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Syncope

Introduction

Syncope is defined as a transient loss of consciousness (T-LOC) due to brief global cerebral hypoperfusion characterized by rapid onset, short duration, and spontaneous complete recovery. Typical syncope is brief, lasting less than 20 seconds in duration. However, syncope rarely may last longer, even as much as several minutes.[1]

This review focuses on identifying the mechanism, planning treatment, and assessing the specific risk to a patient. Figure 1 illustrates syncope within the broader differential for loss of consciousness.

Epidemiology

Syncope is common in the general population, and there is significant variation with age.

- About 1% of toddlers experience vasovagal syncope.[2,3]
- There is a high prevalence of first faints in patients between 10 and 30 years (females 47% vs. males 31%).[4,5] In a community study, only 5% of the subjects reported first episode of syncope above 40 years of age.[6-10]
- The incidence gradually increases with age older than 65 years in both males and females.[9] In the Framingham study, the incidence of syncope shows a sharp rise after the age of 70 years, from 5.7 events per 1000 person-years in men aged 60-69, to 11.1 in men aged 70-79.[7]
- Younger people don't seek medical attention for a fainting spell, and 44% of the patients who present to a medical facility have a mean age of 51 years.[5,6]
- Across all age groups, reflex syncope is the most frequent cause of syncope.
- Cardiovascular disease is the second most common cause.
- Orthostatic hypotension is unusual below the age of 40 but is a frequent cause in the elderly population.
- No cause is identified in up to 30%.
- History and physical exam are more reliable in the young than the elderly.[8-10] Due to the multi-factorial nature of syncope in elderly patients, a fair number are misdiagnosed at initial presentation to the emergency rooms.

Pathophysiology of Syncope

As shown in Figure 2, the central mechanism underlying syncope is the decrease in global cerebral perfusion, which is usually due to a fall in systemic pressure. A sudden cessation of cerebral blood flow for as short as 6-8 seconds has been shown to be sufficient to cause complete LOC.[11] Blood pressure is a product of the cardiac output (CO) and the total peripheral vascular resistance, and a fall in either can compromise cerebral perfusion. In most cases, both of these factors are involved, even if their relative contributions vary considerably. Peripheral resistance is closely regulated by the autonomic nervous system (ANS), which can be affected by various intrinsic or extrinsic factors like drugs, toxins, etc. Cardiac output can be affected by the pump function, intravascular

Executive Summary

- Reflex syncope is the most frequent cause of syncope, followed by syncope secondary to cardiovascular disease. However, no identifiable cause can be associated with 30% of syncopal episodes.
- Vasovagal syncope is known as the "common faint" and is usually preceded by prodromal symptoms of autonomic activation.
- Carotid sinus massage is a relatively safe procedure and can be helpful diagnostically, but it does carry a small risk of neurological and cardiac complications.
- Treatment options have included physical counterpressure maneuvers, drug therapy including alpha agonists and beta-blockers, fludrocortisone, and cardiac pacing.
- Although syncope-related accidents are rare, each state has specific department of motor vehicle or public health department guidelines regarding whether there is a requirement for physician reporting.

volume, cardiac rhythm, and the neural control.

In autonomic failure (ANF), sympathetic vasomotor pathways are unable to increase total peripheral vascular resistance in response to the upright position. Gravitational stress, in combination with vasomotor failure, results in venous pooling of blood below the diaphragm, causing a decrease in venous return and consequently in CO.

From a pathophysiological perspective, syncope can be broadly divided into three main categories: reflex, cardiac, and autonomic or orthostatic. (*See Figure 2.*)

Reflex Syncope (Neurally Mediated Syncope). Reflex syncope refers to a group of conditions in which the normal cardiovascular reflexes that are involved in maintaining circulation become temporarily inappropriate, resulting in vasodilatation and/or bradycardia leading to a fall in BP and global cerebral perfusion.[12]

If hypotension is the predominant finding, the term "vasodepressor type" is used; "cardioinhibitory" when bradycardia or asystole predominate; and "mixed" if both mechanisms are present.

Reflex syncope is further subdivided into:

Vasovagal syncope (VVS), also known as the "common faint": This is commonly seen in young subjects and starts as an isolated episode, mostly benign in nature. It is commonly caused by emotional or orthostatic stress and is usually preceded by prodromal symptoms of autonomic activation (sweating, pallor, nausea).

Situational syncope refers to reflex syncope associated with some specific circumstances like coughing, micturition, post-prandial, etc. In this category, exercise syncope deserves special consideration. Fainting in association with physical exertion is seen in approximately 5% of presentations and increases the risk of a serious cardiac abnormality three-fold relative to non-exertional syncope. In younger people with seemingly normal hearts, benign causes are far more common, but they can have channelopathies, such as long QT syndrome, which may be difficult to diagnose. More likely, though, exercise-induced syncope suggests underlying heart disease such as ischemic heart disease, aortic stenosis, hypertrophic cardiomyopathy (HOCM), or pulmonary hypertension. Post-exercise syncope can occur in young athletes as a form of reflex syncope as well as in middle-aged and elderly subjects as an early manifestation of ANF before they experience typical OH.

