Syncope: Diagnosis and Management

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Abstract: Syncope is defined as transient loss of consciousness due to global cerebral hypoperfusion. It is characterized by having a relatively rapid onset, brief duration with spontaneous and full recovery. The major challenge in the evaluation of patients with syncope is that most patients are asymptomatic at the time of their presentation. A thorough history and physical examination including orthostatic assessment are crucial for making the diagnosis. After initial evaluation, short-term risk assessment should be performed to determine the need for admission. If the short-term risk is high, inpatient evaluation is needed. If the short-term risk is low, outpatient evaluation is recommended. In patients with suspected cardiac syncope, monitoring is indicated until a diagnosis is made. In patients with suspected reflex syncope or orthostatic hypotension, outpatient evaluation with tilt-table testing is appropriate. Syncope units have been shown to improve the rate of diagnosis while reducing cost and thus are highly recommended. (Curr Probl Cardiol 2015;40:51–86.)

Definition

Transient loss of consciousness (T-LOC) or "faint" is a broad term that includes all disorders characterized by transient, self-limited loss of consciousness (LOC). The causes of T-LOC include syncope, epileptic seizures, metabolic disorders, and psychogenic causes. Syncope is defined as a form of T-LOC where the mechanism is transient

Disclosure: M Hamdan is the co-inventor of the software described in this paper and has financial interest in the start-up company that has exclusive rights to the software product (Faint-Algorithm, F2 Solutions Inc., Sandy, Utah).

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global cerebral hypoperfusion. It is characterized by having a relatively rapid onset, brief duration with spontaneous and full recovery.

Epidemiology

Syncope is common in the general population. The first episode presents at characteristic ages in a bimodal distribution with a high incidence in patients between the ages of 10 and 30 years, relatively uncommon in middle-aged adults, and peaking again in patients older than 65 years.[1,2] In the Framingham Heart Study, the overall incidence rate of a first report of syncope was 6.2 per 1000 person-years.[3] The incidence rates increased with age, with a sharp rise at 70 years. The 10-year cumulative incidence was 6%. In another study by Malasana et al, the prevalence of faint over a 1-year period was estimated at 9.5 per 1000 inhabitants, with women having a higher prevalence at the ages of 10-49 years when compared with males and similar prevalence at ages greater than 50 years (Fig. 1).[4] Variations in the reported prevalence of syncope in different studies are likely due to differences in definition, diagnostic methods, and study populations. Nevertheless, approximately one-third of individuals are likely to have a syncopal episode during their lifetime.[5-7]

Syncope is a common problem in the emergency department (ED). Several reports found that 3%-5% of all ED visits and 1%-6% of all hospital admissions were due to syncope.[8-11] The prognosis in patients with syncope depends on the etiology and underlying cardiovascular condition. In the Framingham study, the risk of death was doubled among participants with cardiac syncope compared with those without syncope. Vasovagal syncope

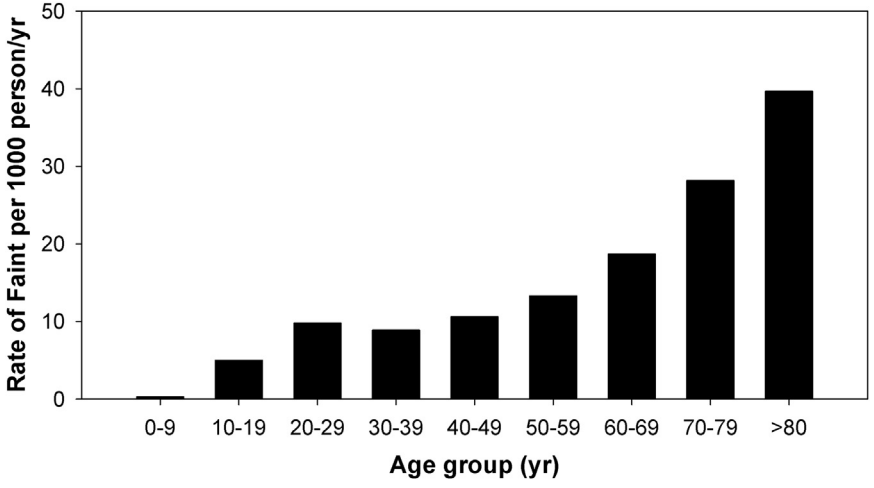

FIG 1. Prevalence of faint in the State of Utah. (Adapted with permission from Malasana et al.[4])

was not associated with an increased risk of any of the major outcomes (Fig. 2).[3] Similarly, Del Rosso et al identified clinical predictors of cardiac syncope and found that during a mean follow-up period of 614 days, patients with likely cardiac syncope, identified as having an Evaluation of Guidelines in Syncope Study (EGSYS) score ≥ 3, had a higher mortality when compared with patients with a score < 3 (17% vs 3%, $P < 0.001$).[12]

Approach to Patients With T-LOC

Initial evaluation of a patient presenting with T-LOC should include careful history, physical examination, orthostatic blood pressure measurement, 12-lead electrocardiogram (ECG), and transthoracic echocardiography. The goal of the initial evaluation is to answer 3 fundamental questions: (1) Is it a syncopal episode? (2) What is the short-term risk? (3) Is the diagnosis certain and if not what is it likely to be?

History

The interviewer should start with a careful history including specific questions aimed at determining the mechanism of LOC. As stated in the

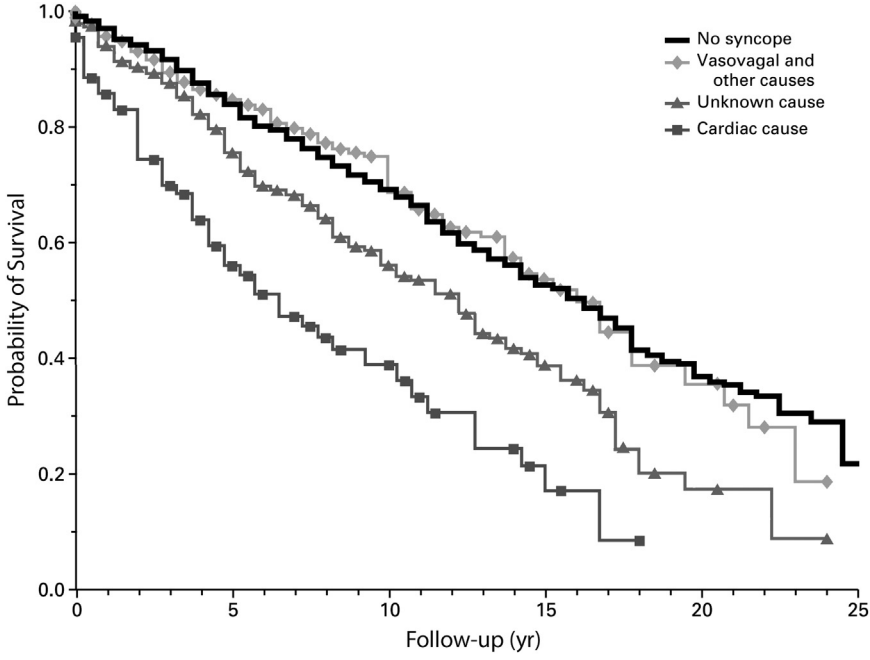

FIG 2. Probability of survival as a function of cause of faint. (Adapted with permission from Soteriades et al.[3])

introduction, T-LOC is due to syncope if the event is relatively rapid in onset and short in duration with spontaneous and complete recovery. If the patient is in the upright position, loss of postural tone must occur, as it is one of the earlier manifestations of cerebral hypoperfusion. If the answer to any of these questions is no, nonsyncopal causes of faint should be considered including neurologic, metabolic, and psychogenic causes. It is important to note that generalized jerky movements can occur with syncope. They are usually characterized as being very short in duration and *always* occurring after the LOC. Unlike with seizure disorders, the patient is oriented within 1-2 minutes after the event.

