Syncope

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Definition

Syncope (from the Greek *Syn* with *koptein,* meaning to cut off) is the sudden, transient loss of consciousness and postural tone with subsequent spontaneous recovery. Before syncope, the patient may experience a variety of prodromal symptoms, typically including the awareness of an impending faint. The latter "near-syncopal" or "presyncopal" state may not always progress to frank loss of consciousness, if the underlying pathophysiologic disturbances that would otherwise culminate in syncope are aborted (either spontaneously or via countermaneuvers, such as assuming the recumbent position). Hypotension with cerebral hypoperfusion distinguishes true syncope from other syndromes, such as hypoglycemia, with which it may be confused. Syncope should also not be confused with sudden cardiac arrest. A person with sudden cardiac arrest loses consciousness suddenly but will die unless they recieve immediate medical attention. However, a person with syncope recovers quickly, almost always without treatment. Although, injuries can occur during a syncopal episode and recurrent episodes can be worrisome.

Most individuals with the "common faint" (vasovagal syncope, described later) do not consult a doctor, and hence the prevalence of syncope is difficult to determine. About one third of adults experience at least one episode of syncope in their lifetime, and syncope accounts for about 3% of emergency room visits and up to 6% of general hospital admissions in the United States [1]. The recurrence rate is as high as 34% on 3-year follow-up [2].

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The range of prognoses in syncope is wide and the main task of the clinician, therefore, is to determine whether the patient has a benign or a life-threatening cause for syncope [3, 4]. One must be concerned about the possibility that the syncopal event actually represents a self-aborted cardiac arrest, with a potentially catastrophic outcome the next time around. Yet even when syncope is not a harbinger of sudden death, it may incur serious secondary morbidity consequent to trauma.

An important caveat to bear in mind for a patient with syncope is recognition that that the actual event has come and gone, leaving the physician to, in effect, "reconstruct" what transpired. Even when abnormalities are uncovered in the course of various diagnostic procedures, it is not immediately evident that the physician has determined the true cause. The physician must integrate all available information, with focused use of diagnostic tests, and then apply sound clinical judgment to arrive at the most reasonable working diagnosis, which will guide therapy selection. Often, only with the passage of time is the accuracy of the hypothesized cause borne out (suppression of further events) or refuted (syncope recurrence)—in which case diagnostic reevaluation is required.

Principal Causes (Table 5.1)

Neurally Mediated Syncope

Patients with these conditions have in common the paroxysmal occurrence of peripheral vasodilatation, bradycardia. or both, which reflects sympathetic withdrawal and hypervagotonia [5].

Vasovagal, vasodepressor, or *neurocardiogenic* syncope—also called the "common faint"—is often caused by a precipitating event such as prolonged standing, hypovolemia (commonly dehydration), fear, severe pain, heat exposure, the sight of blood, strong emotion, or instrumentation; however, it can also occur without obvious cause. In a typical

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Table 5.1 Principal causes of syncope

Neurally mediated syncope
Vasovagal
Situational
Carotid sinus
Orthostatic syncope (drugs, autonomic insufficiency, volume depletion)
Cardiac syncope
Arrhythmic
Structural
Metabolic disturbances
Neurologic, psychiatric disorders
Unexplained etiology

episode of the common faint, there is a prodrome in which the patient may feel unsteady, "feel bad," be confused, yawn, or experience ringing in the ears or visual disturbances (dimming, blurring, or seeing spots). Often there is associated warmth and nausea, sometimes with vomiting; facial pallor and diaphoresis are common. These presyncopal features (typically lasting from 30 to 60 s) are not seen in all patients; the faint may occur suddenly without warning, not allowing time for protection against injury. At the onset of syncope, there is hypotension, often (but not necessarily) accompanied by bradycardia. With protracted hypotension, there may be attendant seizurelike activity (involuntary muscle jerking). On recovery, along with return of consciousness, color returns to the face, blood pressure increases, and bradycardia resolves. Characteristically, consciousness is regained rapidly after the individual is in the supine position, although there is commonly a feeling of postevent fatigue. In patients who have minimal presyncopal warning, telltale symptoms and signs of vasovagal syncope—nausea, warmth, diaphoresis, and pallor—sometimes become apparent only during the recovery phase. The long-term prognosis in neurocardiogenic syncope is generally excellent; however, in some patients, recurrences are frequent and are a major cause for seeking medical attention.

Situational or *reflex* syncope is loss of consciousness during or immediately after coughing, micturition, swallowing, or defecation. Alcohol has been implicated in micturition-related syncope.

Carotid sinus syncope is induced by carotid sinus stimulation, resulting in hypotension, bradycardia, or both. Sensitive individuals, typically elderly men, may develop carotid sinus syncope with tight shirt collars or while shaving the neck.

Orthostatic Syncope

This type of syncope results from orthostatic hypotension, diagnosed by documentation of a 20 mmHg or more fall in systolic blood pressure during the initial 5 min after the patient is in upright position; the associated heart rate either remains unchanged or increases (in contrast to vasovagal syncope). Orthostatic hypotension is a common cause of syncope in the elderly and is exacerbated by medications (as discussed later). Detection of orthostatic hypotension should trigger an investigation for fluid depletion and blood loss, particularly with syncope of new onset. A major intraabdominal hemorrhage (e.g., gastrointestinal or from ectopic pregnancy) can precipitate syncope before overt signs of bleeding are apparent. Autonomic insufficiency is a cause of orthostatic hypotension in diabetic patients, patients with Parkinson's disease, and the elderly.

Cardiac Syncope

A cardiac cause of syncope is seen in about one fifth of patients. Syncope associated with cardiovascular disease portends a much higher risk of mortality than is the case in the absence of underlying structural heart disease. Patients with cardiac syncope are at highest risk of dying within 1–6 months [6]. The 1-year mortality rate is 18–33%, in comparison with that of syncope with noncardiac causes (0–12%) or syncope in patients with no etiology (6%) [7]. The incidence of sudden death in patients with a cardiac cause is substantially higher than in the other two groups. Cardiac causes of syncope include the following:

Arrhythmic syncope results from tachyarrhythmias (ventricular or supraventricular) and bradyarrhythmias. Specific examples include sinus arrest; atrial fibrillation with very rapid conduction over an accessory pathway in patients with Wolff-Parkinson-White syndrome; and sustained monomorphic ventricular tachycardia (VT). Patients with complete heart block may develop self-limiting syncopal episodes in which there is no effective cardiac output as a result of transient asystole or ventricular tachyarrhythmias (Stokes-Adams attacks).