Carotid sinus syncope (CSS). Carotid sinus hypersensitivity (CSH) is defined as a ventricular pause lasting more than 3 second and/or a fall in systolic BP of more than 50 mmHg on carotid sinus massage (CSM). When this abnormal response is associated with spontaneous syncope, it constitutes CSS. It should be noted that CSH is a common finding in older males, but patients with CSS are unusual, especially in those younger than 40 years of age.[13,14] In its rare spontaneous form, it is triggered by mechanical manipulation of the carotid sinuses. In the more common form, no mechanical trigger is found and it is diagnosed by CSM.[15]

The term *atypical form* is used to describe situations in which reflex syncope occurs with uncertain or even apparently absent triggers. The diagnosis then rests less on history-taking alone, and more on the exclusion of other causes of syncope (absence of structural heart disease) and on reproducing similar symptoms with tilt testing.

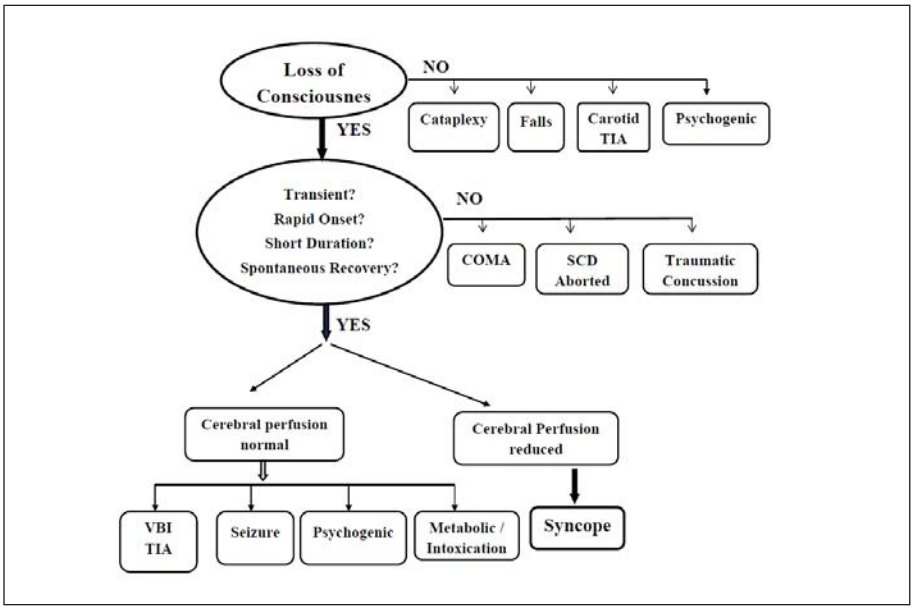
Cardiac syncope can be due to cardiac rhythm abnormalities and/or structural heart disease.

Patients with cardiac syncope appear to do worse than patients with noncardiac syncope (5-year mortality can be as high as 50%, and 1-year mortality can be 30%). Soteriades et al. followed 7814 patients with syncope for 17 years and found a higher mortality rate for patients with cardiac syncope compared with noncardiac syncope.[7] Suzuki et al. studied 912 patients with syncope for an average of 3 years and found the same result.[16]

Arrhythmia. Cardiac rhythm abnormality by itself or in association with an abnormal pump function and vascular tone can cause hemodynamic impairment, leading to a critical decrease in the stroke volume and cerebral blood flow.[17,18] Rhythm abnormalities constitute 13-32% of syncope cases. Bradycardia is seen in about 16% and tachycardia in 6%, but this seemingly small number with VT can lead to sudden death.[7,19,20]

Sick sinus syndrome is a

Figure 1: Illustrates the Differential Diagnoses for Loss of Consciousness Encountered in Clinical Practice



degenerative disease of the sinoatrial node, which affects the initiation of electrical impulse. The most common variant of this is the tachy-brady syndrome.[18]

High degree AV block is another common cause of syncope in which the subsidiary pacemaker tries to take over but the heart rate is relatively slow (25-40 bpm). In addition to directly causing syncope, bradycardia can be a harbinger for polymorphic ventricular tachycardia (VT) by prolonging the repolarization phase.

Tachycardia. Syncope is commonly seen with hemodynamically unstable ventricular tachycardia (VT) and uncommonly with atrial tachycardias.

Torsades de pointes is a specific type of polymorphic VT characterized by a twisting of the ECG axis, preceded by long-short RR-intervals, mostly triggered by an early premature ventricular contraction (R-on-T PVC) in people with congenital or acquired QT interval prolongation. (*See Figure 3.*) This rhythm has the potential to deteriorate into life-threatening ventricular fibrillation.

It is more common in women and is caused by drugs prolonging the QT interval. These drugs belong to different categories (i.e., antiarrhythmics, vasodilators, psychotropics, antimicrobials, non-sedating antihistamines, etc.). The website www.qtdrugs.org is a good reference resource.

Structural Heart Disease. Structural cardiac diseases can cause syncope when circulatory demands outweigh the impaired ability of the heart to increase its output. Most serious (ventricular) arrhythmias occur in the setting of structural heart disease, and syncope in this setting is associated with a much worse prognosis than just about everything else. Middlekauff et al. studied 491 patients with New York Heart Association (NYHA) functional class III or IV disease and noted that, regardless of the cause, 45% of those with syncope died within 1 year, whereas 12% of those without syncope died during the same interval.[21]

Obstructive conditions such as aortic stenosis (AS) and hypertrophied obstructive cardiomyopathy (HOCM) are a greater concern than regurgitant lesions. Syncope as a manifestation of aortic stenosis was first mentioned by Cowper in 1706. In these patients, if the aortic valve is not replaced, the 3-year mortality can be as high as 50%. Severe AS produces a fixed cardiac output, and the drop in peripheral vascular resistance with exercise causes a fall in the systemic blood pressure leading to decreased cerebral perfusion and syncope. An alternative theory is that during exercise, the high pressures generated in the hypertrophied LV causes a vasodepressor response, which causes a secondary peripheral vasodilatation and cerebral ischemia.

