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.

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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?

Purpose:

Syncope may be benign or may be the only warning before an episode causing sudden death. 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.

Neurocardiogenic (vasovagal) syncope is the most common of a group of reflex (neurally mediated) synapses, 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.

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.

Although the cause is still controversial, 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. 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. 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.

Neurocardiogenic syncope may be provoked by prolonged standing, vigorous exercise in a warm environment, fear, emotional distress, or severe pain. Presyncope 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 minutes).
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 on passive tilt at angles between 60 and 70 degrees approaches 90 percent (false positive rate, 10 percent)\(^ {12-15}\); 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).\(^ {16}\)

**Table 1. Indications for Tilt-Table Testing.**

<table>
<thead>
<tr>
<th>Definite indications</th>
<th>Possible indications</th>
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<tbody>
<tr>
<td>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</td>
<td>Differentiation of convulsive syncope from epilepsy</td>
</tr>
<tr>
<td>Unexplained recurrent syncope or a single episode in the presence of organic heart disease after cardiac causes of syncope have been excluded</td>
<td>Assessment of recurrent, unexplained falls</td>
</tr>
<tr>
<td>In a case in which the cause of syncope has been determined but the predisposition to neurocardiogenic syncope may alter the treatment used</td>
<td>Evaluation of recurrent, unexplained near-syncope and light-headedness</td>
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<tr>
<td>Evaluation of recurrent syncope in the setting of autonomic failure or peripheral neuropathies</td>
<td>Evaluation of postexertional syncope when an episode cannot be reproduced by exercise testing</td>
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</table>

\(^{6}\) Information is from Sutton and Benditt.\(^ {12}\)
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, 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 trial 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). In a small randomized trial of patients with neurocardiogenic syncope, 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 stress; however, data on the use of this method are conflicting, and long-term compliance appears poor.

**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 tone 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
have benefit in five of seven controlled studies.\textsuperscript{25-31} However, methodologic limitations, including variability in the number of patients enrolled, make the results difficult to interpret.\textsuperscript{24} For example, one trial included patients with a history of syncope regardless of whether tilt-table testing was positive, finding that raised the possibility of diagnoses other than neurocardiogenic syncope.\textsuperscript{28} The Prevention of Syncope Trial was a well-designed randomized, double-blind study that compared metoprolol (50 mg, 1 to 2 times daily) with placebo in 208 patients with recurrent syncope and positive results on tilt-table testing.\textsuperscript{32} 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 sensation of sodium, the expansion of central blood volume, and the sensitization of alpha receptors in the peripheral vasculature.\textsuperscript{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.\textsuperscript{33}

**Midodrine**

Midodrine hydrochloride, a direct \(\alpha_1\)-receptor agonist and vasoconstrictor approved in the United States for the treatment of symptomatic orthostatic hypotension, is also used for recurrent neurocardiogenic syncope.\textsuperscript{32,34} In a randomized, double-blind, crossover trial,\textsuperscript{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.\textsuperscript{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).\textsuperscript{37} An uncontrolled study of methylphenidate suggested that it might be an effective alternative.\textsuperscript{38} A randomized trial of the vasoconstrictive agent etilefrine, however, showed that it was no better than placebo.\textsuperscript{39}

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**Selective serotonin-reuptake inhibitors**

Because serotonin may have a role in regulating sympathetic nervous system activity,\textsuperscript{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.\textsuperscript{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 (\(P<0.001\)).\textsuperscript{43}

**OTHER THERAPIES**

Transdermal scopolamine was not superior to placebo in a randomized trial involving 60 patients with neurocardiogenic syncope.\textsuperscript{44} Controlled studies are needed to support the use of several other proposed agents, including disopyramide, enalapril, theophylline, and ephedrine.\textsuperscript{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.\textsuperscript{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.\textsuperscript{47} Initial randomized trials showed that the pacemaker was effective in preventing syncope.\textsuperscript{48} However, since subjects were randomly assigned to receive a pacemaker, there was concern that the observed benefit might reflect a placebo effect.\textsuperscript{49}

In two subsequent trials, pacemakers were implanted in all subjects, who were then randomly assigned to have the pacemaker turned on or off.\textsuperscript{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).\textsuperscript{50} Complications included one case each of venous thrombosis, pericardial tamponade, and infection. Preliminary results of the Vasovagal Syncope and Pacing Trial\textsuperscript{53} 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,\textsuperscript{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,\textsuperscript{3} the Heart Rhythm Society (formerly called the North American Society of Pacing and Electrophysiology),\textsuperscript{4} the American College of Cardiology,\textsuperscript{13} and the European Society of Cardiology,\textsuperscript{14}—guidelines that are consistent with the approach discussed here. The European Society of Cardiology has also issued treatment guidelines,\textsuperscript{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 re assurance 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 tending 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. 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 reinitiate medication if her symptoms recurred.

REFERENCES
26. Sheldon R, Rose S, Flanagan P, Koshman ML, Killam S. Effect of beta blockers on the time to first syncope recurrence in pa-
-What would you do to stop bleeding if you seriously cut your hand?

-How would you know if you cut an artery or a vein?

-What is blood pressure? Why are there 2 numbers (ex: 120/80) involved in a blood pressure reading?

-Is it better to have high or low blood pressure? Why?