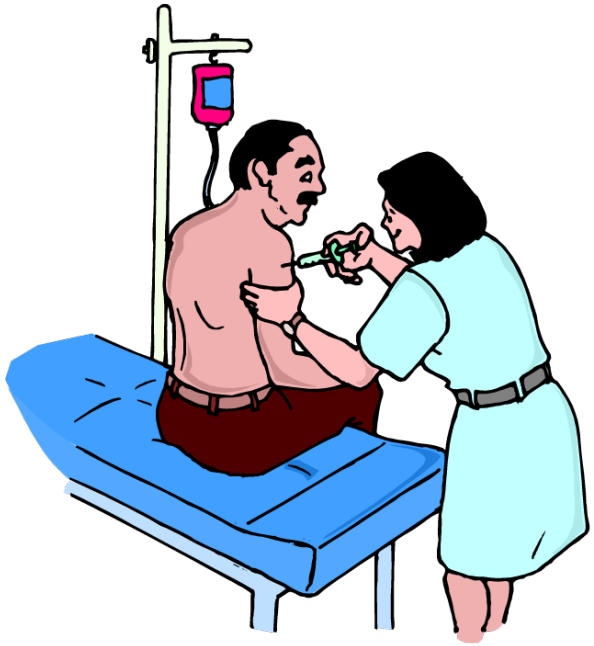

Tajunnanhäiriö-kohtauksen aiheuttaja	Kliininen kuva	Oireen taustalla oleva mekanismi	Huomio
Synkopee	Äkillinen, ohimenevä tajunnanmenetys, joka kestää yleensä sekunneista minuuttiin	Synkopee johtuu aivojen riittämättömästä verenvirtauksesta (ns. globaali hypoperfuusio). Syy voi olla neurologinen (neuraly mediated), sydänperäinen (kardiogeeninen) tai veren tilavuuteen liittyvä (hypovolemia)	Lyhytkestoisia lihasnykäyksiä (myoklonioita) ja äännähtelyä voi esiintyä, potilas kaatuu jos on pystyasennossa
Hermostoperäinen heijaste-synkopee			
Vasovagaalinen synkopee = pyörtyminenb	1. Prekollapsituntemukset: heikotus, kalpeus, kylmänhiki, näön sumeneminen, putkinäkö, huimaus, kuumotus, pahoinvointi, pelko, tarve hengittää raitista ilmaa	Neurovaskulaarinen synkopee - aivorungon välittämä autonomisen hermoston heijaste, joka hidastaa sydämen sykettä ja/tai laajentaa verisuonia ja johtaa pyörtymiseen	Pyörtymiselle altistavia tilanteita ovat mm. verikokeen otto, pitkään seisominen, jännitys
	2. Äkillinen nopeasti ohimenevä tajuttomuuskohtaus, joka yleensä johtaa kaatumiseen (jos potilas seisoo)	Verenpaine ei riitä ylläpitämään aivojen verenvirtausta (aivoperfuusio) pystyasennossa	Tajunnanmenetys pitkittyy jos potilas ei pääse makuuasentoon (pyörtyminen puhelinkopissa) tai alkaa uudelleen jos hänet koitetaan nostaa liian nopeasti pystyyn
Virtsaamis-synkopee	Mikturitiosynkopeessa virtsaaminen johtaa nopeasti ohimenevään pyörtymiseen (tajunnan menetykseen)	Virtsaaminen käynnistää pyörtymiseen johtavan autonomisen hermoston parasympaattisen heijasteen	Mikturiosynkopee on yleisempi miehillä - seisaaltaan virtsaaminen johtaa kaatumiseen
Sinus caroticus synkopee	Karotispoukaman koskettelu tai hieronta aiheuttaa pyörtymisen	Yliherkän karotispoukaman painereseptorien hieronta tai koskettelu käynnistää pyörtymiseen johtavan parasympaattisen hermoston heijasteen	Tiukka kaulus voi johtaa pyörtymiseen tällä mekanismilla
Yskänsynkopee	Yskiminen johtaa nopeasti ohimenevään pyörtymiseen (tajunnan menetykseen)	Yskiminen käynnistää pyörtymiseen johtavan autonomisen hermoston heijasteen, kuten yllä	
Kipusynkopee	Kipu johtaa nopeasti ohimenevään pyörtymiseen (tajunnan menetykseen)	Autonomisen hermoston kipuheijaste johtaa pyörtymiseen	
Autonominen neuropatia	Ylösnousu altistaa tajunnanmenetykselle (ylösnousu makuulta, istuvasta asennosta)	Autonomisen hermostoon normaalit heijasteet eivät toimi - ylösnousun jälkeen verenpaine ei riitä ylläpitämään aivojen verenvirtausta	Ortostatismi voi johtua muustakin syystä kuin autonomisesta neuropatiasta

Tajunnanhäiriö-kohtauksen aiheuttaja	Kliininen kuva	Oireen taustalla oleva mekanismi	Huomio
Hyperventilaatio	Hengityksen kiihtyminen johtaa kollapsiin	Kiihtynyt hengitysfrekvenssi johtaa veren hiilidioksidipitoisuuden laskuun, aivoverisuonet supistuvat, aivoverenkierron vastus lisääntyy ja lopulta verenvirtaus ei enää riitä	Oireistoon kuuluu hapennälkää, pelkoa, sydämen tykytystä, kasvojen ja huulien puutumista
Sydänperäinen synkopee			
Taky- tai bradykardian aiheuttama tajunnanmenetys (kollapsi)	Äkillinen tajunnanmenetys ilman ennakko-oireita, fyysisessä rasituksessa tai makuuasennossa	Rytmihäiriö johtaa riittämättömään aivoperfuusion	Voi alkaa sekä fyysisessä rasituksessa tai levossa
Pitkän QT-oireyhtymän aiheuttama tajunnanmenetys	Äkillinen tajunnanmenetys ilman ennakko-oireita, voi ilmaantua myös makuuasennossa	Pitkä QT-oireyhtymä aiheuttaa rytmihäiriön, joka johtaa riittämättömään aivojen verenvirtaukseen	Voi alkaa sekä fyysisessä rasituksessa tai levossa
Rakenteellisen sydänvian aiheuttama tajunnanmenetys	Äkillinen tajunnanmenetys ilman ennakko-oireita, usein fyysisessä rasituksessa, mahdollinen myös makuuasennossa	Rakenteellinen sydänvika johtaa relatiiviseen virtausesteeseen ja riittämättömään aivojen verenvirtaukseen	Sydänstatuksessa ja EKG:ssa usein poikkeavuuksia
Aorttastenoosin aiheuttama tajunnanmenetys	Äkillinen tajunnanmenetys ilman ennakko-oireita, usein fyysisessä rasituksessa, sydämestä kuluu stenoosin systolinen sivuääni	Aorttaläpän ahtauma johtaa relatiiviseen virtausesteeseen ja riittämättömään aivojen verenvirtaukseen	Sydänstatuksessa ja EKG:ssa usein poikkeavuuksia
Kardiomyopatian aiheuttama tajunnanmenetys	Äkillinen tajunnanmenetys ilman ennakko-oireita, usein fyysisessä rasituksessa, mahdollisesti myös makuuasennossa	Sydämen pumppuvaje johtaa riittämättömään aivojen verenvirtaukseen	Sydänstatuksessa ja EKG:ssa usein poikkeavuuksia
Valtimolaskimo-oikovirtauksen aiheuttama tajunnanmenetys	Rintakipu, rytmihäiriöt, sydämen vajaatoiminta, syädänperäinen kollapsi	Oikovirtaus sydämessä johtaa sydänlihasiskemiaan, riittämättömään pumppausvoimaan ja aivojen verenvirtausvajeeseen	
Muu syy			

Tajunnanhäiriö-kohtauksen aiheuttaja	Kliininen kuva	Oireen taustalla oleva mekanismi	Huomio
Vähentynyt kiertävää veritilavuus (hypovolemia)	Ylösnousu altistaa tajunnanmenetykselle (kollapsille)	Ylösnousun käynnistämät autonomisen hermoston heijasteet eivät riitä kompensoimaan vähentynyttä kiertävää veritilavuutta	Esim. verenvuoto, elimistön kuivuminen
Hypoglykemia	Kollapsi, päänsärky, heikotus, sekavuus, kouristelu, muut hypoglykemian oireet		Potilaalla on yleensä perussairautena diabetes
	Huimaus, pyörrytys, näön hämärtyminen, keskittymisvaikeus, ajatus ei kulje, epätavallinen tai riitaisa käytös, päänsärky, kahtena näkeminen, väsymys, uupumus, uneliaisuus, vaikeissa tapauksissa kouristelu ja tajuttomuus	Hypoglykemian aiheuttamat hermosto-oireet (neuroglukopeeniset oireet), matalan verensokerin aiheuttama keskushermoston toimintahäiriö	Hypoglykemia aiheuttaa myös ns. insuliinituntemuksia (adrenergiset oireet): vapina, käsien tärinä, hermostuneisuus, sydämentykytys (tiheä pulssi), hikoilu, nälän tunne, heikotus

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Syncope

William P. Cheshire Jr, MD, FAAN

ABSTRACT

Purpose of Review: Syncope is a prevalent syndrome with diverse causes, which have in common a sudden transient failure of the autonomic nervous system to maintain blood pressure against the force of gravity at a level sufficient for cerebral perfusion. Neurally mediated syncope is an episodic phenomenon in which autonomic nervous system function is normal the rest of the time. Although relatively benign, syncope increases the risk for injury from falling and can substantially impair patients' quality of life. Recognition of its various clinical presentations and knowledge of the underlying pathophysiology are essential for accurate diagnosis and successful management.