Syncope and pre-syncope occur in approximately 15-25% of patients with hypertrophic cardiomyopathy (HCM). In young patients with HOCM, a history of recurrent syncope is associated with an increased risk of sudden death. Arrhythmias such as paroxysmal atrial fibrillation or ventricular tachycardia are responsible in a minority of these patients, but the exact etiology is unknown.[22]

Subclavian steal is an important differential for arm claudication and syncope. In this condition, there is rerouting of blood flow to the arm through the vertebral artery due to stenosis or occlusion of the subclavian artery. It most often affects the left side and is often asymptomatic in 64%.[23]

Syncope Due to Orthostatic Hypotension or Autonomic Failure (ANF). Abnormalities in the autonomic nervous system (ANS) are commonly manifested as OH. In contrast to reflex syncope, in ANF sympathetic efferent activity is chronically impaired so that vasoconstriction is deficient. There are three categories of ANF.

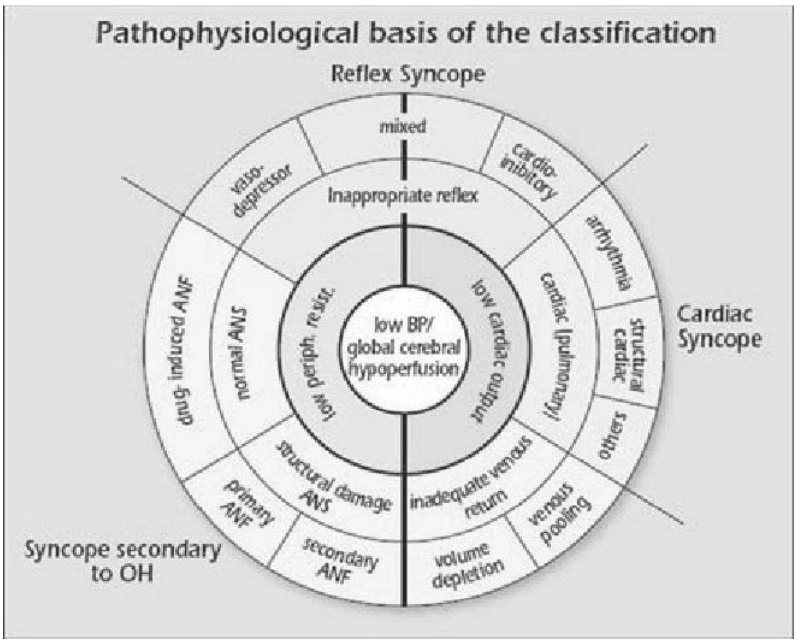
Primary ANF comprises degenerative neurological diseases such as multiple system atrophy, Parkinson's disease, and Lewy body dementia. Premonitory signs are impotence and disturbed micturition, and later movement disorders.

Secondary ANF involves autonomic damage secondary to other diseases, such as diabetes mellitus, amyloidosis, and polyneuropathies.

Drug-induced OH is another frequent cause of OH and is due to a functional abnormality rather than any structural damage.

OH is defined as an abnormal decrease in systolic BP upon standing. In addition to syncope, OH can cause: dizziness/lightheadedness, pre-syncope; weakness, fatigue, lethargy; palpitations, sweating; visual disturbances; hearing disturbances; and pain in the neck region.

Figure 2: Pathophysiological Basis of Syncope



Global cerebral hypoperfusion due to systemic hypotension is at the center, adjacent to low or inadequate peripheral resistance and low CO. ANF: autonomic nervous failure; ANS: autonomic nervous system; BP: blood pressure; OH: orthostatic hypotension. Used with permission from: Guidelines for the diagnosis and management of syncope. *Eur Heart J*. Copyright © 2009 Oxford University Press.

OH can be divided into three types:

Classical OH: A decrease in systolic BP 20 mmHg and in diastolic BP 10 mmHg within 3 minutes of standing. It is seen in patients with pure ANF and hypovolemia.[24]

Initial OH: BP falls immediately on standing to more than 40 mmHg and then rapidly returns to normal, so the period of hypotension and symptoms is short (< 30 seconds).[25]

Delayed (progressive) OH: Mostly seen in the elderly due to age-related impairment of compensatory reflexes and stiffer hearts.[26] Delayed OH is characterized by a slow progressive decrease in systolic BP on assuming erect posture. The absence of a bradycardic reflex (vagal) differentiates delayed OH from reflex syncope.

Psychiatric Causes

Functional attacks is a term used for somatic conditions without a physiological explanation and presumed to have a psychological mechanism. Functional syncope can be seen in:

- Somatization disorders
- Generalized anxiety disorder
- Panic attacks
- Major depressive disorder
- Alcohol and substance abuse.

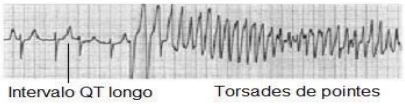
The frequency of such attacks is not known, and in one study, functional T-LOC was noted in 15-20% of cases in specialized epilepsy clinics and in up to 6% in syncope clinics.[27] Pseudosyncope usually lasts longer than syncope. Patients may lie on the floor for many minutes (15 minutes is not unusual). Other clues are a high frequency including numerous attacks in a day, and lack of a recognizable trigger. The hemodynamic parameters such as BP and HR are fairly normal in this condition. The eyes are usually open in epileptic seizures and syncope, but are usually closed in functional T-LOC. Injury does not exclude functional T-LOC; trauma occurred in nearly 50% of pseudoseizures.

