Acute and Long-Term Beta-Adrenergic Blockade for Patients With Neurocardiogenic Syncope

Marilyn M. Cox, MD, FACC, Bruce A. Perlman, MD, Manuel R. Mayor, MD, Todd A. Silverstein, BS, Ester Levin, MD, Lynn Pringle, RN, Agustin Castellanos, MD, FACC, Robert J. Myerburg, MD, FACC

Miami, Florida

Objectives. This study was designed to prospectively evaluate the long-term outcome of drug therapy guided by head-up tilt testing for the management of unexplained syncope and near syncope.

Background. Head-up tilt testing is used to evaluate patients with unexplained syncope. The validity of acute drug testing and the efficacy of long-term oral therapy for prevention of recurrent syncope have not been investigated in large patient groups.

Methods. We studied 296 consecutive patients with unexplained syncope. We challenged patients by head-up tilt testing with and without isoproterenol challenge. The efficacy of intravenous and oral beta-blocker therapy was evaluated by repeat testing. Patients with both positive and negative responses to therapy were followed up for rates of recurrence of syncope.

Results. A total of 193 patients (65%) had a positive tilt test response; 89% of these 193 required isoproterenol challenge to elicit this response. Patients with a positive tilt test result had lower values for heart rate at rest (mean ± SD 69 ± 13 vs. 74 ± 14 beats/min, p = 0.046) and systolic blood pressure (137 ± 28 vs. 145 ± 30 mm Hg, p = 0.0018) at baseline than did the patients with a negative tilt test result. Intravenous propranolol blocked the positive response in 163 (90%) of 181 patients retested. Oral beta-blockers were effective by tilt test criteria in 118 (94%) of 125 patients; 12 (10%) had recurrent clinical symptoms while taking beta-blockers. Eight (42%) of 19 patients who had a negative tilt test response during beta-blocker therapy had recurrent symptoms when they stopped therapy. Three (23%) of 13 patients receiving empiric beta-blocker therapy had recurrent symptoms. The follow-up period for the patients with a positive tilt test result was 28 ± 11 months (range 5 to 48).

Conclusions. Intravenous propranolol is effective in preventing neurocardiogenic syncope diagnosed during head-up tilt testing and predicts the response to oral beta-blocker therapy. Oral beta-blocker therapy prevents recurrent syncope in the majority of patients. Recurrence of syncope is lowest when efficacy of oral beta-blocker therapy is confirmed by repeat head-up tilt testing.

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blocker therapy but did not continue it and in patients who had a negative response on initial head-up tilt tests.

### Methods

#### Patients.** A cohort of 296 consecutive patients referred for evaluation of unexplained syncope or near syncope from 1990 to 1994 were included in this study. All patients underwent a complete history and physical examination, routine blood studies to rule out anemia or electrolyte imbalances, a standard 12-lead electrocardiogram (ECG) and neurologic evaluation, including a computed tomographic scan or magnetic resonance imaging of the brain, as well as an electroencephalogram and carotid artery Doppler studies when deemed appropriate.

#### Head-up tilt testing.** All patients underwent tilt testing in a fasting, nonsedated state after giving written informed consent. All received a minimum of 500 ml of normal saline or lactated Ringer solution intravenously before the test to ensure that they were euvoletic. Patients were placed in a supine position on an electronically controlled tilt table with a foot board for weight bearing, and baseline blood pressure and pulse were recorded after a 5-min equilibration period. Blood pressure was measured by an automatic sphygmomanometer and by a manual mercury sphygmomanometer and by a manual mercury sphygmomanometer when the blood pressure could not be obtained automatically. Heart rate and rhythm were recorded with the use of a three-lead ECG. After baseline blood pressure and heart rate were recorded, the patients were tilted to an 80° angle for a maximum of 10 min, or less if the patient became symptomatic. Blood pressure and heart rate were recorded every minute. A positive test result was defined as syncope, near syncope or extreme lightheadedness associated with hypotension or bradycardia, or both. Patients who remained asymptomatic during the baseline tilt were returned to the supine position and given an isoproterenol infusion in gradually increasing doses to a maximum of 5 μg/min. An equilibration period of 5 min was allowed after each increase in isoproterenol dose.

#### Intravenous drug testing.** Patients with a positive test response were returned to the supine position and allowed to recover. After a minimum of 5 min for equilibration and stabilization, they were given intravenous propranolol in increments of 1 to 2 mg/min to a total dose of 0.2 mg/kg total body weight. After the infusion of propranolol was completed, the patients underwent repeat tilt testing under the same conditions in which the initial positive test result was elicited.