Joseph Alpert: A common error in clinical practice is a diagnosis of seizure disorder in a patient who exhibits tonic-clonic movements during a period of cardiac arrest or marked hypotension. Such movements are the result of cerebral hypoperfusion and are not indicative of a chronic seizure disorder.

Once the diagnosis of syncope is made, historical features about the circumstances surrounding the event are very helpful in identifying the cause and prognosis. On one hand, syncope preceded by prolonged standing, emotional distress, medical instrumentation, or occurring following micturition, defecation, or coughing is likely to be reflex in nature with a benign prognosis. On the other hand, syncope occurring during exercise or in the supine position is likely to be cardiac in nature with poor prognosis. Obtaining a detailed medical history and family history is also very important in the initial evaluation of a patient with syncope. History of cardiac disease as evidenced by abnormal findings on the echocardiogram or ECG is highly suggestive of a cardiac etiology. Similarly, a family history of sudden cardiac death should alert the health care provider about the possibility of inherited arrhythmias such as long QT, short QT, or Brugada syndrome.

Joseph Alpert: A small percentage of families with hypertrophic cardiomyopathy have an increased incidence of sudden death among family members, with this disastrous event occurring even in teenagers and young adults.

Physical Examination

Physical examination should focus on vital signs, including orthostasis and careful evaluation of the cardiovascular (presence of murmur, outflow obstruction, and arrhythmia) and neurologic (muscle weakness or

paresthesia or cranial nerve abnormalities) systems. The presence of orthostatic hypotension with reproduction of clinical symptoms is diagnostic and eliminates the need for unnecessary tests. However, the provider should be aware that early orthostatic hypotension could sometimes be missed in the absence of continuous blood pressure monitoring particularly in patients with rapid blood pressure recovery. Furthermore, active standing is unlikely to help with the diagnosis of delayed orthostatic hypotension. When delayed orthostatic hypotension is suspected, patients should undergo tilt-table testing to make the diagnosis.[13] Therefore, although the presence of orthostatic hypotension is helpful, its absence does not exclude the diagnosis.

Cardiac ECG

An ECG is recommended in every patient who presents with syncope. Although a normal ECG finding has a high negative predictive value,[14] the overall diagnostic yield of an ECG in a patient with syncope is low at 2%-9% and even lower at 0%-3% in patients younger than 40 years. However, as the cost is minimal, its routine use is justified.[7,9,15,16] The ECG provides important information about the rhythm and atrioventricular (AV) conduction. Symptomatic bradyarrhythmias should be considered in patients with sinus bradycardia, a prolonged PR interval, or bundle branch block. Examination of the QRS complex and repolarization may also identify the presence of structural heart disease such as cardiac hypertrophy, arrhythmogenic right ventricular dysplasia, pre-excitation, and inherited arrhythmias. Ventricular ectopy or nonsustained ventricular tachycardia particularly in patients with prior myocardial infarction raises the possibility of ventricular arrhythmias as the cause of syncope. Cardiac ischemia is an uncommon cause of syncope but should be ruled out in the evaluation of patients with risk factors particularly when presenting with chest pain.

Echocardiography

Echocardiography is recommended in patients with syncope as it may help with diagnosis and risk stratification.[2,17] In an era where appropriate use of testing is crucial in health care delivery, it should be noted that the recent American Society of Echocardiography appropriate use criteria document published in 2011 gives a score of 9 for transthoracic echocardiography in the evaluation of patients with lightheadedness, presyncope, or syncope when clinical symptoms or signs consistent with a cardiac diagnosis are noted and a score of 7 when there are no other

symptoms or signs of cardiovascular disease (median score 7-9 indicates that the test is generally acceptable and is a reasonable approach for the indication).[18] Echocardiography can diagnose underlying structural heart disease such as left ventricular dysfunction, hypertrophic cardiomyopathy, or significant aortic stenosis.[19] The finding of structural heart disease does not generally establish the cause of syncope but strongly suggest a cardiac etiology unless the history is typical for reflex-mediated syncope. In the 2009 European Society of Cardiology (ESC) guidelines on syncope management, only a finding of severe aortic stenosis, obstructive tumor or thrombus (eg, atrial myxoma), cardiac tamponade, aortic dissection, or congenital anomaly of the coronary artery is considered diagnostic as a cause for syncope.[2]

Stress Test

Stress testing is not indicated in patients with syncope unless the event occurred during exercise, there is a history of chest pain before the LOC, or the patient has 2 or more risk factors for coronary artery disease.[2,20] In addition to ruling out ischemia, stress testing is useful in diagnosing stress-induced cardiac arrhythmias including exercise-induced tachyarrhythmias such as outflow ventricular tachycardia, polymorphic ventricular tachycardia, and bradyarrhythmias including exercise-induced AV block. The latter invariably occurs in patients with conduction disease and is due to infranodal block.[21]

Joseph Alpert: Some authorities advise stress testing high-risk individuals with hypertrophic cardiomyopathy. Strenuous exercise, especially in competitive athletic endeavors, is not advised for such patients.

Short-Term Risk Assessment

After establishing the diagnosis of syncope, that is, T-LOC was due to transient cerebral hypoperfusion and is not a neurologic, metabolic, or psychological disorder, the provider faces the question of short-term risk assessment. In other words, do you need to admit the patient to the hospital or not? The need for admission should be determined by the short-term risk of having a life-threatening event, syncope recurrence with injury, or death within 7 days of the index event. Although the presence of structural heart disease or abnormal ECG finding increases the likelihood of cardiac syncope, it is important not to equate cardiac syncope with elevated short-term risk and thus the need for hospital admission. Indeed, several studies

have shown that many of the syncope admissions are unwarranted with a low event rate during the short-term cardiac monitoring period.[22]

In this section, we discuss several studies that used risk-scores methods aimed at helping the clinician with risk assessment when evaluating patients with syncope. In addition, we describe a different method that uses a decision-support system in risk assessment.

Risk Stratification Score-Questionnaires

In the *San Francisco Syncope Rule* derivation study,[23] physicians prospectively completed a structured data form when evaluating patients with syncope in the ED ($n = 684$). Serious outcomes, including the occurrence of death, myocardial infarction, malignant arrhythmia, pulmonary embolism, stroke, subarachnoid hemorrhage, significant hemorrhage, or other serious events, which required return to ED and subsequent hospitalization, were monitored during a 7-day period following the index event. The authors found that a rule (San Francisco Rule) that considers patients with an abnormal ECG finding, a complaint of shortness of breath, hematocrit level $<30\%$, systolic blood pressure <90 mm Hg, or a history of congestive heart failure had 96% (95% CI: 92%-100%) sensitivity and 62% (95% CI: 58%-66%) specificity. In a subsequent validation study ($n = 791$), the rule performed well, with a sensitivity of 98% and a specificity of 56%.[24] External validation studies, however, found lower sensitivity and specificity and in some cases no added value to clinical judgment[25-28] with higher rates of admission.[29]

The Rose Rule[30] was a single-center, prospective, observational study of adults presenting to the ED with syncope. A clinical decision rule was devised from 550 patients in a derivation cohort and subsequently tested in a validation cohort consisting of an additional 550 patients. The study was designed to identify risk factors predictive of an adverse event within 1 month after initial presentation to ED with syncope. The authors found that (1) brain natriuretic peptide >300 pg/mL, (2) stool positive for occult blood, (3) oxygen saturation $<94\%$ on room air on initial presentation, (4) hemoglobin <90 g/L, (5) chest pain associated with syncope, (6) bradycardia (heart rate <50 bpm), and (7) Q-wave on ECG predicted the likelihood of adverse outcomes. Of the study population, 7.1% met an end point at the end of 1 month. The sensitivity and specificity of the Rose Rule were estimated to be 87.2% and 65.5%, respectively.