Evaluation and Management

Evaluation involves answering the following key questions:

- Is it a syncopal episode? (*See Figure 1.*)
- Is an etiological diagnosis possible? (*See Figure 2.*)
- Are there high-risk findings suggestive of a recurrence or death?

Figure 3: Classical Torsades de Pointes



There is a short pre-initiating RR interval due to the PVC followed by a long initiating cycle due to the compensatory pause. R-On-T phenomenon is also noted before the induction of this twisting arrhythmia. Used with permission from: http://www.cardiac-risk-assessment.com/ca-blog/what-is-qtc-and-long-qt-syndrome-lqts/

History

In ascertaining if the LOC was indeed syncope, a detailed clinical history, focused on answering some key questions mentioned below, is extremely helpful (positive predictive value 23-50%), but sometimes can be equally difficult.[28-30]

- Was LOC complete with rapid onset and short duration?
- Did the patient recover spontaneously, completely, and without sequelae?
- Did the patient lose postural tone?

If the answers to these questions are positive, the episode has a high likelihood of being syncope. If the answer to one or more of these questions is negative, other forms of LOC need to be excluded. Specific questions relating to the events surrounding the syncopal episode, i.e. preceding, during, and post collapse should be asked. As shown in Table 1, certain findings can be considered diagnostic of a particular etiology.

Further diagnostic workup depends on the above information and can be broadly divided into cardiovascular and neurological.

Carotid Sinus Massage (CSM).

CSM is performed for at least 10 seconds on either side in both standing and lying down positions under hemodynamic and electrocardiographic monitoring. Carotid sinus can be located between the angle of the mandible and the superior border of thyroid cartilage. Firm pressure should be applied without actually occluding the carotid artery. CSH along with fainting constitutes CSS.

Clinically, three types of CSH have been described.

• The cardioinhibitory type comprises 70-75% of cases. The predominant manifestation is a decreased heart rate, resulting in sinus bradycardia, atrioventricular block, or asystole due to vagal action on sinus and atrioventricular nodes. This can be reversed with atropine.

• The vasodepressor type comprises 5-10% of cases and is characterized by a decrease in the vasomotor tone leading to hypotension without a change in heart rate. This response is not abolished with atropine.

• The mixed type comprises 20-25% of cases and is associated with a decrease in both the heart rate and the vasomotor tone.

CSM is a relatively safe procedure but does carry a small risk of neurological (0.17% to 1.0%) and cardiac complications (a few case reports of prolonged asystole, atrial fibrillation, and ventricular tachycardia). Complications are seen mostly in the elderly with atheromatous carotid arteries. Simultaneous bilateral CSM should never be performed. CSM should be avoided in patients with previous TIA, stroke within the past 3 months, carotid artery occlusion, history of VF/VT, or recent myocardial infarction. The relative contraindication includes presence of carotid bruits.[31]

Orthostatic Challenge. Changing from supine to upright position leads to venous pooling in the lower extremities and, if the compensatory mechanisms are abnormal, this could result in a fall in BP and syncope.[32]

Currently, there are two different methods for assessing the response to change in posture: One is active standing, in which patients arise actively from supine to erect, and the other, a passive process, is tilt table testing. The test is diagnostic when there is a symptomatic >20 mm Hg fall in SBP from baseline or > 10 mm Hg in DBP.

Head Up Tilt Testing (HUT). HUT is an accurate and controlled way to test for neurally mediated reflex syncope. Peripheral blood pooling and impaired peripheral vasoconstriction followed by sympathetic withdrawal and vagal overactivity cause hypotension and usually concomitant bradycardia leading to a syncopal episode. A positive HUT is pathognomonic of reflex syncope from prolonged standing but can be seen in other forms of syncope and in patients with sick sinus syndrome.[33]

Indications for HUT testing are shown in Table 2.

Methodology. Tilt testing was introduced into clinical evaluation of patients with syncope of unknown origin by Kenny et al. in 1986.[34] After an overnight fast, a patient is placed on a motorized table with a foot board at one end and is held in place by a single strap over the stomach. After the patient remains supine for 15 minutes, the table is tilted nearly upright to 60-80° for 45 minutes.

With tilting, if vasovagal symptoms develop, vasovagal syncope is confirmed. If they do not occur, a drug (e.g., isoproterenol or sub-lingual nitroglycerin) may be given to induce them. Sensitivity varies from 30-80% depending on the protocol used. The false-positive rate is 10-15%. The following findings are noted:

Vasovagal: A drop in both heart rate and BP;

Cardioinhibitory: Primary significant drop in HR associated with hypotension;

Vasodepressor: A primary decrease in BP with slight increase in HR;

Dysautonomic pattern/Delayed Orthostatic Hypotension response: A gradual decrease in BP with little change in heart rate;

Cerebral Syncope: In some individuals, abnormal baroreceptor responses triggered during orthostatic stress may result in a derangement of cerebral autoregulation leading to cerebral vasoconstriction with resultant cerebral hypoxia and syncope in the absence of systemic hypotension.[35]

POTs (postural orthostatic tachycardia syndrome): This is a clinical diagnosis with significant increase in heart rate (> 30 beats/min) within 10 minutes of head up tilt with little change in BP;

Psychogenic: Syncope with no hemodynamic changes.