Recent Findings: The most effective forms of treatment remain education of patients, avoidance of triggers, physical counterpressure maneuvers, and hydration or intravascular volume expansion. Pharmacologic interventions may be appropriate for some patients but, in general, have limited evidence of efficacy in preventing syncope. Based on the findings of a recent study, the possibility of pulmonary embolism should be considered in patients hospitalized for syncope, whether or not an alternative etiology for syncope is identified.

Summary: This article focuses on the neurologic diagnosis, differential diagnosis, physiology, and management strategies for syncope, with an emphasis on neurally mediated syncope.

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Unlabeled Use of Products/Investigational Use Disclosure: Dr Cheshire discusses the unlabeled/investigational use of beta-blockers, fludrocortisone, and midodrine for the treatment of syncope.

INTRODUCTION

Syncope, which derives from the Greek word meaning *cessation*, refers to the common clinical syndrome of sudden transient total loss of consciousness and postural tone resulting from global cerebral hypoperfusion with spontaneous and complete recovery and no neurologic sequelae.[1] Commonly called fainting, syncope can be thought of as a brain-heart event. Syncope is not a disease, but a syndrome. Whereas syncope can happen to anyone under sufficiently stressful provocative conditions, some people have an innate or acquired predisposition that renders them more susceptible. Presyncope or near syncope refers to a feeling that syncope may be imminent, but loss of consciousness does not occur or is prevented by muscle tensing or by sitting or lying down.

The most common type of syncope is neurally mediated syncope, which involves reflex dysfunction at the interface of the central nervous and cardiovascular systems, leading to hypotension and cerebral hypoperfusion. Neurally mediated syncope encompasses neurocardiogenic syncope, vasovagal syncope, and vasodepressor syncope, with the wording choice depending on which aspect of the physiology is emphasized or is clinically apparent. An international multidisciplinary consensus committee recommends use of the terminology neurally mediated syncope, as the origin of the phenomenon is in the nervous system.[2]

Syncope is typically evaluated and treated by a cardiologist (because of the diagnostic challenge of ruling out potentially life-threatening cardiac arrhythmias or structural heart disease,

KEY POINTS

- Neurally mediated syncope encompasses neurocardiogenic, vasovagal, and vasodepressor syncope. Differing terminologies have evolved because the mechanisms are complex. Currently, neurally mediated syncope is preferred as it acknowledges that the phenomenon originates in the nervous system.
- Syncope is usually evaluated by a cardiologist because of the diagnostic challenge of ruling out potentially life-threatening cardiac arrhythmias or structural heart disease.
- Neurologic expertise is needed to discriminate neurally mediated syncope from seizures, transient ischemic attacks, orthostatic hypotension, psychogenic episodes, and other causes of transient loss of consciousness.
- About 30% to 40% of people will experience syncope during a lifetime. Neurally mediated syncope is the most common cause of transient loss of consciousness among all age groups. Recurrent syncope occurs in about 1 in 6000 people.

among other reasons), but the diagnosis initially may be unclear, for which reason the neurologist may be consulted to help disambiguate syncope from other disorders that it can mimic, such as epileptic seizures or transient ischemic attacks. All neurologists, therefore, ought to be thoroughly familiar with the clinical presentation of syncope. Accurate diagnosis is necessary so that correct treatment strategies may be chosen and so that inappropriate interventions can be avoided.

EPIDEMIOLOGY

The true incidence of syncope in the general population is difficult to estimate because of incomplete reporting and variations in terminology. More than one-half of instances of syncope do not come to medical attention and years later may not be remembered.[3] Even at the time of syncope, amnesia for loss of consciousness is common.[4] In the elderly, the history on which the diagnosis is based may be less reliable, particularly in patients who are cognitively impaired or for unwitnessed events.[5]

Furthermore, some studies do not distinguish between neurally mediated syncope and transient loss of consciousness due to many other causes. The Framingham Heart Study, for example, included in its definition of syncope transient loss of consciousness caused by vasovagal phenomena, cardiac arrhythmias, coronary ischemia, seizures, transient ischemic attacks, orthostatic hypotension, and medications.[6] In a population of 7814 participants, this study found an incidence of 6.2 per 1000 person-years. The most common identifiable cause was vasovagal syncope in 21.2%, followed by cardiac syncope in 9.5%, orthostatic hypotension in 9.4%, medication effects in 6.8%, seizure in 4.9%, and stroke in 4.1% of participants. Following evaluation, the cause of syncope remained unknown in 36.6% of participants.[6]

The lifetime prevalence of syncope in the general population is from 20% to 40% for people up to 60 years of age.[3,7,8] Syncope can occur at any age.[5] For example, a survey of medical students found that approximately one-third recalled a personal history of syncope.[9] A Dutch population-based study found the lifetime cumulative incidence of syncope to be approximately 35%.[3] Almost all patients had experienced their first episode as a teenager or young adult, and the median age of the first episode was 18.[3] Incidence in women is 1.5 times as frequent as in men.[3,8]

The age distribution is bimodal, occurring more frequently in younger and elderly individuals. The younger peak of incidence is represented mostly by females near the age of 15 to 20 years, and the older peak of incidence is represented by both sexes near age 80 years.[3,7] Neurally mediated syncope is the most frequent cause of transient loss of consciousness in the young, who typically experience a benign course, whereas cardiac causes, orthostatic and postprandial hypotension, and medication effects are common in the elderly.[10,11] The increased susceptibility to syncope with advancing years has been associated with age-related physiologic impairment in baroreflex function and cerebral autoregulation combined with medical comorbidities and polypharmacy.[12]

Syncope tends also to cluster in families. A heritable component to syncope has been estimated in at least 20% of cases.[13] Approximately one-third of children with syncope have a family history of syncope, whereas most patients with adult-onset syncope do not.[14] The few reported pedigrees of familial syncope suggest a genetic influence in what is likely a multifactorial phenomenon

with psychological and environmental factors.[9,15]

An estimated 1 in 6000 of the general population experiences recurrent syncopal events.[12] In the Dutch study, the probability of experiencing a second episode was 62%, and the probability of experiencing a third episode after a second episode was 77%.[3] The most reliable predictor of syncope recurrence is the number of syncopal events during the preceding year.[16] Among patients with syncope who have a positive tilt test and three or more lifetime syncopal spells, the probability of recurrence during the succeeding year for those with no history during the preceding year was 7%, for those with fewer than two spells this probability was 22%, and for those with more than six spells this probability was 69%.[17]

Syncope accounts for 1% to 3% of emergency department visits and hospital admissions.[18] Approximately 10% of syncope cases are referred to a specialist.[13] Syncope represents 4% of referrals to neurology outpatient clinics.[19]

PATHOPHYSIOLOGY

Human consciousness requires ongoing cerebral perfusion to sustain neuronal functioning. Sustaining blood pressure at levels sufficient for cerebral perfusion from moment to moment against the force of gravity and in response to dynamic changes in the distribution of blood flow throughout the body requires the proper functioning of a set of coordinated physiologic mechanisms.[20] These include stretch-activated baroreceptors located in the carotid sinus and aortic arch that transmit afferent signals by way of the glossopharyngeal and vagus nerves, respectively, to the nucleus tractus solitarius in the brainstem. This baroreflex center phasically inhibits efferent sympathetic outflow, which can be detected in recordings from muscle sympathetic nerves, while phasically augmenting parasympathetic outflow, which can be detected in recordings of heart rate variability. Cardiopulmonary baroreceptors located in the cardiac ventricular walls and intrathoracic vessels also influence sympathetic outflow. Increased cardiac filling pressures activate the cardiac baroreceptors, resulting in inhibition of sympathetic outflow, whereas decreased cardiac filling pressures result in activation of sympathetic outflow. This sympathetic efferent activity to the peripheral vasculature is essential to maintaining arterial pressure, particularly under conditions of decreased intravascular volume or orthostatic stress.