In the *Short-Term Prognosis of Syncope (STePS) Study*,[31] the authors evaluated short-term and long-term severe outcomes and related risk factors in 676 patients who presented with syncope. Long-term adverse

outcomes were defined as death or the need for major therapeutic procedures. Overall, 41 subjects (6.1%) experienced severe short-term outcomes and 62 (9.3%) long-term severe outcomes including 40 deaths and 22 patients requiring major therapeutic procedures. An abnormal ECG finding, concomitant trauma, absence of symptoms of impending syncope, and male sex were associated with short-term unfavorable outcomes. Long-term severe outcomes correlated with an age >65 years, history of neoplasms, cerebrovascular diseases, structural heart diseases, and ventricular arrhythmias. The authors concluded that risk factors for short-term and long-term adverse outcomes were different and that hospital admission favorably influenced prognosis.

Sun et al[32] assessed the occurrence of a predefined serious event within 30 days after an ED evaluation for syncope or near syncope. In a cohort including 2584 patients, 173 patients (7%) with an age ≥ 60 years experienced a 30-day serious event. High-risk predictors included the following: (1) age greater than 90 years, (2) male sex, (3) history of an arrhythmia, (4) triage systolic blood pressure greater than 160 mmHg, (5) abnormal ECG finding, and (6) abnormal troponin I level result. A low-risk predictor was a complaint of near syncope rather than syncope. By summing high-risk predictors and subtracting low-risk predictors, the authors were able to generate a risk score, which stratified patients into low-risk (event rate = 2.5%, 95% CI: 1.4-3.6), intermediate-risk (event rate = 6.3%, 95% CI: 5.1-7.5), and high-risk (event rate = 20%, 95% CI: 15-25) groups.

In summary, the aforementioned studies were designed to help identify patients with syncope who could be safely discharged from the ED. By design, they all had a good negative predictive value. As a result, the effect on the rate of admission was no change or a slight increase. A summary of the aforementioned studies is provided in Table 1.

Evidence-Based Decision-Support Software

Another approach in risk stratification has been the use of decision-support software to help the physician follow the best evidence-based management as dictated by the guidelines. Unlike the aforementioned studies where risk score methods are used to estimate risk based on few variables, the software incorporates all aspects of history taking, physical examination, and tests' findings and makes a recommendation to admit or not admit according to the most recent guidelines. Of course, the final decision is the result of clinical judgment using all available data. Daccarett et al[33] showed that the use of the guideline-based criteria incorporated into

TABLE 1. Short-term risk assessment studies

Studies	Risk factors	Score or risk level	End points	Results
San Francisco Syncope Study[23,24] ($N = 684$ Derivation Study; $N = 791$ Validation Study)	An abnormal ECG finding Shortness of breath Systolic BP <90 mm Hg Hematocrit level $<30\%$ Congestive heart failure	No risk factors = low risk >1 Risk factor = high risk	Serious events within 30 d of ED visit	Sensitivity = 98% Specificity = 56%
Rose Study[30] ($N = 550$ Derivation Study; $N = 550$ Validation Study)	Brain natriuretic peptide level >300 pg/mL Stool positive for occult blood Oxygen saturation $<94\%$ on room air Hemoglobin level <90 g/L Chest pain associated with syncope Bradycardia (<50 bpm) Q-wave on ECG	Admit if any of the risk factors are present.	Serious events within 30 d of ED visit	Sensitivity = 87% Specificity = 66%
STePS Study[31] ($N = 676$)	Short-term Risk Abnormal ECG finding Trauma Absence of symptoms of impending syncope Male sex Long-term risk Age >65 y Neoplasm Cerebrovascular disease Structural heart disease Ventricular arrhythmias		Serious events within 10 days of ED visit (short-term risk) Serious events from the 11th day up to 1 y (long-term risk)	Short-term risk factors may help ED physicians Long-term and short-term risk factors are different
Sun et al[32] ($N = 2584$) (Age ≥ 60 y)	Age >90 y Male sex History of an arrhythmia	Low risk (-1,0) Intermediate risk (1,2) High risk (3-6)	Serious events within 30 d of ED visit	Event rate = 2.5% (low risk)

TABLE 1. Continued

Studies	Risk factors	Score or risk level	End points	Results
	Triage systolic blood pressure >160 mm Hg Abnormal electrocardiogram finding Abnormal troponin I level result Near Syncope (−1)			Event rate = 6.3% (Intermediate risk) Event rate = 6.3% (high risk)

BP, blood pressure; STePs, Short-Term Prognosis of Syncope.

such software would have allowed a safe 52% reduction in admission rate without a significant difference in the prevalence of serious events in the discharged group. A list of criteria including several ECG findings that should alert the provider about the need to admit the patient for syncope evaluation is provided in Table 2. These short-term high-risk criteria were obtained from the recent guidelines on syncope management where hospital admission or early invasive evaluation is recommended.[2]

If a decision is made to admit the patient, an electrophysiological consult is recommended to assess the need for invasive evaluation and possible ablation or device implantation. If a decision is made not to admit the patient because of the absence of short-term high-risk criteria, the provider needs to make either a "certain diagnosis" or "most likely diagnosis" with the ultimate goal of applying therapy and preventing future recurrences. In the following section, we describe a classification of the different causes of syncope based on the pathophysiology with reference to the commonly accepted criteria for making a diagnosis as published in the most recent guidelines.[2]

Classification of Syncope

The classification of syncope is traditionally based on the underlying pathophysiological mechanism. Data from tilt-table testing indicate that a decrease in systolic blood pressure below 60 mmHg for at least 6-8 seconds is associated with syncope.[34] Therefore, regardless of the mechanism, a common denominator with syncope is a significant decrease in systolic blood pressure resulting in reduction in cerebral blood flow and LOC.

Establishing the mechanism is always a challenge as by definition, the event is transient in nature and thus most patients have an unremarkable

TABLE 2. Faint-Algorithm Admission criteria. (Adapted with permission from 2009 ESC guidelines on Syncope.)[2]

Reason for admission
Cardiac-arrhythmic causes
(1) Sinus bradycardia $<$ 40 bpm or pauses $>$3 sec
(2) Mobitz II or 2:1 second-degree or third-degree atrioventricular block
(3) Alternating left and right bundle branch block
(4) Sustained supraventricular tachycardia
(5) Sustained ventricular tachycardia
(6) Pacemaker (ICD) malfunction with cardiac pauses.
(7) LBBB or RBBB + left or right axis deviation
(8) Long QT pattern
(9) Brugada pattern
(10) ARVD pattern
(11) WPW pattern
Cardiac-ischemic causes
(12) Cardiac ischemia
Cardiovascular and pulmonary structural causes
(13) Prolapsing atrial myxoma, tumor
(14) Severe aortic stenosis
(15) Respiratory insufficiently defined as shortness of breath and O_2 saturation $<$70%
(16) Acute aortic dissection
(17) Pericardial tamponade
(18) Severe hypertrophic obstructive cardiomyopathy (HOCM)
(19) Severe prosthetic valve dysfunction
(20) Sustained ($\geq$2 measurements at $>$5 min) supine systolic hypotension $\leq$80 mm Hg
(21) Severe systolic dysfunction (eg, $<$40%)
(22) History of myocardial infarction with mild LV dysfunction (LVEF $>$ 40%) and absence of criteria for vasovagal syncope or orthostatic hypotension
Noncardiovascular causes
(23) Acute hemorrhage
(24) End-stage diseases (cancer, renal dialysis, etc)
(25) Major physical injuries secondary to syncope
(26) Minor physical injuries *and* symptomatic orthostatic hypotension

ARVD, arrhythmogenic right ventricular dysplasia; ICD, implantable cardioverter defibrillator; LBBB/RBBB, left or right bundle branch block; LV, left ventricular; LVEF, left ventricular ejection fraction; WPW, Wolff-Parkinson-White.

physical exam on presentation. Nevertheless, the principal causes of syncope can be classified into 3 categories: cardiac, reflex mediated, and orthostatic hypotension. A summary of the commonly accepted diagnostic criteria for syncope is provided in Table 3. When diagnostic criteria are met, the diagnosis is made with certainty and no further testing is needed. Examples include a patient with a history consistent with vasovagal syncope, that is, preceded by a known trigger and associated with typical autonomic symptoms, or a patient with syncope occurring soon after

TABLE 3. Established diagnosis at initial evaluation: Commonly accepted diagnostic criteria

Reflex syncope

Classical vasovagal syncope is diagnosed if syncope is precipitated by emotional distress (such as fear, severe pain, instrumentation, or blood phobia) or prolonged standing and is associated with typical prodromal symptoms owing to autonomic activation (intense pallor, sweating, nausea, feeling of warmth, odd sensation in the abdomen, and lightheadedness or dizziness).

