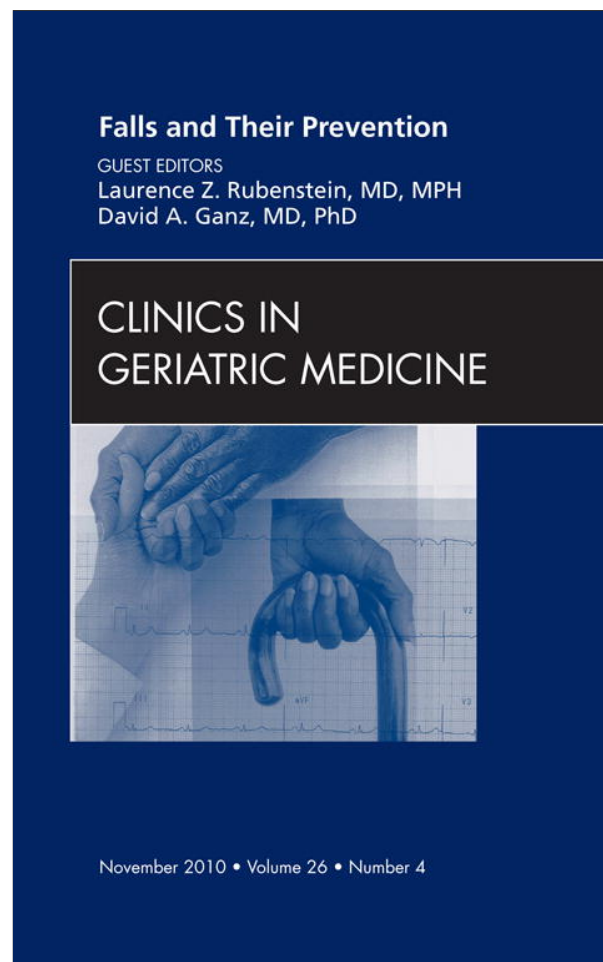


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Cardiac Causes for Falls and Their Treatment

Hilary Cronin, MB, BAO, BCh, MRCP^{a,*},

Rose Anne Kenny, MB, BCh, MD, FRCPI, FRCP^b

KEYWORDS

- Falls • Syncope • Carotid sinus syndrome
- Postprandial hypotension • Orthostatic hypotension
- Vasovagal syncope • Bradyarrhythmia

Falls are a serious medical issue for older people and a major health care and cost priority.^{1–3} The incidence of falls increases steadily from middle age and peaks in persons aged 80 years and older.⁴ One-third of community-dwelling adults aged 65 years and older and up to half of those aged 80 years and older have a fall each year.^{5–7} This increases to more than 60% in long-term care populations.⁸ In more than half of all cases, the falls are recurrent.^{6,9}

Although some falls have a single cause, most are multifactorial, attributed to a complex interaction of intrinsic and extrinsic risk factors superimposed on the normal aging process.^{6,7,9,10} Cardiovascular disorders are increasingly being recognized as risk factors for falls,⁴ with one study reporting that cardiovascular disease accounted for 77% of persons presenting to accident and emergency departments with unexplained or recurrent falls and with falls associated with unexplained loss of consciousness.¹¹ Those with an intrinsic cardiac cause for falling have a higher mortality rate than those with noncardiovascular or unknown causes of falls.¹²

Traditionally, syncope and falls have been considered as 2 separate entities with different definitions (**Box 1**) and causes. Recent evidence suggests, however, that these conditions are not always distinctly separate and, in fact, that there may be considerable overlap between them.^{6,13–16} Determining whether a person who has fallen has had a syncopal event can be difficult in older adults. Half of all syncopal episodes are unwitnessed,¹³ and older adults are more likely to have amnesia for loss of consciousness (in which case the person does not recall syncope) than younger adults.^{11,17,18} In fact, amnesia for loss of consciousness has been observed in half the patients with carotid sinus syndrome (CSS) who present with falls and

^a The Irish Longitudinal Study of Ageing (TILDA), Chemistry Extension, Trinity College Dublin, Dublin 2, Ireland

^b Trinity College Dublin and St James's Hospital, James's Street, Dublin 8, Ireland

* Corresponding author.

E-mail address: croninhi@tcd.ie

Box 1**Traditional definitions of falls and syncope**

Fall: An event whereby an individual unexpectedly comes to rest on the ground or another lower level without known loss of consciousness.²¹

Syncope: A transient loss of consciousness due to transient global cerebral hypoperfusion characterized by rapid onset, short duration, and spontaneous complete recovery.²²

a quarter of all patients with CSS irrespective of presentation.¹⁹ Also, older patients who have gait and/or balance problems may experience balance instability and consequently fall during an episode of transient hypotension. In these cases, older persons may present with recurrent falls rather than syncope.¹³ More recent reports confirm a high incidence of falls in addition to traditional syncopal symptoms in older patients with sick sinus syndrome and atrioventricular conduction disorders.²⁰ Thus, syncope and falls may be indistinguishable and may, in some cases, be manifestations of similar pathophysiologic processes.

International guidelines now cite the importance of a cardiovascular assessment in fall prevention. The American Geriatrics Society panel on falls prevention, in its 2001 evidence-based guidelines, and again in the 2009 update, recommends assessment of basic cardiovascular status, including heart rate and rhythm, postural pulse, and blood pressure (BP), and, if appropriate, heart rate and BP responses to carotid sinus massage.^{21,23} Furthermore, it recommends targeted multifactorial intervention, including treatment of postural hypotension and cardiovascular disorders (including cardiac arrhythmias). Cardiovascular examination as part of a multifactorial falls assessment is also recommended in the National Institute for Health and Clinical Excellence guidelines in the United Kingdom.²⁴

CARDIOVASCULAR CAUSES OF FALLS

Cardiovascular causes of falls and/or syncope can be broadly divided into 3 main categories: neurally mediated causes, orthostatic hypotension (OH), and intrinsic cardiac abnormalities of structure or rhythm (**Box 2**).

Although the most frequent causes of syncope are neurally mediated, regardless of the age of the individual; the underlying pathology differs between younger and older individuals. Older individuals with neurally mediated syncope are far more likely to have CSS or postprandial hypotension than vasovagal syncope (VVS), in contrast with younger individuals (<40 years) who almost exclusively have VVS (**Fig. 1**).^{25,26}

Older adults (>60 years) who fall and/or lose consciousness are also far more likely to have an underlying cardiac cause than younger adults (<40 years) (**Fig. 2**).²⁷

Features in the history that are suggestive of an underlying cardiac cause include previous history of heart disease, symptoms occurring during exercise or while supine, episodes preceded by palpitations, or family history of sudden death. Alboni and colleagues²⁸ demonstrated that a previous history of heart disease predicts cardiac syncope with 95% sensitivity and 48% specificity, and its absence excludes a cardiac cause in 97%. In addition to a detailed history and cardiac examination, a 12-lead electrocardiogram (ECG) is invaluable in the assessment of patients presenting with unexplained falls and/or syncope. ECG abnormalities that suggest the presence of underlying cardiac disease are summarized in **Box 3**.

Cardiac syncope is strongly associated with increased mortality.^{25,29} Soteriades and colleagues²⁵ found that cardiac syncope doubled the risk of death from any cause

Box 2**Cardiovascular causes of falls***Neurally mediated (reflex)*

- Vasovagal syncope:
Mediated by emotional distress: fear, pain, blood phobia
Mediated by orthostatic stress
- Situational syncope:
Coughing, sneezing, micturition (postmicturition)
Gastrointestinal stimulation (swallowing, defecation, visceral pain)
Postexercise
Postprandial
Others (laughing, weightlifting)
- Carotid Sinus Syndrome (CSS)
- Atypical forms (without apparent triggers and/or atypical presentation)

OH

- Primary orthostatic failure:
Pure autonomic failure, multi-system atrophy, Parkinson's disease with autonomic failure, Lewy body dementia
- Secondary autonomic failure:
Diabetes, amyloidosis, uremia, spinal cord injuries
- Drug-induced autonomic failure:
Alcohol, vasodilators, diuretics, antidepressants, phenothiazines
- Volume depletion:
Hemorrhage, diarrhea, vomiting

Intrinsic cardiac disease

- Arrhythmia as primary cause
Bradycardia: sinus-node dysfunction, atrioventricular conduction disease, implanted device malfunction
Tachycardia: supraventricular or ventricular
Drug-induced bradycardia and tachyarrhythmias
- Structural
Cardiac: cardiac valvular disease, acute myocardial infarction/ischemia, hypertrophic cardiomyopathy, cardiac masses (eg, atrial myxoma, tumors), pericardial disease/tamponade
Others: pulmonary embolus, acute aortic dissection, pulmonary hypertension

and increased the risk of fatal and nonfatal cardiovascular events in participants involved in the Framingham study who were followed over a 17-year period (**Fig. 3**).