Autonomic cardiovascular reflexes come into play during the normal physiologic response to assuming the upright posture. The simple act of standing causes a gravitational fluid shift of 300 mL to 700 mL of blood into vascular capacitance beds in the abdomen and lower extremities. Excessive pooling of blood is prevented by adrenergic neurovascular responses that increase peripheral vasoconstriction, neurohumoral responses including release of vasopressin, and the mechanical effect of the muscle pump as lower extremity skeletal muscles, particularly in the thighs, compress capacitance veins. If not for these responses, venous return to the heart would drop, cardiac output would fall, and cerebral perfusion to the reticular activating system would be inadequate to maintain consciousness. Prodromal symptoms occur once mean blood pressure falls below approximately 60 mm Hg.[21] The threshold for unconsciousness is a mean blood pressure below about 50 mm Hg at heart level, which corresponds to 30 mm Hg of cerebral arterial pressure.[21] Below that pressure, unconsciousness occurs usually within 7 seconds.[21]

The pathophysiology of neurally mediated syncope is incompletely

KEY POINTS

- Syncope from all causes accounts for 1% to 3% of emergency department visits and hospital admissions and, depending on the practice setting, about 4% of referrals to neurologists.
- Prodromal symptoms occur once mean blood pressure falls below 60 mm Hg. Interruption of cerebral perfusion for more than 7 seconds causes unconsciousness.

KEY POINTS

- Syncope begins with a chain of events: venous pooling reduces cardiac filling, and the left ventricle becomes hypercontractile, activating ventricular mechanoreceptors that, along with limbic structures, project to the brainstem. The result is sudden withdrawal of sympathetic vascular tone, peripheral vasodilatation, hypotension, and decreased cerebral perfusion.
- Patients with neurally mediated syncope may also have orthostatic intolerance, orthostatic tachycardia, or enhanced cerebrovascular and peripheral vascular responses to hypocapnia when overbreathing.

understood. The neurologic factors that initiate the sequence of autonomic phenomena leading to transient loss of consciousness remain to be fully elucidated and appear to be multifarious.

The traditional model of neurally mediated syncope involves the Bezold-Jarisch reflex, which is a paradoxical aberration of the normal response to orthostasis. The Bezold-Jarisch reflex begins when excessive venous pooling results in decreased preload, leading to decreased ventricular filling. This causes a hypercontractile state with increased ventricular contraction to maintain cardiac output.[22] The hypercontractile left ventricle activates stretch-sensitive mechanoreceptors that respond to wall tension and are located in the inferoposterior aspect of the left ventricle. These receptors supply vagal afferents that project to the nucleus tractus solitarius and, when activated, mediate a sympathetic vasodepressor response with marked peripheral vasodilatation as well as a parasympathetic cardioinhibitory response, resulting in hypotension and bradycardia.

Withdrawal of sympathetic vasopressor tone has long been understood to be the final common pathway leading to transient loss of consciousness.[23] Evidence of persistent muscle sympathetic nerve activity during syncope, however, has challenged this theory and suggests that full withdrawal of muscle sympathetic nerve activity is not an obligatory prerequisite for syncope.[24,25]

Furthermore, sympathetic withdrawal may be preceded by a period of sympathetic excitation reflected in increased serum catecholamine levels, heart rate, and muscle sympathetic nerve activity as well as by decreased sympathetic baroreflex gain.[21,26] Evidence has accumulated for both passive and active mechanisms of the vasodilatory response that precedes loss of consciousness.[27,28] Additional triggering mechanisms may also play a role, depending on the patient and the clinical circumstances. Considered together, it is likely that patients with neurally mediated syncope comprise multiple phenotypes that differ in their autonomic responses to emotional states, norepinephrine availability, baroreflex physiology, and tolerance for sustained orthostatic stress.[1]

Individual susceptibility to neurally mediated syncope may depend not only on differences in orthostatic tolerance but also on enhanced cerebrovascular and peripheral vascular responses to hypocapnia. Patients with a history of neurally mediated syncope were found to have a greater reduction in cerebral blood flow and a greater dilatation of forearm vasculature in response to hypocapnia as compared to healthy individuals.[29] Moreover, investigations combining spirometry with transcranial Doppler have found that patients with neurally mediated syncope demonstrated increased respiratory tidal volumes, decreased end tidal PCO_2, decreased cerebral blood flow velocity, and increased cerebrovascular resistance occurring between 120 and 200 seconds before syncope and preceding the drop in blood pressure.[30] The additive effect of a decrease in cerebral blood flow when arterial pressure has fallen could further accentuate cerebral hypoperfusion.

Recent investigations using voxel-based morphometry have shown decreased volume in the right insular cortex in patients with a history of syncope who had abnormal tilt tests.[31] As the insular cortex plays an important role in interoceptive awareness, visceral states associated with emotional experience, and autonomic control, this finding may be an important clue toward identifying triggering mechanisms at the level of the cerebral cortex.

Furthermore, as hyperventilation is part of the physiologic response to fear and anxiety, hyperventilation-induced hypocapnia may be one of the links between limbic structures and the rapid drop in cerebral blood flow that occurs in neurally mediated syncope.[29]

CLINICAL PRESENTATION

The importance of taking a careful history cannot be overstated, as particular details—even those that the patient might not consider relevant—can be of enormous diagnostic value. The circumstances leading up to loss of consciousness, the patient's subjective symptoms, and physical signs observed by witnesses often provide essential diagnostic clues.

Case 1-1 is a typical instance of neurally mediated syncope, which is the most common form of transient loss of consciousness in healthy adults. Neurally mediated syncope in susceptible individuals is often provoked by factors such as prolonged standing, a warm environment, fear, emotional distress, pain, the sight of blood, venipuncture, or other medical instrumentation.[3,22] Neurally mediated syncope typically, but not invariably, occurs in the upright posture, which allows for venous pooling.

Prodrome

Equally important is soliciting a history of prodromal symptoms and signs, which are often called presyncope. These signs and symptoms may be produced by cerebral hypoperfusion, autonomic activation, or a combination thereof, as outlined in **Table 1-1**. A frequent initial sign of neurally mediated syncope is facial pallor, which is caused by decreased cutaneous blood flow resulting from sympathetically and vasopressin-induced vasoconstriction and systemic hypotension.[32] The patient may report nausea, dizziness, a feeling of warmth or coldness, clammy skin, visual blurring or dimming, difficulty concentrating, weakness, muffled hearing, ears ringing, restlessness, neck ache, or fecal urgency. Further signs of impending syncope may include yawning, sighing, tachypnea, tachycardia, sweating, salivation, pupillary dilatation, and increased sounds of peristalsis.[21,22,27] These symptoms and signs occur gradually from 30 seconds to several minutes prior to syncope.[21,22] As blood pressure continues to fall, symptoms of retinal ischemia may occur, including graying or dimming of the peripheral visual fields and loss of color vision. Once perfusion of the reticular activating formation is no longer adequate, loss of consciousness occurs.[21]

One-third of patients with neurally mediated syncope, especially if older, may not recognize or later recall a prodrome.[22] Whereas the young patient typically presents with prodromal symptoms such as pallor, nausea, warmth, sweating, or lightheadedness, the older patient often presents with unexplained falls.[33] Syncope that occurs abruptly and without a prodrome should arouse suspicion for the possibility of ventricular arrhythmia.[34] Ventricular arrhythmias account for approximately one-fifth of cases of otherwise unexplained syncope and can be associated with structural heart disease.[34]

Unresponsiveness

The loss of consciousness in neurally mediated syncope is typically brief. Syncope induced in healthy volunteers through a sequence of hyperventilation, orthostasis, and Valsalva maneuver resulted in a mean duration of loss of consciousness of 12 seconds.[35] Prolonged unresponsiveness should prompt consideration of an alternative diagnosis, such as vertebrobasilar stenosis or occlusion, epilepsy, subarachnoid hemorrhage, traumatic brain

KEY POINT

- Neurally mediated syncope is frequently preceded by a characteristic prodrome in which the patient may recall symptoms such as nausea, dizziness, feelings of warmth or coldness, visual dimming or blurring, clammy skin, facial pallor, general weakness, decreased hearing, or fecal urgency. Learning to recognize and respond to these symptoms can prevent loss of consciousness.

Case 1-1

A 30-year-old woman presented with a 2-year history of episodes of transient loss of consciousness recurring at a frequency of every 1 to 2 months. All of the episodes had occurred while standing still, often in hot weather, and once while taking a shower. Her initial symptoms consisted of a warm rush, abdominal queasiness, and lightheadedness, progressing to muffled hearing, clammy skin, and dimming of peripheral vision. Family members reported that she then appeared as pale as a sheet of white paper. She found that if she shifted her weight from leg to leg, she felt better, but once symptoms developed, she would lose consciousness if she did not sit down. On one occasion, she fell to the ground and startled onlookers with jerking movements of her arms and legs lasting several seconds. She always regained consciousness within 30 seconds, at which point she was fully oriented. Her muscles did not ache afterward. She had not bitten her tongue, although urinary incontinence occurred during one of the spells. In retrospect, as a child she had fainted once at the sight of blood on the school playground, and as a teenager she had fainted twice following phlebotomy. The neurologic referral letter that the patient brought with her from her primary care physician noted a concern for seizures and included a question as to whether she should be started on antiepileptic medication.