A negative tilt table response

Table 1: Factors Differentiating a Seizure from Syncope[1]

Characteristic	Syncope	Seizure
Preceding symptoms	Nausea, vomiting, feeling cold, sweating, blurred vision, lightheadedness	Aura
During the episode	Very brief if any tonic-clonic movements and they start after the LOC	Prolonged tonic-clonic movements coinciding with the LOC Chewing, lip smacking, frothing, tongue biting, Incontinence
Post event	Generally rapid and full recovery	Prolonged confusion Muscle pains Headache Feeling sleepy

Table 2: Summary of Indications for Tilt Table Testing

Tilt Table Testing Is Warranted In:

- Recurrent or single syncopal episode in a high-risk patient, whether or not the medical history is suggestive of neurally mediated (vasovagal) origin, and
  - No evidence of structural cardiovascular disease
  - Structural cardiovascular disease is present, but other causes of syncope have been excluded by appropriate testing
- Further evaluation of patients in whom an apparent cause has been established (e.g., asystole, atrioventricular block), but in whom demonstration of susceptibility to neurally mediated syncope would affect treatment plans
- Part of the evaluation of exercise-induced or exercise-associated syncope

Reasonable Differences of Opinion Exist Regarding Utility of Tilt Table Testing In:

- Differentiating convulsive syncope from seizures
- Evaluating patients (especially the elderly) with recurrent unexplained falls
- Assessing recurrent dizziness or presyncope
- Evaluating unexplained syncope in the setting of peripheral neuropathies or dysautonomias
- Follow-up evaluation to assess therapy of neurally mediated syncope

Tilt Table Testing Not Warranted In:

- Single syncopal episode without injury and not in a high-risk setting with clear-cut vasovagal clinical features
- Syncope in which an alternative specific cause has been established and in which additional demonstration of a neurally mediated susceptibility would not alter treatment plans

Potential Emerging Indications

- Recurrent idiopathic vertigo
- Recurrent transient ischemic attacks
- Chronic fatigue syndrome
- Sudden infant death syndrome (SIDS)

A summary of principal indications for tilt table testing in the evaluation of syncope based on Benditt et al. Tilt table testing for syncope. *J Am Coll Cardiol* 1996;28:263–275).

does not exclude the diagnosis of reflex syncope. In studies comparing the response to tilt testing with spontaneous syncope recorded by an ILR, while a positive cardioinhibitory response on tilting predicts with a high probability an asystolic spontaneous syncope, the presence of a positive vasodepressor or mixed response or even a negative response does not exclude the presence of asystole during spontaneous syncope.[36,37]

Complications and Contraindications. Tilt testing is safe with no mortality reported. Use of isoproterenol has been associated with some rare ventricular arrhythmias, especially in the presence of ischemic cardiomyopathy, but the use of nitroglycerin has caused only minor side effects such as headache.[38] Atrial fibrillation can be induced during or after a positive tilt test and is usually self-limited.[39]

Contraindications to the administration of isoproterenol include ischemic heart disease, uncontrolled hypertension, left ventricular outflow tract obstruction, and significant aortic stenosis. Caution should be used in patients with known arrhythmias.

Cardiac Rhythm Monitoring. Based on published data, a cardiac etiology can be seen in roughly 20% of syncope cases, and arrhythmias are to blame in most cases. The gold standard for the diagnosis of syncope is when an arrhythmia is recorded during a syncopal episode. The presence of some asymptomatic significant arrhythmias, defined by prolonged asystole (> 3 seconds), rapid supraventricular tachycardias (SVTs) (i.e., > 160 bpm for > .32 beats), or VTs, has been considered by several authors as a diagnostic finding. As a general rule, ECG monitoring is indicated only when there is a high pre-test probability of identifying an arrhythmia associated with syncope. An arrhythmia, usually asystole, is present during syncope in up to 50% of patients older than 40 years with recurrent syncope, no known structural heart disease, and a normal baseline ECG.[40,41] Various modalities are available for ECG monitoring and include:

- 24/48 hour ambulatory Holter Monitoring: Inexpensive to set up, but the true yield can be as low as 1-2% due to paucity of symptoms. In 15% of patients, symptoms were not associated with arrhythmia, and in these patients, a rhythm disturbance could potentially be excluded as a cause of syncope.[42] Holter is useful when symptoms are frequent.
- Event Recorders: These devices have a loop memory that continuously records and deletes ECG. They can be applied for up to a month. When activated by the patient, typically after a symptom has occurred, 5-15 minutes of pre-activation ECG is stored and can be retrieved for analysis. In one study, event monitors were able to diagnose the cause of syncope in up to 25% of enrolled patients.[43]
- Implantable loop recorders (ILR): These can be implanted subcutaneously under local anesthesia and can be left in place for up to 3 years. These devices store retrospective ECG recordings when activated

either by the patient or a bystander, usually after a syncopal episode, or automatically activated in the case of occurrence of predefined arrhythmias. These devices can be very cost-effective in difficult-to-diagnose, infrequent yet clinically significant syncopal episodes. In a study by Krahn et al., 15/16 patients experienced syncope 4 months post implantation.[44] In the RAST trial, combining primary strategy with crossover, the diagnostic yield is 43% ILR vs. 20% conventional. ILR was cost effective by being 26% less expensive than conventional testing.[45]

Electrophysiology Study. Electrophysiology (EPS) is helpful in diagnosing the cause of syncope in patients with structural heart disease. In clinical practice, less than 2% of patients with unexplained syncope evaluated by cardiologists undergo EPS, and even fewer if they are evaluated by other specialists.[43] Sensitivity and specificity of EPS is low, and it is indicated in patients with:

- structural heart disease and an arrhythmic cause for syncope but not a candidate for ICD;
- bundle branch block and undiagnosed syncope;
- Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy and hypertrophic cardiomyopathy;
- high-risk occupations and undiagnosable syncope.

