

CLINICAL PRACTICE

Neurocardiogenic Syncope

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

A 23-year-old nurse presents for evaluation after having had five episodes of syncope at work during the previous three months. All the episodes occurred while she was standing and were characterized by a feeling of light-headedness lasting one to two seconds and then an abrupt loss of consciousness. Two of the episodes caused falls that resulted in facial trauma. The syncope was brief and not associated with incontinence; it was followed by severe fatigue but no confusion. How should the patient be evaluated and treated?

THE CLINICAL PROBLEM

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N Engl J Med 2005;352:1004-10.
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Syncope may be benign or may be the only warning before an episode causing sudden death.¹ Even if the cause is benign, recurrent syncope can result in injury and provokes substantial anxiety among patients and their families, producing a degree of functional impairment similar to that seen in chronic debilitating disorders such as rheumatoid arthritis.²⁻⁴

Neurocardiogenic (vasovagal) syncope is the most common of a group of reflex (neurally mediated) syncopes, characterized by a sudden failure of the autonomic nervous system to maintain blood pressure and sometimes heart rate at a level sufficient to maintain cerebral perfusion and consciousness.⁵⁻⁷ Other conditions in this group include the carotid sinus syndrome and the "situational" syncopes, which occur after urination, defecation, swallowing, or coughing. Syncope accounts for 3.5 percent of all emergency room visits and 1 to 6 percent of all hospital admissions annually in the United States.⁴

Although the cause is still controversial,⁸ neurocardiogenic syncope is believed to occur in persons who have a predisposition to the condition as a result of excessive peripheral venous pooling that causes a sudden drop in peripheral venous return.⁹ This results in a cardiac "hypercontractile" state, which activates mechanoreceptors that normally respond only to stretch. The increase in afferent neural traffic to the brain mimics the conditions seen in hypertension and provokes an apparent paradoxical reflex bradycardia and a drop in peripheral vascular resistance.¹⁰ Mechanoreceptors are present throughout the body (in the bladder, rectum, esophagus, and lungs), and it is thought that the sudden activation of a large number of these receptors also sends afferent signals to the brain, which provokes a similar response.¹

Neurocardiogenic syncope may be provoked by prolonged standing, vigorous exercise in a warm environment, fear, emotional distress, or severe pain. Presyncopal symptoms include weakness, light-headedness, diaphoresis, visual blurring, headache, nausea, and feeling warm or cold; signs include facial pallor, yawning, pupillary dilatation, and nervousness. These signs and symptoms may occur from 30 seconds to several minutes before syncope. However, up to a third of patients (usually older adults) will have little or no prodrome and, in such cases, physical trauma may result from any fall associated with syncope. The loss of consciousness is usually brief (30 seconds to 5 min-

utes) but may be longer, particularly in older patients. Patients may occasionally have seizure-like movements during an episode (“convulsive syncope”). Recovery is rapid, with little if any postictal state, although in older patients, confusion may occur for up to 10 minutes after the event. Afterward, the patient may appear pale and have headache, weakness, or fatigue. For unclear reasons, episodes may occur in clusters, followed by a long event-free period.

STRATEGIES AND EVIDENCE

A detailed history and physical examination are central to the diagnosis,³ which requires ruling out cardiovascular or neurologic disease. Patients should be asked about a family history of cardiovascular disorders or unexplained sudden death. The patient should be asked about the frequency and circumstances of each event (including prodromal symptoms), as well as any precipitating factors, such as prolonged standing, fear, or pain. A situational syncope is suggested if the event occurred with defecation, urination, coughing, or swallowing. The accounts of bystanders are valuable in providing information about the duration of the loss of consciousness, changes in skin color, and associated myoclonic or tonic-clonic activity. The presence of a cardiac or vascular murmur or focal neurologic signs necessitates further investigation, such as echocardiography or brain magnetic resonance imaging. Most experts suggest that standard 12-lead electrocardiography be performed routinely (with attention to rhythm, duration of the QT interval, bundle-branch morphology, and evidence of myocardial ischemia or hypertrophy) and that echocardiography be performed if there is any question about whether the heart is normal.

In the absence of another identifiable cause, a compatible history is often sufficient to make the diagnosis of neurocardiogenic syncope.⁴ However, if the diagnosis remains uncertain, further testing is warranted.