However, cardiac syncope, in general, is eminently treatable, with insertion of a pacemaker and/or antiarrhythmic medication (see later sections). Therefore, it is an important condition to recognize. In any older person presenting with an

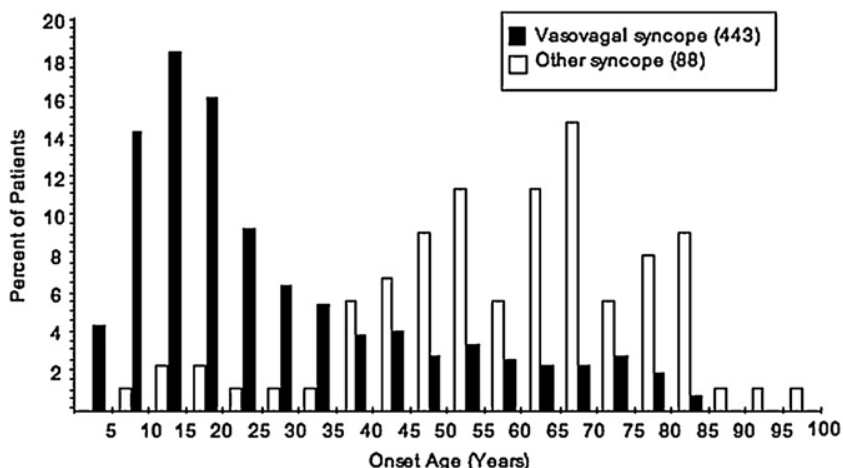


Fig. 1. Comparison of ages of first faint in 443 patients with VVS and 88 patients with syncope of other known cause. (From Sheldon RS, Sheldon AG, Connolly SJ, et al. Age of first faint in patients with vasovagal syncope. *J Cardiovasc Electrophysiol* 2006;17:49–54; with permission.)

unexplained fall or loss of consciousness, it is important to first rule out cardiac causes of syncope.³⁰ An approach to the evaluation of syncope for all age groups is shown in **Fig. 4**.

As a general rule, the most common cardiovascular disorders causing falls and/or syncope in the elderly are CSS, postprandial hypotension, vasovagal syndrome, OH, bradyarrhythmias, and tachyarrhythmias.^{31,32} These are discussed in more detail in the next sections.

CAROTID SINUS HYPERSENSITIVITY AND CSS

Introduction

The carotid sinus is located at the bifurcation of the common carotid artery and contains numerous baroreceptors (**Fig. 5**). In healthy adults, pressure on this area causes a slowing in heart rate and a drop in BP. In some individuals, this response

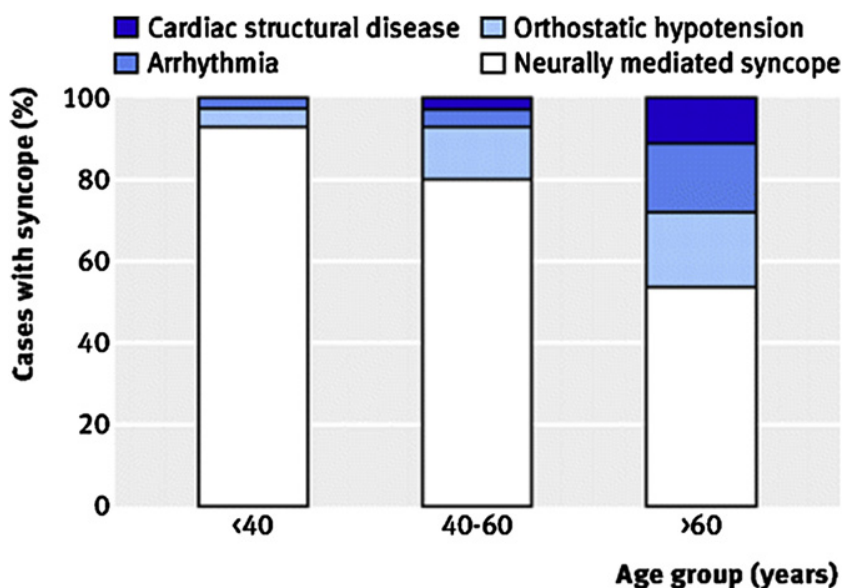


Fig. 2. Causes of syncope by age. (Data from Del Rosso A, et al. Relation of clinical presentation of syncope to the age of patients. *Am J Cardiol* 2005;96(10):1431–5; Parry SW, Tan MP, An approach to the evaluation and management of syncope in adults. *BMJ* 2010;340:c880.)

Box 3**ECG abnormalities suggesting the presence of arrhythmias**

Bifascicular block

- Left bundle branch block (LBBB)
- Right bundle branch block (RBBB) and left anterior or posterior hemiblock
- Atrioventricular block

Sinus bradycardia, sinus pauses

Pre-excitation (shortened PR interval)

Prolonged QT interval

Myocardial ischemia or infarction

Others

- Brugada syndrome (RBBB with ST elevation in leads V1–V3)
- Arrhythmogenic right ventricular dysplasia

is exaggerated, leading to a diagnosis of carotid sinus hypersensitivity (CSH). When CSH is associated with spontaneous recurrent syncope or unexplained falls, it is called CSS.²² Although CSH and CSS are 2 distinct entities, they are often used interchangeably in the literature.

Epidemiology

CSH is a disease of aging and is virtually unknown in people younger than 40 years.³³ The prevalence of CSH increases with age thereafter, from 2.4% in those aged 50 to 59 years to greater than 40% in those older than 80 years.³⁴ Men are more commonly affected than women, and most have coronary artery disease or hypertension.^{27,35} Other hypotensive disorders, such as VVS and OH, coexist in one-third of patients with CSH.^{36–38}

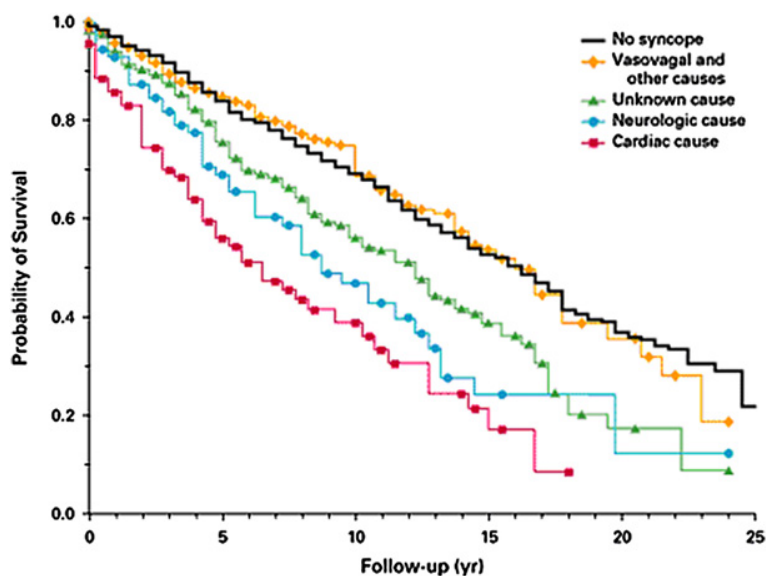


Fig. 3. Kaplan Meier curve showing the overall survival of participants with syncope according to cause, and participants without syncope. (From Soteriades ES, Evans JC, Larson MG, et al. Incidence and prognosis of syncope. *N Engl J Med* 2002;347:878–85; with permission.)