Torsade de pointes is a polymorphic VT that occurs in patients with prolonged ventricular repolarization [long QT syndrome (LQTS)]. LQTS may occur either on a congenital or acquired basis (e.g., hypokalemia or exposure to certain drugs, as described below). Torsade de pointes can readily progress to ventricular fibrillation. Thus, individuals with LQTS are at risk not only for syncope but also for "seizures" (from transient cerebral hypoxia) and sudden death. Other congenital, potentially lethal arrhythmic disorders include Brugada syndrome (ST segment elevation in precordial leads V_1, V_2, and V_3, often with incomplete or complete right bundle branch block) [8], familial catecholaminergic polymorphic VT [9], and arrhythmogenic right ventricular dysplasia with associated ventricular arrhythmias [10]. In some variants of hypertrophic cardiomyopathy, patients may exhibit minimal, if any, cardiac hypertrophy, and yet affected individuals

may be predisposed to sudden death, presumably from sustained ventricular tachyarrhythmias. Another explanation for syncope in hypertrophic cardiomyopathy is the obstructive type in which there is an intraventricular gradient.

Pacemaker and implantable cardiac defibrillator (ICD) malfunction may be a cause of syncope in patients with these devices. With ICDs, however, it should be appreciated that even when a rapid ventricular tachyarrhythmia is successfully treated by the device, syncope may nonetheless occur, depending on the duration of hypotension preceding the termination of tachyarrhythmia. ICD interrogation can provide information about possible tachyarrhythmia occurrence and therapy delivery/outcome coincident with the syncopal event in question.

Structural syncope is caused by valvular stenosis (aortic, mitral, pulmonic), prosthetic valve dysfunction or thrombosis, hypertrophic cardiomyopathy, pulmonary embolism, pulmonary hypertension, cardiac tamponade, and anomalous origin of the coronary arteries. Syncope in aortic stenosis occurs during exertion when the fixed valvular obstruction prevents an increase in cardiac output into the dilated vascular bed of the exercising skeletal muscles. The syncope can occur during exertion or immediately afterward. Syncope can also occur at rest in aortic stenosis when paroxysmal tachyarrhythmias or bradyarrhythmias accompany this valvular abnormality. Aortic dissection, subclavian steal, severe left ventricular dysfunction, and myocardial infarction are other important causes of cardiac syncope. In elderly patients, syncope may be the presenting feature in acute myocardial infarction [11]. Left atrial myxomas or ball-valve thrombi that fall into the mitral valve during diastole can result in the obstruction of ventricular filling and in syncope.

Lastly, cardiac involvement should be excluded in patients with neuromuscular diseases, eg, Duchenne dystrophy. As a result of cardiac involvement, these patients may develop cardiomyopathy, complete AV block, ventricular tachycardia, or ventricular fibrillation leading to syncope.

Metabolic Disturbance

Syncope due to hypoglycemia is the loss of consciousness that accompanies a blood glucose level of less than 40 mg per deciliter and is preceded by tremors, confusion, salivation, hyperadrenergic state, and hunger. Hypoglycemic syncope should be suspected in diabetic patients who take insulin or oral hypoglycemic agents. In contrast to true syncope, the loss of consciousness caused by hypoglycemia is not associated with hypotension, persists even when the patient is in the supine position, and usually does not resolve until the blood glucose level is restored to normal. Hypoadrenalism, which can cause postural hypotension as a result of inadequate cortisol secretion, is an important and treatable, albeit uncommon, cause for syncope and should be suspected when long-term steroid therapy is suddenly discontinued or when there are other stigmata of adrenal insufficiency.

Neurologic Disease

Neurologic conditions can mimic syncope by causing impairment or loss of consciousness; these conditions include transient cerebral ischemia (usually in the vertebrobasilar territory), migraines (basilar artery territory), temporal lobe epilepsy, atonic seizures, and unwitnessed grand mal seizures. Disorders resembling syncope, but without loss of consciousness, include drop attacks (sudden loss of postural tone), cataplexy, and transient ischemic attacks of carotid origin. In neurologic conditions associated with severe pain, such as trigeminal or glossopharyngeal neuralgia, the loss of consciousness is usually caused by vasovagal syncope.

Psychiatric Disorder

Syncope or syncopelike syndromes associated with psychiatric conditions are not associated with increased rates of mortality but have high 1-year recurrence rates (up to 50%) [12]. The association between syncope and psychiatric disorders may be complicated. First, psychiatric disorders may represent comorbidity in a patient with syncope and have no role in syncope occurrence. Second, psychiatric disorders may cause syncope-like states, often involving a conversion reaction. Psychiatric conditions associated with syncope include generalized anxiety and panic disorders (in which hyperventilation leads to cerebral vasoconstriction and possible loss of consciousness), major depression, alcohol and substance abuse, and somatization disorders. Finally, it is possible that recurrent syncope itself may secondarily give rise to psychiatric conditions such anxiety and panic attacks. A diagnosis of syncope resulting from psychiatric disorders is usually made after organic causes have been excluded. Diagnosis may be difficult when patients have both organic and psychogenic seizures.

Unexplained Etiology

Earlier studies reported that, in about half of the patients with syncope, no cause could be determined. However, with the wider use of tilt testing, event monitoring, electrophysiologic studies, and more aggressive investigation of elderly patients and those with suspected psychiatric causes, the proportion of syncope cases in which the cause can be determined has increased.

Keys to the History

A meticulously documented history is critical in the assessment of syncope. For new-onset syncope, the examiner focuses primarily on ruling out underlying structural heart disease and other life-threatening conditions as such as acute myocardial infarction and stroke, which necessitates evaluation in the emergency department. In contrast, the diagnostic assessment of recurrent syncope (Figs. 5.1 and 5.2) involves a broader consideration of causes and is often undertaken in an ambulatory setting. The history and physical examination should identify a cause of syncope in about 45% of patients [13]. These basic elements of a medical evaluation can lead to recognition of ischemic heart disease, heart failure, aortic stenosis, hypertrophic cardiomyopathy, and pulmonary embolism; neurologic causes such as seizure disorder and subclavian steal syndrome; and familial conditions such as long QT syndrome. Emphasis should be placed on the circumstances surrounding the syncopal event, the nature of prodromal and associated symptoms, characterization of the recovery period, medications and drugs, the presence of known cardiac disease, family history (e.g., cardiomyopathy or LQTS), and psychiatric history. Observations from witnesses or a family member may be helpful. In documenting the history, the examiner should focus on the relation of syncopal events to posture, exertion, and palpitations. The examiner should determine the number and chronicity of prior syncopal and near-syncopal episodes; the latter may be more frequent (albeit of shorter duration) than full-blown syncopal events and may provide an opportunity for diagnostic electrocardiographic monitoring to capture a clinically relevant event. Inquiry also should be made into whether the patient has sustained any trauma in association with the symptoms; serious secondary injury warrants a more aggressive diagnostic and treatment strategy aimed at preventing subsequent morbidity.