#### Oral drug testing.** Patients with a positive tilt test result and a beneficial response to intravenous propranolol were started on treatment with either short-acting propranolol, atenolol, metoprolol or nadolol and the dose was titrated to achieve clinical beta-blockade. The choice of oral beta-blocker therapy was not randomized. Once beta-adrenergic blockade was achieved, patients underwent a repeat tilt test at baseline with no isoproterenol stimulation; if isoproterenol had been required during the initial study, they also underwent an additional tilt test performed with the same dose of isoproterenol that had resulted in the initial positive test result.

#### Follow-up.** During follow-up, each patient was contacted by telephone every 3 months, or was seen during regularly scheduled follow-up visits, to evaluate clinical status, including recurrent symptoms and compliance with prescribed beta-blocker therapy. Recurrence of symptoms was defined as syncope or near syncope.

### Statistical analysis.** The Student t test was used to compare results within groups (paired) and among groups (unpaired). Chi-square analysis was used to compare groups when variables were dichotomous.

### Results

#### Study group characteristics.** Among the 296 patients with unexplained syncope or near syncope who underwent head-up tilt testing, 193 (65%) had a positive and 103 had a negative test result (Table 1). Patients with a positive result were younger than patients with a negative result (mean ± SD 53 ± 20 vs. 59 ± 20 years, p = 0.015). The proportion of men and women in each group was similar, as was the distribution of the number of syncopal episodes. Ninety-five percent of patients with a positive tilt test result had a normal ejection fraction compared with 87% of patients with a negative result (p = 0.01). There were no significant differences between the patients with a positive and a negative test result with respect to the presence of mitral valve prolapse, hypertension or coronary artery disease.

#### Initial hemodynamic findings.** Patients with a positive tilt test result had a lower baseline heart rate at rest (69 ± 13 vs. 74 ± 14 beats/min, p = 0.046) and systolic blood pressure at rest (137 ± 28 vs. 145 ± 30 mm Hg (p = 0.0018) than did patients with a negative test result. When subgrouped by gender, there was no significant age difference between women with a positive or negative test result or between men with a positive or a negative test result. However, men in both the positive and negative test result groups were older and had a higher rest systolic blood pressure than that of women.

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### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Head-Up Tilt Test Response</th>
<th>Positive (n = 193)</th>
<th>Negative (n = 103)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>53 ± 20</td>
<td>59 ± 20</td>
<td>0.015</td>
</tr>
<tr>
<td>Male/female ratio (%)</td>
<td>51/49</td>
<td>54/46</td>
<td>NS</td>
</tr>
<tr>
<td>Episodes of syncope</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0, near syncope only</td>
<td>47 (24%)</td>
<td>27 (26%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>24 (12%)</td>
<td>20 (19%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>18 (9%)</td>
<td>14 (13%)</td>
<td></td>
</tr>
<tr>
<td>3 or more</td>
<td>104 (54%)</td>
<td>42 (41%)</td>
<td></td>
</tr>
<tr>
<td>Normal ejection fraction</td>
<td>183 (95%)</td>
<td>89 (87%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>28 (15%)</td>
<td>11 (10%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>21 (11%)</td>
<td>28 (27%)</td>
<td>NS</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>28 (12%)</td>
<td>18 (17%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Unless otherwise indicated, data are expressed as mean value ± SD or number (%) of patients.
Response patterns during initial tilt tests. Among the 193 patients with a positive tilt test result, 144 patients (75%) had a mixed vasodepressor and cardioinhibitory response with both hypotension and bradycardia, and 49 patients (25%) had a pure vasodepressor response during tilt testing. No patient had a pure cardioinhibitory response. The patients with a pure vasodepressor response were significantly older than patients with a mixed response (63 ± 16 vs. 49 ± 20 years, p < 0.0001). Twenty-one patients (11%) had a positive tilt test result at baseline without isoproterenol challenge. Sixty-seven patients (35%) required up to 2 μg/min of intravenous isoproterenol to elicit a positive test result and the remaining 105 patients (54%) required 3 to 5 μg/min of isoproterenol.

Response to therapy. Data were analyzed for response to intravenous propranolol during the initial tilt test and to oral therapy with propranolol, atenolol, metoprolol and nadolol during a second tilt test.

Response to intravenous propranolol. Among the 193 patients who had a positive initial head-up tilt test result, 181 received intravenous propranolol. Of these, 163 (90%) had a negative head-up tilt test result during repeat testing after propranolol administration. Eighteen patients continued to have a positive tilt test result after intravenous propranolol. Two of the 18 had prolonged asystole (19 and 30 s, respectively) during repeat tilt testing after intravenous propranolol; neither had this response during the initial tilt test before administration of propranolol or experienced it clinically.

