Syncope

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Syncope is defined as a transient loss of consciousness (TLOC) attributable to global cerebral hypo-perfusion, further characterized by rapid onset, brevity, and spontaneous recovery.[1] It is a common presentation to the emergency department, accounting for ≈1% of attendances.[2,3] In the United States, 30% to 40% of such patients are subsequently admitted for further investigation at an annual cost of $2.4billion according to the Medicare database.[2,4–6] This relates to multiple expensive, low-yield investigations and unnecessary hospital admissions.[1] Beyond the economic impact, recurrent syncope is associated with significant morbidity[7] with the adverse impact on quality of life similar to other chronic diseases such as rheumatoid arthritis.[8] The prognosis after syncope ranges from relatively benign for vasovagal to poor for ventricular tachyarrhythmia,[9] but invariably creates anxiety and potentially life-changing disruption demanding timely resolution. Management of vasovagal syncope, which is the commonest cause, remains challenging in many.

The 2009 European Society of Cardiology (ESC) guidelines for the diagnosis and management of syncope provide an excellent and comprehensive reference.[1] We will attempt to summarize the key elements in diagnosis and management, while pointing out new diagnostic tools and therapies. Notwithstanding substantive progress, advancement has been more evolutionary than revolutionary with as yet incomplete understanding of the pathophysiology and optimal therapy of reflex syncope in particular.

Epidemiology

Syncope is common, with a similar incidence in men and women.[9,10] The lifetime cumulative incidence of syncope is ≥35%, with peak prevalence of the first episode between ages 10–35.[11] The incidence increases with age, especially after 70 years,[9,10] and is bimodal with peaks at 20 and 80 years.[10]

Etiology

Syncope may be classified as reflex, orthostatic hypotensive, and cardiac. Nonsyncopal causes of TLOC always figure in the differential diagnosis because of obvious similarity in clinical presentation (Table 1). The commonest cause, irrespective of age, sex, or comorbidity, is vasovagal.[9,12] The second commonest cause is cardiac syncope.[9] Carotid sinus syncope and orthostatic hypotension rarely cause syncope in those under the age of 40 years.[1] As many as 50% still remain undiagnosed after clinical presentation.[9,11]

Reflex or Neurally Mediated Syncope

A heterogeneous group of disorders consisting of vasovagal syncope, situational syncope, carotid sinus syncope, and others are generally grouped as reflex or neurally mediated syncope. Although the provoking stimuli differ, they share sequelae of hypotension and vasodilatation with relative or absolute bradycardia. This is thought to be related to abrupt withdrawal of sympathetic and increase in parasympathetic tone.[13] Orthostatic stress is the main trigger for vasovagal syncope.[13] The ventricular theory is widely accepted, postulating that baroreceptors react to a decrease in blood pressure by sympathetic activation leading to greater cardiac inotropy, chronotropy, and peripheral vasoconstriction. In the setting of reduced ventricular filling or preload, excessive wall tension develops within the vigorously contracting empty left ventricle, activating ventricular mechanoreceptors (C fibers), mimicking conditions seen in hypertension. This provokes reflex compensatory bradycardia and vasodilatation, a seemingly paradoxical response to the initiating hypotension.[13] Baroreceptor hypersensitivity is one of many other postulates.[14,15] Strong emotion or physical pain can also trigger vasovagal syncope by poorly understood mechanisms. Some situational syncope appears to be triggered by distension of hollow viscera, including the esophagus, rectum, and bladder, which in turn activates sensory-proprioceptive or specialized afferent nerves resulting in syncope.[13] Carotid sinus syncope typically occurs in the elderly, classically with neck stretching but often without obvious triggers. This is thought to be related to carotid baroreceptor hypersensitivity, potentially verified by carotid sinus massage.[16]

Unfortunately, there is no perfect animal model for reflex syncope, and the periodicity of events in patients is highly variable making study of spontaneous events challenging. The family of reflex syncope is likely mechanistically eclectic.[13]

Orthostatic Hypotension

The common denominator is insufficient peripheral vasoconstriction (physiological or pathological) in response to orthostatic stress. Classical orthostatic hypotension has been arbitrarily defined as a drop in systolic blood pressure of >20 mm Hg or diastolic blood pressure of >10 mm Hg within 3 minutes of standing.[17] Acute hemorrhage or excessive diuresis and rarely Addison disease can lead to orthostatic hypotension. Autonomic insufficiency is frequently related to or aggravated by medication use, advancing age, or diabetes mellitus. Primary autonomic dysfunction is observed in Parkinson disease, Lewy Body dementia, multisystem atrophy, or pure