Circumstances Surrounding Onset

Painstaking attention should be paid to the chronology of symptoms: sudden onset without a prodrome may suggest arrhythmias, whereas protracted autonomic symptoms

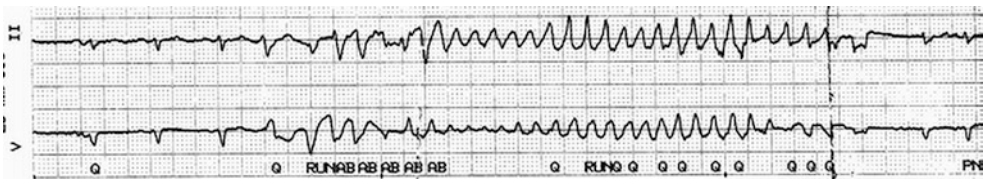

Fig. 5.1 ECG monitor strip revealing nonsustained polymorphous VT in a patient who presented with recurrent syncope. Although the tachycardia resembles torsades, the patient did not have evident LQTS and the onset was not of the "long-short" form. Correction of electrolyte disturbance (marked hypokalemia) appeared to resolve the problem, but an ICD was placed as well. (From Puppala et al. [44]; with permission)

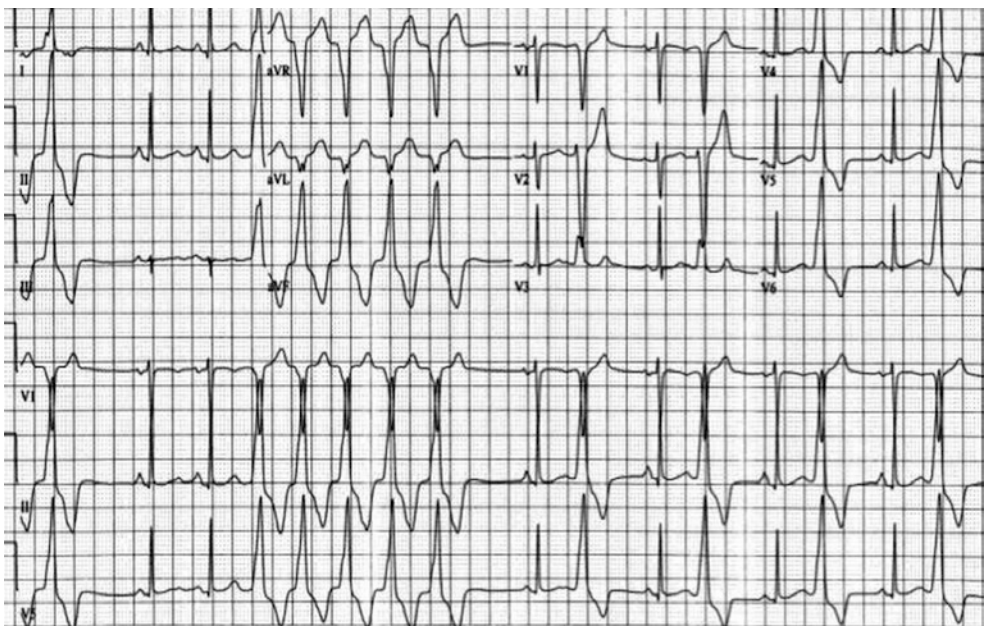

Fig. 5.2 Recordings obtained in a 36-year-old male with a clinically normal heart who presented for evaluation of recurrent syncope. A Holter monitor recording showed frequent ventricular ectopic beats and nonsustained ventricular tachycardia, which correlated well with his symptoms. The morphology of these ventricular ectopic beats on 12-lead ECG was consistent with RVOT origin. He underwent electrophysiological study, and his ventricular arrhythmias were successfully ablated. (From Puppala et al. [44]; with permission)

(pallor, diaphoresis, nausea) in association with a precipitating factor suggest vasovagal syncope. Loss of consciousness after prolonged standing at attention suggests vasovagal syncope, whereas that which occurs immediately on standing is caused by orthostatic hypotension. Situational syncope occurs during or immediately after swallowing, coughing, defecation, and micturition. Alcohol ingestion may be the most important predisposing factor in micturition syncope. Alcohol ingestion has also been implicated in about 10% of syncope cases in young adults, and the syncope in those cases has been attributed to orthostatic stress because of impaired vasoconstriction [14]. Carotid syncope occurs with head rotation while the person is wearing tight collars. Exertional syncope suggests possible structural heart disease such as aortic stenosis, hypertrophic cardiomyopathy, or exercise-induced tachycardias. In highly competitive athletes, vasovagal syncope documented by history and head-up tilt testing has been shown to occur during as well as after exertion [15]. Syncope associated with arm exercise is a feature of subclavian steal syndrome. A history of exertional chest pain, as well as exertional syncope, in an adolescent or young adult raises the possibility of anomalous origin of a coronary artery [16]. Syncope in patients with LQTS may occur in association with physical exertion (particularly swimming), during emotional stress, or in response to sudden, unexpected acoustic stimuli (e.g., sound of an alarm clock or telephone) [17]. Palpitations preceding syncope, especially an awareness of rapid heart beating, suggests an arrhythmic origin – although tachyarrhythmic syncope need not be accompanied by such prodromal symptoms. Features of neurologic syncope include brainstem findings (vertigo, dysarthria, ataxia, visual disturbances), whereas postevent confusion is more likely to be caused by seizures. Loss of consciousness associated with headache indicates migraine or seizures, whereas that associated with throat or facial pain suggests glossopharyngeal or trigeminal neuralgia.

Posture at the Onset of Attack

Vasodepressor syncope typically occurs in the upright position; once the patient is horizontal, the autonomic derangements begin to reverse. In some instances, if the patient returns to the upright position too soon, there can be a recurrent faint. Syncope resulting from arrhythmias and other causes of loss of consciousness that resembles syncope, such as hypoglycemia and hyperventilation, can occur independently of posture. Moreover, syncope caused by pain or emotion-related vasovagal syncope (e.g., after a needlestick or on the sight of blood or injury) need not occur while the patient is upright.

Differentiating Syncope from Seizures

This distinction can be clinically challenging (Table 5.2), and eyewitness accounts are often helpful in discriminating between the two conditions. Both phenomena involve loss of consciousness. As a further confounding factor, myoclonic jerking may occur during the course of true syncope secondary to transient cerebral hypoxia [18]. The best discriminatory features between syncope and seizures are sensorium of the patient after the episode and the patient's age. When a patient older than 45 years is disorientated after an episode, seizures are five times more likely than syncope to have occurred [19]. Older individuals with prolonged disorientation after an episode of loss of consciousness are therefore more likely to have had a seizure. An exception would be arrhythmic syncope with a prolonged hypotensive episode, which may secondarily cause transient cerebral hypoxic injury and postevent disorientation. Other clinical features suggestive of a seizure include cyanotic facial appearance, as opposed to pallor, during the episode; frothing at the mouth; unconsciousness lasting more than 5 min; feeling sleepy after the episode; aching muscles; and tongue biting along the lateral aspect of the tongue. Seizures are also suggested by an aura before the event, horizontal eye movement during the event, and a headache after the episode. Fecal and urinary incontinence can occur in both syncope and seizures but are far more common with seizures. Temporal lobe seizures can easily be mistaken for syncope because they usually lack tonic-clonic movements and are associated with autonomic changes such as flushing and fluctuating changes in the level of consciousness.