Response to oral beta-blockers. Among the 163 patients who had a negative tilt test result after intravenous propranolol, 157 were treated with oral beta-blockers (atenolol in 98, propranolol in 33, metoprolol in 22 and nadolol in 4). All oral beta-blockers except nadolol significantly decreased the rest values for systolic blood pressure and heart rate from pre-drug values (Table 2). One hundred eighteen patients underwent repeat testing while receiving oral therapy, and drug efficacy in this group ranged from 91% to 100% (Table 3). Although atenolol was slightly less efficacious than the other agents, this difference was not statistically significant. Three of the 18 patients who did not respond favorably to intravenous propranolol (excluding the two patients with prolonged asystole) underwent permanent pacemaker implantation to provide pacing back-up for beta-blocker-induced symptomatic bradycardia. After pacemaker implantation the patients were given oral propranolol, 80 to 240 mg daily in divided doses, and had a negative result on repeat head-up tilt testing. One patient who did not respond favorably to intravenous propranolol was given oral propranolol, 40 mg every 6 h, and had a negative response during repeat testing. Seven patients continued to have a positive head-up tilt test result while taking oral atenolol despite adequate beta-blockade; six of these seven were retested with another beta-blocker (propranolol in five and metoprolol in one) and had a negative repeat tilt test result.

Follow-up: recurrence of symptoms. Patients with both positive and negative initial tilt test results were contacted to evaluate long-term outcome and rates of recurrence of syncope in both groups. Recurrence of symptoms (syncope or near syncope) was analyzed with respect to patient age and gender, number of syncopal episodes, presenting symptoms, ejection fraction, underlying heart disease, hemodynamic response during tilt testing, use of isoproterenol during the initial test and type of beta-blocker therapy used. Recurrence of symp-
patients was independent of all these variables except with respect to the beta-blocker nadolol. However, only three patients received nadolol and were retested; a larger sample size is needed to make an accurate assessment of the effect of this beta-blocker. Among patients who used beta-blocker therapy proved effective by tilt testing, only 10% had recurrent symptoms. Among patients who used beta-blocker therapy proved effective by tilt testing, only 10% had recurrent symptoms during a mean follow-up interval of 28 ± 11 months. In contrast, empiric beta-blocker therapy resulted in a 23% recurrence rate, whereas patients who discontinued beta-blocker therapy that had been proved effective had a 42% recurrence rate. Patients who had a positive tilt test result but remained untreated had a 58% recurrence rate.

We analyzed the symptoms and drug compliance history in the 12 patients (10% of 118) who had recurrent symptoms despite drug efficacy-proved by tilt testing. Five of these 12 had been partially non-compliant, decreasing the dose of medication that had resulted in a negative repeat tilt test result. The other seven patients had required multiple medication trials to find a therapeutic regimen that would prevent their symptoms. The actuarial rate of freedom from recurrent syncope was 93% at 3 months, 92% at 6 months and 90% at 1 year in the patients who continued the drug therapy proved effective by tilt testing (Fig. 1).

Eight of 19 patients who discontinued tilt-proved effective therapy had recurrent symptoms. Thus, patients who discontinued beta-blocker therapy that was confirmed to be effective by repeat tilt testing had a significantly higher rate of recurrent syncope than did patients who continued beta-blocker therapy (42% vs. 10%, p = 0.0009). Recurrence was independent of whether or not isoproterenol had been required to evoke a positive test result.

Two patients died: one of unknown causes 12 months after the second tilt test and one of a myocardial infarction 34 months after the second tilt test. Both had been taking their prescribed medication. The mean time of follow-up for all patients was 28 ± 11 months (range 5 to 48). Thirty-five patients were lost to follow-up.

**Figure 1.** Actuarial probability of freedom from recurrent symptoms (syncope or near syncope) among patients whose initially positive tilt test result was followed by a negative result during treatment with oral beta-adrenergic blocking agents. Curve A represents experience in patients who continued beta-blocker therapy; curve B represents those who discontinued therapy. The difference between the two groups was significant (p < 0.0009).