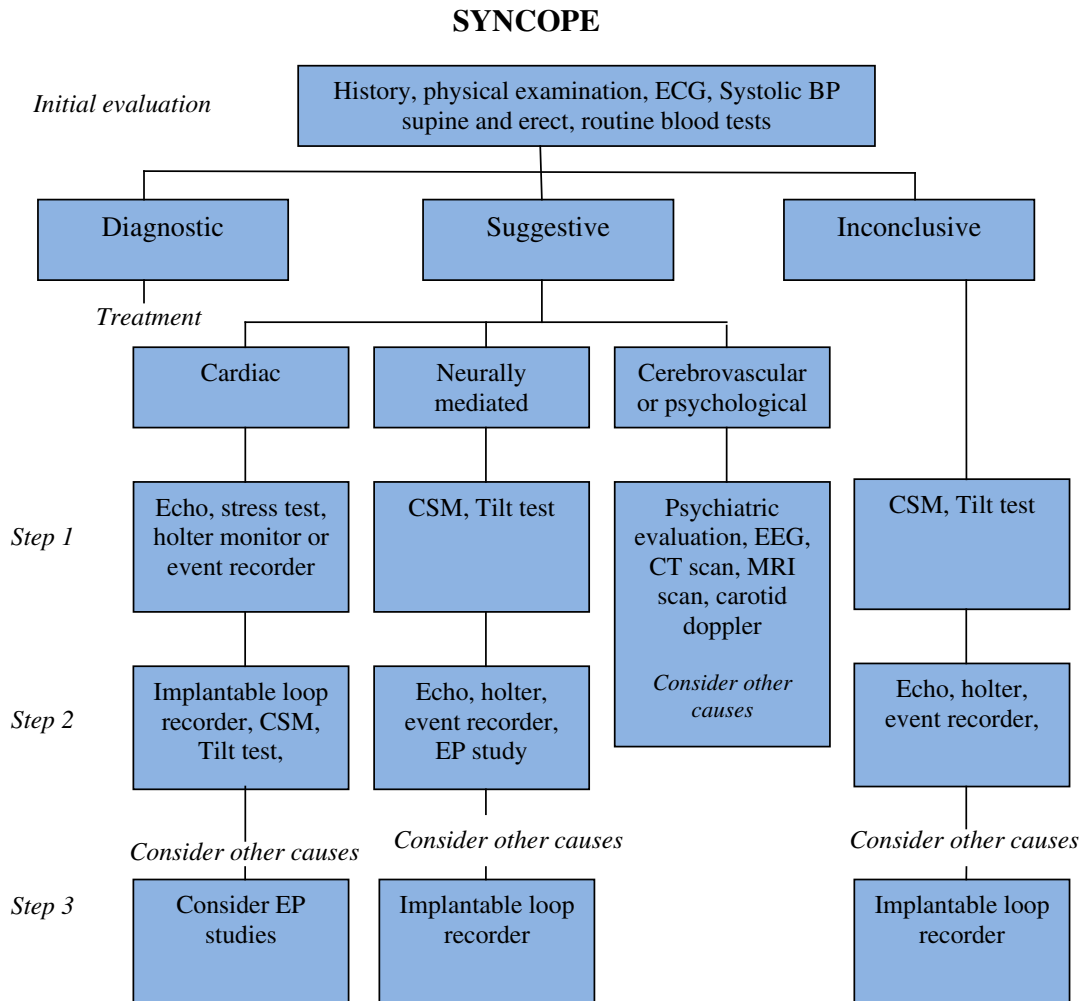


Fig. 4. Proposed approach to the evaluation of syncope for all age groups. CSM, carotid sinus massage; CT, computed tomographic; EEG, electroencephalogram; Echo, echocardiography; EP, cardiac electrophysiological study; Holter, ambulatory cardiac recorder; MRI, magnetic resonance imaging.

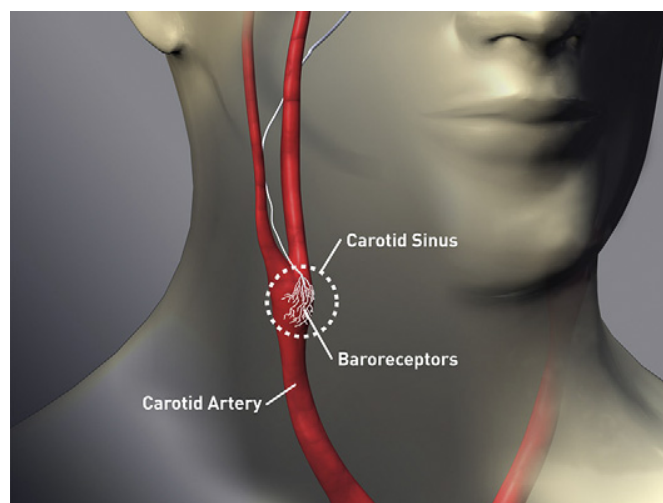


Fig. 5. Anatomic location of the carotid sinus.

Considerable debate exists in the current literature as to whether CSH is indeed a clinically important entity or merely a physiologic observation without clinical sequelae. Kerr and colleagues³⁹ found that 30% of a community-dwelling population who tested positive for CSH were asymptomatic for the disorder. However, more recent neuropathologic research suggests that CSH is associated with neurodegenerative pathology at the cardiovascular center in the brain stem.⁴⁰ Miller and colleagues⁴⁰ demonstrated a significant increase in hyperphosphorylated tau accumulation in baroreflex nuclei in patients with CSH versus age-matched controls. Individuals with CSH have an exaggerated baroreflex response, rather than the loss of baroreflex responses seen in other aging-related autonomic disorders, such as multi-system atrophy or Parkinson disease (PD) with OH. This suggests the dysregulation of baroreflex nuclei in CSH rather than death or loss of neurons. This involvement of neurodegenerative processes is one of the theories proposed to explain why some people with CSH develop syncope and/or falls and others remain asymptomatic.⁴⁰

However, the literature makes it clear that CSS is an important but frequently overlooked cause of falls and syncope in older persons.^{11,15,17,31,41} One prospective study of older patients presenting to an accident and emergency department with unexplained falls found that almost half the patients with nonaccidental falls had cardioinhibitory CSH compared with 13% of the age-matched controls.¹⁸ Another study looking at the causes of recurrent drop attacks in the elderly (defined as a sudden fall event whereby the patient landed on the ground or another level, with no prodrome, no awareness of loss of consciousness, and no overt extraneous triggering event, such as a slip or trip) found that CSH was the underlying diagnosis in 40% of these patients.¹⁵

CSS is associated with significant morbidity; up to 50% of people sustain an injury, including a fracture, during symptomatic episodes.³¹ In a prospective study of falls in nursing home residents, a threefold increase in the fracture rate in those with CSH was observed.⁴² However, CSS is not associated with an increased risk of death. The mortality rate in patients with CSS is similar to that of patients with unexplained syncope and the general population matched for age and sex. Mortality rates are similar for the 3 subtypes of the syndrome.

Presentation

Patients with CSS may present with syncope, presyncope, and/or falls. Although syncope (with or without warning) remains the commonest presentation, accounting for approximately 60% of all cases, more than a quarter of patients with CSS present with unexplained falls.³⁴ Recognized triggers for CSS include mechanical stimulation of the carotid sinus (such as head turning, tight neckwear, neck pathology), vagal stimuli (such as prolonged standing), postprandial state, straining, micturition, defecation, looking or stretching upwards, and exertion. However, in a significant number of people, no triggering event can be identified.

Evaluation

Carotid sinus sensitivity is assessed by measuring heart rate and BP response to carotid sinus massage (CSM). This procedure requires 2 people, one to perform CSM and the other to record the ECG and BP readings.⁴³

The examiner first locates the carotid sinus by finding the maximal point of carotid pulsation between the angle of the mandible and the superior border of the thyroid cartilage. Using 1 or 2 fingers, the examiner then firmly rubs along a 2-cm stretch of the carotid artery (centered over the carotid sinus) in an up-and-down motion for 5 seconds (**Fig. 6**). Simple pressure over the carotid sinus does not reliably reproduce

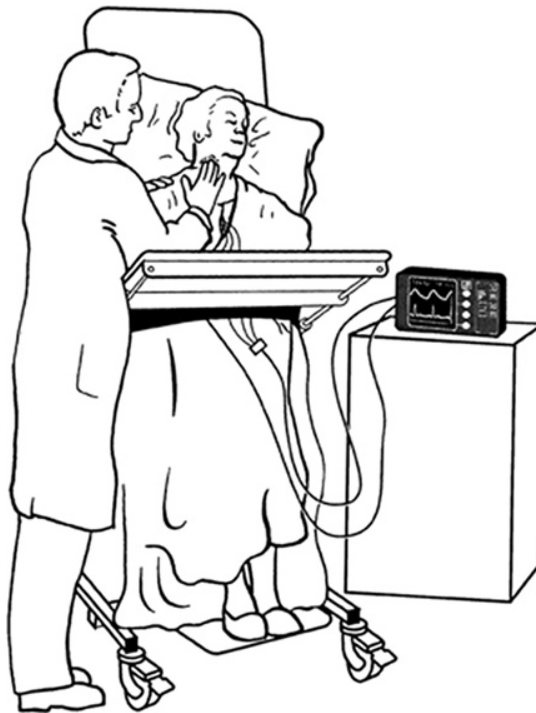


Fig. 6. Demonstration of CSM in the upright position.

a response. The maximum decline in heart rate usually occurs within 5 seconds of the onset of massage and the maximum decline in BP, within 20 seconds. There is no fixed relationship between the degree of heart rate slowing and the degree of decline in BP. By convention, CSM is conducted on the right side in the supine position first, followed by the left supine.⁴³ If the test is negative in the supine position, it should be repeated in the upright position with the patient tilted at 70° on a tilt table with a footplate. This improves diagnostic sensitivity (because up to one-third of patients only achieve a diagnostic response during upright CSM) and facilitates better evaluation of the vasodepressor component.^{19,44–46}

The test is considered positive if there is 3 seconds or more of asystole (cardioinhibitory subtype), a decline in systolic BP (SBP) of 50 mm Hg or more (vasodepressor subtype), or both (mixed subtype) in tandem with symptom reproduction. Cardioinhibition and vasodepression are more common on the right side. In patients with cardioinhibitory CSS, more than 70% have a positive response to right-sided CSM, alone or in combination with left-sided CSM. Symptom reproduction during CSM is preferable for a diagnosis of CSS. This reproduction of symptoms aids in attributing the episodes to CSS, especially in patients with unexplained falls who deny loss of consciousness. However, it may not always be possible to reproduce symptoms, particularly in older patients with amnesia for loss of consciousness. In these difficult cases, it is reasonable to diagnose CSS if no other attributable cause of unexplained falls or syncope can be found after a systematic approach has been undertaken.⁴⁷

Although CSM is a useful test, it has some limitations. First, as a technique, it is crude, unquantifiable, and prone to both intra- and inter-observer variations. Second, an abnormal response to CSM may not always be reproducible, thus necessitating repetition of the procedure if the diagnosis is strongly suspected.