Age at Onset

In younger individuals (younger than 30 years), common causes (Table 5.3) include neurally mediated syncope, undiagnosed seizures, Wolff-Parkinson-White syndrome and other supraventricular tachycardias, hypertrophic cardiomyopathy,

Table 5.2 Characteristics of syncope versus seizures

Clinical features	Syncope	Seizures
Loss of consciousness precipitated by pain, micturition, exercise, pain, defecation, or stressful events	+	–
Sweating and nausea before or during the event	+	–
Aura	–	+
Tongue biting	–	+
Clonic or myoclonic jerks or rhythmic movements	+/–	++
Disorientation after the event	–	+
Slowness in returning to consciousness	–	+
Unconscious >5 min	–	+

Table 5.3 Causes of syncope by age

Age	Causes
Youth (<30 years)	Neurally mediated syncope
	Situational
	Alcohol
	Undiagnosed seizures
	Cardiac syncope:
	Hypertrophic cardiomyopathy
	Coronary artery anomalies
	WPW syndrome, other SVT
	Long QT syndrome and other inherited arrhythmic disorders
Middle-aged (30–65 years)	Neurally mediated syncope
	Cardiac (arrhythmic, mechanical/obstructive)
Elderly (>65 years)	Neurally mediated syncope
	Cardiac (arrhythmic, mechanical/obstructive)
	Drugs: Antihyperhypertensive medications, antidepressants, etc. (see text for list)
	Orthostatic hypotension

SVT supraventricular tachycardia, *WPW* Wolff-Parkinson-White

LQTS and other inherited arrhythmic disorders, and congenital coronary anomalies [16].

In middle-aged individuals, typical causes of syncope are neurally mediated and cardiac (arrhythmic, mechanical/obstructive) in origin.

Syncope in the elderly (older than 65 years) may be overlooked when the episode is described by the patient simply as a "fall," owing to postsyncope retrograde amnesia [4]. In the elderly, the cause of syncope is often multifactorial, and older patients tend to have serious arrhythmias (sustained VT in the setting of cardiomyopathy), orthostatic hypotension, or neurologic disorders that are contributory [3]. Elderly patients are also prone to neurally mediated syncope related to known triggers, such as micturition, defecation, coughing, laughing, swallowing, and eating. Postprandial hypotension (secondary to splanchnic vascular volume shifts) can result in syncope during or after a meal. Another confounding factor in this age group is polypharmacy: Many medications at therapeutic doses cause postural hypotension. Aortic stenosis, myocardial infarction, and carotid sinus hypersensitivity are other conditions that predispose to syncope in the elderly. Carotid sinus hypersensitivity has been suggested to be responsible for syncope or "falls" in the elderly [4]. The multifactorial nature of syncope in older patientsoften necessitates a management approach aimed at correcting many of these factors simultaneously.

Other Historical Clues

Cardiac syncope must be kept in mind in patients with structural heart disease, particularly ischemic heart disease with left ventricular dysfunction. A family history of sudden death (including accidental drownings) or seizures is a feature of hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia, LQTS, Brugada syndrome and catecholaminergic polymorphic VT. A history of LQTS is particularly important in syncope precipitated by medications (to be described).

Features of the history that suggest syncope caused by VT or atrioventricular (AV) block (odds ratio greater than 5) are male gender, age older than 54 years, three or fewer episodes of syncope, and a 6-s or shorter duration of warning before syncope [20].

Drugs

Drugs can frequently cause syncope, particularly in the elderly. Antihypertensive and antidepressant medications are the most commonly implicated agents. Culprit antihypertensive agents include doxazosin, clonidine, hydralazine, prazosin, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers. Other drugs associated with syncope are morphine, nitroglycerin, phenothiazines, perioperative amiodarone, calcium channel blockers (e.g., nifedipine), citrated blood, aggressive diuretic therapy, interleukin-2, protamine, and quinidine. Documentation of drug-induced syncope may require ambulatory monitoring of blood pressure.

Drug history is also important in patients with syncope who are suspected of having LQTS. After exposure to drugs that prolong ventricular repolarization, even previously asymptomatic gene carriers may suddenly develop syncope or cardiac arrest caused by torsade de pointes. A detailed list of QT-prolonging drugs can be found at *www.qtdrugs.org*. A partial list of such drugs known to precipitate syncope caused by torsade de pointes include (a) *cardiac drugs,* such as quinidine, procainamide, sotalol, disopyramide, amiodarone, and dofetilide, and (b) *noncardiac drugs,* such as macrolide antibiotics, tricyclic antidepressants, phenothiazines, methadone, some antihistamines, and cisapride. Of note, QT-prolonging drugs are prone to induce torsade de pointes more frequently in women than in men [21, 22].

Pregnancy

Syncope is relatively common in pregnancy [3], but its exact mechanism and prognosis remain unclear. In the third trimester, syncope can occur even in the supine position as a result of compression of the aorta and inferior vena cava in the abdomen by the enlarged uterus. Pregnant women with known cardiac disease, palpitations or arrhythmias, exertional syncope, or pathologic murmur merit further evaluation.