TILT-TABLE TESTING

Tilt-table testing is the only method for the diagnosis of neurocardiogenic syncope that has undergone rigorous evaluation.¹¹ Indications for testing are summarized in Table 1, and Figure 1 demonstrates how the test is performed. A positive test is one that provokes a hypotensive episode that reproduces the patient’s symptoms. The specificity of a negative test

Table 1. Indications for Tilt-Table Testing.*

Definite indications

Unexplained recurrent syncope or a single episode in the absence of organic heart disease either associated with injury or in settings that pose a high risk of injury
 Unexplained recurrent syncope or a single episode in the presence of organic heart disease after cardiac causes of syncope have been excluded
 A case in which the cause of syncope has been determined but the predisposition to neurocardiogenic syncope may alter the treatment used

Possible indications

Differentiation of convulsive syncope from epilepsy
 Assessment of recurrent, unexplained falls
 Evaluation of recurrent, unexplained near-syncope and light-headedness
 Evaluation of recurrent syncope in the setting of autonomic failure or peripheral neuropathies
 Evaluation of postexertional syncope when an episode cannot be reproduced by exercise testing

* Information is from Sutton and Benditt.¹²

on passive tilt at angles between 60 and 70 degrees approaches 90 percent (false positive rate, 10 percent)^{11,13-15}; the sensitivity of the test is uncertain since there is no “gold standard.” Detailed descriptions of protocols for testing and test characteristics are available elsewhere.^{13,14} The reproducibility of the test (in a time period ranging from hours to weeks) is 80 to 95 percent for an initially negative result but lower for an initially positive response (30 to 90 percent).¹⁵ Tilt-table testing may not produce hemodynamic effects and changes in heart rhythm that are the same as those occurring during spontaneous episodes (as documented by implantable loop recorders).¹⁶

IMPLANTABLE LOOP RECORDERS

Implantable loop recorders are small recording devices that are placed in a subcutaneous pocket and can store about 45 minutes of retrospective electrocardiographic recording. The device can record automatically or be activated by the patient after a syncopal event.¹⁶ Because of the need for surgical implantation and the cost, this device is generally reserved for patients with recurrent syncope in whom the diagnosis remains uncertain despite conventional evaluation. In such cases, a diagnostic yield of 25 to 40 percent has been reported with the use of the device during a period of 8 to 10 months.¹⁷ It is presently uncertain which patients are most likely to benefit from the placement of a loop recorder.

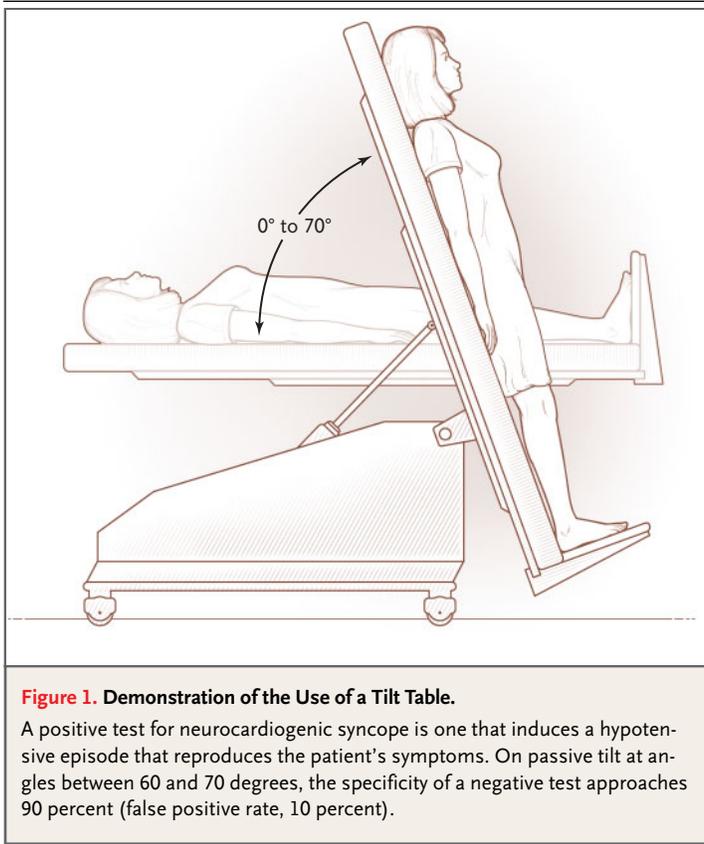


Figure 1. Demonstration of the Use of a Tilt Table.