Neurologic examination, including measurement of blood pressure supine and standing, was normal. ECG was normal. Her tilt test (**Figure 1-1**) showed a typical vasodepressor response in which blood pressure and pulse pressure precipitously declined over about 1 minute and dropped below the threshold where cerebral blood flow could be sustained in the upright posture.

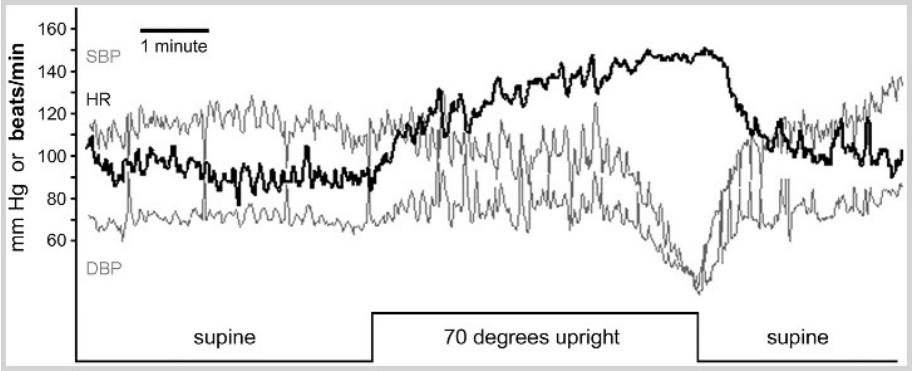

FIGURE 1-1 Blood pressure profile during tilt testing in syncope. Beat-to-beat systolic blood pressure (SBP, *upper gray line*) and diastolic blood pressure (DBP, *lower gray line*) and heart rate (HR, *black line*) acquired by photoplethysmography at baseline and during 70 degrees of head-upright positioning for 5 minutes on a tilt table. The tracing is from a patient similar to the patient in **Case 1-1** with neurally mediated syncope and shows a gradual increase in heart rate preceding a vasodepressor response with a simultaneous drop in SBP and DBP.

Comment. This case exemplifies a typical history of a patient with neurally mediated syncope and illustrates the importance of making the correct diagnosis and distinguishing the benign myoclonus of convulsive syncope from the tonic-clonic movements of epilepsy.

injury, intoxication, hypoglycemia, or, if medical causes are excluded, psychogenic pseudosyncope.

An important exception to this rule is the patient who loses consciousness and is prevented from reaching a recumbent posture to restore circulation to the brain. For example, the patient who faints while strapped to a wheelchair or who slides off a toilet and is wedged upright between the plumbing fixture and the wall may continue

TABLE 1-1 Prodromal Symptoms and Signs of Syncope[a]

▶ **Autonomic Instability**
Lightheadedness
Nausea
Warm feeling
Chill
Facial pallor
Clammy skin
Yawning or sighing
Tachypnea
Mydriasis
Tinnitus
Increased peristalsis
Salivation
Restlessness
Fecal urgency
▶ **Cerebral Hypoperfusion**
Lightheadedness
Inability to focus mentally
General weakness
Muffled hearing
Color vision desaturation
Dimming of vision
Tunnel vision
Swaying posture

[a] Data from Wieling W, et al, Brain.[21] *brain.oxfordjournals.org/content/132/10/2630.long*.

to be deprived of adequate cerebral perfusion and may sustain a longer duration of unconsciousness or, in some cases, watershed cerebral infarction. Falling as the result of syncope is a risk factor for hip fractures in elderly patients. As many as 10% of syncopal episodes lead to injury.[8]

Ictal-Appearing Phenomena

Distinguishing the ictal-appearing phenomena of neurally mediated syncope from those of an epileptic seizure is one of the history-taking skills that a neurologist must master. Myoclonic jerks have been reported in between 12% and 90% of syncopal events and consist of multifocal arrhythmic jerks involving proximal and distal muscles.[16,35] Unlike the myoclonus in an epileptic seizure, which is cortical in origin, this *convulsive syncope* is believed to result from inadequate brainstem perfusion.[36] Opisthotonus, or head turning, is occasionally seen.[21,35] These movements, which are common in syncope, are sometimes mistaken by witnesses for epileptic seizures. A key distinguishing feature is that, whereas the onset of tonic or clonic behavior of a seizure precedes falling, the myoclonus of syncope begins after the patient has fallen. These episodes are also more brief than seizures, lasting about 1 to 15 seconds.[21] Distinguishing features of convulsive syncope and epilepsy are listed in **Table 1-2**. A number of educational videos are available at *syncopedia.org* that show the ictal-appearing aspects of syncope.

The eyes usually remain open during syncope and may initially deviate upward.[21,35] Downbeat nystagmus has also been described. The mechanism is thought to be vestibular disinhibition as a consequence of cerebellar hypoperfusion.[37] Breathing usually continues during unconsciousness and may appear shallow, slow, or deep. Rare cases of apnea have been described in patients who were asystolic for more than 30 seconds.[21] The pulse pressure diminishes, which may render peripheral pulses briefly undetectable.

Transient focal neurologic deficits have been observed in as many as 5% of patients with syncope, particularly in those with frequent syncope, a history

KEY POINTS

- The acute response to someone with syncope should never be to support the person in an upright posture, as this prolongs cerebral hypoperfusion. The person should be gently placed in a recumbent posture with the legs elevated to restore circulation to the brain.
- Brief, multifocal, arrhythmic, myoclonic jerks are observed in up to 90% of patients at the time of syncope. These are caused by brainstem hypoperfusion and may be mistaken for epilepsy.

TABLE 1-2 Distinguishing Convulsive Syncope From Epilepsy

Characteristic	Convulsive Syncope	Epileptic Seizure
Onset of myoclonus	Follows loss of consciousness	Immediate
Eye deviation	Upward	Lateral
Myoclonus rhythm	Arrhythmic jerks	Rhythmic jerks
Myoclonus pattern	Multifocal jerks briefly involving bilateral proximal and distal muscles	Unilateral or asymmetric jerks may exhibit neuroanatomic evolution or generalized tonic-clonic behavior
Myoclonus duration	1–15 seconds	30 seconds to 2 minutes
Urinary incontinence	May occur	May occur
Postictal presentation	Postictal fatigue but no confusion	Postictal confusion

KEY POINT

- Recognizable forms of situational syncope are variations of neurally mediated syncope and include syncope associated with fear or anxiety, Valsalva maneuvers, medical instrumentation, micturition, defecation, coughing, swallowing, laughing, glossopharyngeal neuralgia, and carotid sinus stimulation.

of childhood syncope, delayed diastolic recovery during active standing, or concomitant carotid or vertebrobasilar artery stenosis.[38] Urinary incontinence occurs in approximately 10% to 25% of cases, whereas fecal incontinence is rare.[21] Headache often immediately follows neurally mediated syncope and may result from postsyncopal cerebral reperfusion or hyperperfusion.[39]

SITUATIONAL SYNCOPE

A number of situational or reflex forms of syncope are recognized. In these variations of neurally mediated syncope, specific triggering factors provoke or contribute to a vasodepressor or vasovagal response.[5] Neurally mediated syncope is commonly triggered by, for example, medical instrumentation procedures including IV catheter insertion, blood donation, or phlebotomy.[27] Presyncopal symptoms occur after blood donation in 2% to 5% of donors and in 5% to 10% of those younger than 19 years of age. Syncope occurs in four out of 1000 blood donors.[40] Apprehension, anxiety, fear, and young age are the strongest predictors of neurally mediated syncope and presyncope in voluntary blood donors.[41]

Postexertional Syncope

Postexertional syncope occasionally occurs in the young athlete shortly after cessation of exercise.[42] The athlete typically has been exercising vigorously in a hot environment and through sweating has depleted intravascular fluid volume. Neurally mediated syncope heralded by nausea, dizziness, and weakness occurs when the patient is standing upright, while muscular and cutaneous vascular beds are still open but skeletal muscles are no longer contracting and compressing lower extremity veins.

Micturition Syncope

Micturition syncope is a common form of situational syncope in middle-aged men. Syncope occurs most frequently during the evening hours, is typically without recalled premonitory symptoms, and occurs especially in men taking vasodilators or after drinking alcohol.[43,44] The mechanism is multifactorial and includes orthostasis, vasodilatation, activation of mechanoreceptors in the bladder wall, and increased intrathoracic pressure.[44]

A second type of excretory syncope is defecation syncope, which is more

common in elderly women and is often associated with premonitory symptoms of abdominal cramping, nausea, and a strong urge to defecate.[43,44]

Tussive or Cough Syncope

Tussive or cough syncope consists of loss of consciousness following a vigorous cough or episode of repeated coughing. Patients susceptible to cough syncope include middle-aged men with obstructive airway disease, children with asthma, or patients with a Chiari malformation or intracerebral mass lesion, where the generation of very high intrathoracic and intracerebral pressures causes cerebral hypoperfusion.[45] The increased intrathoracic pressure in cough syncope has a staccato pattern in contrast to the sustained pressure that occurs in forced micturition or when straining at stool.

