Usefulness of a Tilt Training Program for the Prevention of Refractory Neurocardiogenic Syncope in Adolescents

A Controlled Study

Enrico Di Girolamo, MD; Cesare Di Iorio, MD; Luigi Leonzio, MD; Panfilo Sabatini, MD; Antonio Barsotti, MD

Background—Recurrent syncope represents a debilitating disorder and quality of life deteriorates as a function of recurrence of symptoms. Although the administration of β-blockers, vasoconstrictors, fludrocortisone, and serotonin reuptake inhibitors may be helpful in preventing episodes, many patients are intolerant of or respond poorly to these agents. Orthostatic training has been reported to be effective in preventing refractory syncope. Thus, to determine whether a tilt training program could prevent symptoms in adolescents, the following controlled study was undertaken.

Methods and Results—Forty-seven consecutive adolescents (18 male and 29 female, mean age 16.0 ± 2.2 years) with recurrent syncope and positive head-up tilt test refractory to previous traditional therapies were distributed between 2 groups, depending on their consent (24 patients) or refusal (controls, 23 patients) to enter the program. Orthostatic training was started, in the presence of a family member, with a series of 5 in-hospital sessions. The 24 patients and their relatives were then instructed to perform the tilt training at home by standing against a wall twice a day for a planned duration of up to 40 minutes, depending on the in-hospital orthostatic tolerance. Head-up tilt response was reevaluated after 1 month, and the clinical effect was noted over a mean follow-up of 18.2 ± 5.3 months (range 15 to 23); 26.1% of patients in the control group and 95.8% of patients in the training group became tilt-negative (P < 0.0001). Spontaneous syncope was observed in 56.5% versus 0% in the control and training group, respectively (P < 0.0001).

Conclusions—Orthostatic training was found to significantly improve symptoms of adolescents with neurocardiogenic syncope unresponsive to or intolerant of traditional medications. Twice-a-day training sessions of 40 minutes were well accepted by patients. (Circulation. 1999;100:1798-1801.)

Key Words: syncope ■ baroreceptors ■ nervous system, autonomic ■ reflex

Neurocardiogenic syncope is defined as a sudden, transient loss of consciousness due to neurally mediated hypotension and bradycardia that annually accounts for up to 3% of all emergency room visits. Survival prognosis seems to be excellent but quality of life deteriorates as a function of recurrence of episodes. The importance of identifying susceptibility to vasovagal reactions in patients with unexplained syncope is readily evident given the frequency with which vasovagal syncope appears to be responsible for patient symptoms. Head-up tilt test was introduced in clinical practice in 1986; to date it represents the only diagnostic tool for evaluation of unexplained syncope to have been subjected to sufficient clinical scrutiny to assess its effectiveness in this setting. The exact pathophysiology of neurocardiogenic syncope remains incompletely understood; therapy has largely been empiric, based on the mechanisms commonly believed to lead to neurocardiogenic fainting, ie, a reflex triggered by enhanced ventricular unmyelinated vagal C-fibers (mechanoceptor) activity in response to a sympathetically mediated increase in contractility in a preload-reduced left ventricular chamber. Moreover, several neurotransmitters such as catecholamines, opioid peptides, arginine-vasopressin, nitric oxide, adenosine, and 5-hydroxy-triptamine are believed to facilitate vasovagal reactions by inhibiting the neuroadrenergic system. Neurocardiogenic syncope, to date, lacks adequate prophylactic therapy, and some patients (23% in our series) who have recurrent episodes do not respond to or are intolerant of the available pharmacological agents commonly used to solve this problem (eg, β-blockers, vasoconstrictor, vagolytic, negative inotropic, mineral corticoid, or selective serotonin reuptake inhibiting drugs). Recently, we reported tilt table test as having some therapeutic effects, and orthostatic training seems to be effective in preventing recurrent syncope. Thus, to determine whether a tilt training program would prevent refractory neurocardiogenic syncope in adolescents, the following controlled study was undertaken.
Methods

Study Population
Forty-seven consecutive adolescents (18 male and 29 female, mean age was 16.0±2.2 years) with recurrent refractory syncope and positive nitrate-potentiated head-up tilt test were referred for study. Cause of syncope remained unexplained despite a complete history and physical examination, cardiologic and neurologic assessment, computed axial tomography (8 patients) or magnetic resonance (15 patients) of the brain (if indicated), carotid sinus massage, blood pressure determination (both supine and orthostatic), 12-lead ECG, chest x-ray, routine laboratory tests, 2-dimensional echocardiography, and 24-hour Holter monitoring exercise stress test. Each of the patients was unresponsive to or intolerant of previous therapies.