Situational syncope is diagnosed if syncope occurs during or immediately after specific triggers:

- Micturition (postmicturition)
- Postexercise
- Postprandial
- Cough and sneeze
- Others (eg, laughing, brass instrument playing, and weightlifting)

Orthostatic syncope is diagnosed when the history is consistent with the diagnosis and there is documentation of orthostatic hypotension during an active standing test (usually defined as a decrease in systolic blood pressure $\geq$20 mm Hg or a decrease of systolic blood pressure to $<$90 mm Hg) associated with syncope or presyncope (a fall $>$30 mm Hg is needed in hypertensive subjects).

Arrhythmia-related syncope is diagnosed by ECG (including ECG monitoring) when there is

- Sinus bradycardia $<$40 bpm or repetitive sinoatrial blocks or sinus pauses $>$3 s
- Second-degree Mobitz II or third-degree atrioventricular block
- Alternating left and right bundle branch block
- Paroxysmal supraventricular tachycardia or ventricular tachycardia
- Pacemaker or ICD malfunction with cardiac pauses

Cardiac ischemia-related syncope is diagnosed when symptoms are present with ECG evidence of acute ischemia with or without myocardial infarction

Cardiovascular syncope is diagnosed by echocardiography performed at initial evaluation when syncope presents in patients with prolapsing atrial myxoma or other intracardiac tumors, severe aortic stenosis, pulmonary hypertension, pulmonary embolus or other hypoxic states, acute aortic dissection, pericardial tamponade, obstructive hypertrophic cardiomyopathy, and prosthetic valve dysfunction

standing with documented symptomatic early orthostatic hypotension during an active standing test. However, in most instances, the diagnosis is not certain, and the caring physician must make a likely diagnosis and decide on the diagnostic approach and future management. In this section of the article, we review the main characteristics of each type of syncope.

Cardiac Syncope

Definition. Cardiac syncope includes syncope due to arrhythmias or structural heart disease including pulmonary embolism. Arrhythmias are by far the most common cause of cardiac syncope. The prevalence of cardiac syncope increases with age.[1] Absence of prodromes is always concerning for a cardiac etiology particularly in the elderly. Predictors of

cardiac syncope include the presence of structural heart disease or abnormal ECG finding, syncope during exercise, syncope in the supine position, and the presence of palpitations immediately before the LOC. Del Rosso et al developed a diagnostic score to help identify patient with a likely cardiac cause for their syncope: the EGSYS score.[12] The authors analyzed the clinical features of syncope using a standard 52-item form. In a validation cohort of 260 patients, the predictive value of symptoms or signs was evaluated and a point score was developed, which was then validated in a cohort of 256 other patients. The outcome measurements, early (1 month) and late (2 years), were death rate and syncopal relapses. The 6 risk factors identified in the EGSYS study that were predictive of adverse outcomes included the following: (1) abnormal ECG finding or heart disease or both, (2) palpitations before syncope, (3) syncope during effort, (4) syncope in the supine position, (5) absence of autonomic prodromes, and (6) absence of predisposing and precipitating factors. To each variable, a score from +4 to −1 was assigned to the magnitude of regression coefficient. A score ≥ 3 identified cardiac syncope with a sensitivity of 95% and 92% and a specificity of 61% and 69% in the derivation and validation cohorts, respectively (Fig. 3).[12] The mortality at 2 years was noted to be 2% in patients with a score < 3 and 21% in patients with a score ≥ 3.

Differential Diagnosis. In patients with a history suggestive of cardiac syncope, the differential diagnosis include bradyarrhythmias, tachyarrhythmias, and decreased cardiac output due to structural heart disease such as hypertrophic cardiomyopathy, aortic stenosis, mitral stenosis, atrial myxoma, or reduction in preload as seen with pulmonary emboli and severe pulmonary hypertension.

Joseph Alpert: Syncope in patients with severe valvular aortic stenosis and hypertrophic cardiomyopathy is particularly worrisome, and such individuals should be urgently considered for aortic valve replacement in the case of aortic stenosis and implantable cardioverter defibrillator placement in patients with hypertrophic cardiomyopathy.

Cardiac syncope due to myocardial ischemia or injury is rare but easily diagnosed with a 12-lead ECG and cardiac enzymes. In patients with no evidence of structural heart disease, bradyarrhythmias or supraventricular tachyarrhythmias should be suspected. It should be noted that syncope with supraventricular arrhythmias usually occurs shortly after tachycardia onset before the baroreflex has a chance to compensate for the decrease in

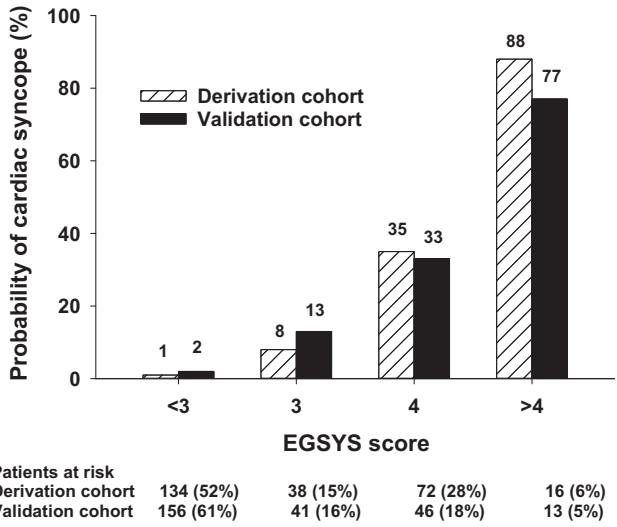

FIG 3. Probability of cardiac syncope according to the EGSYS score. (Adapted with permission from Del Rosso et al.[12])

blood pressure.[35,36] In patients with a depressed left ventricular function or a substrate for a tachyarrhythmia such as a ventricular scar, ventricular arrhythmias should be ruled out. In the latter group, invasive assessment with an electrophysiological study is indicated followed by prolonged monitoring as needed.

Joseph Alpert: In hot, dry climates, patients on fixed doses of antihypertensive agents may vasodilate and dehydrate resulting in hypotension and syncope. We have observed a number of such patients during the summer months here in Arizona. Reduced doses of antihypertensive agents should be considered for such individuals when ambient temperatures are high and humidity is low.

Management. In patients suspected of having cardiac syncope who meet any of the high-risk short-term criteria listed in Table 2, in-hospital monitoring is indicated. The diagnostic yield of invasive electrophysiologic testing is highly dependent on the pretest probability and the programmed stimulation protocol. Positive results occur predominantly in patients with structural heart disease.[37] In patients who do not require hospital admission, the guidelines recommend Holter monitoring in patients with frequent syncope or presyncope (≥ 1 per week), external loop recorders when the duration between the events is ≤ 4 weeks, and implantable loop recorder (ILR) in patients with less frequent events, that is, ≥ 4 weeks apart. The average diagnostic yield with an ILR is

approximately 26%-51% over an observation period of 10-18 months. Furukawa et al[38] demonstrated that prolonging the monitoring period up to 4 years increased the diagnostic yield with a cumulative diagnostic rates of 30%, 43%, 52%, and 80% at 1, 2, 3, and 4 years, respectively. Of note, 26% of the diagnoses were made after 18 months. Therefore, when cardiac syncope is suspected, cardiac monitoring should be performed and extended until a diagnosis is made.

