Case: A 75-year-old woman was referred for recurrent syncope. Over the past 12 months, she had had 10 episodes of brief (less than 1 minute) loss of consciousness with rapid recovery. She has known coronary artery disease and underwent coronary artery bypass grafting 2 years ago. She had diabetes mellitus that was well controlled with insulin. Her physical examination was normal, including orthostatic blood pressures. She has been admitted several times to different hospitals for the evaluation of recurrent syncope. Electrocardiograms have shown left bundle-branch block. Holter monitoring, electroencephalograms, and head computed tomography scans have been negative. Neurology consult believed that there was not a neurological cause for her loss of consciousness. A thallium stress test was negative for ischemia, and an echocardiogram showed normal ventricular function.

Syncope is a sudden temporary loss of consciousness associated with a loss of postural tone and spontaneous recovery not requiring electrical or chemical cardioversion. Syncope has a large differential diagnosis, is difficult to evaluate, and can be disabling. There are subsets of syncopal patients with a high risk of sudden death. The central issues in the evaluation of syncope are establishing the cause of syncope, deciding whether the patient needs to be admitted, and treating the causes of syncope effectively to reduce recurrences and potentially improve patient outcomes.

Is It Syncope?
The first issue to resolve is whether the patient had syncope. Dizziness, presyncope, drop attacks, and vertigo are easily distinguished from syncope because these symptoms do not lead to loss of consciousness. Seizures, however, are often difficult to distinguish from syncope. Features useful in separating seizure and syncope are precipitants, prodromal symptoms, complaints during the spell, and symptoms after the episode. Loss of consciousness precipitated by pain or occurring after exercise, micturition, defecation, and stressful events is generally due to syncope, whereas aura may precede a seizure. Symptoms such as sweating and nausea during the episode are associated with syncope. A long duration of loss of consciousness (>5 minutes), disorientation after the event, and slowness of return to consciousness suggest a seizure. Syncope can result in seizure-like activity, but when rhythmic movements (such as clonic or myoclonic jerks) are reported, seizure is the likely diagnosis.

How Often Are Causes of Syncope Established?
The Table shows the estimated mean prevalence of the causes of syncope from population-based studies. Although the most common etiologies included vasovagal/situational, cardiac arrhythmias, and orthostatic hypotension, there was a wide range of occurrence. Reasons for variability included aggressiveness of diagnostic testing, diagnostic criteria for causes, patient populations (eg, all patients, emergency room visits, hospitalized patients), and whether patients with a likely seizure disorder were excluded. In approximately 39% of patients, the cause of syncope was not established. It should be noted that these studies were conducted in the 1980s, when tilt-table testing or loop event monitoring was not available. It is likely that the use of tilt testing, event monitoring, and attention to psychiatric illnesses as causes of syncope lead to a higher proportion of patients receiving the correct diagnoses.

Two studies (reported in 2000 and 2001) from Europe employed diagnostic algorithms and prospective evaluation using newer diagnostic modalities. Unexplained syncope was found in 14% to 17.5% of patients. Neurally mediated syncope was the most common cause in both studies and was diagnosed in 35% to 38% of patients; psychiatric illnesses were diagnosed in up to 5.6% of the patients. These studies should be replicated in the US populations.

Prognosis and Risk Stratification
The presence of heart disease in patients with syncope has been identified as the most important factor in prognosis and
risk stratification. Although population-based studies conducted in the 1980s showed that patients with a cardiac cause of syncope had a higher 1-year mortality (18% to 33%) than patients with a noncardiac cause (0% to 12%) or patients with an unknown cause (6%), subsequent studies have shown that the higher mortality is largely due to underlying cardiovascular disease in patients with cardiac syncope. A study comparing patients with and without syncope matched for cardiac disease and other important clinical variables found that cardiac syncope was not a significant predictor of overall or cardiac 1-year survival. Rather, underlying heart disease, especially congestive heart failure, was found to be the significant survival predictor. Similarly, a study of hospitalized syncope patients found that the risk of dying was not associated with cardiac cause but correlated with age and comorbid illnesses, which included cardiovascular diseases. In a study of patients with advanced heart failure, poor left ventricular function was associated with high risk of sudden death regardless of the cause of syncope.

A study of risk stratification used the occurrence of important cardiac arrhythmias or death in the year after presentation with syncope as an outcome. The 4 factors that were predictors are age ≥ 45, a history of heart failure, a history of ventricular arrhythmias, and an abnormal ECG. Patients with none of the predictors had 4% to 7% risk of this outcome as compared with 58% to 80% in patients with 3 or 4 risk factors.

The presence of underlying heart disease in patients with syncope predicts a worse prognosis. Attempts should be made to detect, define, and treat the underlying structural heart disease in syncope patients to reduce the probability of mortality and sudden death.

### Diagnostic Evaluation

Although several guidelines have been published for the diagnostic approach to patients with syncope, none has been validated prospectively and none applies to every clinical situation encountered. Most guidelines do not specify the level of detail needed to create a structural evaluation tool for these patients. Therefore, these guidelines provide only a framework to approach the diagnostic evaluation of this difficult problem. Deviation from guidelines and situational modification of approach are often needed to deal with the heterogeneity of patients presenting with syncope.