Echocardiography and Other Imaging Techniques. Echocardiography is an easy and non-invasive way to evaluate for the structural and functional hemodynamic data, particularly in patients with known structural cardiac disease. Echocardiography plays an important role in risk stratification on the basis of left ventricular ejection fraction.

Transoesophageal echocardiography, computed tomography (CT), and magnetic resonance imaging (MRI) may be performed in selected cases (e.g., aortic dissection and hematoma, pulmonary embolism, cardiac masses, pericardial and myocardial diseases, congenital anomalies of coronary arteries).

Exercise Stress Testing. Exercise-induced syncope is infrequent but, as mentioned above, it can be a harbinger of a life-threatening condition. Exercise testing is not routinely indicated in the general population but should be performed in most cases of exertional syncope both as a means of reproducing the symptoms and in evaluating for arrythmias (QT response to stress and recovery can also be assessed) in this setting. Some causes of cardiac syncope and sudden cardiac death precipitated by exercise include: ischemic heart disease, HOCM, dilated cardiomyopathy, ARVC, inherited channelopathies, and certain congenital anomalies of coronary circulation.

Neurological Evaluation. *Electroencephalography.* EEGs are normal in syncope[46], but an interictal normal EEG cannot rule out epilepsy, and must always be interpreted in a clinical context. An EEG is not recommended when syncope is the most likely cause of T-LOC, but it is when epilepsy is the likely cause or when clinical data are equivocal. If recorded during a provoked attack, the EEG may be useful to differentiate psychogenic pseudosyncope.

Computed Tomography, Magnetic Resonance Imaging, and Carotid Duplex. These are performed mostly to exclude causes other than syncope and are not recommended for routine evaluation of syncope.

Psychiatric Evaluation

A detailed history is the most important, and documenting attacks is very helpful; parameters to assess are posture and muscle tone (video recording or neurological investigation), BP, HR, and EEG. During tilt testing, the combination of apparent unconsciousness with loss of motor control, normal BP, HR, and EEG rules out syncope and most forms of epilepsy.

Treatment

The main goals of treatment include prolonging survival, avoiding injuries, and preventing recurrences. Figure 4 illustrates the treatment of syncope based on pathophysiology.

Treatment of Reflex Syncope and Orthostatic Intolerance. Treatment of reflex syncope and orthostatic intolerance nvolves educating the patient regarding the benign nature of this problem, explaining how to avoid triggers, early recognition of prodromal symptoms, and performing maneuvers to abort the episode in a timely fashion.

Physical Counterpressure Maneuvers. Two clinical trials have shown that isometric PCMs of the legs (leg crossing) or of the arms (hand grip and arm tensing) are able to induce a significant BP increase during the phase of impending reflex syncope that allows the patient to avoid or delay losing consciousness in most cases.[47,48] The results have been confirmed in a multicenter prospective trial that assessed the effectiveness of PCMs in daily life in 223 patients aged 38-53 years with recurrent reflex syncope and recognizable prodromal symptoms.[49]

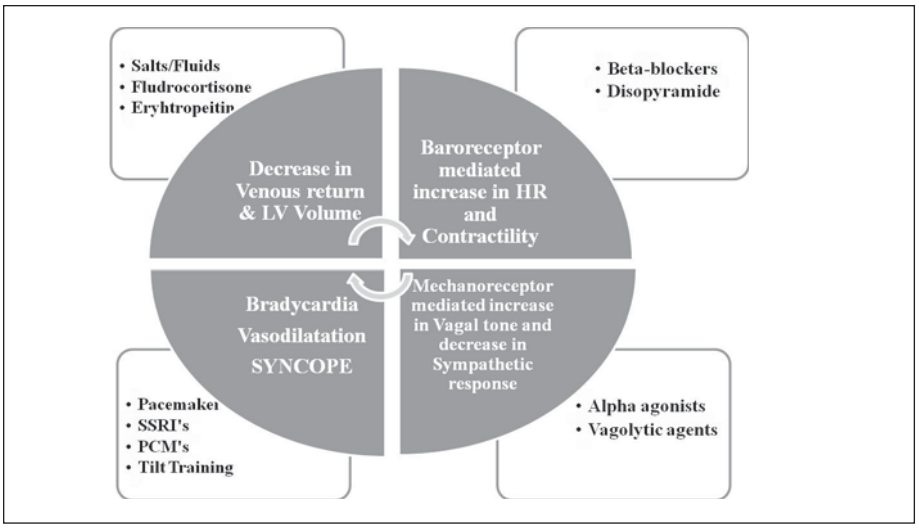
Tilt training is effective in highly motivated young patients with recurrent vasovagal symptoms triggered by orthostatic stress, but its success has not been shown in controlled studies.[50,51]

Drug Therapy. To date many drugs have been tested in the treatment of reflex syncope and include beta-blockers, disopyramide, scopolamine, theophylline, ephedrine, etilefrine, midodrine, clonidine, and serotonin reuptake inhibitors.