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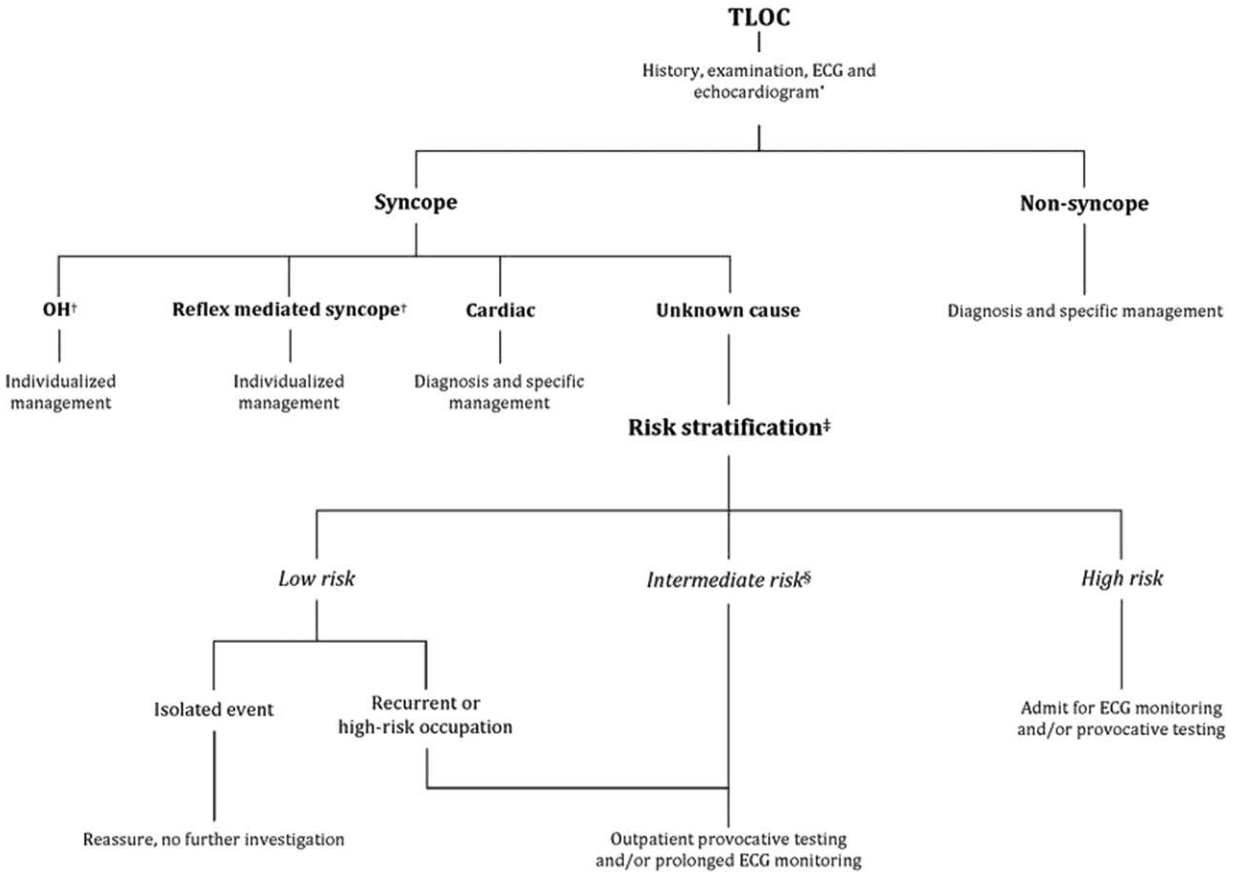

* Echocardiogram is reasonable in selected cases where cardiac disease is suspected.
† Denotes a presumptive diagnosis in the absence of other abnormalities on evaluation.
‡ Denotes the use of the ESC or CCS risk stratification guidelines (Table 2).
§ Denotes the presence of 1 or more minor CCS criteria. The urgency of further testing is determined accordingly.

Figure. Algorithm for the investigation of transient loss of consciousness (TLOC). OH indicates orthostatic hypotension.

autonomic failure. Orthostatic hypotension may also trigger reflex mediated syncope.[18]

Cardiac Syncope

Cardiac syncope is most often arrhythmic. Syncope during tachycardia is related to rate but modulated by the specific arrhythmia (supraventricular/ventricular), preload conditions, posture, left ventricular function, and adequacy of vascular adaptation.[19] Sinus node dysfunction or AV block may cause bradycardia directly or after tachycardia termination (tachy-brady). Syncope attributable to sinus node dysfunction or AV block is often related to vascular adaptation to sudden rate drop, because most patients with fixed bradycardia have normal or elevated systolic blood pressure. Tachycardia may trigger vasovagal syncope.[20] Bradycardia may prolong the QT interval in susceptible individuals and trigger torsade de pointes. Fixed or dynamic mechanical obstruction to cardiac output especially with exertion is less frequent.

