tr>
<tr>
<td>Systolic BP drop, %</td>
<td>49 ± 6.3</td>
<td>10 ± 1.0</td>
<td>46 ± 6.0</td>
<td>12 ± 2.0</td>
</tr>
<tr>
<td>Time to tilt symptoms, min</td>
<td>13.9 ± 1.9</td>
<td>...</td>
<td>6.2 ± 0.9</td>
<td>...</td>
</tr>
</tbody>
</table>

ISO indicates provocative isoproterenol test; HR, heart rate; and BP, blood pressure.

### Table 3. Electrical Course of ATP Test

<table>
<thead>
<tr>
<th>Phase</th>
<th>ATP Positive (Pause &gt; 10 s)</th>
<th>ATP Negative (Pause ≤ 10 s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Mean ± SEM</td>
<td>n</td>
</tr>
<tr>
<td>I</td>
<td>8</td>
<td>55</td>
</tr>
<tr>
<td>II</td>
<td>8</td>
<td>55</td>
</tr>
<tr>
<td>III</td>
<td>8</td>
<td>27</td>
</tr>
<tr>
<td>IV</td>
<td>8</td>
<td>53</td>
</tr>
<tr>
<td>Resting HR, bpm</td>
<td>8</td>
<td>64</td>
</tr>
<tr>
<td>Reflex tachycardia (phase V), bpm</td>
<td>8</td>
<td>64</td>
</tr>
<tr>
<td>HR change, %</td>
<td>8</td>
<td>64</td>
</tr>
</tbody>
</table>

Measure of the 5 successive phases of ECG response to ATP for responders (ATP Positive) and nonresponders (ATP Negative) as defined by duration of phase III cardiac pause on ATP. For nonresponders, only the 27 patients with a cardiac pause were used in the phase III calculation. Durations of phases I through IV are expressed in seconds (mean ± SD). Phase V (reflex tachycardia) heart rate (HR) is expressed in bpm.
choice. From this preliminary study, we observed the following:

1. Because typical vasovagal circumstances were absent at the time of symptoms in half of the patients, appropriate testing must be used to determine the presence of vagal dominance.
2. Tilt tests reproduced spontaneous symptoms in 57% of patients, similar to the percentage reported in the literature; most positive tests were the result of provocation with isoproterenol.
3. The ATP test was positive in 8 patients (11%), who were 14 years older on average and more frequently had underlying cardiopathy than the ATP-negative patients. If one assumes that these 8 were the only patients with cardioinhibition, most vasovagal syndromes were of vasodepressive origin in this study population, which was young relative to the previous study.
4. Both tests were positive in 3 patients, which suggests that a few patients were subject to vasovagal attacks via both mechanisms.
5. Both tests were negative in 26 patients; these patients might be considered to have had neither mechanism at the time of testing. However, if diagnostic tests were repeated, 1 of these mechanisms might eventually be revealed.

**Tilt Test**

Since 1986, wide use of tilt testing has reproduced hypotensive symptoms in >50% of tested patients, especially in young populations. The significant drop in blood pressure is usually followed by mild bradycardia but rarely by significant bradycardia or asystole. The present study used the most widely accepted tilt test procedure for both initial passive and secondary provocative tests.

Given both the diversity of physiopathological mechanisms potentially responsible for vasovagal manifestations and the provocative rationale for tilt testing, the different protocols should not reliably reproduce symptoms. The predictive value of the tilt test declines as the time interval between spontaneous symptoms and testing increases. Also, absent a "gold standard," we cannot determine the sensitivity of the test without making strong assumptions. Moreover, provocative testing with isoproterenol increases test sensitivity while decreasing specificity. Similarly, other provocative agents such as nitroglycerin, edrophonium, epinephrine, and nitroprusside yield equivocal results.

Some patients who initially tested negative on the tilt test (identifiable perhaps by an isolated, significant drop in blood pressure) might become positive at later repeat testing or by use of another provocative agent.

**ATP Test**

Unlike other adenosine nucleotides, ATP triggers a vagal reflex in animals that is immediately followed by cardioinhibition. In humans, the vagal action of ATP can reveal patients with abnormal cardiovascular hypersensitivity to vagal stimulation. However, there is no evidence that ATP itself plays a role in the spontaneous symptomatic episodes, and it may therefore be misleading to label the underlying condition “ATP sensitivity,” as has been suggested recently.

In the present study, the percentage of patients with positive ATP tests (11%) was lower than that reported in a previous study (41%). Because age and probability of a positive ATP test are strongly associated, this discrepancy most likely stems from the 9-year age difference between the 2 study populations; 65.0 ± 1.9 years in the present study versus 73.6 ± 0.6 years in the previous study. It is also consistent with the 14-year age difference in the present study between positive and negative ATP responders (77.6 ± 3.2 versus 63.4 ± 2.0 years, respectively; Table 1) and with the similarity between mean ages of the positive ATP responders in the previous and present studies (77.2 ± 0.7 versus 77.6 ± 3.2 years; P = 0.8986).

The severest form of the disease is often called malignant vasovagal syndrome, although the definition varies by author. According to the British Pacing and Electrophysiology Group, it is severe syncpe with bradycardia or asystole during tilt testing and justifies implantation of a permanent pacemaker. We submit that patients in whom both tests are positive may also suffer from malignant vasovagal syndrome. Because pacemaker therapy frequently fails (48% to 73% of

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**TABLE 4. Spontaneous Symptoms versus Symptoms During ATP Test**

<table>
<thead>
<tr>
<th>Spontaneous Symptoms</th>
<th>ATP Positive (Pause &gt;10 s)</th>
<th>ATP Negative (Pause ≤10 s or No Pause)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Symptoms</td>
<td>Presyncope</td>
</tr>
<tr>
<td>Presyncope (n=16)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Syncope (n=25)</td>
<td>2 (25%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Presenting spontaneous symptoms and ATP-provoked symptoms, by response to ATP testing.