Alpha agonists have proven somewhat effective by their ability to cause peripheral vasoconstriction. Midodrine was studied in three small, open-label, randomized trials in patients affected by very frequent hypotensive symptoms (> 1 syncope/month).[52-54] The major limitation of midodrine is frequent dosing and the side effect profile. Elderly males are particularly inconvenienced by urinary outflow problems.

Fludrocortisone is a mineralocorticoid used in young adults with reflex syncope. It has shown some benefit in a few non-randomized trials.[55] The results of a large multicenter,

Figure 4: Treatment of Syncope Based on the Pathophysiological Mechanism



international, randomized, placebo-controlled study (POST II) looking at the effectiveness of fludrocortisone in the prevention of neurally mediated syncope is awaited.[56]

Beta-blockers have been presumed to lessen the degree of ventricular mechanoreceptor activation owing to their negative inotropic effect in reflex syncope. This theory has not been supported by the outcome of clinical trials. A rationale for use of beta-blockers in other forms of neurally mediated syncope is lacking, and they may worsen bradycardia in CSS.[57-59]

Paroxetine was shown to be effective in one placebo-controlled trial, which included highly symptomatic patients from one institution.[60] This has not been confirmed by other studies. Paroxetine may reduce anxiety, which precipitates events. Being a psychotropic drug, its use in patients without psychiatric disease requires caution.

Cardiac Pacing

Cardiac pacing is mostly considered for patients with carotid and vasovagal syndromes with a predominant cardioinhibitory component. Pacing will have no effect on the vasodepressor component, which is often the dominant factor in these conditions, explaining why syncope still recurs during long-term observation in approximately 20% of the paced patients.

Pacing in Vasovagal Syncope. Effectiveness of pacing in VVS has been studied in five multicenter randomized controlled trials; three non-blinded[61-63] gave positive results and two blinded[64,65] gave negative results. The strongest supporting evidence was provided by the North American VPS[62] and the European VASIS and SYDIT trials.[61,63] In these trials, a total of 338 patients were included based mostly on the tilt table results; syncope recurred in 21% of paced vs. 44% of unpaced patients. The Second Vasovagal Pacemaker Study (VPS II)[64] and the Vasovagal Syncope and Pacing trial (SYNPACE)[65] gave totally different results. They diverged from the previous trials in that patients in the control arm received a permanent pacemaker programmed "off." Although there was a 30% reduction in recurrence in the two groups, the VPS II study failed to demonstrate significant superiority of pacing. In the SYNPACE trial, syncope recurred in 50% of patient assigned to pacing "on" and in 38% of patients assigned to pacing "off." To answer the limitations associated with tilt table testing, in the ISSUE II trial, patients > 40 years with a high likelihood of VVS received an implantable loop recorder and those who experienced syncope with concomitant long pauses received a pacemaker.[66] The results were clearly in favor of pacing, but unfortunately ISSUE II was not a randomized trial and a final conclusion cannot be drawn. A recent meta-analysis of all studies suggested a nonsignificant 17% reduction in syncope with pacing.[67] In conclusion, pacing plays a small role in therapy for reflex syncope, unless severe spontaneous bradycardia is detected during prolonged monitoring. Moreover, this condition frequently affects young patients in whom we have to be cognizant of the long-term problems associated with pacemakers. Cardiac pacing may have a role in a selected proportion of elderly patients affected by severe recurrent unpredictable VVS.

Carotid Sinus Syndrome and Pacing. Pacing was considered a therapeutic option for CSS in the early 1970s when some case reports demonstrated that recurrence of syncope was abolished after implantation of a pacemaker.[68] As we discussed, CSH without fainting is not considered diagnostic of CSS. Recent work suggests that in patients who have a > 3 second pause on CSM but no symptoms may benefit from pacing.[69] The first randomized trial comparing pacing to no pacing in 60 patients was reported in 1992.[70] After a mean follow-up of 36 ± 10 months, syncope recurred, respectively, in 9% and 57% of the patients in pacing and control groups ($P < 0.0002$).

Orthostatic Hypotension and Orthostatic Intolerance Syndromes. Even a small increase in the BP can help to ameliorate the symptoms. Expansion of intravascular volume is an important goal. In the absence of hypertension, patients should be instructed to take sufficient salt and water intake, targeting 2-3 L of fluids per day and 10 g of NaCl.[71] Sleeping with the head of the bed elevated prevents nocturnal polyuria, maintains a more favorable distribution of body fluids, and ameliorates nocturnal hypertension.[72]

Abdominal binders or graduated compression stockings are effective and should be routinely recommended.[73] PCMs such as leg crossing and squatting should be encouraged

in patients with warning symptoms.[74]

The alpha-agonist midodrine (5-20 mg taken three times daily) increases BP and can ameliorate the symptoms of OH.[75] Fludrocortisone (0.1-0.3 mg once daily) stimulates renal sodium retention and expands fluid volume. Caution is necessary for possible side effects of hypernatremia, hypokalemia, hyperglycemia, congestive heart failure, and hypothalamic-pituitary-adrenal axis suppression when used chronically. Hypertension in the recumbent position is an important risk of fludrocortisone treatment in patients with orthostatic hypotension and is not volume-dependent but is related to increased peripheral-vascular resistance. The evidence in favor of fludrocortisone is from a small observational study (in combination with head-up sleeping) and one double-blind trial.[76,77]

Additional and less frequently used treatments, alone or in combination, include desmopressin in patients with nocturnal polyuria, octeotride in post-prandial hypotension, erythropoietin in anemia, frequent small meals, and judicious exercise of leg and abdominal muscles, especially swimming.