Prognosis and Recurrence

Prognosis is determined by the underlying etiology, specifically the presence and severity of cardiac disease. Untreated, mortality can be >10% at 6 months,[9] whereas vasovagal and other reflex mediated syncope have a generally favorable prognosis.[9]

An estimate of the composite mortality between 7 and 30 days after presentation for syncope according to a recent review of the literature is 0.7%.[21] The risk increases to ≈10% at 1 year. An average 7.5% of patients with syncope referred to the emergency department will have a severe nonfatal outcome (defined as a new diagnosis, clinical deterioration, syncope recurrence with injury, or a significant therapeutic intervention) while in the emergency department.[21] A further 4.5% will have a severe nonfatal outcome in the after 7-30 days. Only half these events are attributable to cardiovascular causes.

Syncope most frequently occurs as an isolated event with recurrence restricted to ≈20% of cases.[9] Cardiac syncope has the highest risk of recurrence (multivariable-adjusted hazard ratio 30).[9] Recurrence of vasovagal syncope is best predicted by the frequency of events in the preceding year with rates of 7%, 22%, and 69% in those with 0, <2, or >6 syncopal events, respectively in the preceding year.[22] This was demonstrated to be a better predictor of vasovagal syncope recurrence in the ensuing year than the cumulative lifetime episodes or the remote (before the preceding year) frequency of syncopal

Table 1. The Causes of Loss of Consciousness and Their Prevalence

Causes of Loss of Consciousness (LOC)		
Syncope		Prevalence (%)
Reflex mediated syncope	Carotid sinus syndrome	1
	Situational syncope (cough, micturating etc.)	3
	Vasovagal syncope	14
Orthostatic hypotension	Primary autonomic dysfunction	11
	Secondary autonomic dysfunction (drugs/DM/amyloid)	
	Acute massive hemorrhage	
	Addison's disease	
Cardiac	Tachyarrhythmia and bradyarrhythmia	14
	Hemodynamic/valvular (eg, hypertrophic obstructive cardiomyopathy, aortic stenosis, pulmonary hypertension or massive PE)	3
Nonsyncope		
Seizures		7
Drop attacks†		
Fall†		
Vertebrobasilar TIA	Left subclavian Steal syndrome	
Metabolic	Medication/drug overdose	7
	Hypoglycemia	
	Hypo/hypernatremia	
	Hypoxia/Hypercapnia	
Pseudo-syncope†		1
Unknown		39

DM indicates Diabetes mellitus; PE, pulmonary embolism; and TIA, transient ischemic attack. Adapted from Schnipper JL, Kapoor WK. Diagnostic evaluation and management of patients with syncope. *Med Clin North Am.* 2001;85:423–456.

†Loss of consciousness is only apparent not literal.

events.[22] In essence, patients with vasovagal syncope often have clustering of events separated by long periods of quiescence.

The Initial Assessment

A focal point of investigation is identification of the patient potentially at risk for sudden death, that, is risk stratification (Table 2). This can be achieved by history, ECG, and assessment for structural heart disease. A normal ECG and absence of structural heart disease are generally prognostically favorable. The patient with a single episode of syncope without injury can be generally reassured if the preliminary workup (ECG and echocardiogram) is normal; further investigation is rarely productive (Figure).

The history, physical examination, and the 12-lead ECG are the usual starting points to investigation. An account by a witness is often extremely helpful and worthy of pursuit. The ECG is infrequently diagnostic (yield <5%)[23] but prognostically useful and may provide clues of varying significance such as conduction defect, preexcitation, QT prolongation, Brugada pattern, etc. Key historical features are as follows:

1. The Circumstance
   a. Vasovagal syncope is classically triggered by pain, medical procedures, prolonged standing, or hot or crowded surroundings[24,25] but frequently occurs without an obvious trigger.
   b. Syncope during cough, micturition, defecation, or swallowing suggests situational syncope, while shaving or neck extension suggests carotid sinus syndrome.
   c. Syncope during exertion is generally worrisome, although syncope shortly after exertion is relatively common in vasovagal syncope.
   d. Provocation by sudden noise, strong emotion or exercise suggests long QT syndrome.
2. The Prodrome
   a. Vasovagal syncope is classically associated with a prodrome of warmth, diaphoresis, nausea, ringing in the ears, or abdominal pain. The prodrome is often consistent in an individual.
   b. Vasovagal syncope in the elderly often lacks significant warning, in part because retrograde amnesia is common.[26,27]
   c. A very brief or absent prodrome is more typical of arrhythmia. Palpitations suggest tachyarrhythmia but are often nonspecific.
   d. TLOC associated with déjà vu, jamais vu, sensory aura, olfactory hallucinations, preoccupation, or behavior changes suggests seizure.[28]
3. During TLOC
   a. Syncope involves brief TLOC, generally <5 minutes and typically <30 seconds.
   b. Pallor or diaphoresis suggest vasovagal syncope.[24]
   c. Cyanosis suggests cardiac syncope.[24]
   d. Unusual posturing, head turning, tongue biting, or rhythmic limb jerking are more consistent with seizures.[28–30] This notwithstanding, syncope can cause seizure-like motor activity and seizures may also cause arrhythmia.[31–33]
   e. Psychogenic (pseudo syncope) may result in atypical features such as resistance to attempts to open the eyes or bizarre movements or inconsistencies.
4. The Postdrome
   a. Syncope attributable to transient bradycardia or tachycardia is generally associated with relatively rapid recovery of mentation whereas vasovagal syncope frequently results in more protracted symptoms of fatigue, nausea, and somnolence from minutes to hours.[24,25] Prolonged fatigue after the episode often hours in duration is more typically vasovagal.
   b. TLOC involving postictal confusion and transient neurological deficit suggests seizure.[28]
5. Associated cardiac disease
6. Family history of syncope or untimely sudden death
7. Medications (prescription or other)

Historical criteria for vasovagal syncope have been identified in patients with[24,25] and without[24] structural heart disease

Table 2. High-Risk Features in Syncope That Should Prompt Admission or Early Intensive Evaluation

High-Risk Features in Syncope
ESC guidelines[1]
Severe structural or coronary artery disease: Heart failure, previous myocardial infarction, low left ventricular ejection fraction
ECG features of arrhythmic syncope: Bifascicular block (complete LBBB, RBBB with left hemifasciclar block) or other interventricular conduction delay with QRS duration ≥120ms, nonsustained VT, inadequate sinus bradycardia (<50 bpm) or sinoatrial block in absence of negative chronotropic medications or physical training, pre-excited QRS complex, prolonged or short QT interval, Brugada pattern, negative T waves in right precordial leads, epsilon waves and ventricular late potentials suggestive of Arrhythmogenic right ventricular cardiomyopathy.
Clinical features of arrhythmic syncope: Syncope during exertion, palpitations at the time of syncope or family history of SCD
Important comorbidities: Severe anemia or electrolyte disturbance
CCS guidelines[21]
Abnormal ECG: Any tachyarrhythmia, bradyarrhythmia, conduction disease. New ischemia or old infarct
History of cardiac disease: Ischemic, arrhythmic, structural, obstructive or valvular
Hypotension: Systolic BP <90 mm Hg
Heart failure: Current state or past history
Minor risk factors: Age >60, dyspnea, anemia (hematocrit <0.3), hypertension, cerebrovascular disease, family history of SCD (<50 yr), specific situation (syncope during exertion, while supine, or without prodrome)

The Canadian Cardiac Society (CCS) guidelines echo those of the European Society of Cardiology (ESC), with the addition of minor criteria. Patients with ≥1 minor criteria may be considered for urgent cardiology assessment as either an inpatient or outpatient within 2 wk. Although the rationale for urgent cardiology assessment in high-risk patients is to reduce early mortality, there are no data to support this presumption. bpm indicates beats per minute; LBBB, left bundle branch block; RBBB, right bundle branch block; SCD, sudden cardiac death; and VT, ventricular tachycardia.

as well as to distinguish between seizures and syncope.[28] A point scoring system considers both the presence and absence of key historical features in coming to a diagnosis. Key historical features, although not intended for interpretation in isolation, are listed in Table 3.

The physical examination although less useful should focus on the following:

1. Heart rate (<50bpm).[1]
2. Orthostatic hypotension: Assessed in the supine position followed by active standing for 3 minutes, preferably using a manual sphygmomanometer. A fall in systolic blood pressure (BP) of ≥20 mm Hg, diastolic BP of ≥10 mm Hg, or systolic BP to < 90 mm Hg compared with baseline is considered diagnostic, particularly if associated with symptoms.[1]
3. Heart failure.
4. Valvular heart disease.
5. Focal neurological deficits.
6. Carotid sinus massage is reasonable in patients >40 years with syncope of unknown etiology after initial evaluation.[1] Contraindications include myocardial infarction or stroke within 3 months and the presence of carotid bruits. Continuous ECG monitoring and ideally beat-to-beat BP monitoring is necessary. Carotid sinus massage is performed initially in the supine position, with consecutive gentle rhythmic (1.5 Hz) massage of the right followed by left carotid body for 5–10 seconds.[33] The carotid sinus is typically located at the upper border of the thyroid cartilage medial to the sternocleidomastoid muscle; alternatively, the point of maximum carotid pulsation can be used to account for anatomic variations. An asystolic pause of ≥3 seconds or fall in systolic BP of ≥50 mm Hg is considered positive, suggesting carotid sinus hypersensitivity. If negative, the test may be repeated in the 60 to 70° head up tilt position. ESC guidelines require the reproduction of symptoms to define carotid sinus syndrome. The current definition of carotid sinus hypersensitivity is regarded by some to be too sensitive and lacking specificity.[33] Revised criteria of asystole >6 seconds or fall in systolic BP below 60 mm Hg lasting for ≥6 seconds have been suggested, yet await prospective validation.[33]