The European Society of Cardiology’s Guidelines on Management (Diagnosis and Treatment) of Syncope provides an up-to-date recommendation on the evaluation of syncope. Important features of this guideline include:

1. Initial evaluation (history, physical examination, orthostatic blood pressure, and ECG) helps divide patients into 2 groups, those with a certain or suspected diagnosis and those with unexplained syncope. In patients with a suspected diagnosis, further evaluation is needed to confirm or exclude the causes under consideration.

### Causes of Syncope

<table>
<thead>
<tr>
<th>Type or Cause of Syncope</th>
<th>Mean Prevalence, % (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reflex mediated</td>
<td>14 (8–37)</td>
</tr>
<tr>
<td>Vasovagal</td>
<td>3 (1–8)</td>
</tr>
<tr>
<td>Situational</td>
<td>3 (0–7)</td>
</tr>
<tr>
<td>Cough</td>
<td>1 (0–5)</td>
</tr>
<tr>
<td>Micturation</td>
<td>7 (3–32)</td>
</tr>
<tr>
<td>Defecation</td>
<td></td>
</tr>
<tr>
<td>Swallow</td>
<td></td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>11 (4–13)</td>
</tr>
<tr>
<td>Medications</td>
<td>3 (0–7)</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>1 (0–5)</td>
</tr>
<tr>
<td>Neurological</td>
<td>5 (0–7)</td>
</tr>
<tr>
<td>Migraines</td>
<td></td>
</tr>
<tr>
<td>Transient ischemic attacks</td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td></td>
</tr>
<tr>
<td>Subclavian steal</td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td></td>
</tr>
<tr>
<td>Organic heart disease</td>
<td>3 (1–8)</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>14 (4–26)</td>
</tr>
<tr>
<td>Bradycardiac arrhythmias</td>
<td></td>
</tr>
<tr>
<td>Sinus node disease</td>
<td></td>
</tr>
<tr>
<td>Second- or third-degree heart block</td>
<td></td>
</tr>
<tr>
<td>Pacemaker malfunction</td>
<td></td>
</tr>
<tr>
<td>Drug induced</td>
<td></td>
</tr>
<tr>
<td>Tachycardiac arrhythmias</td>
<td></td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td></td>
</tr>
<tr>
<td>Torsade de pointes</td>
<td></td>
</tr>
<tr>
<td>Supraventricular tachycardia</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5 (0–7)</td>
</tr>
<tr>
<td>Including carotid sinus syncope, hypoglycemia, hyperventilation</td>
<td></td>
</tr>
</tbody>
</table>
confirmed, no further testing is needed, the diagnosis is made, and treatment is initiated. If the diagnosis is not confirmed, these patients are approached as unexplained syncope.

2. In patients with unexplained syncope, structural heart disease or abnormal ECG is used to stratify patients for additional testing. Whether all patients with unexplained syncope should undergo echocardiography or stress testing has not been addressed by available studies. Clinical evaluation alone may suffice in many patients in this group, but further testing should be done if there is any question about possible underlying cardiac disease.

In patients with structural heart disease or abnormal ECG, arrhythmias are the major concern. Holter monitoring, electrophysiological testing, and loop event monitoring are used in the evaluation of these patients. Loop recording devices have made it possible to capture arrhythmias during recurrent symptoms, thus allowing the diagnosis of arrhythmic syncope to be made with greater certainty. Symptom correlation is generally not possible with electrophysiological testing. Loop monitoring is the test of choice when bradyarrhythmia is a consideration. Insertable loop recorders are the diagnostic test of choice to detect bradyarrhythmias in patients with rare recurrent symptoms.18

3. In patients with no structural heart disease and a normal ECG, neurally mediated syndromes are the major consideration. Treatment of neurally mediated syncope is recommended only when syncope is recurrent or severe, and tilt testing should generally be reserved for these patients.19 In patients older than 50 years, carotid massage should be performed because carotid sinus syncope is a disease of the elderly. In young patients with recurrent syncope and multiple other somatic complaints, psychiatric illnesses (somatization disorder, major depression, anxiety, and panic disorders) should be considered, even with a positive tilt test.

Protocols for tilt testing have been studied extensively. Findings show that chemical stimulation with agents such as isoproterenol or nitroglycerine is needed to achieve high rates of positive responses in unexplained syncope (60% to 70%).17 Positive response rates and specificity are similar for protocols that use either agent.20 Sublingual nitroglycerine use with tilt testing seems to be simpler and better tolerated, especially in the elderly and in those with coronary artery disease. The specificity of the protocols using high-dose isoproterenol infusion is poor, and these protocols should be avoided.21,22 There is still a great deal of difficulty in reproducing the results of a positive tilt test on subsequent days, and thus it is difficult to use repeat tilt testing in treatment planning.