The interpretation of symptoms in a patient monitored for cardiac syncope has to be done with caution. Several studies have shown that presyncope was much less likely to be associated with an arrhythmia when compared with syncope.[39-45] Therefore, although the presence of a significant arrhythmia at the time of presyncope is helpful, its absence does not rule out the presence of an arrhythmia at the time of syncope. As such, presyncope should not be considered a surrogate for syncope.

Given the aforementioned considerations and according to the recent guidelines, a diagnosis is made with cardiac monitoring if the patient has a recurrence of syncope with or without an arrhythmia or ECG documentation of one of the following arrhythmias: sinus arrest >3 seconds while awake, Mobitz II or III AV block, or rapid supraventricular or ventricular arrhythmia lasting greater than 32 beats with a rate ≥ 160 bpm. It is important to note that recurrence of syncope with documentation of the absence of an arrhythmia is helpful as it excludes the presence of cardiac syncope. The differential diagnosis in such instances includes reflex syncope with a vasodepressor response, orthostatic hypotension, and psychogenic syncope. Tilt-table testing is helpful in dissecting the mechanism in these patients.

Reflex Syncope

Definition. Reflex syncope is a term used in reference to a heterogeneous group of conditions where normal reflexes that control circulatory homeostasis become "overactive," resulting in vagotonia and peripheral sympathetic inhibition. The former leads to bradycardia and possible asystole whereas the latter results in vasodilation. The combination results in hypotension and syncope. It is important to note that some patients might experience significant hypotension in the absence of any change in heart rate during monitoring and as such might have their episodes of T-LOC dismissed as being nonsyncopal because of the absence of rhythm abnormalities. Therefore, it is important not to exclude the diagnosis of syncope based on cardiac monitoring alone in patients suspected of having reflex syncope. In such cases, history taking and tilt testing as discussed previously are helpful in establishing the diagnosis.

Classification of Reflex Syncope. Classification of reflex syncope is based on either the efferent or afferent limb of the reflex. The Vasovagal Syncope International Study (VASIS) classification following tilt testing is an example of classification based on the efferent response with type 2 indicating a cardioinhibitory response with and without asystole, type 3 indicating a vasodepressor response, and type 1 a mixed response.[46] Classification based on the afferent limb includes situations such as cough, swallow, micturition, or defecation syncope. The different types of reflex-mediated syncope are summarized as follows:

- "*Vasovagal or neurocardiogenic syncope*" is the most common type of reflex-mediated syncope. It usually occurs following prolonged standing, that is, orthostatic stress, pain, anxiety, or medical instrumentation. Patients frequently experience a sensation of increased warmth, nausea, lightheadedness, and pallor before the syncopal event. Palpitations are common with reflex-mediated syncope, as patients often experience a hyperadrenergic state before the activation of the reflex that leads to sinus bradycardia or asystole.[47] Unlike patients with cardiac syncope due to a tachyarrhythmia, patients with vasovagal syncope have palpitations for 2-3 minutes before the LOC. Patients with cardiac syncope due to a tachyarrhythmia usually experience LOC within seconds after the onset of palpitations.[48] It is important to note that in some instances, vasovagal syncope might not be preceded by any prodromes. This is particularly true in the elderly where the presentation is often atypical. In such instances, the health care provider should still be suspicious of the diagnosis if the LOC occurred following a known trigger and the patient has no evidence of abnormalities on ECG or structural heart disease. Fatigue after the event is common in patients with vasovagal syncope. In one study, up to 94% of patients with vasovagal syncope reported fatigue (66% severe fatigue) after syncope compared with 16% in patients with ventricular tachycardia and 0% in patients with AV block. This feature of the clinical history is helpful in differentiating reflex syncope from cardiac syncope particularly in patients with no structural heart disease.

  The need for tilt-table testing in patients suspected of having vasovagal syncope depends on the history. If a known trigger precedes the syncopal event and the patient gives a history of autonomic symptoms, the diagnosis of vasovagal syncope is certain, and no further testing is needed. In the absence of a known trigger or autonomic symptoms, tilt-table testing is helpful in confirming the diagnosis. It is important to note that a negative tilt-table test result does not exclude the diagnosis of vasovagal syncope and that the type of response during tilt testing does not always correlate with the hemodynamic changes occurring during a clinical event.

- "*Carotid sinus syncope*" is the second most common type of reflex syncope and occurs most commonly in the elderly population and men.[49-51] The diagnosis is usually made when the patient gives a history of syncope following mechanical manipulation of the carotid sinuses. However, in most instances, the diagnosis is made with carotid sinus massage (CSM) in a patient with syncope and no clear triggers. A CSM is considered positive when the patient has 3 seconds or more of asystole or a decrease in systolic blood pressure greater than 50 mmHg.[52] Patients with positive CSM findings and no syncope are labeled as having carotid sinus hypersensitivity. Patients with positive CSM findings and syncope have carotid sinus syndrome.
- "*Situational syncope*" is a third category of reflex syncope that includes syncope following a variety of activities such as coughing, swallowing, micturition, and defecation.[53,54] Also included under this category is post-exercise syncope. Possible mechanisms include increased intrathoracic pressure resulting in a sudden decrease in venous return and decrease in cardiac output, vagal surge with subsequent bradycardia and asystole, and vasodilation resulting in hypotension.

Treatment of Reflex Syncope. Once the diagnosis of reflex-mediated syncope is made, attention should be turned to treatment. Treatment falls into 3 main categories: lifestyle modification (nonpharmacologic intervention), pharmacologic therapy, and pacemaker therapy.

- "Lifestyle modification" and instructions on how to perform counterpressure maneuvers are the first line of therapy in patients with reflex syncope. Patients should be counseled on the importance of preventing dehydration, avoiding excessive heating, and maintaining adequate salt intake. In some patients, salt supplementation may be helpful (2 g of sodium chloride 3 times a day for 2 weeks followed by 1 g 3 times a day). Elastic compression stockings that are waist high providing a minimum of 30 mmHg of ankle counterpressure as well as sleeping with the head of the bed elevated approximately 6 inches to decrease nocturnal diuresis have also been shown to be useful in alleviating symptoms.[55] The importance of recognizing the prodromal symptoms is crucial in avoiding injuries. Once recognized, patients should be instructed on how to perform isometric counterpressure maneuvers to avoid syncope or "buy time" until they could find a place to rest. Isometric arm counterpressure maneuvers including handgrip for 2 minutes starting at the time of symptom-onset has been shown to increase systolic blood pressure on an

average of >10 mmHg leading to a dramatic reduction in syncope (5% vs 47% in the control arm).[56] Similarly, leg crossing and muscle tensing for at least 30 seconds at the onset of symptoms has been shown to increase systolic and diastolic blood pressure during tilt testing, abating symptoms and preventing syncope.[57]