Emergency Department Decision Rules and Syncope Units

Risk stratification of patients presenting to the emergency department determines the need for admission resulting in clinical decision rules. The focus of these risk scores is prognosis, not necessarily diagnosis, with the goal of identification of individuals who can be safely discharged. The San Francisco Syncope Rule has been prospectively validated in a large tertiary referral emergency department.[34,35] The pneumonic CHESS (history of Congestive cardiac failure, Hematocrit <30%, abnormal ECG, complaint of Shortness of breath and a triage Systolic BP of <90 mm Hg) lists high risk features. The San Francisco Syncope Rule has a sensitivity and specificity of 98% and 56%, respectively for predicting adverse 30-day outcomes.[35] Other decision rules recognize the importance of an abnormal ECG, history of cardiovascular disease, and increasing age (>45–65 years) in predicting adverse 1-year outcomes.[36,37] Emergency department syncope decision rules help standardize acute management but ultimate reduction in mortality or costs remains to be verified[21,38]

Another structured and systematic approach to the investigation of syncope in the emergency department is the syncope unit. These units are staffed by physicians who have preferential access to specialist consultations and testing. The SEEDS trial was a randomized control trial comparing the evaluation of patients with syncope (of intermediate risk for a cardiac cause) in a syncope unit compared with standard care.[39] The presumptive diagnostic yield was significantly higher in the patients randomized to the syncope unit (67% versus 10%, $P<0.001$). The hospital admission rate and total length of

Table 3. Salient Features Obtained on History Taking That Help Differentiate Between the Commonest Causes of Syncope and Other Nonsyncopal Causes of Transient Loss of Consciousness

Relevant History and Findings	
Vasovagal syncope	Provoked by prolonged standing classically in a hot, or crowded environment or associated with pain or medical procedure.
	Syncope at rest, after exercise.
	Prodrome of nausea, diaphoresis, dyspnea or warmth (often absent in older population)
	Brief LOC (<5min)
	Postdrome of somnolence or fatigue lasting minutes to hours
Cardiac syncope	Syncope at rest or exertion
	Brief or absent prodrome
	Rapid recovery
	Brief LOC (<5min)
	May be preceded by palpitations
Seizures	Prodromal aura (eg, odd smell), preoccupation, déjà vu or jamais vu
	Tongue bitten
	Head turning to one side during LOC
	Unusual posturing during LOC
	Postictal confusion
	Coarse, rhythmic and synchronous limb jerking of ≈1min beginning before or coinciding with LOC.
Pseudo-syncope	Prolonged LOC >15-20min
	Lack of injury in spite of the frequency of episodes
	Resists eye opening during LOC
	Known psychiatric disorder

LOC indicates loss of consciousness.

patient-hospital days was >50% lower in patients randomized to the syncope unit. There was no difference in all-cause mortality or syncope recurrence rates.

The 2009 ESC guidelines provide for a systematic framework for the investigation of syncope. The EGSYS-2 study used online interactive decision making software based on these guidelines to provide a standardized care pathway.[40] Use of this software provided a presumptive diagnosis in 98% of cases, with 50% of patients not requiring any testing beyond the initial evaluation. In a nonrandomized comparison with usual care consisting of generic implementation of the ESC guidelines, the EGSYS software guided approach resulted in significantly higher diagnostic yields, lower hospitalization rates, shorter in hospital stays, and fewer tests performed.[41] This translated into a 19% lower mean cost per patient and 29% lower mean cost per diagnosis compared with standard care (P=0.001).