Complications from CSM are uncommon but include cardiac arrhythmias and neurologic sequelae. Fatal arrhythmias are extremely uncommon and have generally only occurred in patients with underlying heart disease undergoing therapeutic rather than diagnostic massage. Digoxin toxicity has been implicated in most cases of

ventricular fibrillation. Neurologic complications result from occlusion of or embolization from the carotid artery. Several authors have reported cases of hemiplegia after carotid sinus stimulation, often in the absence of hemodynamic changes. However, in a prospective series of 1000 consecutive cases, no patient had cardiac complications and 1% had transient neurologic symptoms that resolved.^{48–50} Persistent neurologic complications were uncommon, occurring in 0.04%.^{48–50} Pooled data of 7319 patients who underwent CSM^{33,48,49} showed a neurologic complication rate of 0.29% (21 patients).²² CSM should not be performed in patients who have had a recent (within 3 months) cerebrovascular event or myocardial infarction. It should also be avoided in patients with carotid bruits unless carotid Doppler studies have excluded significant stenosis.⁴⁸

Management

It is prudent to treat patients with a history of 2 or more symptomatic episodes, because there is a high rate of injury. The need for intervention in those with a solitary event should be assessed on an individual basis, taking into consideration the severity of the event and the patient's comorbidity.

Treatment options depend on the underlying subtype of CSS, whether cardioinhibitory, vasodepressor, or mixed. Early studies of CSS revealed that a cardioinhibitory response was the most common, accounting for up to 70% of cases, with mixed and vasodepressor response each accounting for 15%.^{51–53} However, more recent studies have highlighted the much higher prevalence of the vasodepressor component than was previously known.^{31,44} This is important when considering pacemaker therapy, because those with prolonged vasodepressor response to CSM are at a high risk of recurrence despite pacemaker therapy and need a more complex therapeutic approach.⁴⁴

Initial studies demonstrated a beneficial effect of cardiac pacing in patients with cardioinhibitory CSS.^{41,45,54} In a single-center randomized control trial of 175 patients (mean age 73 years) with cardioinhibitory CSH and recurrent unexplained falls (Syncope and Falls in the Elderly Pacing and Carotid Sinus Evaluation [SAFEPACE 1]), cardiac pacing reduced subsequent fall events by 70% and injurious events by 75%.⁴¹ Because of these positive studies, the European Society of Cardiology (ESC) guidelines currently recommend dual-chamber cardiac pacing for patients with symptomatic cardioinhibitory CSS.²² However, 2 studies published since the release of the 2009 ESC guidelines have failed to demonstrate this benefit. SAFEPACE 2, a multicenter trial of 141 patients (mean age 78 years) randomized to receive an implantable loop recorder (ILR) or a dual-chamber pacemaker found no significant difference in fall rates between the 2 groups.⁵⁵ The population studied was older and frailer than in the SAFEPACE 1 study. Another by Parry and colleagues⁵⁶ also failed to demonstrate significant reduction in fall rates in older patients with CSH who were paced, although this study was underpowered because of high attrition rates. Both these studies, however, highlight the need for further work in this area.

If a patient with CSS is referred for pacing, dual-chamber pacing is the treatment of choice. Atrial pacing is contraindicated in view of the high prevalence of sinoatrial and atrioventricular block in patients with CSH. Ventricular pacing abolishes cardioinhibition but fails to alleviate symptoms in a significant number of patients because of aggravation of a coexisting vasodepressor response or development of pacemaker-induced hypotension, called pacemaker syndrome. The latter occurs when ventriculoatrial conduction is intact, as is the case for up to 80% of patients with the syndrome. As dual-chamber pacing maintains atrioventricular synchrony, there is no risk of pacemaker syndrome.

Treatment of vasodepressor CSS is less successful because of poor understanding of its pathophysiology. There are still no randomized studies examining the treatment of dominant vasodepressor CSS. Fludrocortisone, a mineralocorticoid widely used in the treatment of OH, is used in the treatment of vasodepressor CSS with good results, but its use is limited in the longer term by adverse effects (**Table 1**). Midodrine, an α -blocker, has been mainly studied in the treatment of OH; however, a small randomized controlled trial suggests good benefit for patients with CSS (see **Table 1**).⁵⁷ Other agents reported to be useful include ephedrine and dihydroergotamine; however, long-term use of these agents is limited by side effects and poor tolerance.

POSTPRANDIAL HYPOTENSION

Introduction

Postprandial hypotension was first described in 1977 in a patient with advanced Parkinson's Disease (PD).⁵⁸ It is defined as a decrease in SBP of 20 mm Hg or more or a decrease in SBP to less than 90 mm Hg from 100 mm Hg or higher within 2 hours of a meal.⁵⁹ It is a common but often under-recognized condition among older adults. Postprandial hypotension is particularly common among elderly institutionalized patients, with prevalence rates ranging from 25% to 67%.^{60–63} It is also common in patients with diabetes mellitus,^{64,65} essential hypertension,⁶⁶ and PD.⁶⁷ Polypharmacy is another well documented risk factor for postprandial hypotension,^{60,61} as is the use of diuretics.^{60,66} OH, at one time thought to be a risk factor for postprandial hypotension, seems instead to be additive rather than synergistic with postprandial hypotension.^{68,69} The type and time of meal have also been implicated.⁶⁰ Carbohydrate-rich meals cause more postprandial hypotension than meals composed mainly of protein or fat. Also, warm meals (50°C) appear to cause a greater decrease in postprandial BP than meals served cold (5°C).⁷⁰ Although postprandial hypotension can occur after any meal, breakfast and lunch appear to be associated with more pronounced decreases in BP.^{61,71} Although it is difficult to quantify the clinical

Medication	Dose & Frequency	Side Effects	Caution
Midodrine	2.5 mg thrice daily; can be titrated up gradually depending on symptoms and BP to a maximum dose of 45 mg/d	Hypertension, gastrointestinal symptoms (particularly diarrhea), pilomotor erection, and central nervous system toxicity. These usually respond to dose reduction	Contraindicated in persons with coronary heart disease, heart failure, urinary retention, and thyrotoxicosis. Use cautiously in elderly patients who are taking medications that decrease heart rate, such as β -blockers and calcium-channel blockers
Fludrocortisone	0.1–0.2 mg/d	Hypertension, edema, cardiac failure, depression, and hypokalemia	

significance of a decline in BP after meals, postprandial hypotension is associated with recurrent syncope and falls in older persons,^{61,62,72} as well as coronary events and stroke.⁷³ Postprandial hypotension also predicts all-cause mortality in older adults.⁷⁴ In a prospective study of 179 older adults (mean age 83.2 ± 7.0 years) followed over 4.7 years, the relative risk of all-cause mortality increased by 13% for every 10 mm Hg decrease in postprandial SBP. Participants with a postprandial drop in SBP of 20 mm Hg or greater had the worst survival rate (**Fig. 7**).⁷⁴

Presentation and Diagnosis

In most fit as well as frail older people, most postprandial hypotensive episodes go unnoticed. However, in older patients presenting with syncope or falls, it is important to have a high index of suspicion and to inquire specifically about hypotensive symptoms after meals. Twenty-four hour ambulatory blood pressure monitoring, along with careful documentation of each meal is the cornerstone of diagnosis.