Baseline Head-Up Tilt Test
Patients underwent head-up tilt test between 10 AM and 12 AM, after a 12-hour fasting period. After baseline blood pressure and heart rate values measurement, each patient was tilted to 60° for up to 45 minutes.17 If syncope developed during the tilt, the patient was immediately lowered to the supine position and the study ended. If no symptoms developed, the test was prolonged for up to 20 minutes after 5 mg sublingual isosorbide dinitrate (Carvasin, Wyeth) administration.18 Blood pressure was recorded by an automatic sphygmomanometer on the right arm while heart rate was monitored by a 12-channel ECG. A positive head-up tilt test was defined as the provocation of hypotension, bradycardia, or both, associated with a loss of consciousness that reproduced the patients’ clinical episodes.19 The study was performed according to the guidelines of the institutional committee on human research. All patients (ie, their parents) were informed about the study and signed a consent form.

Previous Therapies
In each of the 47 patients, traditional therapies were either ineffectual or poorly tolerated. Failure was defined as the clinical recurrence of syncope. Patients were unresponsive to or intolerant of 75 mg daily etilefrine (19 patients), 80 mg daily propranolol (15 patients), and either etilefrine or propranolol (11 patients). The other patients underwent 0.2 mg daily fludrocortisone (1 patient) or 20 mg daily etilefrine (19 patients), 80 mg daily propranolol (15 patients), and either etilefrine or propranolol (11 patients). The other patients were treated with 75 mg daily propranolol (5 patients), 75 mg daily atenolol (4 patients), 0.2 mg daily fludrocortisone (1 patient), or a combination of noradrenergic agents. Medications were all discontinued in both control and placebo groups before the study started.

Tilt Training Program
After diagnostic head-up tilt, the pathophysiology of neurocardiogenic syncope and the end points of the program were explained to each of the patients. Patients were then distributed between 2 follow-up groups, depending on their consent (24 patients) or refusal (no compliance; controls, 23 patients) to enter the program.

Orthostatic training was then started with a series of 5 in-hospital sessions for a planned duration of between 10 and 50 minutes (once a day for 5 days), with an increase of test duration of 10 minutes per day. If syncope developed during the test, the patient was immediately lowered to the supine position and the study ended. A family member participated in all the in-hospital head-up tilt sessions. At hospital discharge, the 24 patients and their relatives were instructed to perform the tilt training at home by standing against a wall (with the united ankles 15 cm from the wall)20 twice a day for a planned duration of up to 40 minutes, depending on the orthostatic tolerance during in-hospital tilting. The sessions were performed in a comfortable and safe environment to avoid the risk of physical trauma, and were completed under the supervision of a family member.20 One month after the initiation of the tilt training program, the response to head-up tilt test was reevaluated in the same laboratory at approximately the same time of day using the same protocol of baseline test. None of the patients in either the control or training groups were given instructions about increasing their salt intake as a protective measure to avoid symptoms. Patients or their relatives were seen or contacted by telephone every month, and recurrence of spontaneous syncope was evaluated over a mean period of 18.2±5.3 months. Each of the 47 patients had a follow-up of at least 15 months (range 15 to 23).

Results

Patients Characteristics
Mean age, ratio between male and female sex, duration of symptoms, severity (recurrence) of attacks, and baseline blood pressure and heart rate values were not different in the 2 groups (Table 1). During the baseline head-up tilt test, syncope occurred after a mean test duration of 27.6±19.9 minutes in the control group as compared with 29.1±12.2 minutes in the training group (\(P=0.756\)). All patients who agreed to the program achieved a 40-minute tilt training tolerance within 1 month.

Head-Up Tilt Test Reevaluation
At tilt test repeat, acute tilt-induced syncope was observed in 73.9% (18 patients) versus 4.2% (1 patient) in the control and tilt training group, respectively (\(P<0.0001\)). However, the patient in the training group reported a significant increase of spontaneous syncope (Table 2).