A positive test for neurocardiogenic syncope is one that induces a hypotensive episode that reproduces the patient's symptoms. On passive tilt at angles between 60 and 70 degrees, the specificity of a negative test approaches 90 percent (false positive rate, 10 percent).

TREATMENT

In cases in which syncope occurs only under exceptional circumstances, management primarily entails education of the patient and the patient's family regarding the nature of the disorder and predisposing factors to be avoided (such as extreme heat, dehydration, and drugs that may precipitate syncope, such as alcohol and vasodilators). Patient should be instructed to lie down at the onset of any prodromal symptoms.

Isometric contractions of the arm and leg muscles have been proposed as potential methods to abort syncopal episodes in patients with recurrent neurocardiogenic syncope, by activating the skeletal-muscle pump to augment venous return. In one study,¹⁸ 21 patients increased their mean systolic blood pressure (from 65 to 106 mm Hg) and aborted syncope by crossing their legs and tensing their muscles for 30 seconds before tilt-table testing that would otherwise have provoked syncope. Another small randomized, single-blind crossover trial¹⁹ showed that intense gripping of the hands and tensing of the arms for two minutes at the onset of tilt-induced symptoms raised systolic blood pressure,

which fell in patients who did not perform the maneuver; syncope occurred in 37 percent of the patients, as compared with 89 percent who did not perform the maneuver. During clinical follow-up, 94 of 95 impending syncopal events were reportedly aborted by hand gripping and arm tensing.

Increasing fluid and salt intake may prevent further syncopal episodes. A reduced frequency of syncopal episodes was reported among adolescents with neurocardiogenic syncope who increased fluid intake (almost 2 liters in the morning, followed by enough fluid to keep the urine clear).²⁰ In a small randomized trial of patients with neurocardiogenic syncope,²¹ daily supplementation with 120 mmol of sodium (about 7 g of salt) for eight weeks increased both blood pressure during tilt-table testing and plasma volume, as compared with placebo, although effects on symptoms were not reported. Some practitioners have advocated "tilt training" (standing for 10 to 30 minutes each day against a wall) to "desensitize" patients to the effects of orthostatic stress²²; however, data on the use of this method are conflicting, and long-term compliance appears poor.²³

HIGH-RISK PATIENTS

For patients who experience sudden recurrent and unpredictable episodes of syncope of neurocardiogenic origin, particularly those who have had recurrent injuries or whose occupations place them or others at severe risk for injury or death from syncope, prophylactic therapy is appropriate. The goal of therapy is to reduce both the frequency and the severity of syncopal events and to prevent fall-related injuries.

Although a variety of agents are used to prevent recurrent neurocardiogenic syncope (Table 2), there are limited data from randomized controlled trials to support their use, and no drug has been approved by the Food and Drug Administration for this indication.²⁴

BETA-BLOCKERS

Beta-blockers have been used for many years as therapy for neurocardiogenic syncope. The proposed mechanisms include a diminished activation of the left ventricular mechanoreceptors that are believed to be responsible for the withdrawal of sympathetic tone²⁴ and a blunting of the increased serum epinephrine levels that occur before syncope. Although beta-blockers were reported to be effective in several uncontrolled studies, they did not

Table 2. Potential Therapies for Neurocardiogenic Syncope.

Treatment	Use and Dosage	Problems
Lifestyle changes		
Fluid intake	About 2 liters/day	Poor compliance, frequent urination
Salt intake*	120 mmol/day	Edema, gastrointestinal upset
Physical maneuvers*	Isometric arm contraction; leg crossing	Unable to use in absence of prodrome
Tilt training	10–30 min/day of standing	Poor compliance
Drugs and devices		
Midodrine*	2.5–10 mg 3 times daily	Nausea, scalp pruritus, hypertension
Fludrocortisone	0.1–0.2 mg daily	Bloating, hypokalemia, headache
Beta-blockers*	Drugs such as metoprolol (50 mg 1 to 2 times daily)	Prosyncope, fatigue, bradycardia
Selective serotonin-reuptake inhibitors*	Drugs such as paroxetine (20 mg daily) or escitalopram (10 mg daily)	Nausea, diarrhea, insomnia, agitation
Permanent cardiac pacing**†	DDD mode with rate-drop algorithm	Invasive, expensive; infection, bleeding, thrombosis

* This treatment has been reported to be effective in at least one randomized clinical trial. For beta-blockers, other randomized clinical trials showed no benefit.