Helpful Signs on Physical Examination

Clinical signs are not readily apparent, and findings depend on the underlying cause of syncope. Clinical examination should be targeted to identify underlying causes suspected from the history. Physical examination is most useful in diagnosing syncope caused by postural hypotension, cardiovascular conditions, and neurologic diseases. Preliminary assessment includes the following:

- Recording of the heart rate: Severe bradycardia may suggest second- or third-degree heart block, whereas tachycardia should trigger an investigation of ventricular or supraventricular tachyarrhythmia. "Postural orthostatic tachycardia syndrome," with associated symptoms of near syncope, may overlap with the clinical picture of vasovagal syncope [23]. Postural orthostatic tachycardia should be suspected when there is an increase of 30 beats per minute within 5 min of standing, accompanied by symptoms of orthostatic intolerance (lightheadedness, dizziness, near syncope).
- Recording of supine and erect blood pressure for orthostatic hypotension: Erect blood pressure should be recorded at least 3 min after the patient stands upright. Orthostatic hypotension should be suspected when there is a 20-mmHg fall in systolic blood pressure or a 10-mmHg fall in diastolic blood pressure within 5 min after the patient stands upright. Patients with autonomic insufficiency typically lack a compensatory sinus tachycardia.
- Assessment of pulse deficit and blood pressures in the arms when aortic dissection is suspected.
- Auscultation of the heart for ejection systolic murmur of aortic stenosis and hypertrophic cardiomyopathy and for gallops.
- Pulmonary examination includes assessment of respiratory rate and other findings to help exclude tension pneumothorax, congestive heart failure, and chronic obstructive pulmonary disease.
- Carotid sinus massage is useful in elderly patients with suspected carotid sinus syncope. It is best performed with a cardiac monitor but should be deferred in a patient with carotid bruits; in the setting of a recent myocardial infarction, stroke, or transient ischemic attacks; or in patients with a history of VT. Before massaging the carotid sinus, the physician should ensure that there are no carotid bruits and then massage one side at a time, 5 s per attempt. The massage should be performed with the patient both supine and erect. An abnormal test result is associated with a pause of greater than 3 s with or without prolonged hypotension. The test result is more meaningful if the patient's symptoms of presyncope are reproduced. The reproducibility of the test is enhanced when the symptoms are elicited with the patient in both the supine and erect positions, usually with a tilt table.
- Neurologic examination and auscultation for carotid bruit should be performed when a stroke or focal neurologic deficits are suspected.

Diagnostic Tests

The investigation of syncope is limited by fact that there are no diagnostic gold standards against which the diagnostic tests can be assessed. For example, the detection of coronary artery disease in a patient who has fainted does not necessarily imply that such a pathologic process is the cause of syncope.

- **Baseline Laboratory Tests:** Routine laboratory testing is not warranted, and these tests should be performed only if suggested by the history or clinical examination findings. Useful measurements include blood glucose to exclude hypoglycemia and hematocrit to exclude blood loss. Hypokalemia and hypomagnesemia should be ruled out if QT prolongation is observed. Pregnancy testing should be considered in women of childbearing age, particularly before head-up tilt testing or electrophysiologic testing.
- **Twelve-Lead ECG** should be recorded in all patients with syncope, and rhythm strips recorded by paramedics should be reviewed. Although yield of the ECG is low, there is no risk, and the test is relatively inexpensive. Moreover, abnormalities such as previous myocardial infarction, nonsustained VT, or bundle branch block may guide further evaluation. These findings, however, do not necessarily point to a unique cause. For example, a patient with bifascicular block and prior myocardial infarction may turn out to have VT rather than AV block as the cause of syncope [4]. Left ventricular hypertrophy may suggest underlying cardiomyopathy. A completely normal ECG implies a more favorable prognosis and tends to reduce (but does not absolutely exclude) the likelihood of a ventricular tachyarrhythmic origin. The ECG is particularly useful in identifying acute ischemia; sinoatrial conduction disturbances; bundle branch/bifascicular blocks; second- or third-degree heart block; supraventricular tachycardia; nonsustained VT; accessory pathways with ventricular preexcitation [e.g, Wolff-Parkinson-White syndrome, with short PR interval and slurred QRS upstroke ("delta wave")]; prolonged QT interval; ST segment elevation in the right precordial leads (V_1, V_2, and V_3), possibly with incomplete/ complete right bundle branch block (Brugada syndrome; Chap. 16); and, on occasion, the "epsilon waves" of arrhythmogenic right ventricular dysplasia, with associated T wave inversions, in the right precordial leads.

- For diagnosing LQTS, a rate-corrected QT (QTc) of more than 0.44 s (in the absence of bundle branch block) has traditionally been considered prolonged. However, it should be recognized that in normal persons, the upper 95% confidence limit for QTc is 0.46 s in women and 0.45 s in men [24]. Thus, although longer intervals are probably truly abnormal, QTc values of 0.42 to 0.46 s are diagnostically equivocal, because both LQTS gene carriers and noncarriers may exhibit QTc intervals in that normal/borderline range [25]. The QTc is calculated as $QT / \sqrt{RR}$, where the QT (traditionally measured in lead II) and RR intervals are measured in seconds. Because computerized ECG measurements are not always reliable, manual assessment of QTc in patients with syncope is advisable. Care should be taken to avoid inclusion of the U wave in the measurement of QT interval [26]. Certain T wave morphologic features, particularly "notches"/"humps", may also be present in LQTS patients even with borderline or normal QTc intervals [26, 27].
- **Exercise Stress Testing** is useful for diagnosing underlying myocardial ischemia when an ischemic substrate is suspected to be the cause of arrhythmogenic syncope. In addition, it may be useful in the detection of rate-dependent AV block, exercise-induced tachyarrhythmias (such as familial catecholaminergicpolymorphic VT [9]), or exercise-associated syncope [15]. Before exercise testing, all patients with exertional syncope must have an echocardiogram to rule out aortic stenosis or hypertrophic cardiomyopathy. In young patients and athletes, congenital anomalous coronary arteries should also be considered prior to exercise testing.
- **Echocardiogram:** Echocardiogram is particularly useful when structural heart disease, such as aortic stenosis, hypertrophic cardiomyopathy, left ventricular dysfunction, right ventricular dysplasia, or pulmonary hypertension, is suspected [28] (Table 5.4). Right ventricular wall motion and function should be explicitly assessed when the examiner tries to exclude right ventricular dysplasia by echocardiography; if any question about this diagnosis remains, computed tomographic scan and/or cardiac magnetic resonance imaging should be considered.
- **Head-up tilt table testing** (Table 5.5) is useful in patients suspected of having neurally mediated syncope and low suspicion of cardiac syncope. Patients are tilted passively to an angle of 60 to 70° for 20 to 45 min, depending on the protocol utilized, with frequent or continuous monitoring of vital signs. The procedure may involve the use of a provocative agent, such as isoproterenol or nitroglycerine, to augment the sensitivity of the test, when initial results are negative. It is generally accepted that occurrence of hypotension (*vasodepressor* response)—often, but not necessarily, accompanied by bradycardia (*cardio-*

Table 5.4 ACC/AHA recommendations for echocardiography

Class I: There is evidence and/or general agreement that echocardiography is useful and effective
Syncope in a patient with clinically suspected heart disease
Periexertional syncope
Class IIa: The weight of evidence/opinion is in favor of usefulness/efficacy
Syncope in a patient in a high-risk occupation (e.g., a pilot)
Class IIb: Usefulness/efficacy is less well established by evidence/opinion
Syncope of occult etiology with no findings of heart disease on history or physical examination
Class III: There is evidence and/or general agreement that echocardiography is not useful and in some cases may be harmful
Recurrent syncope in a patient in whom previous echocardiographic or other testing was demonstrated as a cause of syncope
Syncope in a patient for whom there is no clinical suspicion of heart disease
Classic neurogenic syncope