---

**TABLE 5. Tilt-Test Results versus ATP Test Results**

<table>
<thead>
<tr>
<th>Tilt-Test Results</th>
<th>ATP Test Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive (Pause &gt;10 s)</td>
</tr>
<tr>
<td></td>
<td>(n=8)</td>
</tr>
<tr>
<td>Passive positive tilt (n=16)</td>
<td>2</td>
</tr>
<tr>
<td>Passive negative tilt (n=56)</td>
<td>6</td>
</tr>
<tr>
<td>ISO positive tilt (n=25)</td>
<td>1</td>
</tr>
<tr>
<td>ISO negative tilt (n=31)</td>
<td>5</td>
</tr>
<tr>
<td>Passive or ISO positive tilt (n=41)</td>
<td>3</td>
</tr>
<tr>
<td>Passive or ISO negative tilt (n=31)</td>
<td>5</td>
</tr>
</tbody>
</table>

Combined results of tilt and ATP tests. ISO indicates provocative isoproterenol test.
patients have symptom recurrence) in patients in whom pacemakers are implanted because of malignant vasovagal syndrome identified by tilt testing, and because a positive tilt test may not always reflect spontaneous symptoms in all patients, those patients with positive tilt and ATP tests (thus identifying both “vaso” and “vagal” mechanisms) may have truly malignant vasovagal syndrome and therefore may be better treated with both drugs and pacemaker. However, confirmation of such speculation awaits larger trials incorporating both diagnostic and therapeutic outcomes. Finally, as with the tilt test, without any gold standard for cardioinhibitory reflex of vagal origin, the sensitivity of the ATP test cannot be estimated.

**Patient Age and the Evolution of Vasovagal Syndrome**

This preliminary study shows that although age does not increase the probability of a positive tilt test among vasovagal patients, it does increase the probability of a positive ATP test. This finding suggests that the prevalence of vasodepression does not change with age, but cardioinhibition becomes increasingly prevalent as patients age. Additionally, individuals vary in cardiovascular sensitivity to vagal stimulation. These observations suggest a hypothesis for the evolution of vasovagal syndrome: (1) Hypersensitivity to vagal stimulation may start in youth, with some degree of instability in orthoparasymathetic regulation identified by circumstantial vasodepressive symptoms and reproduced by tilt testing. (2) With aging, this regulation may deteriorate because of fibrotic degeneration or a decrease in perfusion of the autonomic nervous tissue. The autonomic nervous system may become overly reactive to neurohormonal inputs, especially those of vagal origin. Perhaps, after a phase of inotropic and vascular dysregulation, vagal input subsequently alters chronotropic and dromotropic properties. Thus, tilt testing alone would be more appropriate initially because it identifies abnormal vasodepression prevalent in the younger population; in the later phase, ATP testing becomes appropriate as well because it identifies individuals with pathological cardioinhibitory reflex of vagal origin, a more prevalent condition in the older population.

**Therapeutic Strategy Inferences**

Although not addressed by this study, therapeutic strategies may be tentatively proposed. Patients with a positive tilt test and a negative ATP test should either receive drug therapy or simply be monitored. Generally, results with temporary cardiac pacing have been mixed, leading Petersen and Sutton to discourage pacing therapy. However, early clinical experience with a dual-chamber “rate-drop–sensing algorithm” suggested some improvement of symptoms. Patients with positive ATP tests and negative tilt tests should receive dual-chamber pacemakers, on the basis of an estimated 85% reduction in symptom recurrence. Patients with both positive tilt and ATP tests represent a more difficult group to treat, requiring permanent pacing therapy and tilt-evaluated drug therapy. In patients with evidence of cardiac inhibition during tilt testing, both temporary and permanent cardiac pacing have reduced symptom severity. A rate-drop–sensing algorithm may improve the follow-up results. Finally, no specific therapy can be recommended for patients with negative results on both tests.

**Study Limitations**

Small and limited in scope, this study provides only preliminary estimates of parameters in the joint use of ATP and tilt-table tests. It raises some important questions, notably how to manage patients with negative results on both tests and whether a significant blood pressure drop should be an additional criterion of tilt-test positivity. The results point to the need for larger studies that can define more precisely the underlying mechanism of vasovagal symptoms in populations with a wider age distribution and that ultimately can identify explicit criteria for successful therapy.

**Conclusions**

In patients with syncope or presyncope of vasovagal origin, the objective of testing is to select optimal therapy. Two major mechanisms of vasovagal syndrome may be assessed by tilt testing, which is designed to reproduce symptoms usually associated with a vasodepressive mechanism, and by ATP testing, which identifies patients with abnormal cardioinhibitory under vagal stimulation. In the present study, both tests combined to indicate a positive diagnosis in 46 (64%) of the 72 patients. Tilt testing reproduced symptoms in 41 mostly younger patients. The ATP test was positive in 8 mostly older patients, from whom also had positive tilt-test results. Finally, 26 patients had negative results on both tests; with no identified mechanism, therapy for these patients remains uncertain. Larger studies using both tests are needed to gain knowledge about the mechanisms of vasovagal syndrome and its multiple manifestations, to reassess the criteria for tilt test positivity and the definition of the malignant form of vasovagal syndrome, and to define the optimal use of both diagnostic tools for improving therapy in vasovagal syndrome.

**References**


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