- "Pharmacologic therapy" is indicated when patients continue to be symptomatic despite lifestyle modifications. Indications for drug therapy include the presence of multiple events or a single event resulting in injury.[2] Medical therapy includes mineralocorticoids, vasoactive agents, acetylcholinesterase inhibitors, and serotonin antagonists.[2,58-64] Beta-blockers have not been shown to be effective in 4 of 5 randomized trials and thus are no longer commonly used in the treatment of vasovagal syncope. Having said that, the authors still find them useful in patients with vasovagal syncope and other indications for beta-blocker therapy such as inappropriate sinus tachycardia, postural orthostatic tachycardia syndrome, and elderly patients with a history of hypertension where the use of mineralocorticoids and vasoactive agents is prohibited. A summary of the pharmacologic agents used in vasovagal syncope is provided in Table 4.
- "Pacemaker therapy" aimed at blunting the cardioinhibitory component of reflex-mediated syncope has been evaluated in many trials with significant controversy. This should not come as a surprise as pacing only addresses 1 component of the reflex, namely, the cardioinhibition with no effect on vasodilation. Earlier studies showed benefit, but they were not blinded or placebo controlled. Therefore, the results might have been due to ascertainment bias or placebo effect of pacemaker implantation or both. Subsequent randomized trials showed no added value. Recently, the ISSUE 3 trial[65] renewed interest in pacing in patients with significant cardioinhibitory response defined as ≥ 3 seconds of asystole with syncope or ≥ 6 seconds of asystole without symptoms during prolonged monitoring. It is important to note that patients enrolled in the ISSUE 3 trial were ≥ 40 years old and had at least 3 events in the past 2 years. In addition, the presence of asystole was required during monitoring independent of the tilt results. In fact, a positive tilt-table test result was a predictor of poor response to pacing. In an editorial, the authors speculated that this may be explained by the presence of "hypotensive susceptibility" in patients with a positive tilt table test result and thus a greater propensity for a vasodepressor response during clinical events.[66] Table 5 summarizes the trials evaluating the use of permanent pacemaker therapy in reflex-mediated syncope.[65,67-72] Most experts defer implantation of a permanent pacemaker as a last resort only after exhausting other therapies.

TABLE 4. Drug therapy in the treatment of vasovagal syncope

Class	Agents	Mechanism	Comments
Mineralocorticoid	Fludrocortisone	Expands fluid volume and may promote peripheral vasoconstriction through increased alpha receptor sensitivity	May be limited by peripheral edema and weight gain
Vasoconstrictive agents	Midodrine	Alpha adrenergic vasoconstriction	2009 ESC Class IIb recommendation. May be limited by supine hypertension
Serotonin antagonists	Fluoxetine, paroxetine, and venlafaxine	Downregulate postsynaptic receptor density and thereby blunt effects of serotonin in mediating sympathetic withdrawal	Paroxetine was shown to be effective on a placebo-controlled trial[58]
Beta-adrenergic blockers	Metoprolol, propranolol, atenolol, and nadalol	Negative inotropic effects may lessen the degree of cardiac mechanoreceptor activation during periods of reduced venous return. Decreases vasodilation owing to peripheral effect	2009 ESC Class III recommendation. May be helpful in patients with concurrent IST, POTS, and older patients with hypertension

IST, inappropriate sinus tachycardia; POTS, postural orthostatic tachycardia syndrome

The 2012 ACC/AHA/HRS device guidelines update[73] stated that permanent pacing may be considered for significantly symptomatic neurocardiogenic syncope associated with bradycardia documented spontaneously or at the time of tilt-table testing (Class IIb). They also advised that permanent pacing is not indicated for situational vasovagal syncope in which avoidance behavior is effective and preferred (Class III). The 2013 ESC Guidelines on cardiac pacing[74] have similar recommendations, with a Class IIb recommendation for tilt-induced cardioinhibitory response with recurrent frequent unpredictable syncope and age >40 years after alternative therapy has failed. Cardiac pacing was not recommended in the absence of a documented cardioinhibitory reflex (Class III).

As with the treatment of vasovagal syncope, patients with carotid sinus syndrome syncope should be educated on nonpharmacologic measures or lifestyle modification. Avoidance of accidental manipulation of the carotid sinus with either manual manipulation or tight neck collars should be avoided. In patients who have a predominately cardioinhibitory response, pacing has been shown to be effective. Indeed, patients with carotid sinus syndrome have a high prevalence of asystole during prolonged monitoring[75,76] and fewer recurrences after pacing when compared with patients

TABLE 5. Pacing therapy in the treatment of vasovagal syncope

Trial (Year)	Methods	Population	Intervention	Results
VPS-I (1999)[69]	Randomized, nonblinded, non–placebo-controlled pilot study	≥6 Lifetime episodes of syncope AND positive tilt-table test finding with relative bradycardia	DDD pacemaker with rate-drop response vs no pacemaker	There was a marked reduction in the risk of syncope in pacemaker patients (RRR = 85.4% (95% CI: 59.7%-94.7%, $P <$ 0.0001)
VASIS (2000)[46]	Randomized, nonblinded, multicenter trial	≥3 Syncopal episodes in the last 2 y VASIS type 2A or 2B cardioinhibitory response to head-up tilt testing Age ≥40 y, or if <40 y, proven refractoriness to conventional drug therapy	DDI at 80 bpm with hysteresis vs no pacemaker	Syncope recurrence at 5% in the pacemaker group vs 61% in the nonpacemaker arm ($P =$ 0.0006)
SYDIT Trial (2001)[67]	Randomized, multicenter trial	Age >35 y ≥3 Episodes in preceding 2 y Positive tilt-table response with relative bradycardia	DDD pacing with rate-drop response vs atenolol 100 mg daily	First recurrence of syncope was 4.3% in the pacing arm vs 25.5% in drug arm ($P =$ 0.004)
VPS-II (2003)[70]	Randomized, double-blind, multicenter trial	Age >19 y ≥6 Episodes ever, or >3 episodes in past 2 y Positive tilt-table test result with a heart rate *x* BP product <6000/min *x* mm Hg	Pacer in all patients with DDD + rate-drop response vs ODO mode	First recurrence of syncope at 33% in DDD group vs 42% in ODO group ($P =$ 0.14)
SYNPACE (2004)[71]	Randomized, double-blind, placebo, multicenter trial	Age ≥18 y >6 Episodes ever with the last one occurring within 6 mo At least 1 recurrence within 12 mo following positive tilt test result Significant cardioinhibitory component during tilt test	Pacer in all with DDD + rate-drop response vs OOO mode	During a median of 715 d of follow-up, 50% recurrence in DDD group vs 38% in the OOO group ($P =$ NS)
ISSUE 3 (2012)[65]	Double-blind, randomized,	Age ≥40 y	Pacer in all with DDD pacing +	2-Y syncope recurrence rate

TABLE 5. Continued

Trial (Year)	Methods	Population	Intervention	Results
	placebo-controlled, multicenter trial	≥3 Syncopal episodes in past 2 y ≥3 s Of asystole with syncope or ≥6 s asystole without syncope	rate-drop response vs sensing only	was 21% with pacing ON vs 49% with pacing OFF (RRR = 57%, $P = 0.039$)

Pacemaker setting- atria AND ventricle are paced OR inhibited; NS, non significant; RRR, relative risk ratio; SYDIT, SYncope DIagnosis and Treatment study; SYNPAC, vasovagal SYNcope and PACing trial; VASIS, Vasovagal Syncope International Study; VPS, Vasovagal Pacemaker Study.

without pacing therapy.[77,78] Accordingly, in the most recent guidelines, it is stated that permanent pacing is indicated for recurrent syncope caused by spontaneously occurring carotid sinus stimulation that induces >3 seconds of asystole (Class I) and is reasonable for syncope without provocative events in patients who have a hypersensitive cardioinhibitory response of 3 seconds or longer (Class IIa).

Orthostatic Hypotension

With the assumption of the upright position, 500-800 mL of blood is displaced from the thorax to the abdomen and lower extremities, resulting in decreased cardiac filling. Unloading of the baroreceptors in turn leads to an increase in heart rate (10-15 bpm) and a slight elevation in diastolic blood pressure owing to reflex sympatho-excitation. With prolonged standing, there is an increase in capillary pressure leading to additional fluid shift and activation of the renin-angiotensin-aldosterone system.