ACC/AHA American College of Cardiology/American Heart Association
Adapted from Cheitlin et al. [28]

Table 5.5 ACC recommendations for tilt-table testing

Class I: Tilt-table testing is warranted
Recurrent syncope or single syncopal episode in a high-risk patient whether the medical history is suggestive of neurally mediated (vasovagal) origin or not and
No evidence of structural or cardiovascular disease or
Structural cardiovascular disease is present but other causes of syncope have been excluded by appropriate testing
Further evaluation of patients in whom an apparent cause has been established (e.g., asystole, atrioventricular block) but in whom demonstration of susceptibility to neurally mediated syncope would affect treatment plans
Part of the evaluation of exercise-induced or exercise-associated syncope
Class II: Conditions in which reasonable differences of opinion exist regarding tilt table testing
Differentiating convulsive syncope from seizures
Evaluating pateints (especially the elderly) with recurrent unexplained falls
Assessing recurrent dizziness or presyncope
Evaluating unexplained syncope in the setting of peripheral neuropathies or dysautonomias
Follow-up evaluation to assess therapy of neurally mediated syncope
Class III: Conditions in which tilt-table testing is not warranted
Single syncopal episode, without injury and not in a high-risk setting, with clear-cut vasovagal clinical features
Syncope in which an alternative specific cause has been established and in which additional demonstration of a neurally mediated susceptibility would not alter treatment plans
Relative contraindications to tilt-table testing
Syncope with clinically severe left ventricular outflow obstruction
Syncope in the presence of critical mitral stenosis
Syncope in the setting of known critical proximal coronary artery stenoses
Syncope in conjunction with known critical cerebrovascular stenoses

ACC American College of Cardiology
Adapted from Benditt et al. [1]

inhibitory response)—during head-up tilt is akin to spontaneous vasovagal syncope.

About half of the patients with unexplained syncope have a positive test result with passive tilt; after the administration of isoproterenol, the overall response rate increases to 64% [29]. The exact mechanism of enhanced response with isoproterenol remains to be determined but probably involves vasodilatation as well as stimulation of afferent myocardial mechanoreceptors. The sensitivity of the tilt test is 32% to 85%, whereas the overall specificity is about 90% [1]. Note that a "negative" tilt test can occur even in the presence of an obvious case of neurally mediated syncope, and a "positive" test can occur when syncope is clearly due to other causes [1].

The procedure is not advisable for pregnant women, patients with hypertrophic cardiomyopathy, aortic stenosis and the elderly because hypotension is especially detrimental to these patients. The test is not indicated for individuals who have had a single episode of syncope that is characteristic of vasovagal syncope and during which no injury was sustained. Head-up tilt testing is recommended for patients with recurrent syncope in the absence of cardiac cause.

- **Ambulatory Electrocardiographic (Holter) Monitoring for 24 to 48 H:** This type of monitoring (Table 5.6) is used to detect arrhythmogenic causes of syncope [30]. The yield of this investigation is enhanced when a record is obtained during an episode of syncope (a rare, fortuitous occurrence). The optimal duration for monitoring is not known; however, several studies have suggested that it is not cost effective to monitor for periods longer than 48 h [30]. In general, culprit tachyarrhythmias or bradycardias are sporadic and transient, and continuous ambulatory recordings are thus often unrewarding. Nonetheless, Holter monitoring is recommended for patients with a high pretest probability of arrhythmias, such as patients with structural heart disease, an abnormal ECG, brief sudden loss of consciousness without a prodrome, or palpitations associated with syncope. Holter monitoring is most likely to be informative in patients with frequent (virtually daily) episodes of presyncopal symptoms. Nondiagnostic arrhythmias found during Holter monitoring (i.e., those not correlated with symptoms of presyncope or syncope) usually do not require treatment; this issue frequently arises with regard to premature ventricular complexes, which are commonly seen in the normal population (see Chap. 3).
- **Event Monitors** (see Chap. 3) are useful when patients have presyncopal symptoms every few days to weeks. The devices commonly utilize a "memory loop" to store ongoing ECG signals, which can be "frozen" into memory by patient activation (in response to symptoms) and subsequently retrieved for transtelephonic transmission and analysis. Event monitors are typically used for 2- to 4-week periods at a time and are therefore more likely than the Holter monitors to capture an arrhythmia. Loop-type monitors are especially valuable for detecting fleeting arrhythmias. In about 8–20% of patients, event monitors detect arrhythmias with symptoms; in an additional 27%, symptoms are present without arrhythmias [31]. Patients who use event monitors usually must be capable of activating the device and performing the transtelephonic transmissions; the former capability is not necessary when an "auto-triggered" device with prespecified rate criteria is utilized. Patient-activated event monitoring is a particularly useful diagnostic modality when syncope is associated with prodromal palpitations or dizziness, or when there are also episodes of near-syncope. For syncope that occurs suddenly, however, the patient is not likely to have time to signal a symptom; in these cases, an "auto-triggered" device is the preferred type of event monitor.
- **Implantable Loop Recorders** are helpful in recurrent syncope that is undiagnosed after initial investigations including Holter monitoring and electrophysiologic testing [32]. These subcutaneous implantable recorders allow electrocardiographic monitoring for periods up to 18 months. The devices are single-lead ECG systems and, when activated by patients, can store rhythms recorded for several minutes before and after the device is activated. Newer generation devices can be programmed to record rhythms automatically, on the basis of prespecified upper and lower rate thresholds. As with pacemakers and ICDs, the stored recordings can be retrieved by radiotelemetry-based interrogation of the device. More important, implantable loop recordings can lead to a correct diagnosis, thereby avoiding misdirected therapy

Table 5.6 ACC/AHA recommendations for ambulatory electrocardiography

Class I: There is evidence and/or general agreement that ambulatory electrocardiography is useful and effective
Patients with unexplained syncope, near syncope or episodic dizziness in whom the cause is not obvious
Class IIb: Usefulness/efficacy is less well established by evidence/opinion
Patients with symptoms such as syncope, near syncope, episodic dizziness or palpitation in whom a probable cause other than an arrhythmia has been identified but in whom symptoms persist despite treatment of this other cause
Class III: There is evidence and/or general agreement that the ambulatory electrocardiography is not useful and in some cases may be harmful
Patients with symptoms such as syncope, near syncope, episodic dizziness, or palpitation in whom other causes have been identified by history, physical examination or laboratory tests

ACC/AHA American College of Cardiology/American Heart Association
Adapted from Crawford et al. [30]

that is based on a presumed, but erroneous, cause of syncope.