**Patients with an initial negative tilt test result.** Among the 103 patients who initially had a negative tilt test result, 4 died of unknown causes and 36 were lost to follow-up. The remaining 67 patients were followed up a mean of 25 ± 12 months (range 6 to 52). Eleven (16%) of the 67 had recurrent syncope or near syncope: 2 with ventricular tachycardia, 1 with a pacemaker and hypertension, 1 with epilepsy, 1 with a conversion disorder, 1 with an aortic valve replacement and 1 with chronic obstructive pulmonary disease. One patient had syncope only in association with extreme pain. Three patients were given therapy for presumed neurocardiogenic syncope (beta-blockers in two, aminophylline in one) in the absence of a positive tilt test result. Of the 38 asymptomatic patients, 18 had subsequently received therapy prescribed by other physicians for various indications. Nine (24%) had permanent pacemakers for bradycardia indications, two were receiving beta-blockers, three oral aminophylline, two fludrocortisone, one ephedrine and one meclizine. Although the incidence of recurrent syncope tended to be greater among the patients who had an initial negative tilt test result than among those with an initial positive test result who were effectively treated with beta-blockers (16% vs. 10%), the rate of recurrent syncope was not significantly different between the two groups.

**Discussion**

Head-up tilt testing has become a widely used diagnostic tool for the evaluation of syncope, and it is now thought that many patients with unexplained syncope have abnormal neurocardiac reflexes as the underlying mechanism of syncope (2). However, some investigators (12) have questioned the validity of the concept and the specificity of the testing procedure. To address these issues, we performed a large prospective study using head-up tilt testing as the primary diagnostic tool for the evaluation and management of syncope. Our analyses include the results of both acute intravenous and long-term oral beta-blocker therapy. Among the 193 patients who had a
positive test result, from the group of 296 consecutive patients studied, the response to the acute intravenous administration of the noncardioselective beta-blocker propranolol was used to guide oral beta-blocker therapy, and oral drug efficacy was confirmed by both repeat head-up tilt testing during oral therapy and long-term clinical follow-up.

**Patient characteristics.** The incidence of a positive tilt test result (65%) in our patients is similar to that reported by others (6,13). Few data have been provided on the characteristics of patients with a positive tilt test result. In this study, we found that such patients were significantly younger and had significantly lower rest levels of heart rate and blood pressure, possibly reflecting a higher vagal tone at rest. A mixed vaso-depressor and cardioinhibitory response was the most common hemodynamic response; however, patients with a pure vasodepressor response were significantly older, possibly suggesting that lack of appropriate sympathetically mediated peripheral vasoconstriction is a factor in older patients with neurocardiogenic syncope.

**Use of isoproterenol.** The majority of patients (89%) in this study required isoproterenol challenge to elicit a positive test result. Similarly, Sheldon and Killam (14) reported that 66 of 100 patients referred for unexplained syncope had a positive tilt test result and that >90% of these 66 had required isoproterenol to produce syncope or near syncope. In that study, >60% of patients who had a positive test result required a dose of 5 μg/min of isoproterenol. In the present study, 35% of patients required up to 2 μg/min of isoproterenol and 54% of patients required 5 μg/min to elicit a positive test result. In contrast, Sra et al. (5) reported that only 12 (35%) of 34 patients required isoproterenol to elicit a positive test result, whereas Waxman et al. (3) reported that 12 (60%) of 20 patients required isoproterenol. This discrepancy may be explained by the variability inherent in smaller patient numbers or by selection bias.

In a recent review, Kapoor et al. (15) analyzed five studies utilizing 80° tilt testing and isoproterenol challenge and found that 24 (34%) of 70 control subjects had a positive test result. Although a high incidence of false positive tests is a valid concern, this may not be a factor in our study because the recurrence of symptoms among patients not compliant with oral beta-blocker therapy proved effective by tilt testing was independent of the need for isoproterenol to elicit an initial positive test result.

**Responses to intravenous beta-blockade.** Overall, 90% of our patients responded beneficially to acute administration of intravenous propranolol and had a negative repeat tilt test result on the same day. The observation that acute intravenous administration of a beta-adrenergic blocker prevents the hypotension or bradycardia, or both, that characterizes a positive head-up tilt test result has been made by other investigators (3,5,7) and reinforces the theory that an increase in adrenergic tone is an important triggering mechanism for episodes of neurocardiogenic syncope. In contrast to a 90% beneficial response rate to beta-blocker therapy in the present study, Sra et al. (5) reported that only 13 (50%) of 26 patients who had a positive tilt test result and underwent acute repeat tilt testing after intravenous metoprolol responded beneficially. We also observed that 9 (43%) of 21 patients who had a positive tilt test result without isoproterenol challenge responded beneficially to intravenous propranolol, indicating that beta-adrenergic blocker therapy is beneficial in patients who do not require beta-adrenergic stimulation for a positive test result. Similarly, Sra et al. (7) reported that 6 (35%) of 17 patients who had a positive tilt test result without isoproterenol challenge responded beneficially to the short-acting cardioselective beta-adrenergic blocker esmolol. The higher proportion of our patients responding to intravenous propranolol, with or without isoproterenol challenge during repeat tilt testing, may be explained by the fact that a nonselective beta-adrenergic blocker crosses the blood-brain barrier and thus may be more effective in the acute treatment of neurocardiogenic syncope. This suggests not only that cardiac and peripheral autonomic reflexes are important, but also that central nervous system reflexes may be involved. In selected patients, a primary role of central nervous system mechanisms has been suggested and therefore penetration of the blood-brain barrier may be more important than previously realized. This concept is supported by the fact that valproic acid (16), an anticonvulsant agent, and fluoxetine hydrochloride, an antidepressant (17), have been shown to be effective in some patients with neurocardiogenic syncope.