Laughter (Gelastic) Syncope

Laughter (gelastic) syncope is a rare phenomenon in which a subjective humorous stimulus triggers transient loss of consciousness. Proposed mechanisms include increased intrathoracic pressure from sustained or hearty laughter, vasodepressor or vasovagal reflexes, and possible neuroendocrine effects triggered by limbic circuits.[46]

Swallow (Deglutition) Syncope

Also rare is swallow (deglutition) syncope, in which stimulation of stretch-sensitive mechanoreceptors in the esophagus causes a vagal reflex that inhibits the cardiac conduction system.[47] Facial flushing and palpitations may precede loss of consciousness.[48] Whether the vagal reflex results from overly sensitive afferent or excessive efferent vagal activity is uncertain. Many of these patients will have an underlying condition such as esophageal spasm, esophageal stricture, or achalasia.[47]

Glossopharyngeal Neuralgia

Patients with glossopharyngeal neuralgia may experience not only paroxysmal stabbing oropharyngeal or tympanic pain, but also syncope triggered by swallowing. A proposed mechanism is abnormal connections between brainstem pathways involved in glossopharyngeal and vagal nerve function.[49]

Carotid Sinus Syncope

Carotid sinus syncope, another subtype of neurally mediated syncope in the older patient, occurs in response to mechanical compression or stretching of the carotid sinus as the result of direct pressure, massage, or turning of the head. Premonitory symptoms may be absent.[5,11,50]

COMORBIDITIES

Neurally mediated syncope often coexists with other forms of orthostatic intolerance. Approximately one-third of patients with postural tachycardia syndrome (POTS) also have a history of neurally mediated syncope.[51] In a large series of patients with POTS demonstrated by a 30 beats/min rise in heart rate without hypotension on tilt testing, tachycardia was followed by a symptomatic vasodepressor or vasovagal response in 6% of patients.[52]

Migraine is also a frequent comorbidity in one-third to one-half of patients with neurally mediated syncope.[53] Evidence of endothelial dysfunction in both disorders suggests that arterial hypersensitivity to nitric oxide may be a common feature.[54]

DIFFERENTIAL DIAGNOSIS

The clinical approach to detecting the cause of syncope proceeds through a methodical consideration of how well the patient's presentation accords with or diverges from potential alternative diagnoses.

KEY POINTS

- Potentially serious cardiac causes of syncope include ventricular tachycardia, aortic stenosis, hypertrophic obstructive cardiomyopathy, atrioventricular block, subclavian steal syndrome, Brugada syndrome, and inherited and acquired QT interval abnormalities.
- Laceration of the lateral aspect of the tongue, but not the tip, from biting during an episode of loss of consciousness should prompt suspicion for a generalized tonic-clonic epileptic seizure.
- Ictal bradycardia and ictal asystole are rare phenomena in which a temporal, insular, or frontal cortex seizure focus activates central autonomic pathways to cause an episode of neurally mediated syncope.

Cardiac Arrhythmia

In the evaluation of syncope, care must be taken not to miss a potentially life-threatening alternative diagnosis. Of particular concern is the possibility of cardiac syncope. In the Framingham Heart Study, cardiac syncope was associated with a high risk of subsequent cardiac morbidity and mortality, whereas neurally mediated syncope was not associated with an increased risk of death.[6] Syncope that occurs during exertion (ie, exercise-induced syncope) should arouse suspicion for ventricular arrhythmia, hypertrophic obstructive cardiomyopathy, atrioventricular block, aortic stenosis, or subclavian steal syndrome.[55] Abrupt loss of consciousness occurring at rest and without a prodrome may signal sudden arrhythmic death syndrome. Many such cases are caused by inherited cardiac ion channel abnormalities that predispose the patient to potentially fatal arrhythmias. Specific types include Brugada syndrome (a genetic defect in the sodium ion channel that predisposes to ventricular arrhythmia and sudden cardiac death), inherited or acquired long QT syndrome, short QT syndrome, and catecholaminergic polymorphic ventricular tachycardia. History gathering should include inquiring whether a family history of sudden cardiac death exists.

Pulmonary Embolism

Neurologists need to also be aware of the possibility of pulmonary embolism as a potential life-threatening cardiopulmonary cause of syncope in elderly patients, whether or not an alternative explanation for syncope is identified. In a 2016 study assessing for the presence of pulmonary emboli in 560 patients admitted for syncope (mean age 76 years), Prandoni and colleagues[56] identified pulmonary embolism in 12.7% of patients who had an alternative explanation of syncope and in 25.4% of patients who did not have an alternative explanation.

Epilepsy

Differentiating between seizure and syncope is sometimes difficult, particularly if the patient's memory of the event is incomplete and no witnesses are available. Oral automatisms, jacksonian march, amnesia, and postictal confusion are among the key clinical features that can point to a diagnosis of epilepsy. Biting with laceration of the lateral aspect of the tongue, rather than the tip, is highly specific for a generalized seizure.[57] The presence or absence of urinary incontinence has no diagnostic value.[58] In uncertain cases, additional testing such as EEG, brain imaging, tilt testing, or video-EEG monitoring may be needed to reach a diagnosis.[59]

Sometimes the diagnosis is not seizure or syncope, but both. Epileptic discharges of temporal or frontal lobe origin or those that involve deeper structures such as the insula may influence the central autonomic network.[60] Ictal tachycardia is quite common, occurring in approximately 80% to 90% of seizures, whereas ictal bradycardia and asystole are rare.[60,61] Ictal asystole secondary to a nongeneralized epileptic seizure is a rare cause of syncope and has been seen in 0.3% to 0.5% of patients with refractory epilepsy who underwent video-EEG monitoring.[61,62] In some cases, ictal syncope may be the first manifestation of epilepsy.[63–65] Loss of consciousness typically occurs when the duration of asystole exceeds 6 seconds.[62,66] The clinical spectrum of ictal bradyarrhythmias includes ictal and postictal asystole, ictal bradycardia, ictal and postictal atrioventricular conduction block, ictal and postictal atrial flutter or fibrillation, and postictal ventricular fibrillation.[62]

Seizure onset in these cases is most frequently temporal. Postictal cardiac arrhythmias have potential relevance for sudden unexpected death in epilepsy (SUDEP).[67] Seizure localization studies in patients with ictal arrhythmias have implicated the temporal, insular, and frontal cortices. Some studies have reported left-sided predominance,[68] whereas others have found no consistent laterality.[69]

Cerebrovascular Disease

Loss of consciousness may occur during transient ischemic attacks caused by basilar artery stenosis or occlusion. Unlike neurally mediated syncope, these patients typically manifest focal neurologic signs, such as dysarthria, pupillary abnormalities, vertigo, or other cranial nerve deficits. Loss or decreased level of consciousness correlates strongly with poor outcome.[70,71]

Autonomic Failure

Neurally mediated syncope is distinct from the orthostatic syncope of autonomic failure, which is exemplified in **Case 1-2**. Neurally mediated syncope typically occurs in patients who otherwise have a normally functioning autonomic nervous system and typically develops gradually under conditions of prolonged orthostatic stress. Orthostatic syncope, on the other hand, occurs in patients with adrenergic failure who have severe orthostatic hypotension that results in transient loss of consciousness within moments of standing up.[2] The majority of patients with orthostatic hypotension, however, do not present with loss of consciousness.

An important exception is the syndrome of initial orthostatic hypotension, which is an exaggerated transient fall in blood pressure occurring in some adolescent and older patients within the first 30 seconds of standing.[2] Defined as a decrease in systolic blood pressure of more than 40 mm Hg or diastolic blood pressure of more than 20 mm Hg with symptoms of cerebral hypoperfusion within 15 seconds of standing, initial orthostatic hypotension is believed to indicate a transient mismatch between cardiac output and peripheral vascular resistance occurring during a rapid postural change, which may lead to presyncope or syncope.[72]

Medications

Medications are another common factor in orthostatic syncope, particularly in the elderly. Drugs that can cause or contribute to orthostatic hypotension include diuretics, alpha$_1$-blockers, beta-blockers, calcium antagonists, angiotensin-converting enzyme inhibitors, and centrally acting antihypertensives.

Cataplexy

Syncope must also be distinguished from cataplexy, which, in patients with narcolepsy, consists of the sudden uncontrollable onset of skeletal muscle paralysis during wakefulness. Strong emotion such as laughter triggers the episodes of cataplexy, during which the patient has facial and limb muscle weakness for as long as 1 to 2 minutes while remaining fully conscious. The weakness evolves over many seconds, more slowly than in neurally mediated syncope, and patients are areflexic during the episode.[73]

Psychogenic Pseudosyncope

Case 1-3 is a typical instance of psychogenic pseudosyncope, which is a psychiatric disorder wherein apparent transient loss of consciousness occurs in the absence of true loss of consciousness. Prevalence rates are higher in women.[74] The psychogenic events are often amenable to suggestion and can be induced by tilt testing, measurement of blood pressure while standing, repetitive squatting, or mental status

KEY POINTS

- Orthostatic syncope secondary to orthostatic hypotension is distinct from neurally mediated syncope. Patients with neurogenic orthostatic hypotension caused by autonomic failure typically experience hypotension immediately on standing and every time they stand.
- Medications that can cause orthostatic hypotension may contribute to syncope in the elderly.
- Neurally mediated syncope is distinct from cataplexy, in which consciousness is maintained while motor strength and tendon reflexes are transiently lost.
- Psychogenic pseudosyncope can be a diagnosis of inclusion when continuous blood pressure monitoring excludes hypotension or bradycardia during a typical episode of apparent unconsciousness. EEG monitoring during symptoms is also needed if seizures are suspected.