Definition. Orthostatic hypotension occurs when there is a reduction in intravascular volume or impairment in the baroreflex due to intrinsic (autonomic dysfunction) or extrinsic (drug therapy) factors resulting in a decrease of >20 mmHg in systolic blood pressure. Syncope occurs when there is significant reduction in blood pressure and cerebral hypoperfusion leading to T-LOC.

Classification of Orthostatic Hypotension. When the decrease in blood pressure occurs within 3 minutes of standing with reproduction of clinical symptoms, the diagnosis is "early orthostatic hypotension." Causes of early orthostatic hypotension include hypovolemia, drug side effects, and autonomic dysfunction. It is important to note that in some cases, blood pressure decreases immediately after standing, that is,

within 30 seconds with rapid and spontaneous recovery owing to a healthy baroreflex. In such instances, the diagnosis can be missed unless the test is performed with continuous blood pressure monitoring. When the decrease in blood pressure occurs following prolonged standing with reproduction of clinical symptoms, the diagnosis is "delayed orthostatic hypotension."

It is important not confuse neurocardiogenic syncope with delayed orthostatic hypotension. In the former group, patients have a normal early response with an appropriate increase in heart rate and no change in blood pressure until the vasovagal reflex is activated resulting in cardioinhibition, vasodilation, and hypotension. In the latter group, the response to orthostatic stress is abnormal from the beginning. Patients exhibit an early and gradual decline in blood pressure immediately after standing without any significant change in heart rate. Once the decrease in blood pressure becomes significant, symptoms of cerebral hypoperfusion manifest including syncope without the typical autonomic symptoms seen with vasovagal events. Therefore, delayed orthostatic hypotension is characterized by a slow and gradual decrease in blood pressure with no significant change in heart rate. The mechanism is impairment of the compensatory reflexes owing to aging, hypertension, diabetes, and other causes of autonomic dysfunction.

Treatment of Orthostatic Hypotension. Treatment of orthostatic hypotension starts with volume expansion and elimination of offending agents. In the absence of hypertension, patients should be encouraged to drink 2-3 L of fluids per day and increase salt intake.[79] In addition, they should be instructed to sleep with the head of the bed elevated to decrease nocturnal diuresis.[80] Lastly, compression stocking should be prescribed to minimize venous pooling.[81] If the aforementioned interventions fail to control symptoms, then the use of Florinef (0.1-0.3 mg daily), a mineralocorticoid that stimulates renal sodium retention,[82,83] and midodrine (2.5-10 mg 3 times a day), an alpha agonist,[84-86] are recommended. In our practice, we always start with Florinef as the effects of an alpha agonist are not likely to be significant if the patient is already vasoconstricted due to hypovolemia.

Joseph Alpert: As in so many conditions, therapy should be individualized and titrated to prevent excessive increases in lying blood pressure or volume overload or both. This caveat is particularly relevant with geriatric patients.

Patients with orthostatic hypotension and supine hypertension pose a challenge to health care providers. Impairment of the baroreflex is most likely contributing to both problems with inability to vasoconstrict in the upright position and inability to vasodilate in the supine position. Sleeping with the head of the bed elevated has been shown to help with the management of nocturnal hypertension.[80] The authors find propranolol (10-40 mg twice a day), a nonselective beta-blocker to be useful in the treatment of hypertension owing to its peripheral effects. Indeed, other antihypertensive agents including diuretics and vasodilators often exacerbate the orthostatic hypotension problem. Pyridostigmine (30-60 mg 3 times day), an acetylcholinesterase inhibitor, has also been shown to be helpful in the treatment of orthostatic hypotension.[64] By increasing the availability of acetylcholine at ganglionic nicotinic acetylcholine receptors, it is postulated to result in an increase in sympathetic ganglionic transmission and ultimately systemic resistance. Lastly, nitroglycerin patch starting with a low dose of 100 μg at bedtime can help control the supine hypertension and allow the uptitration of vasoactive agents during daytime. However, caution should be taken when waking up to go to the bathroom.

A summary of the approach to patients with syncope including initial evaluation, short-term risk assessment, and syncope classification is provided in Figure 4.

Special Considerations in the Elderly

Advanced age is associated with increased susceptibility to syncope due to impairments of heart rate and blood pressure regulation and increased incidence of cardiac arrhythmias.[87,88] In addition, cerebral autoregulation is impaired with aging particularly in the presence of hypertension rendering moderate declines in blood pressure of any cause symptomatic.[89]

The most common causes of syncope in the elderly are reflex syncope including carotid sinus syndrome, orthostatic hypotension, and cardiac arrhythmias such as sick sinus syndrome and AV block.[90] Aortic stenosis, pulmonary emboli, and cardiac ischemia are rare causes. It is important to note that significant overlap exists between syncope and falls in the elderly.[2,11,15,16,32] Because of amnesia and frequent absence of witnesses, patient with recurrent LOC might present with falls. Furthermore, transient drop in blood pressure might result in loss of postural tone and a fall without any true LOC. Therefore, a careful assessment of the cardiovascular system is recommended in patients with unexplained falls.

In the following section, we discuss entities that merit attention in the elderly. The definitions have already been covered in the section on

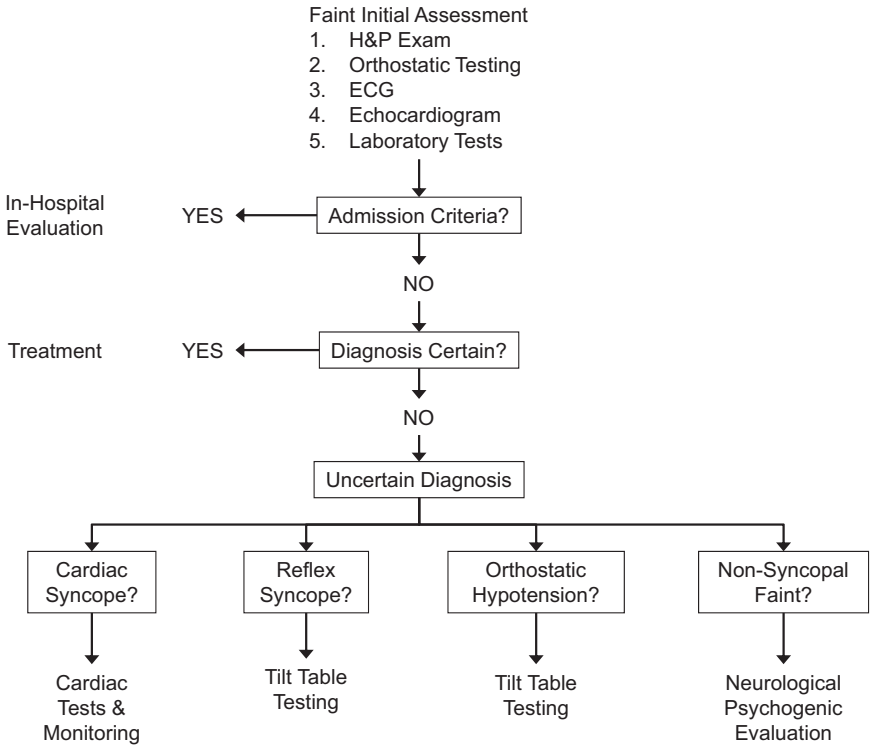

FIG 4. Approach to patients with syncope. (Adapted with permission from Brignole et al.[114])

"Classification of Syncope." Therefore, we focus on specifics related to the elderly patient presenting with syncope.

Orthostatic Hypotension

Orthostatic hypotension is the cause of syncope in 4.2%-30.5% of patients older than 65 years.[90] Main reasons for the increased incidence include (1) reduction in thirst, (2) reduction in the ability to preserve sodium and water, (3) impairment of the baroreflex, (4) impairment of autonomic dysfunction, and (5) polypharmacy. Indeed, it is estimated that one-third of people older than 65 years are taking 3 or more prescribed medications. Medications including antihypertensive agents and postprandial state aggravate the problem.