Diagnosis of TLOC of Unknown Etiology After Initial Assessment: Complementary Roles of Provocative and Monitoring Strategies

The initial evaluation leads to a certain or suspected diagnosis in 50% of cases.[40] An echocardiogram may be used in the initial assessment when there is clinical suspicion of heart disease, especially if, because of body habitus or chronic obstructive pulmonary disease, it is difficult to rule out structural or valvular heart disease on clinical examination. An exercise stress test is recommended if syncope is exercise related, suggesting long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, ischemia, and others. The diagnosis in the patient without a diagnosis after initial assessment has improved considerably but remains challenging.[1]

Monitoring Strategy

This involves varying durations of ECG monitoring in the hope of obtaining the ECG and in future other monitored parameters during a clinical episode. Arguably, this is the gold standard in the investigation of suspected arrhythmic syncope, establishing a symptom-rhythm correlation. Furthermore concomitant sinoatrial slowing or arrest and atrioventricular conduction delay or block may suggest a reflex mediated mechanism. Although documentation of sinus rhythm during syncope does not establish a diagnosis, it does rule out arrhythmia. This informs prognosis and suitably directs further investigation. An obvious disadvantage of a monitoring strategy is the potential for serious injury or death with a subsequent event, so it is generally inappropriate when ventricular tachycardia (VT) or ventricular fibrillation is suspected. Furthermore, the time course of recurrence is unpredictable.[9,42]

Provocative Strategy

Provocative testing aims to establish a diagnosis expeditiously in a controlled environment. The major drawback of such testing is poor sensitivity or specificity. A positive response only implies but does not prove the cause of the clinical event. In reality, both monitoring and provocative tests are used, guided by the frequency of syncope and the perceived risk of serious injury or sudden death.

Head Up Tilt Test

Head Up Tilt Test is most useful in the patient with intermediate risk of vasovagal syncope. It is not helpful with obvious vasovagal syncope by other criteria. A positive test consists of hypotension with relative or overt bradycardia or frank asystole. A positive test is frequently labeled as a cardioinhibitory, vasodepressor, or mixed response,[18] although the response is not necessarily the same during spontaneous syncope or even reproducible on repeat testing.[43,44] Head Up Tilt Test may diagnose orthostatic hypotension, characterized by a failure to compensate for upright posture with a progressive fall in BP. The test can be accelerated with provocative agents, such as intravenous isoproterenol or sublingual nitroglycerine. The reported sensitivity for vasovagal syncope ranges from 26% to 80%,[45] with specificity approaching 90%.[46–51] The specificity of the test is most believable if a patient's unique prodrome is reproduced. A positive test can be useful as confirmation of the clinical diagnosis combined with reinforcing potentially useful patient strategies such as counterpressure maneuvers.[52]

Electrocardiographic Monitoring

Electrocardiographic recording during a clinical episode provides the most direct evidence implicating or disproving arrhythmia. Hospital-based telemetry or fortuitous ECG recording were the first options available.

The Holter monitor routinely provides 24 to 48 hours of monitoring. This can be extended theoretically but is limited practically to 2 weeks or so. The diagnostic yield is poor because expected recurrence is in the range of months to years in most individuals. In 1 study, the yield of electrocardiographic abnormalities was 24% at 48 hours,[53] but only 1 of 95 patients had syncope during 72 hours of monitoring. This highlights the uncertainty of interpreting asymptomatic abnormalities unless compelling.

The external loop recorder permits, practically speaking, monitoring for up to 4 weeks. The external loop recorder records in a looping fashion, saving data if manually or autoactivated for arrhythmia. The diagnostic yield in 1 trial was 21% at 48 hours, 50% at 15 days, and 90% at 33 days.[54] Limitations include improper device application, irritation from the electrode adhesive, poor contact during exercise, and the need for a modest degree of technical proficiency to activate the device or transmit data. Gula et al[54] reported that a patient's ability to operate an automated teller machine predicted their ability to send a test transmission and activate the device during symptoms.

The Mobile Cardiac Outpatient Telemetry device continuously records a surface ECG. The device is coupled to a processor for automated detection of arrhythmia and transtelephonic transmission to a monitoring station. Mobile Cardiac Outpatient Telemetry has some appeal in patients with suspected malignant arrhythmia. Unfortunately, external electrodes are still limiting. In a randomized trial of syncope and presyncope, Mobile Cardiac Outpatient Telemetry had a greater diagnostic yield than external loop recorder.[55]

The main advantages of implantable loop recorders (ILR) are long recording times, freedom from external electrodes, and obviating patient participation in recording. The latest generation of ILRs have a 3-year battery life and are capable of automatic activation as well as remote data transmission. The PICTURE registry demonstrated an ILR diagnosis in 78% of patients with syncope recurrence during an average follow-up of 10 months.[56] The major disadvantage of the current ILR is the need for a minor surgical procedure. This notwithstanding, a strategy of primary ILR monitoring versus usual investigation in recurrent unexplained syncope has been demonstrated to be more efficacious and cost effective.[51]