Treatment

Nonpharmacologic treatment options include a reduction in the simple carbohydrate content of food, replacing it with complex carbohydrates, high-protein, and high-fat foods. Drinking water before a meal has been shown to attenuate the decrease in BP in patients with autonomic failure and in elderly patients.^{75,76} Advising patients to eat smaller, more frequent meals has also been shown to help with symptoms.^{77,78} Clinical trials involving pharmacologic treatments are sparse and mostly limited to patients with autonomic failure and the asymptomatic healthy elderly. Some medications that may be of use include fludrocortisone (see **Table 1**), indomethacin, octreotide, and caffeine. Given orally along with food, caffeine prevents hypotensive symptoms in fit and frail older people but should preferably be given in the mornings, because tolerance develops if it is taken throughout the day.^{79,80} Octreotide, given as a single premeal subcutaneous injection has also been shown to be of benefit in elderly patients with postprandial hypotension, but its use is limited by high cost, QT prolongation, and abdominal and injection site pain.^{81,82} Other pharmacologic

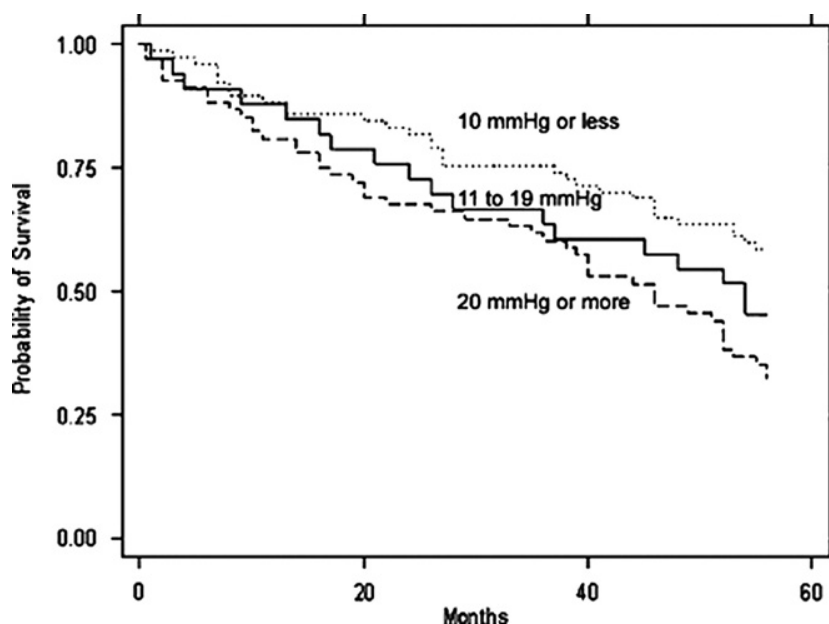


Fig. 7. Kaplan-Meier survival analysis by degree of postprandial changes in SBP. (From Fisher AA, Davis MW, Srikusalanukul W, et al. Postprandial hypotension predicts all-cause mortality in older, low-level care residents. *J Am Geriatr Soc* 2005;53:1313–20; with permission.)

agents that seem promising are the α -glucosidase inhibitors (acarbose or voglibose) and guar gum.^{83–85} However, because of the high incidence of gastrointestinal side effects, their use is also currently limited.

VVS

Introduction

VVS is an exaggerated tendency toward the common faint caused by a sudden and profound hypotension with or without bradycardia.

Epidemiology

VVS can occur at any age, but the age distribution shows 2 distinct peaks—the largest one between ages 20 and 29 years and a second smaller one in those older than 70 years.⁸⁶ In older adults, the prevalence ranges from 10% in community-dwellers to 23% in an elderly institutionalized population.^{25,47,87,88} In specialist syncope clinics, it is even higher.^{89,90} It is estimated that up to 30% of the general population will suffer a VVS episode at least once in their lifetime. Although the natural history of VVS in a younger population tends to be benign,⁹¹ VVS in the older person has been linked with advanced malignancy and other terminal conditions as well as higher mortality.^{29,92–95}

Presentation

The hallmark of VVS is hypotension and/or bradycardia sufficiently profound to produce cerebral ischemia and loss of neural function. VVS most commonly occurs in the standing position but may also present while sitting or, exceptionally, when supine. In most patients, the manifestations occur in 3 distinct phases: a prodrome (or aura) phase, loss-of-consciousness phase, and post-syncopal phase. Common precipitating factors include extreme emotional stress, anxiety, trauma, physical pain or anticipation of physical pain (eg, anticipation of phlebotomy), warm environment, and prolonged standing. Some people experience symptoms in specific situations, such as micturition, defecation, sneezing, and coughing. Although a precipitating factor or situation is identifiable in most young patients, several studies have demonstrated that older patients are far less likely to report these precipitating factors.^{27,86,96} Prodromal symptoms vary from individual to individual but include weakness, nausea, visual distortion, sweating, palpitations, chest pain, extreme fatigue, visual and auditory hallucinations, dizziness, vertigo, headache, abdominal discomfort, dysarthria, and paresthesias. Older patients are less likely to present with the typical symptoms of impending syncope and are more likely to present with unexplained falls.⁹⁶ The duration of the prodrome varies greatly from seconds to several minutes and the syncopal period is usually brief. A significant proportion of people develop involuntary movements during the syncopal period (usually myoclonic jerks, but tonic-clonic movements also occur); thus VVS may masquerade as a seizure. In general, recovery is rapid, but older patients can experience protracted symptoms, such as confusion, disorientation, nausea, headache, dizziness, and a general sense of ill health, following a syncopal episode.

Given that there are significant differences in the clinical presentation of VVS between older and younger patients, an accurate diagnosis of VVS is less likely to be made based on historical features alone in older patients.⁹⁶ Often, older patients presenting with transient loss of consciousness or unexplained falls need more intensive investigation to establish a diagnosis.

Evaluation

In addition to the clinical history and witness statements, the most valid current technique for diagnosing VVS is the head-up tilt test.⁹⁷ This test uses the strong orthostatic stimulus of head-upright tilting and maximal venous pooling to reproduce VVS in susceptible individuals. Subjects are tilted head-up for 40 minutes at 70° (Fig. 8).

Heart rate and BP are measured continuously throughout the test using phasic or noninvasive beat-to-beat BP monitoring. Most phasic BP monitors use arterial photoplethysmography to capture beat-to-beat BP measurements and are more sensitive for detection of transient declines in BP. A test is considered diagnostic or positive if symptoms are reproduced with a decline in SBP of more than 50 mm Hg or a drop in SBP to lower than 90 mm Hg, which may be in addition to significant heart rate slowing. VVS can be broadly classified into 3 subtypes depending on the BP and heart rate response: cardioinhibitory (bradycardia), vasodepressor (hypotension), or mixed (both). The cardioinhibitory response is defined as asystole in excess of 3 seconds or heart rate slowing to less than 40 beats per minute (bpm) for a minimum of 10 seconds.

The sensitivity of head-up tilting can be further improved by provocative agents that accentuate the physiologic events leading to VVS. The agent of choice is nitroglycerin, which, by vasodilatation, acts to reduce venous return, thereby enhancing the vaso-vagal reaction in susceptible individuals.

In people with atypical symptoms (such as extremely short prodrome or no warning at all, syncopal episodes that occur while seated, marked palpitations, or urinary or fecal incontinence during an event), it is advisable to rule out underlying arrhythmias. For those in whom the syncopal episodes occur frequently (every 2–3 weeks), external loop recording is helpful and can aid diagnosis by capturing brady- or tachyarrhythmias at the time of the syncopal episode. When the episodes are less frequent, an implantable loop recorder (ILR) can be used to track underlying arrhythmias. These small medical devices are inserted subcutaneously beneath the clavicle and record the heart rhythm on a continual loop. They are capable of automatically detecting and storing unusual rhythms and can also be activated at will by the person following a fall and/or syncopal episode. These manual activations can be done up to 20 minutes after an

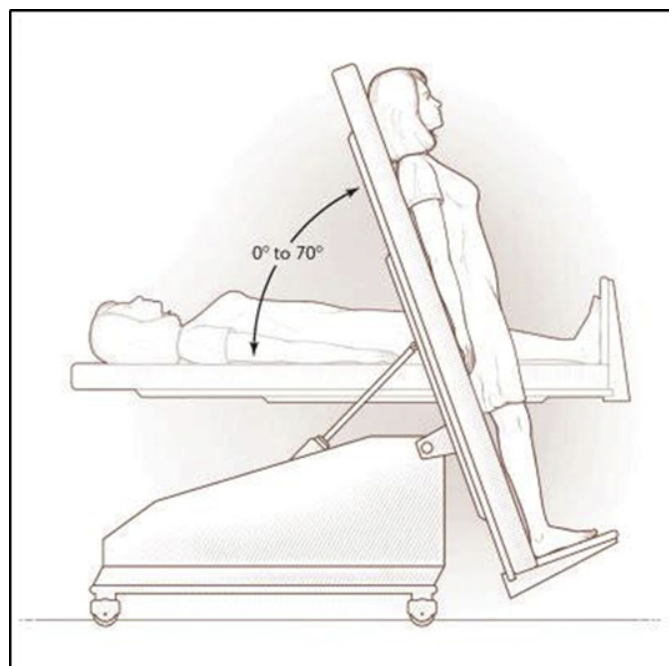


Fig. 8. Tilt table testing.

event, making them particularly useful in older people who may take longer to recover after a syncopal episode than younger ones. The automated and manual activations can then be downloaded and interpreted by a clinician. Typically, these devices are left in situ for up to 18 months or until symptom-rhythm correlation is established.

Management

The mainstay of treatment for VVS is avoidance of precipitating factors, increasing fluid intake, and being educated regarding evasive actions, such as lying down during prodromal symptoms. Physical countermeasures (such as leg crossing or arm tensing) have also been shown to be helpful in avoiding or delaying loss of consciousness.^{98,99} Elastic support hose, relaxation techniques (biofeedback), and conditioning using repeated head-up tilt as therapy have been used successfully as adjuvant therapies. In older people, often the only necessary intervention is withdrawal or modification of culprit medications. Twenty-four hour ambulatory BP monitoring is useful in helping to tailor both the dose and the frequency of antihypertensive medications. Older adults with hypertension who develop syncope, orthostatic or vasovagal, while taking antihypertensive drugs present a difficult therapeutic dilemma and should be treated on an individual basis.