4. Patients without heart disease who have a normal ECG and a single or very rare syncopal episodes are likely to have had neurally mediated syncope. Because treatment is not recommended for patients with rare episodes of neurally mediated syncope, tilt testing is not likely to contribute to changes in management. This group of patients is heterogeneous, however, and rare episodes may have other causes such as seizures, supraventricular tachycardias, or bradycardias.23 The diagnosis of these entities generally requires follow-up and reevaluation on recurrence, including discussion with witnesses.

5. Elderly patients with syncope may have multiple possible etiologies because they may have cardiovascular and other comorbid diseases, may be taking multiple medications, and often have chronic orthostatic hypotension.24 Independent, mobile, and cognitively normal elderly patients should be evaluated to arrive at a single diagnosis as the cause of syncope. In frail elderly, however, invasive or extensive testing may not be possible or tolerated. When multiple abnormalities are identified, they should be treated with the presumption that the syncope may be multifactorial.

6. Syncope evaluation integrates clinical assessment with the results of diagnostic testing to arrive at a plausible diagnosis to explain the patient’s symptoms. If the evaluation is negative, it is often useful to review the entire work-up. It may be particularly useful to review the history with the patient and obtain additional information from witnesses. Repeat physical examination findings and follow-up of subtle abnormalities may also prove valuable.

Management

There are no controlled trials studying the comparative advantages and disadvantages of managing patients with syncope on an outpatient basis as compared with an inpatient basis. Patients should be admitted to the hospital if a rapid diagnostic evaluation is deemed necessary because of concerns about serious arrhythmias, sudden death, and newly diagnosed serious cardiac disease (eg, aortic stenosis, myocardial infarction). Patients with gastrointestinal bleeding, severe orthostatic hypotension, and pulmonary embolism may also be admitted for treatment. Most patients without heart disease can be effectively evaluated and managed as outpatient.

Treatment of patients with syncope focuses on the underlying cause of the symptom. For neurally mediated syncope, treatment can include patient education, tilt training (ie, repeated frequent tilting until the patient’s positive response becomes negative), pharmacological agents, and dual chamber pacing. All patients should be instructed on how to prevent episodes by avoiding triggers such as prolonged standing, heat, large meals, fasting, lack of sleep, alcohol, and dehydration. Vasodilators should be discontinued because they may increase susceptibility to vasovagal syncope. Patients should also be instructed about maneuvers that prevent loss of consciousness, to assume a supine position on premonitory symptoms, and to avoid activities that may lead to serious injury.

The effectiveness of drug therapy in preventing recurrent neurally mediated syncope is open to question.17,25 Although volume expansion with increased salt and fluid intake, moderate exercise, and tilt training are relatively safe measures, their effectiveness has not been demonstrated by randomized controlled trials. One short-term randomized trial and a large number of uncontrolled studies of β-blockers claim effectiveness of these drugs, but several controlled trials did not show effectiveness.26–28 The vasoconstrictive agent etilephrine was ineffective in a randomized European trial.29 Milodrine was shown to be beneficial in a small randomized trial when compared with no treatment, but there was no placebo arm to the study.30 A randomized trial of paroxetine showed reduced recurrences at 2 years but needs further confirmation.31

Three randomized trials have assessed permanent pacemakers.32–34 In one, treatment using pacemakers with rate-drop
response algorithm in patients with severe symptoms (6 or more lifetime episodes) and bradycardia on tilt testing showed 85% relative risk reduction for recurrent syncope. Another study showed that 5% of patients in the pacemaker arm experienced recurrence of syncope as compared with 61% in the no-pacemaker arm during a mean follow-up of 3.7 years. A placebo effect of the pacemaker has not been excluded in these studies. A study comparing pacemakers to atenolol showed lower recurrent rates of syncope at 2 years in the pacemaker treated group. Pacemakers may be a treatment option in patients with severe recurrent syncope and with a cardioinhibitory response on tilt testing. Placebo-controlled studies are needed to determine the role of pacemakers in neurally mediated syncope.

Conclusions

Initial clinical evaluation is crucial in the approach to patients with syncope. The presence of structural heart disease or abnormal ECG helps to stratify patients into those with a higher likelihood of cardiac syncope. Cardiac evaluation is recommended in those patients with structural heart disease or an abnormal ECG. In patients without structural heart disease but with a normal ECG, neurally mediated syndromes are the likely causes and can be further evaluated with tilt testing and carotid massage in the appropriate patients.

The case presented earlier had left bundle-branch block on ECG, and thus the main factors in the differential diagnosis were arrhythmias such as complete atrioventricular block or ventricular tachycardia. The patient had an external loop event recorder placed for a month. When the patient returned for a follow-up office visit, she had not had a syncopal episode for 1 month, illustrating a common problem with the use of loop event monitoring. The patient then underwent electrophysiological testing that did not show evidence of a conduction abnormality or inducible ventricular tachycardia. An external loop event recorder was placed again, and several days later the patient had a syncopal episode with concurrent complete atrioventricular block on monitoring. She underwent a permanent pacemaker placement and has not had syncope in follow-up of more than 2 years.

References

Current Evaluation and Management of Syncope
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