Case 1-2

A 58-year-old man with diabetes mellitus was referred for evaluation of three episodes of transient loss of consciousness. Two episodes occurred immediately upon standing when he got out of bed in the morning, and the third occurred while emptying his bladder in a standing position in the middle of the night. With each episode, he felt lightheaded just before he lost consciousness, and he had sustained a small contusion on his forehead when he fell during the third episode. Blood glucose by finger stick was normal right after each episode. On further questioning, over the past year he frequently felt fatigued and lightheaded with graying of his vision and had a strong urge to sit down whenever he had been standing for longer than 1 to 2 minutes. ECG, echocardiogram, and coronary catheterization were normal.

His neurologic examination was notable for decreased sensation and hyporeflexia below the knees. His blood pressure was 162/84 mm Hg supine and 110/70 mm Hg standing, with a heart rate of 68 beats/min in both positions. His tilt test showed a profound drop in systolic and diastolic blood pressure from baseline values immediately upon reaching the upright posture and continuing until he was returned to the supine position, a typical profile of severe, neurogenic orthostatic hypotension (**Figure 1-2**).

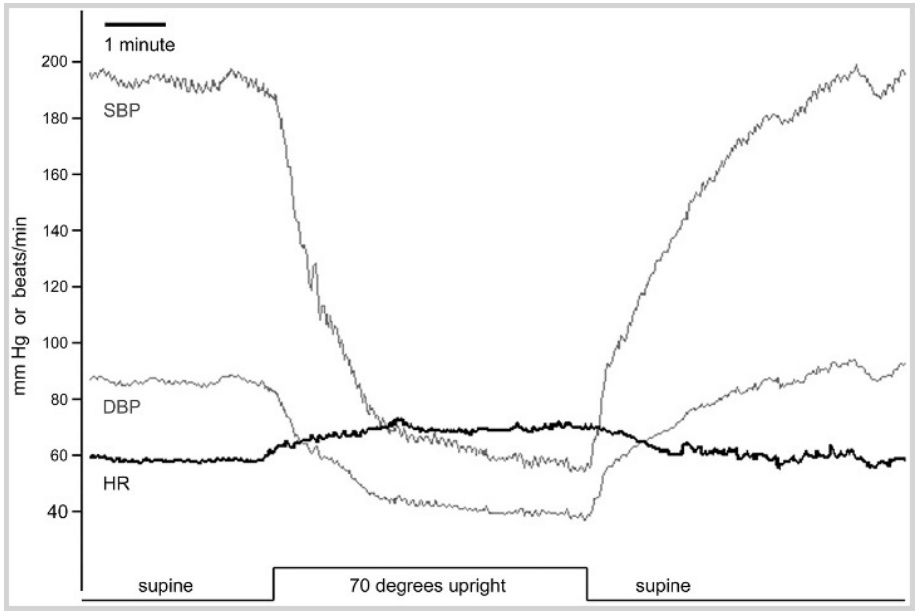

FIGURE 1-2 Blood pressure profile during tilt testing in orthostatic hypotension in a patient similar to the patient in **Case 1-2**. Beat-to-beat systolic blood pressure (SBP, *upper gray line*) and diastolic blood pressure (DBP, *lower gray line*) and heart rate (HR, *black line*) acquired by photoplethysmography at baseline and during 70 degrees of head-upright positioning for 5 minutes on a tilt table. This patient has orthostatic hypotension caused by diabetic autonomic neuropathy. The drop in blood pressure occurs immediately on assuming the upright posture and does not recover until the patient is returned to the horizontal posture.

Comment. This patient has orthostatic syncope as the result of neurogenic orthostatic hypotension. In this clinical context, the most likely cause is diabetic autonomic neuropathy. Note that hypotension occurs almost immediately upon standing, in contrast to the hypotension in neurally mediated syncope in **Case 1-1**, which developed after being upright for several minutes. Another distinguishing feature is that the heart rate increases slightly, although much less than it would in a healthy individual, in response to orthostatic hypotension, whereas in neurally mediated syncope the heart rate decreases as a manifestation of increased vagal outflow.

Case 1-3

A 34-year-old woman presented to the neurology clinic seeking another opinion regarding her 5-year history of recurrent episodes of transient loss of consciousness. The episodes occurred unpredictably, many times each day, and often when she was sitting at home watching television or lying in bed. If a spell occurred while she was standing, she would fall to the ground, but falling never resulted in bodily injury. She was not aware of any warning symptoms. Her boyfriend stated that she looked as if she were falling asleep yet was unresponsive and unarousable, and her eyes were shut, sometimes so tightly that he could not open them to check on her pupils. The duration of unresponsiveness varied from 1 to 30 minutes. Evaluations by multiple physicians including internists, cardiologists, pulmonologists, gastroenterologists, and allergists had all been unrevealing. Normal test results prior to her neurologic consultation included electrolytes, glucose, complete blood cell counts, thyroid function testing, ECG, EEG, prolonged cardiac monitoring, and echocardiogram and cerebrovascular imaging, among others.

Neurologic examination was normal. Subsequent neurologic evaluation included autonomic testing, during which a typical spell was reproduced while the patient was upright on the tilt table (**Figure 1-3**).

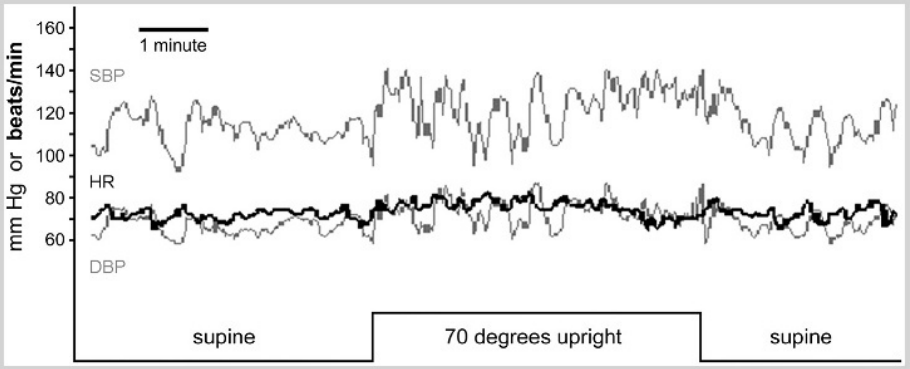

FIGURE 1-3 Blood pressure profile during tilt testing in a patient similar to the patient in **Case 1-3** and consistent with psychogenic pseudosyncope. Beat-to-beat systolic blood pressure (SBP, *upper gray line*) and diastolic blood pressure (DBP, *lower gray line*) and heart rate (HR, *black line*) acquired by photoplethysmography at baseline and during 70 degrees of head-upright positioning for 5 minutes on a tilt table. The tracing shows that blood pressure and HR remain stable during apparent loss of consciousness, which occurred after being upright for 4 minutes and continued for several minutes after return to the supine position.

Comment. Demonstration of normal blood pressure and heart rate during a typical symptomatic episode is strong evidence against neurally mediated syncope and is consistent with psychogenic pseudosyncope.

examinations.[74] In contrast to neurally mediated syncope, in which the eyes remain open, patients with psychogenic pseudosyncope almost always close their eyes.[74,75] The duration of apparent loss of consciousness in psychogenic pseudosyncope is often longer and can continue for several minutes.[74] The diagnosis of psychogenic pseudosyncope requires excluding organic pathology but can also be a diagnosis of inclusion if proven by the demonstration of normal blood pressure, heart rate, and EEG during an episode.[74] The EEG in psychogenic pseudosyncope typically shows a normal posterior-dominant alpha rhythm with no suppression of background waveforms.[76] Whereas in neurally mediated syncope the blood pressure and heart rate drop, in psychogenic pseudosyncope the blood pressure and heart

rate are normal or may increase beginning several minutes prior to the event.[74] Most cases of psychogenic pseudosyncope are classified as conversion disorder, which is not a voluntary deception by the patient but rather the physical manifestation of internal stressors.[77] The key clinical features that distinguish syncope from psychogenic pseudosyncope are listed in **Table 1-3**.

Metabolic

The differential diagnosis of transient loss of consciousness also includes acute metabolic disturbances such as hypoglycemia, hypothermia, hypoxia, and intoxication. Chronic adrenal failure also can cause hypotension, which can present with transient loss of consciousness.