† Recent well-controlled randomized trials showed no benefit. DDD denotes dual-chamber cardiac pacing.

have benefit in five of seven controlled studies.^{25–31} However, methodologic limitations, including variability in the number of patients enrolled, make the results difficult to interpret.²⁴ For example, one trial included patients with a history of syncope regardless of whether tilt-table testing was positive, a finding that raised the possibility of diagnoses other than neurocardiogenic syncope.²⁸ The Prevention of Syncope Trial was a well-designed randomized, double-blind study that compared metoprolol with placebo in 208 patients with recurrent syncope and positive results on tilt-table tests.³¹ At one year, there was no overall difference in syncope-free periods between the groups. A post hoc analysis showed benefit in the subgroup of patients who were more than 42 years of age, but this finding requires confirmation in other studies.

FLUDROCORTISONE

Fludrocortisone is a synthetic mineralocorticoid that causes the retention of sodium, the expansion of central blood volume, and the sensitization of alpha receptors in the peripheral vasculature.³² In uncontrolled studies, the drug has appeared effective in reducing recurrent neurocardiogenic syncope. One randomized trial that compared fludrocortisone with atenolol in adolescents with neurocardiogenic syncope showed similar results for the two drugs, although no placebo group was studied.³³

VASOCONSTRICTORS

Midodrine hydrochloride, a direct α_1 -receptor agonist and vasoconstrictor approved in the United States for the treatment of symptomatic orthostatic hypotension, is also used for recurrent neurocardiogenic syncope.^{32,34} In a randomized, double-blind, crossover trial,³⁵ patients receiving midodrine (5 mg three times daily) for one month had significantly more symptom-free days (mean difference, 7.3) and a better quality of life than the placebo group and were significantly less likely to experience tilt-induced syncope. Another small trial comparing a single dose of midodrine with placebo also showed a significant reduction in the occurrence of tilt-induced syncope.³⁶ A six-month randomized trial comparing midodrine with salt-and-fluid therapy showed a significantly higher rate of resolution of symptoms with midodrine (81 percent vs. 13 percent).³⁷ An uncontrolled study of methylphenidate suggested that it might be an effective alternative.³⁸ A randomized trial of the vasoconstrictive agent etilefrine, however, showed that it was no better than placebo.³⁹

SELECTIVE SEROTONIN-REUPTAKE INHIBITORS

Because serotonin may have a role in regulating sympathetic nervous system activity,^{40,41} selective serotonin-reuptake inhibitors have been proposed as a potential therapy, and open-label studies have

shown that these agents may reduce recurrent neurocardiogenic syncope.^{41,42} In a randomized placebo-controlled trial, 82 percent of the patients who were randomly assigned to receive paroxetine were free of syncope for 25 months, as compared with 53 percent of the placebo group ($P < 0.001$).⁴³

OTHER THERAPIES

Transdermal scopolamine was not superior to placebo in a randomized trial involving 60 patients with neurocardiogenic syncope.⁴⁴ Controlled studies are needed to support the use of several other proposed agents, including disopyramide, enalapril, theophylline, and ephedrine.^{24,32}

In uncontrolled studies involving patients in whom emotional stimuli such as the sight of blood or a needle provoke syncope, biofeedback has been effective in “desensitizing” the person to the psychological stressor and reducing the risk of recurrent syncope.^{45,46}

CARDIAC PACING

The implantation of a permanent dual-chamber pacemaker has been proposed for patients with recurrent neurocardiogenic syncope that is refractory to other therapies, on the basis of the observation that roughly one third of patients have substantial bradycardia or asystole during tilt-induced and spontaneously recorded syncope.⁴⁷ Initial randomized trials showed that the pacemaker was effective in preventing syncope.⁴⁸ However, since subjects were randomly assigned to receive a pacemaker, there was concern that the observed benefit might reflect a placebo effect.⁴⁹