In people who have frequent syncopal episodes and/or short warnings or in those whose quality of life is being affected by the syncope, drug therapy may be required.

The best evidence exists for midodrine, which has demonstrated short- and medium-term therapeutic success in small, randomized controlled trials (see **Table 1**).¹⁰⁰

Although fludrocortisone is widely prescribed for VVS, the clinical trials conducted to date have been in pediatric patients. The first randomized controlled clinical trial to address the effectiveness of fludrocortisone in the treatment of VVS in adults is currently under way (Second Prevention of Syncope Trial [POST II]).¹⁰¹ Until such time as the outcome of that trial is available, the usefulness of fludrocortisone in the prevention of VVS will remain unclear. However, in the absence of contraindications, it is reasonable to give symptomatic patients a trial of fludrocortisone, as a monotherapy or in combination with midodrine (see **Table 1**). To date, there is no convincing evidence to support the use of serotonin antagonists, such as fluoxetine and sertraline hydrochloride, in the treatment of VVS.¹⁰² The use of cardiac pacing for VVS remains controversial. Initial observational and open-label randomized trials showed impressive and highly significant benefits of 80% to 87% relative risk reduction with pacing.¹⁰⁰ However, 2 double-blind studies failed to find a benefit.^{103,104} Whether the subset of patients with VVS who have asystolic pauses during syncope might benefit from pacing is unresolved. The second International Study on Syncope of Uncertain Etiology (ISSUE 2) used ILRs to test whether therapy targeted to the findings of the recorders could prevent syncope. ISSUE 2 implanted ILRs in 417 patients with recurrent syncope and followed them until their next syncope or for a maximum of 2 years.¹⁰⁵ Further treatment was assigned based on the ECG findings during the episode. This resulted in 57 patients receiving a pacemaker for asystole. The patients who received pacing had a 1-year recurrence rate of 10%, compared with 41% in the 50 patients who did not receive a specific treatment, and a 90% relative risk reduction for syncope. Although highly impressive, the study was limited by the absence of a blinded control group. In an effort to resolve the question of the efficacy of targeted therapy, ISSUE 3, a placebo-controlled double-blind study was designed and is currently under way.¹⁰⁶ This study implants ILRs in patients with frequently recurrent, suspected VVS. Patients with asystolic pauses have a pacemaker implanted with double-blinded randomization to active pacing or sensing only.

OH

Introduction

Orthostatic or postural hypotension is arbitrarily defined as a 20-mm Hg decline in systolic BP or a 10-mm Hg decline in diastolic BP within 3 minutes of assuming an upright posture from a supine position.¹⁰⁷ OH implies abnormal BP homeostasis and is a frequent observation with advancing age.

Epidemiology

The reported prevalence figures for OH vary widely depending on the definition of OH, the patient selection, and the methodology used to measure postural BP changes. Despite these variations, it is clear that the prevalence of OH increases with advancing age. Prevalence of OH is 9.4% in individuals aged 50 years, increasing to 14.8% in individuals aged 65 to 69 years and to 26% in those older than 85 years.^{25,108} In frail elderly individuals living in nursing homes, the prevalence of OH is even higher.^{109,110}

OH is an important cause of unexplained falls and syncope, accounting for 14% of all diagnosed cases in a large series. In a tertiary referral clinic dealing with unexplained syncope, dizziness, and falls, 29% of patients older than 65 years had OH as a possible attributable cause of symptoms.¹¹¹ OH is associated with significant morbidity mainly from the falls, fractures, and injuries that occur as a result.¹⁰⁸ OH is also associated with increased mortality in older adults.^{112,113}

Pathophysiology

The cardiovascular system responds to maintenance of an upright posture in 3 phases: (1) an initial heart rate and BP response, (2) an early phase of stabilization, and (3) a response to prolonged standing. All 3 phases are influenced by normal aging. The maximum increase in heart rate and the ratio between the maximum and minimum heart rate in the initial phase decline with age, implying a fairly fixed heart rate irrespective of posture. BP and cardiac output are adequately maintained on standing in active, healthy, well-hydrated, and normotensive older adults, despite a blunted heart rate response because of decreased vasodilatation and reduced venous pooling during the initial phases and increased peripheral vascular resistance after prolonged standing. However, in older persons with hypertension and cardiovascular disease receiving vasoactive drugs, these circulatory adjustments to orthostatic stress are disturbed, rendering them vulnerable to postural hypotension.

Prolonged exposure to hypertension in the cardiovascular system further increases the risk of hypotension by impairing baroreflex sensitivity and reducing ventricular compliance. A strong relationship between supine hypertension and OH has been reported among unmedicated institutionalized older persons.¹¹⁴ Hypertension increases the risk of cerebral ischemia from sudden declines in BP. Older persons with hypertension are more vulnerable to cerebral ischemic symptoms, even with modest and short-term postural hypotension, because the threshold for cerebral autoregulation is altered by prolonged elevation of BP. Also, antihypertensive agents impair cardiovascular reflexes and further increase the risk of OH.

Etiology

OH can be broadly divided into acute and chronic (**Fig. 9**).

Acute OH usually develops over a short period of time and is more symptomatic at the outset. Typically, it results from acute conditions, such as dehydration, sepsis, medications, myocardial ischemia, and adrenal insufficiency. In contrast, chronic OH develops gradually over a much longer period of time, and the individual is often

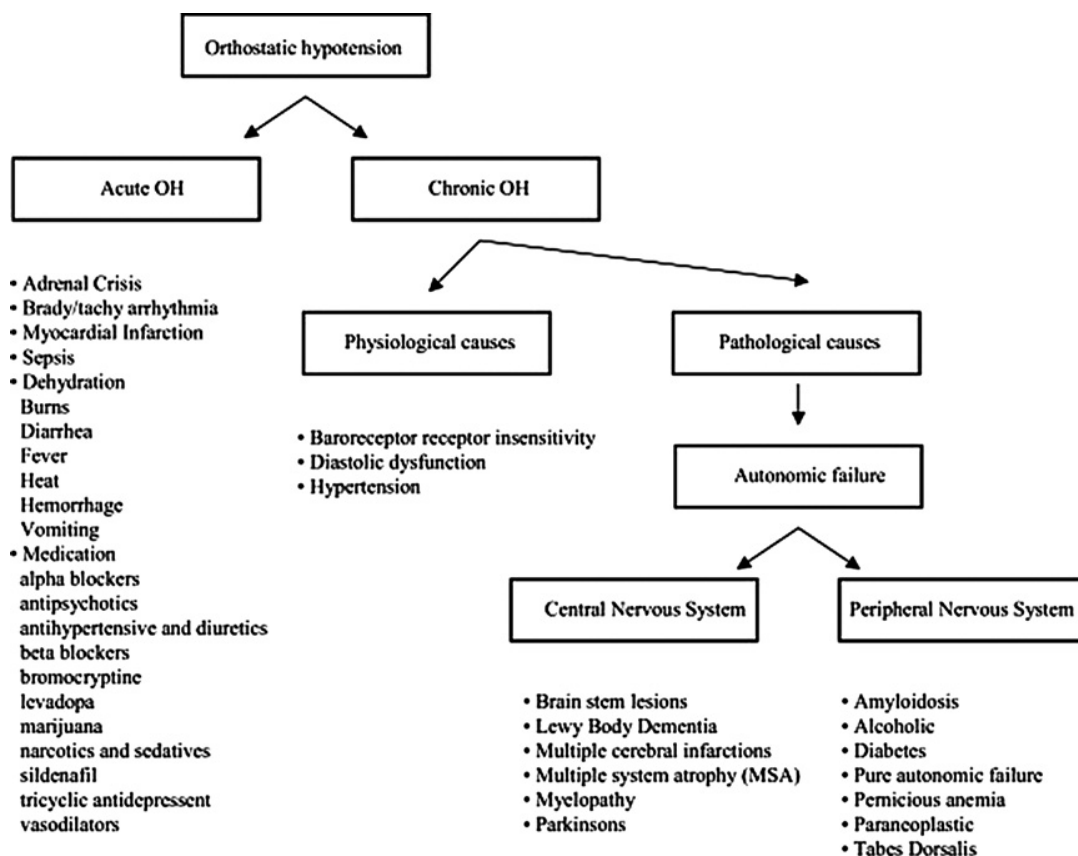


Fig. 9. Causes of OH. (From Gupta V, Lipsitz LA. Orthostatic hypotension in the elderly: diagnosis and treatment. *Am J Med* 2007;120(10):841–7; with permission.)

asymptomatic during the initial period. Both physiologic and pathologic causes may be responsible for the development of chronic OH. Physiologic changes that normally occur with aging predispose older individuals to symptomatic OH in the face of common everyday stressors, such as posture change, new medications, meals, acute illness, or fluid restriction. Pathologic disease in the central and/or peripheral nervous system resulting in autonomic insufficiency may also cause chronic OH.