DIAGNOSTIC TESTING

Autonomic nervous system testing in the evaluation of syncope is useful in the diagnosis of orthostatic hypotension, POTS, and baroreflex failure.[78] Baroreflex failure occurs when lesions of afferent baroreceptive nerves in the carotid sinuses or their central connections impair the dynamic buffering of blood pressure, resulting in marked volatility of blood pressure.

An important element in the evaluation of the patient with suspected orthostatic hypotension is assessment of adrenergic function. This is achieved by continuous monitoring of beat-to-beat blood pressure, performed noninvasively by photoplethysmography, during the physiologic challenges of a Valsalva maneuver and head-up tilt test. The rate and completeness of recovery of blood pressure during the Valsalva maneuver and the temporal profile of blood pressure during head-up tilt test at 60 degrees to 80 degrees are reliable indicators of adrenergic function and diagnosis of adrenergic failure.

When an autonomic laboratory is not available, valuable diagnostic information can be gained at the bedside. Orthostatic vital signs consist of measuring blood pressure and heart rate after the patient has rested in the supine position for several minutes

TABLE 1-3 Distinguishing Syncope From Psychogenic Pseudosyncope

Characteristic	Neurally Mediated Syncope	Psychogenic Pseudosyncope
Prodrome	Pallor, sweating, yawning	None
Eyes	Open	Closed
Myoclonus	Frequent	Rare
Motor activity	Limp	Limp, may move against resistance
Duration of unresponsiveness	Less than 1 minute	Often longer than 1 minute
Blood pressure	Decreased	Normal or mildly elevated
EEG	Suppression of background	Normal or increased myogenic artifact
Symptoms after event	Pallor, sweating	Continued semiresponsiveness

EEG = electroencephalogram.

and then again after 1 to 3 minutes of active standing, all while observing the patient carefully for symptoms of dizziness or signs of diminished alertness.

Diagnosis of initial orthostatic hypotension requires either beat-to-beat blood pressure measurements or rapid assessment by manual sphygmomanometry, as it often recovers too quickly to be detected by automated devices using arm cuffs. Furthermore, as the phenomenon occurs during active, but not passive, standing, tilt testing is of limited diagnostic value.[72]

Whereas heart rate data are easily captured by ambulatory devices, a current obstacle to the use of wearable biosensors in predicting neurally mediated syncope is the inability to capture continuous ambulatory blood pressure measurements.[79] Neurologists should be aware of the severe limitations of automated devices that generate rapid data about autonomic function but do not measure beat-to-beat blood pressure, expiratory pressure, or respiratory effort, as these cannot provide valid interpretations of adrenergic or vagal function.[78] Such devices lack controlled conditions and are not recommended for clinical assessments.[80]

Tilt Testing

The head-up tilt test, also known as the tilt table test (**Figure 1-1**), has been well established as a provocative maneuver in the diagnosis of neurally mediated syncope.[81] The rationale of tilt testing is to reproduce the orthostatic pooling of blood that, along with emotional and other factors, triggers neurally mediated syncope. Active standing, although a lesser orthostatic stress, has also been used with some success as a diagnostic test for neurally mediated syncope and requires the patient to stand quietly for 7 to 15 min without moving the legs.[82] Tilt testing should not substitute for a thorough history.[81]

The Heart Rhythm Society recommends tilt testing at the class IIa level of evidence for assessment of patients with suspected neurally mediated syncope who lack a confident diagnosis after the initial assessment. The Heart Rhythm Society also recommends tilt testing when differentiating between convulsive syncope and epilepsy, when establishing a diagnosis of pseudosyncope, and when evaluating patients with suspected neurally mediated syncope who have no clear diagnostic features.[1]

Assessment of orthostatic hypotension on the tilt table is usually accomplished within the first 3 minutes of monitoring, but a longer duration of head-up tilt is required to detect most cases of neurally mediated syncope.[2] A baseline resting phase of at least 10 minutes supine is necessary. Opinions vary as to the ideal duration of the test; most laboratories utilize 30 to 45 minutes. Three hemodynamic patterns may be seen in neurally mediated syncope. The vasodepressive pattern consists of a progressive fall in blood pressure. In contrast to the immediate fall in blood pressure that occurs in orthostatic hypotension, the vasodepressor response occurs after the patient has been upright for some time. The cardioinhibitory pattern consists of pronounced bradycardia of less than 40 beats/min or asystole of more than 3 seconds. The mixed pattern consists of a combined vasodepressor and cardioinhibitory response.[81] The end point of the test is the development of pronounced hypotension, bradycardia, or presyncope, although some prefer to provoke loss of consciousness.[81] The sensitivity of passive head-up tilt testing cannot be precisely determined because the clinical diagnosis of neurally mediated syncope is usually presumptive.[83] In patients with unexplained syncope, passive tilt testing has an

KEY POINT

- Provocative tilt testing with the goal of reproducing syncope is well established in the diagnosis of neurally mediated syncope. Methodologies differ, and variations designed to increase the sensitivity may also decrease the specificity of diagnosis. Positive tilt tests can occur in normal healthy persons.

KEY POINTS

- EEG during neurally mediated syncope initially shows a slowing of background rhythms followed by high-amplitude delta activity that may progress to flattening consistent with cerebral hypoperfusion.
- Caution is recommended when interpreting tilt test results in patients whose symptoms are not typical of neurally mediated syncope, as it is important to recognize that a positive tilt test can occur in normal individuals.
- As no gold standard test exists for reaching a diagnosis of neurally mediated syncope, and as positive tilt tests can occur in normal individuals, it may be argued that, after excluding alternative diagnoses, a careful history, including interviewing reliable witnesses, is the most useful diagnostic tool.

estimated sensitivity of 25% to 75% and a specificity of 90% to 100%.[83]

Provocative Agents

The sensitivity and thus the diagnostic yield of tilt testing can be enhanced, albeit with loss of specificity, by the use of pharmacologic provocation such as IV infusion of isoproterenol to increase the heart rate. Various incremental or standard dose protocols have been described.[84] The improved sensitivity is approximately 60% to 85%, whereas specificity declines to approximately 35% to 83%, depending on the study population and conditions of testing.[81,83] A potentially confounding variable is insertion of the IV catheter, which itself can provoke neurally mediated syncope in susceptible individuals. Many centers avoid that effect by using sublingual nitroglycerin as the provocative drug, which has a rapid onset of action and promotes the conditions for neurally mediated syncope by causing venous pooling. Sensitivity of tilt testing using nitroglycerin is approximately 51% to 81%, and specificity is 85% to 94%.[85] The diagnostic yield of tilt testing with isoproterenol versus nitroglycerin was comparable in a direct comparison study.[86]

Electroencephalogram

Some laboratories combine EEG with tilt testing in order to assess cerebral cortical activity concomitantly with blood pressure changes during symptomatic events. EEG during neurally mediated syncope initially shows a slowing of background rhythms followed by high-amplitude delta activity that may progress to flattening consistent with cerebral hypoperfusion.[21,87] A classic finding in neurally mediated syncope is what Gastaut and colleagues[88] called the ''slow-flat-slow'' pattern, in which attenuation of alpha rhythm progresses to slow activity of increasing amplitude, then disappearance of slow wave activity with a flat EEG tracing, the duration of which depends on the length of time that cerebral blood flow is interrupted. Recovery proceeds in reverse order.[88] An example of an EEG recording during a neurally mediated syncopal event is depicted in **Figure 1-4**.

Limits to Testing

Caution is recommended when interpreting tilt test results in patients whose symptoms are not typical of neurally mediated syncope, as it is important to recognize that a positive tilt test can occur in normal individuals. In a study of a total of 150 volunteers without a history of syncope who were subjected to head-up tilt testing at 60, 70, or 80 degrees for a maximum of 20 minutes, a positive result with provocation of hypotension occurred in 8%, 8%, and 20% of those who underwent passive testing and in 12%, 12%, and 40% of those who received isoproterenol infusion, respectively.[89] The frequency of vasodepressor responses increased with progressively higher doses of isoproterenol infusion, occurring in 56% of subjects who received 5 mcg/min and tilted to 80 degrees.[89]

Not only does a negative tilt test not exclude a diagnosis of neurally mediated syncope, but a positive tilt test does not exclude a diagnosis of epilepsy.[90] As no gold standard test exists for reaching a diagnosis of neurally mediated syncope, and as positive tilt tests can occur in normal individuals, it may be argued that, after excluding alternative diagnoses, a careful history, including interviewing reliable witnesses, is the most useful diagnostic tool. With that in mind, Sheldon and colleagues[91] developed an 118-item structured questionnaire that assessed symptom burden, provocative situations, presyncopal symptoms, symptoms typical of seizures,