Electrophysiological Study

Electrophysiological study (EPS) is intended to uncover an underlying propensity to arrhythmia. Tachycardia induction is attempted with programmed stimulation, sensitive for some arrhythmias (ie, VT with previous myocardial infarction) but not for others (eg, long QT syndrome). The specificity of other observed arrhythmias may be unclear, such as ventricular fibrillation with more aggressive stimulation techniques.[57] Arrhythmias such as sustained supraventricular tachycardia and monomorphic VT are sufficiently uncommon in an asymptomatic population that they are generally considered as probably causative when induced. The yield of EPS for VT in particular is greatest in patients with structural heart disease.[58] Accordingly, EPS is not recommended in the setting of a normal heart with no other suggestion of arrhythmia.[1,45] The sensitivity of an EPS for VT in patients with previous myocardial infarction and syncope is estimated at 90% to 95%.[59,60] Noninducibility during EPS in such patients predicts a low risk of sudden death.[59] Noninducibility is less predictive with nonischemic dilated cardiomyopathy.[61–63] EPS is relatively insensitive for identifying bradyarrhythmia, especially paroxysmal AV block.[59,64–66] The finding of a baseline H-V interval >100 ms or infra-Hisian block during incremental atrial pacing is predictive of progression to heart block.[1,67]

The role for EPS in the investigation of syncope has diminished with the availability of modern monitoring technologies and trials suggesting a mortality benefit of ICD in patients with low left ventricular ejection fraction.[68,69]

Adenosine Triphosphate Test

Adenosine triphosphate (ATP) modulates arterial tone, AV and SA node function, cardiac inotropy and dromotropy as well as baroreceptor function though a variety of receptors, and may play a role in the pathophysiology of vasovagal syncope.[70,71] This forms the basis for measurement of endogenous ATP levels and characterization of the response to intravenous ATP in such patients. Limited data support higher ATP levels in tilt positive patients with unexplained syncope, and a dose response correlating higher ATP levels with earlier time to symptoms on Head Up Tilt Test.[72] Conversely, ATP levels were found to be lower in patients with idiopathic paroxysmal AV block compared with age- and sex-matched healthy controls in a small study.[66]

Administration of intravenous ATP with unexplained syncope has been studied with conflicting results. A positive response is variably defined as either a pause (AV or SA block) greater than 10 seconds (ignoring escape beats)[73] or an R-R interval >6 seconds.[43,44] A positive ATP test correlates poorly with the mechanism of spontaneous syncope as documented by ILR,[43,44] but patients with unexplained syncope with a positive ATP test had a better response to dual chamber pacing than those with a negative test.[74] These discrepancies are explained in part by the different demographic to which the test is applied, the variable use of adenosine which is not identical to ATP, and the definition of a positive response.[74]

Although the current ESC guidelines (2009) do not recommend the use of the ATP test in clinical practice, it is worthy of further study.[74]

Neurological Investigations

Historically, EEG and brain imaging were often reflexive with TLOC.[75] They have very low yield (2% to 4%) and are best considered only when there are historical or other clues suggesting seizure or neurological event.[1,75,76]

Treatment

The goals of treatment are to reduce mortality, injury, and recurrences. Treatment is obviously best directed at correction of the underlying cause when this is possible. However, preventative or curative treatment directed at the underlying cause may be incomplete or not possible. The ICD has a clear role in the patient with syncope when a life-threatening ventricular arrhythmia is either detected or suspected. A full discussion of the indications is beyond the scope of this review, which is largely covered by recent syncope and device guidelines.[1,77]

A specific mechanistic preventive measure remains elusive in most reflex mediated syncope or orthostatic hypotension. Accordingly, treatment necessitates multiple measures, which in totality may reduce frequency and associated morbidity.

Vasovagal Syncope

Lifestyle Changes

Lifestyle modification constitutes a foundation of management. Avoiding triggers where possible is obvious. Liberal dietary salt and regular water intake is useful where feasible. Alcohol can be contributory and medication with diuretic or vasodilatory properties should be scrutinized. Enhancing fitness and moderate exercise training may be beneficial.[78]

Physical Counterpressure Maneuvers

When clear prodromal symptoms are present, the primary objective is usually to sit or lie down to avoid injury. Maneuvers to raise blood pressure can be taught. These physical counterpressure maneuvers include leg crossing, squatting, tensing of legs and buttocks, and others have been suggested.[52] Physical counterpressure maneuvers reduced the recurrence of syncope by 39% compared with conventional treatment in 1 randomized trial.[52]

Tilt Training

This consists of progressively longer periods of prescribed upright posture and has been recommended in patients who have a high symptom burden and are motivated, because compliance is typically poor.[79–81] Long-term benefit has yet to be demonstrated with attrition of compliance the rule.

Pharmacological Treatment

Many agents have been prescribed for vasovagal syncope, but results are disappointing. Conflicting data from small, short-term, nonrandomized, or uncontrolled trials abound, with a paucity of high-quality randomized placebo-controlled trial data.