Follow-Up
Before entering the protocol, the patients in the control group had an overall mean of 7.9±3.2 yearly syncopal episodes and the patients in the training group, 8.6±3.8 (\(P=0.499\)). Spontaneous syncope recurrence during a 15-month follow-up was 56.5% (13 patients) versus 0% (0 patients) in the control and tilt training group, respectively (\(P<0.0001\)) (Table 2). One patient (4.2%) in the training group experienced a promptly reverted episode of presyncope, secondary to an obvious and

### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Tilt Training</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>23</td>
<td>24</td>
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<tr>
<td>Age, y</td>
<td>16.1±2.1</td>
<td>15.8±2.3</td>
<td>0.885</td>
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<tr>
<td>Sex (M/F)</td>
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<td>9/15</td>
<td>0.499</td>
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<tr>
<td>No. of episodes/year</td>
<td>7.9±3.2</td>
<td>8.6±3.8</td>
<td>0.490</td>
</tr>
<tr>
<td>Duration of history, y</td>
<td>3.1±1.2</td>
<td>3.4±1.7</td>
<td>0.638</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
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<td>114.4±13.6</td>
<td>0.530</td>
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<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>69.6±9.8</td>
<td>71.3±8.6</td>
<td>0.424</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>81.2±7.7</td>
<td>83.1±8.4</td>
<td>0.756</td>
</tr>
<tr>
<td>Time to tilt-syncope, min</td>
<td>27.6±19.9</td>
<td>29.1±12.2</td>
<td>0.756</td>
</tr>
</tbody>
</table>

### Statistical Analysis
Results are expressed as mean±SD. Patients were classified as positive or negative for both the head-up tilt study and their clinical course on the basis of whether or not their symptoms occurred. The response rate of the 2 groups was compared by \(\chi^2\) test, whereas other continuous data were expressed as mean±SD and compared by Student’s \(t\) test. \(P<0.05\) was considered significant. For multiple statistical comparisons to baseline, \(P<0.025\) was considered significant.

### Results

### Head-Up Tilt Test Reevaluation

At tilt test repeat, acute tilt-induced syncope was observed in 73.9% (18 patients) versus 4.2% (1 patient) in the control and tilt training group, respectively (\(P<0.0001\)). However, the patient in the training group reported a significant increase of test duration, with a mean delay of symptoms onset of up to 52 minutes (\(P<0.001\)), and nitrate challenge was required to provoke syncope (Table 2).

### Follow-Up

Before entering the protocol, the patients in the control group had an overall mean of 7.9±3.2 yearly syncopal episodes and the patients in the training group, 8.6±3.8 (\(P=0.499\)). Spontaneous syncope recurrence during a 15-month follow-up was 56.5% (13 patients) versus 0% (0 patients) in the control and tilt training group, respectively (\(P<0.0001\)) (Table 2). One patient (4.2%) in the training group experienced a promptly reverted episode of presyncope, secondary to an obvious and

### TABLE 2. Recurrence of Tilt-Induced and Spontaneous Syncope

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Tilt Training</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tilt-induced syncope</td>
<td>73.9%</td>
<td>4.2%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Spontaneous syncope</td>
<td>56.5%</td>
<td>0%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
avoidable triggering situation (sauna session). No patients reported feeling worse during follow-up. Twice daily orthostatic training sessions of 40 minutes were well accepted by patients. Two patients failed to comply with the training program after 18 and 20 months, respectively, and syncope reappeared within 2 months (5 and 7 weeks).

**Discussion**

Recurrent syncope can be a severely disabling disorder, and quality of life deteriorates as a function of the severity and recurrence of episodes. Survival prognosis seems to be excellent, but these episodes may produce a serious psychological discomfort for adolescents and prevent them from obtaining education or employment. Also, social interactions may be severely restricted.