Medications are an important cause of OH in older adults. Cardiac medications cause OH by working in various ways, including volume depletion (diuretics), reduction in systemic vascular resistance and venodilation (vasodilators, particularly nitrates and α -blockers), centrally acting antihypertensives (alpha-methyldopa, labetalol), ventricular tachycardia associated with a prolonged QT interval (amiodarone, sotalol, and flecainide), and cardiac arrhythmias (digoxin). In addition to cardiac drugs, psychoactive medications (such as tricyclic antidepressants, barbiturates, phenothiazines, and monoamine oxidase inhibitors) are also associated with an increased risk of OH, because of their central effects causing hypotension or cardiac arrhythmias. In the presence of polypharmacy, which is common in the older person, it becomes difficult to identify a single culprit drug, because of the synergistic effect of different drugs and drug interactions. Thus, all drugs should be considered as possible contributors to orthostasis.

OH occurs in up to two-thirds of individuals with PD,^{115,116} and the prevalence of symptomatic OH may be as high as 20%.¹¹⁵ Although this is due mainly to impaired baroreflex function and autonomic failure, certain medications used to treat PD, namely L-dopa, selegiline, and the dopamine agonists, may result in or contribute to OH.^{117–119} Although it is well-recognized that patients with PD have a higher risk of falling than the general population, whether these falls are associated with OH or

not remains controversial. Although some studies have found an association,^{120,121} others have failed to do so.^{122,123} Cognitive impairment, in particular, abnormal attention and executive function, is more common in individuals with PD and OH than those with PD alone, suggesting a possible causal association with hypotension, including watershed lesions.¹²⁴

Presentation

The clinical manifestations of OH are due to hypoperfusion of the brain and other organs. Depending on the degree of decline in BP and cerebral hypoperfusion, symptoms can vary from dizziness to syncope. In elderly people, disturbed speech, visual changes (ranging from blurred vision to total visual loss), falls, confusion, and impaired cognition are more commonly seen.¹⁰⁸ Precipitating factors for OH include a rapid positional change, prolonged recumbency, warm environment, raised intrathoracic pressure (coughing, defecation and micturition), physical exertion, and vasoactive drugs.

Evaluation

The diagnosis of OH involves a demonstration of a postural decline in BP after active standing. OH can be further subdivided according to the BP and heart rate response to active standing (**Figs. 10** and **11**):

- Classic OH: decrease in SBP of 20 mm Hg or greater and in diastolic BP of 10 mm Hg or greater within 3 minutes of standing (see **Fig. 10**, right panel).¹⁰⁷
- Initial OH: characterized by a BP decrease immediately on standing of more than 40 mm Hg.¹²⁵ BP then spontaneously and rapidly returns to normal so that the period of hypotension and symptoms is short (see **Fig. 10**, left panel).
- Delayed (progressive) OH: characterized by a slow progressive decrease in SBP on standing. The absence of a bradycardic reflex (vagal) differentiates delayed OH from neurally mediated (reflex) syncope. Delayed OH is not uncommon in the elderly (see **Fig. 11** lower panel).

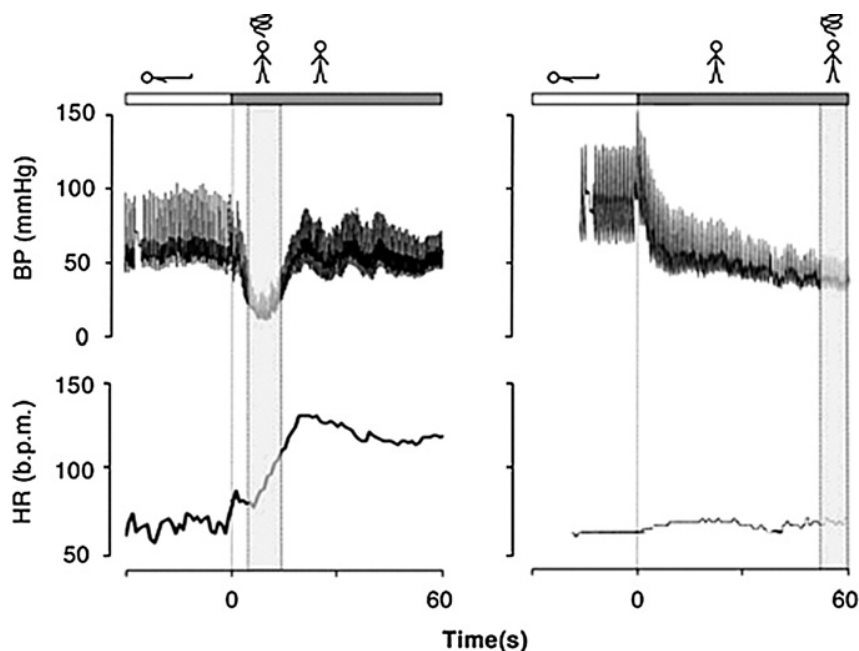


Fig. 10. Left panel shows initial OH with right panel showing classic OH.

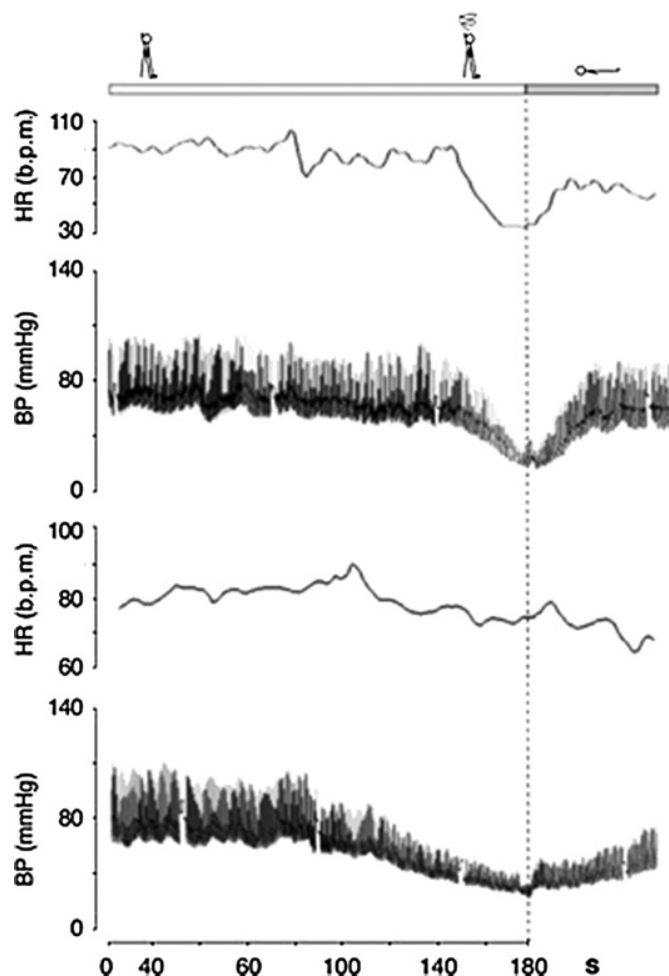


Fig. 11. Reflex syncope induced in young person (*upper panel*) and delayed hypotensive response in older person (*lower panel*).

Reproducibility of OH depends on the time of measurement and on autonomic function. The procedure should be conducted during the morning after maintaining supine posture for at least 10 minutes. The diagnosis may be missed on casual measurement during the afternoon.¹²⁶ Patients with PD are more likely to suffer from delayed (progressive) OH (see **Fig. 11** lower panel), and in these cases, the BP decline is often delayed by longer than the recommended 3 minutes; therefore, any evaluation for OH in a patient with PD should include measurements of BP for up to 5 minutes after positional change.

Traditionally, BP is measured using a sphygmomanometer, either manually or using an automated cuff. These methods only detect hypotension that is sustained. A far more sensitive method for detecting transient declines in BP involves the use of phasic BP measurements (described earlier). It is more appropriate to carry out an active stand rather than using a head-up tilt to diagnose OH, because the active stand more readily represents the physiologic α -adrenergic vasodilatation due to calf muscle activation on standing. Once a diagnosis of postural hypotension is made, the evaluation involves identifying the cause or causes of orthostasis mentioned earlier.