In two subsequent trials, pacemakers were implanted in all subjects, who were then randomly assigned to have the pacemaker turned on or off.^{50,51} The Vasovagal Pacemaker Study II showed no significant reduction in the time to a first recurrence of syncope with dual-chamber pacing during six months of follow-up (relative risk reduction, 30 percent; 95 percent confidence interval, -33 to 63 percent).⁵⁰ Complications included one case each of venous thrombosis, pericardial tamponade, and infection. Preliminary results of the Vasovagal Syncope and Pacing Trial⁵¹ showed no significant difference in the frequency of syncope between the group with pacing and that without pacing, although the subgroup of patients who had asystole in response to a tilt-table test at baseline had a significantly longer time to a first recurrence of syncope with pacing than did patients in the subgroup without pacing.

Given the lack of consistent data from randomized trials to support its use and the potential complications, pacing is not recommended as first-line therapy. However, it may have a role for some patients, specifically those who have little or no prodrome, those in whom other forms of therapy fail, and those who have profound bradycardia or asystole during syncope. For such patients, cardiac pacing may increase the amount of time from the onset of symptoms to a loss of consciousness,⁵² thereby providing time for the patient to take evasive action (i.e., lie down).

GUIDELINES

Guidelines on the evaluation of syncope have been issued by the American College of Physicians,³ the Heart Rhythm Society (formerly called the North American Society of Pacing and Electrophysiology),⁴ the American College of Cardiology,¹³ and the European Society of Cardiology¹⁴ — guidelines that are consistent with the approach discussed here. The European Society of Cardiology has also issued treatment guidelines,¹⁴ but these do not recommend any particular medication; the recommendations regarding pacing antedated the recent negative results of controlled trials.

AREAS OF UNCERTAINTY

The pathophysiology of neurocardiogenic syncope remains uncertain. There are few data available on the natural history of this disorder, and the results of a few large randomized trials guide decision making regarding the optimal therapy. The appropriate role for implantable loop recorders in the diagnostic evaluation of syncope is still being defined.

SUMMARY AND RECOMMENDATIONS

In the case of a patient presenting with syncope, a detailed history (with attention to any personal or family history of cardiac disease or associated symptoms and possible precipitants) and a physical examination (particularly for signs of cardiac disease) are often sufficient to categorize the event with a high likelihood as neurocardiogenic. To rule out cardiovascular disease more definitively, I routinely obtain an electrocardiogram (looking for abnormalities such as the long-QT syndrome or bundle-branch block).

In a case such as the one described in the vi-

gnette, given the severe episodes of syncope (with minimal prodrome and associated with injury), I would recommend additional evaluation, including an echocardiogram (to rule out structural heart disease) and tilt-table testing to provide reassurance that these episodes were caused by neurocardiogenic syncope, even while recognizing that a false positive test is possible.

The first line of therapy for neurocardiogenic syncope is education regarding adequate salt and fluid intake (roughly 2 liters a day of fluid) and, if prodromal symptoms occur, physical maneuvers such as gripping of the hands and tensing of the arms and legs. Although the value of "tilt training" is controversial, I would recommend that the patient stand for a short period each day with her back against a wall, starting with 5 minutes of standing and increasing to 15 to 30 minutes a day.

In cases in which there is little or no prodrome,

and in which episodes have been associated with physical injury, such as that of the patient described, I would also start prophylactic medication. I would first try midodrine at 5 mg orally three times daily (because of its rapid onset of action) and then increase the dose to 10 mg orally three times daily if syncope or near-syncope recurred.⁵³ If episodes were reduced in severity and frequency but were still occurring, I would consider the addition of fludrocortisone at 0.1 mg orally daily (even though supporting data from randomized trials are lacking) or the use of a selective serotonin-reuptake inhibitor (on the basis of limited data from clinical trials). Although data are lacking on the optimal duration of therapy, I would taper and ultimately discontinue medication if the patient remained asymptomatic on treatment for one year (an arbitrary end point) but would follow the patient and reinstitute medication if her symptoms recurred.

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