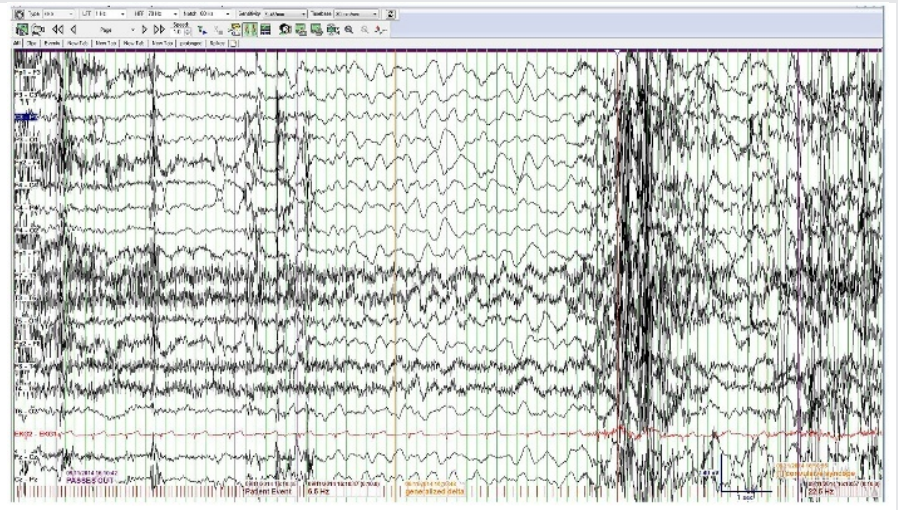

FIGURE 1-4 EEG during neurally mediated syncope. A 24-channel EEG including a single-channel ECG tracing obtained during video-EEG monitoring of a 24-year-old woman with neurally mediated syncope hospitalized for evaluation of spells of uncertain etiology. Note the gradual buildup of high-amplitude delta slowing and the intermixed myogenic artifact in the last 2 to 3 seconds of the tracing during a clinical attack of convulsive syncope.

Courtesy of William O. Tatum IV, DO, FAAN.

bystander observations, and relevant medical history. The questionnaire correctly classified 90% of 418 patients in a tertiary care clinic with a history of syncope, diagnosing neurally mediated syncope with 89% sensitivity and 91% specificity.[91] Building on those results, others have proposed the use of interactive decision-making software with the goal of developing a standardized approach to improve the diagnostic speed and accuracy while minimizing costs.[92,93]

DRIVING

When advising the patient who has had a syncopal episode whether and when it would be safe to return to driving, it should not be supposed that syncope does not occur in the seated posture. Although sitting is a lesser orthostatic stress than standing, 3% to 10% of patients with neurally mediated syncope experience episodes while driving an automobile.[94] Possible factors include the relatively confined conditions as compared to casual sitting, relaxation of lower extremity muscles permitting venous pooling, the warm environment of the car, or emotional excitement while driving.[95–97] Patients who experienced syncope while driving are more likely to have hypertension.[94]

Epidemiologic data suggest that the risk of vehicular accidents overall in patients with syncope does not differ substantially from that in the general population.[5] An international survey of cardiologists who had treated more than 11,500 patients with neurally mediated syncope retrospectively estimated the risk of subsequent motor vehicle accidents to be very low at 0.1% to 0.2%.[98]

Some patients may, however, be at increased risk. In a case-control study of 3877 patients evaluated for syncope, the most common cause was neurally mediated syncope in 1389 (35.8%), 142 (10.2%) of whom had syncope while driving.[96] Among patients with syncope

KEY POINT

- The most effective strategies for managing patients with syncope are avoidance of triggers, education to recognize and respond to prodromal symptoms, physical counterpressure maneuvers, and salt and fluid intake to expand intravascular volume.

while driving, the recurrence rate of syncope was 12.0% and 14.1% at 6 and 12 months, respectively, and the actuarial rate of recurrence of syncope while driving was 0.7% at 6 months and 1.1% at 12 months, with a cumulative probability of 7% over 8 years of follow-up. The rates of recurrence of syncope were similar regardless of whether the initial event had occurred while driving.[96]

In a survey of 104 patients with syncope, 3 reported having had syncope while driving.[99] Of those advised not to drive, only 9% followed that advice and, when contacted 3 to 6 months later, only 79% remembered the medical advice they had received on whether to stop driving.[99]

Guidelines of the American Heart Association, the North American Society of Pacing and Electrophysiology, and the European Society of Cardiology task force on driving stratified neurally mediated syncope into mild, with no restrictions on private drivers, and severe, with a recommendation for restriction of driving until symptoms are controlled. Neurally mediated syncope was defined as severe if it was frequent, occurred during high-risk activity, was recurrent, or was unpredictable. For patients lacking a prodrome, for elderly drivers, or for commercial drivers, more stringent restrictions were recommended, to be weighed according to the specifics of each case.[5,98]

Neurologists should exercise good medical judgment when advising the patient with syncope whether or when to return to driving. Unless the neurologist is confident that the risk of recurrence is minimal, it is best to restrict driving. As for epilepsy, the legal requirements for physicians to report loss of consciousness to the Department of Motor Vehicles and the medical criteria for when the patient may return to driving or flying after syncope are determined by each state.[97]

TREATMENT

The most effective strategies for managing patients with syncope are the avoidance of triggering factors, the use of counterpressure maneuvers, and intravascular volume expansion.[1,100,101] It is also important to educate patients about the shift in blood volume that occurs with standing and how their nervous system and cardiovascular system normally work together to respond. Once the patient learns to recognize the premonitory symptoms that signal a decrease in blood pressure, syncope often can be avoided by sitting or lying down.

Recommended treatment for posturally related syncope includes increasing dietary salt intake to at least 10 g (180 mmol) daily with the goal of expanding intravascular plasma volume to improve orthostatic tolerance.[102,103] How long to continue salt supplementation and whether doing so might increase the long-term risk of hypertension as much as for the general population are unknown.[104] Medications that can cause hypotension should be withdrawn if clinically indicated.[1]

Physical counterpressure maneuvers have been shown to improve orthostatic tolerance and to be effective interventions in patients with neurally mediated syncope who have a sufficiently long duration of prodromal symptoms.[105] Shifting weight from one leg to the other, leg crossing, heel raises, marching in place, and whole-body tensing, especially with clenching of the leg muscles and buttocks, are among the practical measures that activate the ''muscle pump,'' translocating blood from the legs back to the heart. Similarly, emergency countermeasures during impending loss of consciousness include squatting, bending over as if to tie shoes, sitting with the head between the knees, or lying down with the legs raised.[105]

No consistent or compelling evidence exists to suggest the efficacy of pharmacologic agents in preventing neurally mediated syncope.[1,100] However, relatively few well-designed clinical trials have been published, but several are worth noting because the results may be relevant to some patients.[11,106] As syncope is often preceded by increased sympathetic outflow with catecholamine release, beta-blockers have been widely prescribed with the goal of preventing syncope, although evidence of their effectiveness has been mixed.[107] In an observational cohort study of 153 patients with neurally mediated syncope, 52 of whom received beta-blockers, subgroup analysis showed that patients aged 42 years or older experienced a 48% reduction (95% confidence interval of 0.12 to 1.92) in neurally mediated syncope recurrence, whereas younger patients did not.[108] Another preventative approach has been the α_1-adrenergic receptor agonist midodrine, with the goal of maintaining peripheral vascular tone and preventing vasodilatation. Evidence warranting moderate confidence has found that midodrine decreased the risk of syncope recurrence by 37% (95% confidence interval of 20.8 to 47.4).[109] Yet another preventative approach has been the mineralocorticoid fludrocortisone with the goal of expanding intravascular volume. In a randomized, double-blind, placebo-controlled trial in 211 patients followed for 1 year, fludrocortisone showed a trend toward significance with a relative risk reduction of 26% (P=.066).[110] The current guidelines of the European Society of Cardiology assign a class IIb recommendation for midodrine and a class III recommendation against the use of beta-blockers in the treatment of recurrent syncope.[5] Tilt testing is not recommended for the purpose of predicting the response to specific medical treatments.[1] The role for cardiac pacing in treating neurally mediated syncope remains controversial.[101] Current American College of Cardiology and American Heart Association guidelines exclude pacemaker implantation as first-line therapy but allow consideration in some patients who have little or no prodrome prior to loss of consciousness, those with documented profound bradycardia or asystole, and those in whom other therapies have failed.[111]

CONCLUSION

Syncope is a frequent concern among patients seeking neurologic consultation and care. Whereas neurally mediated syncope is considered benign in comparison to other causes of abrupt loss of consciousness, such as epilepsy, stroke, and cardiac syncope, recurrent neurally mediated syncope increases the risk for injury and can substantially impair patients' quality of life. The crucial clinical task of distinguishing benign from potentially serious causes is best achieved through a collaborative approach involving the neurologist and cardiologist in partnership with the patient.

USEFUL WEBSITES

American Autonomic Society
americanautonomicsociety.org

Dysautonomia International
dysautonomiainternational.org

National Dysautonomia Research Foundation
ndrf.org

Syncopedia
syncopedia.org

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