Management

The goal of treatment for symptomatic OH is to improve cerebral perfusion. Nonpharmacologic interventions, including avoidance of precipitating factors for low BP, increased fluid intake, elevation of the head of the bed at night by at least 20°, and

application of graduated pressure from an abdominal support garment or from stockings, should be tried in the first instance.^{127–130} In the absence of hypertension, individuals should be instructed to take sufficient salt, up to 10 g/d.¹³¹ Physical countermeasures, such as leg crossing and squatting, should be encouraged in patients with warning symptoms who are able to perform these maneuvers.¹²⁹ Whenever possible, medications known to contribute to OH should be eliminated or reduced. Although there have been reports to suggest that increasing heart rate during postural change by tachypacing may be of benefit to some patients,^{132,133} in general, these benefits are short lived, probably because venous pooling and vasodilatation dominate. Many medications have been used with varying success to raise BP in OH, including fludrocortisone, midodrine, ephedrine, desmopressin (DDAVP), octreotide, erythropoietin, and nonsteroidal anti-inflammatory agents. One of the most potent agents is fludrocortisone (see **Table 1**), which reduces salt loss and expands blood volume.^{134,135} Although this drug, in general, is well tolerated, older adults may be poorly tolerant to high doses over long periods. If the patient remains symptomatic, midodrine (see **Table 1**) may be effective.^{136–138} Because of its short half-life, midodrine needs to be given 3 times a day. For best results, the morning dose should be given early and the evening dose, no later than 6 PM. Combination therapy of fludrocortisone and midodrine using lower doses of both agents (due to synergistic effects) is also beneficial. DDAVP has potent antidiuretic and mild pressor effects, and intranasal doses of 5 to 40 µg at bed time are useful. The main side effect of DDAVP is water retention, and it can also be used in combination with fludrocortisone with good synergistic effect. Whatever pharmacologic treatment is chosen in the treatment of OH, it is imperative to monitor patients frequently for supine hypertension, electrolyte imbalance, and congestive heart failure. Twenty-four hour ambulatory BP monitoring is extremely useful in many cases, allowing medications to be targeted to particular times of the day and also to monitor for supine hypertension. If a person with OH also has concurrent supine hypertension, particularly at night, one treatment option is applying a nitroglycerine patch after going to bed, removing it in the morning, and taking midodrine with or without fludrocortisone 20 minutes before rising. This is effective provided that the older person remains in bed throughout the night; therefore, nocturia is an important consideration.

ABNORMALITIES OF CARDIAC RHYTHM

The incidence of cardiac syncope increases sharply with age,²⁵ primarily because of underlying arrhythmias (see **Fig. 2**).¹³⁹ Cardiac arrhythmias (brady- and tachyarrhythmias) are an important cause of syncope and unexplained falls in the elderly. Electrophysiological studies and ECG monitoring in highly selected subgroups of patients have suggested that 45% to 80% of cases of syncope classified as being of unknown causes could be assigned a cardiac cause.^{140–143} In younger individuals, the real arrhythmic problem is frequently secondary to other conditions, such as in the case of bradyarrhythmias associated with neurally mediated reflex syncope (VVS). In older adults, and particularly those with evidence of structural heart disease, arrhythmias are more likely to be due to a primary cardiac cause (such as sick sinus syndrome).

Bradyarrhythmias

Sinus node dysfunction

Sinus node dysfunction is characterized by any of several types of rhythm disturbances, including sinus/junctional bradycardia, sinus pauses, and episodes of supraventricular tachyarrhythmia (most commonly paroxysmal atrial fibrillation). In intrinsic

sick sinus syndrome, the sinoatrial node is damaged because of abnormal automaticity or sinoatrial conduction abnormalities. Sinus node dysfunction should be suspected in an older person presenting with unexplained falls or syncope who demonstrates severe sinus bradycardia (heart rate persistently <50 bpm), atrial tachycardias with slow ventricular rates, long asystolic pauses, or episodes of sinoatrial block. Although many studies have demonstrated the link between sick sinus syndrome and syncope, the first study to link sick sinus syndrome specifically with falls was that of Mitchell and colleagues.¹⁴⁴

Diagnosis and treatment As with all arrhythmias, documenting a clear correlation between symptoms and abnormal cardiac rhythm is the key to the diagnosis. Conventional 24-hour ECG monitoring (Holter) has a low diagnostic yield, because the chance of recording a symptomatic arrhythmic event during such a recording is low. In those who have frequent episodes (at least once every 2–3 weeks), an external loop recorder may be sufficient to capture the underlying arrhythmia. However, in most cases, the episodes are less frequent and so necessitate the implantation of an ILR (as discussed earlier).

In patients with sinus node dysfunction and a history of unexplained falls/syncope, implantation of a pacemaker has been shown to improve symptoms, with atrial pacing favored over dual-chamber or single-chamber ventricular pacing. Despite adequate pacing, the recurrence rate of symptoms is high at 20% because of the frequent association of a vasodepressor reflex mechanism with sinus node disease. In those individuals with paroxysmal atrial tachycardias associated with sinus node dysfunction, pharmacologic treatment with antiarrhythmic drugs may be required.

Atrioventricular conduction disorders

Although less common than sinus node dysfunction, bradycardia as a result of intermittent atrioventricular (AV) block is among the more important causes of syncope and/or unexplained falls. As a general rule, the more severe forms of AV block (Mobitz Type II second-degree AV block, third-degree AV block, or alternating LBBB and RBBB) are most closely related to falls and syncope. In these cases, the cardiac rhythm may become dependent on (often unreliable) escape pacemaker sites. Syncope or unexplained falls may occur, because there is a long delay before these subsidiary sites begin to 'fire'.

Diagnosis and treatment As with sinus node dysfunction, ILRs are often necessary to capture the underlying abnormal heart rhythm. Cardiac pacing remains the treatment of choice for syncope or recurrent falls associated with symptomatic AV block.

Tachyarrhythmias

Supraventricular tachycardias

Supraventricular tachycardias rarely cause syncope or falls. However, light-headedness or dizziness may occur at the onset of episodes of tachycardia, which, in susceptible individuals, may be sufficient to cause a fall. Although atrial fibrillation and atrial flutter are rare causes of unexplained falls and/or syncope,¹⁴⁵ the risk increases in patients who are dehydrated or exposed to hot environments and in individuals with left ventricular outflow obstruction (eg, hypertrophic obstructive cardiomyopathy [see next section], severe aortic stenosis). Also, individuals with atrial flutter are at particularly high risk of developing rapid ventricular rates during exertion, which may lead to hypotension, falls, or syncope. Treatment of supraventricular tachycardias primarily involves the use of antiarrhythmic medications, but in certain circumstances, ablation therapy may be required.

Ventricular tachycardias

Ventricular tachycardias most often occur in individuals with structural heart disease, particularly ischemic heart disease and dilated cardiomyopathies.^{28,146} They are a rare cause of unexplained falls; however, if found, they warrant urgent attention and medical treatment. Specific treatment includes antiarrhythmic drugs and implantable defibrillators.

Medications Causing Arrhythmias

Several drugs can cause brady- and tachyarrhythmias. Many antiarrhythmic drugs can cause bradycardia as a result of their specific effect on sinus node function or AV conduction. With the rising incidence of dementia,¹⁴⁷ the use of cholinesterase inhibitors has increased rapidly over the past 5 years.¹⁴⁸ The cardiovascular effects of cholinesterase inhibitors are complex, but they generally augment vagal influences on the heart and promote bradycardia that can result in syncope and/or falls. In a recent paper, Gill and colleagues¹⁴⁹ demonstrated that the use of cholinesterase inhibitors is associated with increased rates of syncope, bradycardia, pacemaker insertion, and hip fracture in older adults with dementia. Older people with dementia are already particularly susceptible to syncope and fall-related injuries,¹⁵⁰ and treatment with cholinesterase inhibitors may worsen these deficits.

Syncope and/or falls due to torsades de pointes is not uncommon, particularly in women, and is caused by drugs prolonging the QT interval. These include antiarrhythmic drugs, vasodilators, psychotropic drugs, antimicrobials, and non-sedating antihistamines.

ABNORMALITIES OF CARDIAC STRUCTURE

Intrinsic structural cardiac abnormalities, such as aortic stenosis or hypertrophic obstructive cardiomyopathy, may be uncovered in up to 5% to 10% of unselected patients with unexplained falls or syncope.¹⁵¹ In general, however, the relationship between structural cardiac disease and syncope/falls is indirect, by virtue of increased susceptibility to tachy- or bradyarrhythmias or hypotension of other cause (eg, low cardiac output, acute myocardial infarction). Syncope is of considerable concern in the setting of fixed or dynamic obstruction to left ventricular outflow. In such cases, symptoms are often provoked by physical exertion but may also develop if an otherwise benign arrhythmia should occur (eg, atrial fibrillation).¹⁵²

Treatment

The treatment of syncope and/or falls in the setting of structural heart disease depends on the nature and severity of the underlying structural abnormalities and the apparent mechanism (ie, arrhythmia, hemodynamic abnormality) leading to the fall/syncope. Treatment in general is aimed at ameliorating the underlying structural defect, and patients should be referred to a specialist cardiology unit for further investigation and management.

SUMMARY

Cardiovascular disorders are a common cause of falls and syncope in older adults.^{4,25} It is important to recognize these conditions because they are associated with an increased mortality, yet most are easily treatable. Given that these conditions may present in various ways to various specialists, it is important that all physicians involved in the care of older people are familiar with the conditions described earlier. Given the significant overlap between falls and syncope and the high level of

knowledge that is required in this area, the obvious question is how much training in geriatric medicine should cardiologists receive and how much cardiology training should geriatricians receive. This important training issue needs to be addressed as a matter of some urgency.

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