In individuals prone to neurocardiogenic syncope, the assumption of passive upright posture leads to gravitationally mediated venous pooling of blood in the lower limbs. This downward displacement of intravascular volume leads to a relevant impairment of cardiac output, and arterial baroreceptor reflexes are activated, resulting in a reflex increase in sympathetic stimulation.\(^4\text{-}^7\) The sympathetically mediated increase in contractility in a preload-reduced left ventricular cavity is believed to activate unmyelinated vagal C-fibers (ventricular mechanoreceptors). Stimulation of these receptors produces a large afferent signal to the brain stem, and inhibition of sympathetic outflow occurs.\(^4\text{-}^7\)

Several neurotransmitters are believed to facilitate vasovagal reactions by inhibiting the neuroadrenergic system. Cat-echolamines, opioid peptides, arginine-vasopressin, nitric oxide, adenosine, and serotonin have all been reported to play an important role in the modulation of central nervous blood pressure and heart rate regulation, thus fluctuations in central levels of some of these molecules are supposed to facilitate the pathogenesis of neurocardiogenic syncope.\(^8\text{-}^{14}\)

Several studies have been undertaken to evaluate the efficacy of pharmacological or electrical therapies on neurocardiogenic syncope, but a real gold standard of head-up tilt-guided therapy has not been established yet. Therapy has largely been empiric, based on the mechanism that is currently believed to be responsible for fainting.\(^12\text{-}^{14},^{20\text{-}22}\) Nevertheless, irrespective of \(\beta\)-blocking, vasoconstrictor, vago-lytic, antipurinergic, negative inotropic, mineral corticoid, serotonin reuptake inhibiting, and cardiac pacing therapies, several patients continue to experience episodes of syncope (refractory syncope). Recently, midodrine has been indicated to be an effective treatment for neurocardiogenic syncope and, apart from \(\beta\)-blockers, it is fast becoming the treatment of choice in these patients.\(^23\) Unfortunately, when the present study was designed these data were not available. Furthermore, young patients are notoriously difficult to treat and long-term drug administration is often poorly accepted by patients and their parents. In our series we studied 47 adolescents with recurrent syncope who had previous ineffectual or poorly tolerated ethylephrine, propranolol, fludro-cortisone, or paroxetine therapies. The clinical recurrence of syncope, irrespective of therapy, encouraged patients (and their relatives) to agree to the training program.

All the patients who performed regular tilt training became asymptomatic during follow-up and only 1 patient (4.2%) experienced syncope during repeat head-up tilt test. Conversely, 56.5% of the patients in the control group still continued to experience syncope. The therapeutic effect of the training program seems to be time-dependent, because syncope reappeared within 2 months in the 2 patients who failed to comply with the proposed training program. These data conform to those reported by Ector et al.\(^16\)

The mechanisms by which tilt training improves symptoms in adolescents with refractory neurocardiogenic syncope remains unclear. Morillo et al observed a reduction of acute tilt-induced syncope in patients subjected to multiple head-up tilt test to evaluate both reproducibility and therapy, and a reconditioning of baroreceptor or mechanoreceptor response was suggested to be responsible for this phenomenon.\(^22\) During peripheral venous pooling, an appropriate compensatory cardiopulmonary baroreceptor reflex-mediated sympathetic activity occurs.\(^5\) In patients prone to neurocardiogenic syncope, these compensatory mechanisms are followed by a paradoxical sympathetic withdrawal.\(^5\) We believe that the daily performance of orthostatic training may have a desensitizing effect on the cardiopulmonary receptors that are believed to trigger the neurocardiogenic reaction. Moreover, patients with recurrent syncope often suffer severe psychological burden; the information about the benignancy of the disorder associated with regained self-confidence of the patients may produce a powerful positive psychological impact,\(^15\text{-}^{16}\) which may contribute to the therapeutic effects of orthostatic training.

**Study Limitations**

This study was not randomized. Selection of patients was based on their consent or refusal to enter the training sessions. The enthusiastic motivation of those who complied with the self-training program may have represented a powerful placebo, thus contributing to the positive therapeutic effects of the program.

**Conclusions**

The tilt training program was found to correct the excessive autonomic reflex activity of neurocardiogenic syncope. We conclude that a self-training program may represent an effective and well accepted therapy in adolescents with recurrent neurocardiogenic syncope who are unresponsive to or intolerant of traditional tilt-guided medication. Major series and longer follow-up periods are needed to resolve the question of the role of orthostatic training in the prophylaxis of refractory neurocardiogenic syncope.

**Acknowledgment**

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**References**


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