Beta Blockers

Small, randomized trials of β-blockers have provided conflicting results.[82–84] The Prevention of Syncope Trial (POST) was a relatively large multicenter, randomized, double-blind, placebo-controlled study of β-blocker use in vasovagal syncope.[85] No benefit was found. A recent meta-analysis demonstrated a statistically significant difference in response in those aged <42 years and ≥42 years (test of interaction P=0.007).[86] β-Blocker use reduced syncope recurrence in those aged ≥42 years by 48% but increased the risk in those aged < 42years by 58%.[86] Accordingly, the cautious use of β-blockers is reasonable in older patients with vasovagal syncope, particularly when hypertension in present.

Fludrocortisone

Fludrocortisone is a mineralocorticoid analogue that expands plasma volume and sensitizes peripheral α-adrenergic receptors, augmenting vasoconstriction. A small randomized, placebo-controlled trial of fludrocortisone and salt in pediatric vasovagal syncope found it to be ineffective.[87] The Second Prevention of Syncope Trial (POST II) trial will soon report more rigorous data.[88]

Alpha Agonists

Alpha agonists may theoretically reduce venous pooling and counterbalance reflex-mediated arterial vasodilation to prevent syncope. A number of small trials yielded conflicting results,[1] but 2 well-conducted randomized, controlled trials failed to show efficacy.[89,90] Three placebo-controlled randomized, controlled trials have shown efficacy of Midodrine in the treatment of orthostatic hypotension.[91–93] Use of this class of drugs is limited by the need for frequent dosing.

Selective Serotonin Reuptake Inhibitors

Fluctuations in central serotonin levels are believed to facilitate vasovagal syncope though modulation of cerebral blood pressure and heart rate regulation. Grubb et al[94] proposed that selective serotonin reuptake inhibitors reduce vasovagal syncope by downregulating postsynaptic central serotonin receptor levels, blunting the response to abrupt changes in central serotonin levels. In the only randomized, double-blind, placebo-controlled trial of selective serotonin reuptake inhibitors, paroxetine reduced the recurrence of vasovagal syncope by 82.4% compared with 47.1% in the placebo arm (P<0.001) over 2 years.[95] Paroxetine was well tolerated with few side effects. Other selective serotonin reuptake inhibitors such as fluoxetine and sertraline are less well tolerated when used for vasovagal syncope.[94,96] Clinical experience has not replicated the dramatic results of the one randomized trial.

Device Therapy

It is intuitively tempting to consider pacing in vasovagal syncope but the role of pacing in this context remains small and controversial. On the basis of limited yet compelling randomized, controlled trials data, permanent pacing is indicated (class IIa) in carotid sinus syndrome.[97,98]

The first 3 randomized trials of permanent pacing in vasovagal syncope demonstrated a benefit.[99–101] These were all unblinded, lacked placebo-control, and were terminated prematurely when a large favorable treatment effect was observed. The VPSII and SYNPACE trials were the first double blind randomized, controlled trials of permanent pacing in neurally mediated syncope designed to address these limitations.[102,103] All patients received pacemakers, and the control arm devices were functionally programmed off. In contrast to the open label trials, there was no significant difference in the rate of recurrent syncope over a 6-month follow up period.

ISSUE 3 targeted patients with spontaneous bradycardia/pauses detected by monitoring and implanting pacemakers in this group. It is the only positive, double-blind, randomized, placebo-controlled trial of dual chamber permanent pacing in patients with severe neurally-mediated syncope documented by loop recorder, targeting frequent syncope, age >40 with ILR documented spontaneous symptomatic asystolic pauses of >3 seconds or asymptomatic pauses >6 seconds.[104] There was a 57% (P<0.05) relative risk reduction for recurrent syncope in the arm with the pacemaker switched on, observed over 2 years of follow up. There is a residual risk of syncope that speaks to the inability of pacing to overcome the vasodepressor component of the reflex, universally present to some degree. Approximately 9% of patients with vasovagal syncope referred qualified for an attempt at pacing based on the ISSUE 3 selection criteria. Thus pacemakers play a minor role

in vasovagal syncope, but should be considered in those with recurrent syncope and documented spontaneous bradycardia.

Conclusion

Syncope is a common problem that affects all age groups. Although prognosis is generally favorable, it can lead to significant morbidity, reduced quality of life, and a burden on resources. An accurate history remains paramount. Technical innovation in monitoring and better understanding of provocative tests have greatly improved the diagnosis of TLOC, but our understanding of the commonest cause, neurocardiogenic syncope, leaves room for improvement, and management remains challenging in many individuals.

Disclosures

Dr Klein serves as a consultant to Medtronic.

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