The 2009 European Society of Cardiology syncope guidelines include the following recommendations for use of ILRs: ILR is indicated for early phase evaluation in patients with recurrent syncope of uncertain origin, absence of high-risk criteria, and a high likelihood of recurrence within the battery life of the device; an ILR is recommended in patients who have high-risk features in whom a comprehensive evaluation did not demonstrate a cause of syncope or lead to a specific treatment; an ILR should be considered to assess the contribution of bradycardia before embarking on cardiac pacing in patients with suspected or certain reflex syncope with frequent or traumatic syncopal episodes [33].

- **Signal-Averaged Electrocardiogram**: The routine use of signal-averaged ECG is not recommended until further studies are available regarding the utility of this diagnostic modality.
- **Electrophysiologic Testing:** Electrophysiologic (EP) testing (Table 5.7) can aid in uncovering as yet undocumented arrhythmic propensities that may give rise to syncope [34]. EP testing involves intracardiac electrical stimulation and monitoring of electrophysiologic parameters to detect bradyarrhythmias and tachyarrhythmias. Most protocols, for induction of tachyarrhythmias, consist of delivery of up to three extrastimuli at one or two sites in the ventricle. Isoproterenol is used to increase the sensitivity for detecting tachyarrhythmias, but it reduces specificity. Parameters that are usually evaluated include sinus node function, AV conduction, and the inducibility of supraventricular and ventricular arrhythmias. Sustained VT is an important abnormality identified in patients with syncope and structural heart disease [35]. Other abnormalities that can be detected include His-Purkinje block and sinus node dysfunction. By comparison, the induction of nonsustained ventricular tachycardia, polymorphic ventricular tachycardia, and ventricular fibrillation is less helpful, as these findings may be nonspecific and may represent "nonclinical" responses. In patients with structural heart disease, such as coronary artery disease, cardiomyopathy, and valvular or congenital heart disease, the diagnostic yield of this procedure is as high as 50%, whereas in the absence of structural heart conditions, the yield is about 10% [36].

Limitations of EP testing include the possibility of not identifying an arrhythmic cause; lack of informativeness for all patient populations, with poor negative predictive value in patients with reduced left ventricular function [37]; and possible detection of multiple abnormalities, with difficulty in proving which is etiologic for syncope. A negative EP test result (with no demonstrable induction of sustained VT or ventricular fibrillation) is generally predictive of a low risk of sudden death [38]. However, unexplained syncope in nonischemic dilated cardiomyopathy may still reflect an occult propensity to ventricular tachyarrhythmias despite a negative EP study result; indeed, prophylactic implantable defibrillators have been shown to reduce mortality rates in this setting [39, 40].

Patients whose hearts appear normal clinically, with normal ECG and normal echocardiogram, should rarely undergo EP testing, whereas patients with structural heart disease, such as myocardial infarction or congestive heart failure, or those with other anatomic abnormalities that might predispose to arrhythmic syncope (e.g., Wolff-Parkinson-White syndrome) should be considered for the procedure early in the diagnostic cascade. Although EP tests are relatively safe in the assessment of syncope, fewer than 3% of the patients may develop significant morbid conditions, including cardiac perforation, arteriovenous fistula, pulmonary embolism, and myocardial infarction [36].

- **Pacemakers and Implantable Cardiac Defibrillators:** These devices must be tested when device malfunction is suspected.
- **Routine Nonselective Neurologic Testing:** These types of tests, such as head-computed tomography, electroencephalogram, and carotid Doppler studies, are all too often performed routinely. These laboratory evaluations rarely provide diagnostic information unless clinical features suggest a neurologic condition; therefore, they should be selectively performed as directed by clinical data.
- **Psychiatric assessment** is usually made only after other investigations have excluded structural heart disease. In such cases, the hyperventilation maneuver (open-mouthed deep respiration for 2–3 min for possible precipitation of syncope) and other screening instruments for mental disorders may be useful [41].

Table 5.7 ACC/AHA recommendations for electrophysiologic testing

Class I: There is evidence and/or general agreement that electrophysiologic testing is useful and effective
Patients with suspected structural heart disease and syncope that remains unexplained after appropriate evaluation
Class II: There is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of electrophysiologic testing
Patients with recurrent unexplained syncope without structural heart disease and a negative head-up tilt test
Class III: There is evidence and/or general agreement that the electrophysiologic testing is not useful and in some cases may be harmful
Patients with a known cause of syncope for whom treatment will not be guided by electrophysiologic testing

ACC/AHA American College of Cardiology/American Heart Association
Adapted from Zipes et al. [34]

When to Admit, When to Refer, and to Whom

The threshold for admitting a patient with syncope is relatively low (Table 5.8). All patients with a first episode of syncope—excluding a classic case of vasovagal syncope in a young patient with history and physical examination findings negative for any acquired or familial cardiac disorder and with a normal ECG—should be referred to the exclude life-threatening conditions as discussed earlier. Patients with recurrent syncope may also require hospitalization for a variety of reasons—for example, if their syncope has not previously been evaluated or treated, especially if cardiopulmonary disease is suspected or there is an untreated known or suspected arrhythmic cause; if there is a family history of sudden death; if there is a history of or concern regarding possible secondary injury; if the recent clinical events represent failure of treatment for syncope (especially of cardiac origin); or if pacemaker or ICD malfunction is suspected [4]. Patients with recurrent syncope that remains unexplained after initial medical evaluation or with syncope of known or suspected cardiac origin, should be referred to a cardiologist or electrophysiologist to aid in the in the diagnosis and management of the patient.

Table 5.8 ACP indications for hospital admission in patients with syncope

Indicated (associated with such adverse outcomes as myocardial infarction, stroke, or arrhythmias)
History of coronary artery disease, congestive heart failure, or ventricular arrhythmia
Accompanying symptoms of chest pain
Physical signs of significant valve disease, congestive heart failure, stroke, or focal neurologic disorder
Electrocardiographic findings: Ischemia, arrhythmia (serious bradycardia or tachycardia), increased QT interval or bundle branch block
Often indicated
Sudden loss of consciousness with injury, rapid heart action, or exertional syncope
Frequent spells, suspicion of coronary disease or arrhythmia (for example, use of medications associated with torsade de pointes)
Moderate to severe hypotension
Older than 70 years of age

ACP American College of Physicians
Adapted from Linzer et al. [36]

Syncope and Driving

Although the incidence of syncope-related motor vehicle accidents is low [4, 41], syncope can have devastating consequences on the patient and others involved in such an accident. Therefore, when a patient is undergoing evaluation for syncope, the physician must carefully consider the implications regarding driving restrictions, taking into account pertinent laws of the relevant state or country, the chances of recurrent syncope, whether syncope occurs when the patient is standing up or on sitting down, and the presence of a prodrome (which might give the patient time to avoid injury). Guidelines for determining length of driving restrictions, if any, are available [42].