Syncope in the Elderly

Some points to consider in the management of elderly with syncope:

- OH is not always reproducible in older adults (particularly medication and age-related). Therefore, orthostatic BP should be repeated, preferably in the morning and/or promptly after syncope.
- CSM is particularly important to perform even if non-specific CSH is present without history of syncope.
- Tilt testing is well tolerated and safe, with positivity rates similar to those observed in younger patients, particularly after nitroglycerin challenge.
- Twenty-four-hour ambulatory BP recording is very helpful.
- Due to the high frequency of arrhythmias, an ILR may be especially useful in the elderly with unexplained syncope.

Driving and Syncope

Contrary to common belief, syncope-related accidents are uncommon.

- In a survey of 104 patients, syncope while driving occurred in 3%, and only 1% crashed their vehicles.
- Among those advised not to drive, only 9% followed this advice.[78]
- In 3877 consecutive patients evaluated for syncope, 380 (9.8%) had syncope while driving and involved a reflex mechanism (37%) or cardiac arrhythmia (12%).
- The cumulative probability of recurrence while driving was 7% in 8 years.

For public safety, the risk of syncope-mediated driving accidents is about 0.8% per year, which is substantially less compared to accidents in the high-risk groups, i.e., young (16-24 years) and elderly drivers. Please refer to your state's DMV laws for specific information and recommendations.

Prognosis

"Syncope begets itself," meaning the number of episodes of syncope during life is the strongest predictor of recurrence.

Structural heart disease and cardiac arrhythmias are major risk factors for SCD and overall mortality in patients with syncope.[79-81] OH closely trails cardiac disease and is associated with a two-fold higher risk of death owing to the severity of co-morbidities in this cohort of patients.[82] Conversely, young patients in whom structural or electrical heart disease has been excluded and who have reflex syncope have an excellent prognosis.[7]

Major morbidity, such as fractures and motor vehicle accidents, were reported in 6% of patients, and minor injury, such as laceration and bruises, in 29%. In patients presenting to an ED, minor trauma was reported in 29.1% and major trauma in 4.7% of cases; the highest prevalence (43%) was observed in older patients with carotid sinus syndrome (CSS).[83]

Hospitalization related to OH increases progressively with age: 4.2% of 65- to 74-year-old patients and 30.5% of patients older than 75 years. A significant impact on quality of life is seen particularly in the elderly and ranges from loss of confidence, depressive illness, fear of falling, and subsequent institutionalization.[84,85] Female gender, presence of co-morbidity, number of episodes of syncope, and presence of pre-syncope seemed to be associated with poorer quality of life. Finally, it should be stressed that, while syncope occurs intermittently, its threat of recurrence continuously impairs quality of life.

Economic Considerations

In the United States, estimated total annual costs for syncope-related admissions in 2004-2005, derived from the Medicare database, were $2.4 billion, with a mean cost of $5400 per hospitalization.[86] In the United Kingdom, the overall cost per patient was £611, with 74% attributed to the costs of hospital stay.[87] These costs continue to increase and could be attributed to the following:

- Approximately 1% of referrals to the ED are for syncope; of these, more than 40% are hospitalized, with a median in-hospital stay of 5.5 days and hospitalization costs account for more than 75% of the total expenses.[88]
- A wide range of conditions may cause syncope. The absence of a gold standard clinical test able to provide a certain, easy, and cheap diagnosis, and the widespread inappropriate use of multiple but inefficiently directed diagnostic tests ("shotgun approach") results in overuse of medical resources and increased costs.

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Physician CME Questions

17. Initial history, physical exam, and ECG can diagnose the cause of syncope in what percentage of patients?
    A. 15%
    B. 25%
    C. 45%
    D. 65%

18. Which of the following is accurate regarding syncope?
    A. The most common cause is cardiac.
    B. The most common cause is neurologic.
    C. History is generally not useful in determining cause.
    D. Transient ischemic attacks are unlikely to cause syncope if involving the anterior circulation.

19. A 23-year-old woman presents for evaluation of recurrent syncope. She has never injured herself. Her most recent episode occurred while standing in line at a store. She became warm, sweaty, and lightheaded. She then lost consciousness. She recovered and went to a local ER for evaluation. She developed recurrent syncope while having an IV inserted. Her ECG monitor at the time revealed a 6-second period of asystole. What recommendations would you make for management?
    A. Initiate beta-blocker therapy.
    B. Increase salt and fluid intake.
    C. Insert permanent pacemaker.
    D. Initiate midodrine.

20. A 65-year-old man reports episodes of fainting that occur during arm exercises for a rotator cuff injury. This suggests:
    A. exercise-induced syncope
    B. carotid sinus syndrome
    C. subclavian steal syndrome
    D. secondary autonomic failure

21. Classic symptoms of orthostatic syncope include all of the following *except*:
    A. blurred vision
    B. tunnel vision
    C. dizziness
    D. vertigo

CME Answer Key
17. C; 18. D; 19. B; 20. C; 21. D

Primary Care Reports

CME Objectives

Upon completion of this activity, participants should be able to:

- summarize recent, significant studies related to the practice of primary care medicine;
- evaluate the credibility of published data and recommendations related to primary care medicine;
- discuss the advantages and disadvantages of new diagnostic and therapeutic procedures in the primary care setting.

CME Instructions

Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the questions at the end of the article. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to evaluate their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. *After completing this activity, you must complete the evaluation form that will be provided at the end of the semester and return it in the reply envelope provided to receive a credit letter.* When your evaluation is received, a credit letter will be mailed to you.

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