Postprandial Hypotension

Postprandial hypotension is defined as a decrease in systolic blood pressure $\geq$ 20 mmHg or less than 90 mmHg from a baseline of $\geq$

100 mmHg within 2 hours after a meal. Its prevalence in institutionalized elders is 25%-38% and higher in patients with Parkinson disease.[91-94] Risk factors include polypharmacy, diuretics, meals rich in carbohydrate, and several comorbid conditions including diabetes mellitus, hypertension, Parkinson disease, autonomic dysfunction, and end-stage renal disease on hemodialysis. Postprandial hypotension is more common following breakfast and lunch, and the degree of blood pressure decrease is positively correlated with age and morning blood pressure.

Patients with postprandial hypotension can present with syncope, falls, and even coronary events and stroke. The mechanism appears to be inadequate compensation for the normal physiological postmeal decrease in blood pressure. The diagnosis is made based on ambulatory blood pressure monitoring and symptoms. Treatment options include lifestyle modification and pharmacotherapy including drinking water up to 500 ml before meals, decreasing carbohydrate consumption, and having small and frequent meals.

Vasovagal Syncope

Vasovagal syncope has been reported in up to 31% of patients older than 65 years who presented with syncope.[1,95,96] The classical prodrome in older patients is usually short or nonexistent. The length of time between symptom onset and presentation is shorter than what is seen with younger patients.[97,98] Chronic treatment with angiotensin-converting enzyme inhibitors, calcium channel blockers, beta-blockers, and nitrates is associated with an increased susceptibility to a hypotensive response to orthostatic stress.[99] Up to 77% of patients with dementia and 57% of patients with Alzheimer disease have neurocardiovascular instability and thus should be evaluated for orthostatic hypotension and reflex syncope when presenting with syncope or falls.[100] Indeed, because of amnesia, the presentation might be a fall, a transient ischemic attack, or even a seizure when the actual mechanism is cerebral hypoxia.

In the elderly, tilt testing is often required to confirm the diagnosis because of the lack of typical features or nonexistent prodromes. The sensitivity of drug-free passive tilt testing decreases with age, thus the need for pharmacologic challenge.[101]

Carotid Sinus Hypersensitivity

Carotid sinus hypersensitivity is defined as an abnormal heart rate and blood pressure response to CSM in the absence of syncope. Its prevalence increases with age and in patients with unexplained falls[102] and

dementia.[103,104] Given its high prevalence in the elderly, it has been investigated as a possible cause for syncope and falls and has been a target for intervention. Although pacing has been shown to be beneficial in patients with syncope and significant cardioinhibitory response to CSM, its use in patients with unexplained falls has not been established. The SAFE PACE Trial[49] evaluated the use of pacing in 175 patients seen in an emergency facility because of a fall without LOC. They were randomly assigned to a dual-chamber pacemaker (DDD with rate-drop response) or no therapy. The primary outcome was the number of falls during a 12-month follow-up period. Pacing significantly reduced the mean frequency of falls by 66% (4.1 vs 9.3 per year for controls) in patients with nonaccidental fall. Subsequent randomized double-blinded trials, however, showed no significant reduction in falls with pacing.[49,50] Accordingly, the most recent ESC guidelines gave a Class III recommendation for pacing in patients with unexplained falls. It is recommended to proceed with prolonged monitoring, that is, ILR at the end of the conventional workup instead of empiric pacing.

Use of Syncope Units

Despite several published guidelines, significant variability exists in our approach and management of patients with syncope in both the ED and outpatient setting. In specific, there has been overuse of expensive tests such as brain imaging and underuse of inexpensive tests such as tilt-table testing and CSM. With these practices, the rate of admission has been high and the rate of diagnosis low. Several models of syncope units have been established to address this problem and have shown promise.

Kenny et al[105] introduced in Newcastle, UK, a dedicated syncope and falls day-case facility that provided rapid access for patients presenting both in the outpatient setting and from the ED. It provided a multi-disciplinary approach for the evaluation and management of patients with T-LOC and falls in the elderly. A geriatrician, internist, or general practitioner supervises the clinic with access to non-invasive testing. This model evolved over the years to include defined protocols that have been shown to reduce the number of admissions and increase the rate of diagnosis while reducing cost.[106] A recent study from the Newcastle Rapid Access Falls and Syncope Service including 80 new patients aged ≥ 65 years who presented for the first time with LOC showed a diagnostic rate of 92.5%.[106]

Brignole et al introduced in Italy a syncope unit run by cardiology with the main purpose of standardizing the approach to patients with syncope.

This model was very successful and now has been adopted in several Italian hospitals. Overall, 279 patients treated in hospitals with syncope units were compared with 274 patients treated in control hospitals.[107] The use of tests was significantly different in the study group when compared with the control group, with fewer brain imaging and echocardiogram examinations and more tilt testing and CSM. Brignole et al[108] recently reported their experience with 941 consecutive patients referred to the syncope units of 9 Italian hospitals. A diagnosis was established early in 21% of patients and within 45 days in another 61% of patients with a mean of 2.9 $\pm$ 1.6 tests per patients.

Investigators at the Mayo Clinic tested the hypothesis that a designated syncope unit in the ED improved the diagnostic yield and reduced hospital admission for patients with syncope who are at intermediate risk for an adverse cardiovascular outcome.[109] In total, 103 intermediate-risk patients with syncope who presented to the ED were randomized to "syncope unit" evaluation vs "standard care." The patients in the syncope unit had telemetry for 6 hours, hourly vital signs, orthostatic blood pressure checks, and immediate availability to echocardiogram, tilt-table test, and electrophysiology consultations. The authors found that the rate of diagnosis was higher in the "syncope unit" arm when compared with the "standard care" arm (67% vs 10%, $P < 0.001$). In addition, the rate of admission was much lower at 43% vs 98%, respectively. Actual survival and survival free from recurrent syncope was not different between the groups.

Our group recently introduced the Faint and Fall Clinic model first at the University of Utah and subsequently at the University of Wisconsin where a new algorithm derived from the most recent ESC guidelines is incorporated in the management of patients with fainting spells or falls. A cardiologist and a geriatrician supervise the clinic with access to neurology services. With the use of a standardized approach, the rate of admissions decreased from 20% to 4% ($P < 0.001$), and the rate of diagnosis at 45 days increased from 45% to 57% ($P = 0.09$) in the total population studied and from 39% to 57% in the outpatient subgroup ($P = 0.02$). In addition, we found that the number of tests was significantly lower in the standardized group when compared with the conventional group (1.9 $\pm$ 1.0 vs 2.6 $\pm$ 1.2, $P = 0.001$).[110]

In summary, the adoption of a standardized approach in the management of patients presenting with syncope has been shown to decrease the number of unnecessary admissions[105,109,110] and improve the rate diagnosis.[108,110,111] Structured pathways have been adopted in both virtual and fixed clinics and have consistently shown improvement in patient care with a decrease in cost per diagnosis.[112,113] In 2009, the ESC with the

endorsement of the Heart Rhythm Society recommended the establishment of formal syncope units with access to syncope experts.[2] The success of such units require having (1) the "right" specialist, (2) standardized assessment, which could be facilitated with the introduction of an interactive decision-making software, and (3) core equipment with access to specialized tests.

Summary

Syncope remains a major health care problem with significant financial burden. In most patients, the etiology can be determined with a thorough history and physical examination including orthostatic assessment. When cardiac syncope is suspected, monitoring is indicated until a diagnosis is made. In patients with suspected reflex syncope or orthostatic hypotension, outpatient evaluation with tilt-table testing is appropriate. Strong considerations should be given to the creation of syncope units as they have been shown to improve the rate of diagnosis while reducing cost by decreasing the number of unnecessary admissions and tests used.

Joseph Alpert: The authors are to be congratulated on this excellent and clinically relevant monograph. Syncope is a very common and frequently a very serious event with many seniors suffering severe head and limb trauma.

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