Another explanation of our greater success with beta-adrenergic blockers may be related to dose. In our study, doses of intravenous propranolol were based on total body weight rather than an empiric dose; thus, patients may have been subjected to more complete beta-adrenergic blockade. However, 10% of patients in this study did not respond beneficially to acute administration of intravenous propranolol. In three patients, underlying conduction system disease interfered with administration of adequate doses of propranolol to achieve beta-adrenergic blockade; after pacemaker implantation full beta-blockade was achieved in these patients and their tilt test response converted from positive to negative with a combination of beta-blocker and pacemaker therapy. Another possible explanation for lack of a beneficial response to acute intravenous propranolol therapy in some patients is drug-induced hypotension caused by overmedication with propranolol. This was a factor that at least one patient who responded beneficially to oral therapy but not to intravenous therapy. We did not specifically test for discordance between the response to oral and intravenous therapy in this study.

**Response to oral beta-blockade.** It has been generally accepted that oral beta-adrenergic blocker therapy provides effective treatment for neurocardiogenic syncope, but the number of patients evaluated during long-term follow-up is limited. We performed repeat head-up tilt testing on oral beta-blockers in 125 patients and the drug efficacy ranged from 91% to 100% during repeat testing (Table 3). The type of oral beta-blocker therapy was not randomized in this study, but the cardioselective and noncardioselective agents had similar efficacies. Oral beta-blocker therapy significantly decreased the
rest values of systolic blood pressure and heart rate from pretreatment values.

Recurrence of syncope. During a mean long-term follow-up period of 28 ± 11 months, 90% of patients remained symptom free on beta-blocker therapy guided by tilt testing. When repeat tilt testing was not used to guide beta-blocker therapy, 77% of patients remained symptom free. In contrast, patients with a positive tilt test result who responded beneficially to oral beta-blocker therapy during repeat tilt testing but discontinued therapy had a high (42%) recurrence rate. Similarly, in patients who did not undergo repeat tilt testing or receive empiric beta-blocker therapy, the recurrence of syncope was 58%, indicating that the majority of patients with neurocardiogenic syncope benefit from beta-blocker therapy.

Our results are similar to those of Natale et al. (11), who demonstrated that tilt test–guided therapy was most effective and yielded a 6% recurrence rate of symptoms among 234 patients, 145 of whom were receiving beta-blocker therapy. Empiric therapy in their study provided a 30% rate of recurrence of symptoms and patients without therapy had a 67% recurrence rate. In our study the recurrence rate of syncope was 16% among patients who had a negative tilt test result at initial evaluation. Forty-eight percent of these patients had an identifiable cause of syncope that could be treated.

Conclusions. In a large cohort of patients undergoing head-up tilt testing, 65% of patients referred because of unexplained syncope or near syncope had a positive head-up tilt test result and intravenous propranolol proved very effective in blocking the abnormal neurocardiac reflex during head-up tilt testing. Patients with a positive head-up tilt test result are younger and have significantly lower rest values for heart rate and blood pressure than do patients who have a negative tilt test result, suggesting a higher vagal tone at rest in patients with a positive result. In addition, the response to intravenous propranolol accurately predicts the response to oral beta-blockers, either selective or noncardioselective, in 90% of the patients. Beta-blockers are generally well tolerated during long-term therapy, and the recurrence of syncope is lowest (10%) in patients who remain on therapy guided by tilt testing. Beta-blocker treatment is slightly less effective when not guided by tilt testing. The rate of recurrence of syncope is high (42%–58%) in patients who discontinue therapy, indicating that beta blockers are clearly beneficial. In patients with a negative tilt test result, the recurrence rate of syncope is 16%.

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References