Conclusions

The approach to syncope requires that both the science and art of medicine come together. A major challenge in the evaluation of syncope is that it is a transient symptom, not a disease, with causes ranging from benign to life-threatening. There is rarely an opportunity to capture a spontaneous episode during diagnostic evaluation, and there is no gold standard test for establishing the diagnosis. Syncope in the elderly is especially problematic, in view of its multifactorial causation. However, with the appropriate use of history, physical signs, and diagnostic tests (Fig. 5.3), patients with life-threatening syncope can be identified with a high degree of accuracy, and a diagnosis can be established, overall, in about 75% of patients with syncope [43]. This allows appropriate treatment to be initiated in these patients. For those in whom syncope recurs without clear explanation, especially after institution of what initially appears to be appropriate therapy based on thorough evaluation, further observation and investigation over time (e.g., through use of an implantable loop recorder) may reveal the underlying cause.

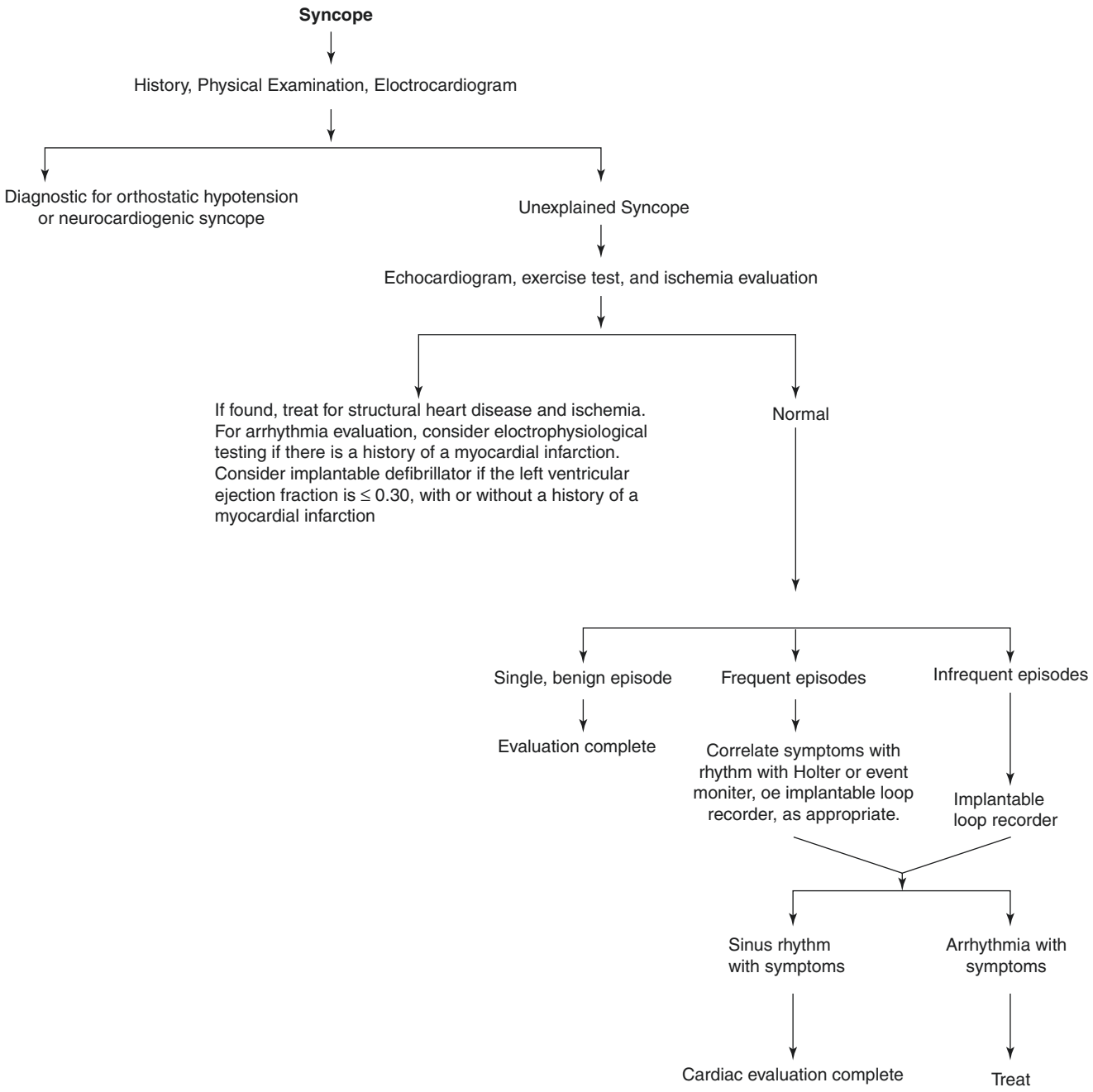

Fig. 5.3 Flow chart for the diagnostic approach to the patient with syncope. (From Strickberger et al. [45]; with permission)

Practical Points

- Patients with a first episode of syncope should evaluated for life-threatening conditions.
- The multifactorial origin of syncope in the elderly often necessitates management approaches aimed at correcting many of these factors simultaneously.
- Key questions during initial evaluation include the following: (a) Is the loss of consciousness attributable to syncope or another cause? (b) Is cardiac disease absent or present? (c) Are there clues in the history suggesting the diagnosis? (Brignole et al. 2004 [4]).
- After return of consciousness, rapid restoration of normal sensorium is the rule in syncope, whereas persistent confusion (more than 5 min) suggests a seizure.
- Ventricular arrhythmias should be suspected in patients with underlying structural heart disease, particularly ventricular involvement.
- ECG findings suggestive of an arrhythmic cause of syncope include sinoatrial dysfunction; second- or third-degree AV block; bifascicular block; Q waves (prior myocardial infarction); delta wave; prolonged QTc; Brugada sign; and right precordial T wave inversion with epsilon wave (ARVD).
- Evaluation for LQTS should include manual measurement of QTc and a search for T wave morphologic abnormalities (e.g., "notches" in left precordial or limb leads or both).
- Event monitors have a higher yield than do Holter monitors for identifying possible arrhythmic causes of near syncope.
- Electroencephalogram, head computed tomographic scan, and carotid ultrasonography should be reserved for cases of syncope in which clinical features suggest a neurologic etiology.
- Patients with clinically normal hearts and with normal ECG and echocardiogram should rarely undergo EP testing, whereas patients with structural heart disease, such as myocardial infarction, congestive heart failure, or ventricular preexcitation, should be considered for the procedure early in the diagnostic cascade.
- Implantable loop recorders are helpful in documenting recurrent but infrequent syncope that is undiagnosed after initial investigations, including Holter monitoring and electrophysiologic testing.

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