Common Syndromes of Orthostatic Intolerance

abstract

The autonomic nervous system, adequate blood volume, and intact skeletal and respiratory muscle pumps are essential components for rapid cardiovascular adjustments to upright posture (orthostasis). Patients lacking sufficient blood volume or having defective sympathetic adrenergic vasoconstriction develop orthostatic hypotension (OH), prohibiting effective upright activities. OH is one form of orthostatic intolerance (OI) defined by signs, such as hypotension, and symptoms, such as lightheadedness, that occur when upright and are relieved by recumbence. Mild OI is commonly experienced during intercurrent illnesses and when standing up rapidly. The latter is denoted “initial OH” and represents a normal cardiovascular adjustment to the blood volume shifts during standing. Some people experience episodic acute OI, such as postural vasovagal syncope (fainting), or chronic OI, such as postural tachycardia syndrome, which can significantly reduce quality of life. The lifetime incidence of ≥ 1 fainting episodes is $\sim 40\%$. For the most part, these episodes are benign and self-limited, although frequent syncope episodes can be debilitating, and injury may occur from sudden falls. In this article, mechanisms for OI having components of adrenergic hypofunction, adrenergic hyperfunction, hyperpnea, and regional blood volume redistribution are discussed. Therapeutic strategies to cope with OI are proposed. *Pediatrics* 2013;131:968–980

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KEY WORDS

syncope, postural tachycardia syndrome, orthostatic hypotension, autonomic nervous system, hypocapnia

ABBREVIATIONS

ANS—autonomic nervous system
BP—blood pressure
CBF—cerebral blood flow
CBFv—cerebral blood flow velocity
CNS—central nervous system
CO—cardiac output
HR—heart rate
IOH—initial orthostatic hypotension
NET—norepinephrine transporter
NOH—neurogenic orthostatic hypotension
OH—orthostatic hypotension
OI—orthostatic intolerance
POTS—postural tachycardia syndrome
VVS—vasovagal syncope

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Upright posture (orthostasis) stresses regulatory capabilities of the circulatory system¹ including an intact heart, intact vascular structure and function, adequate blood volume, and intact physical pumps comprising the skeletal muscle pump (leg muscles that compress leg veins) and the respiratory-abdominal muscle pump, which enhances systemic venous return during respiration.^{2,3} Upright stance causes dependent venous pooling. Muscle pumps propel blood back to the heart when upright and during exercise.² Enabling the skeletal muscle pump forms an important class of physical countermeasures against orthostatic intolerance (OI).^{4,5}

Apart from muscle pumps, rapid orthostatic circulatory adjustments depend on the autonomic nervous system (ANS) comprising sympathetic and parasympathetic arms forming a framework for heart rate (HR) and blood pressure (BP) stability. The myogenic response⁶ and flow-dependent mechanisms⁷ primarily act to ensure tissue-level perfusion and autoregulation. The sympathetic arm acts through its primary vascular neurotransmitter norepinephrine⁸ and cotransmitters neuropeptide Y and ATP⁹ to produce arterial vasoconstriction and venoconstriction, increase cardiac contractility and HR, stimulate adrenal epinephrine release, and control the neuroendocrine and vascular function of the kidney and long-term BP control. The parasympathetic arm, via vagal nerve efferents, contributes most to HR changes at rates less than the intrinsic rate.¹⁰ Recent work indicates strong vagal influences on sympathoexcitation¹¹ and important effects on nitrgergic (nitric oxide containing nerves) vasodilation of the large cerebral arteries.¹² Endocrine and local systems (eg, nitric oxide, local angiotensin) impact the vascular milieu but are slower to develop, often acting to modulate or set tonic activity of the ANS.⁹ Autonomic

control of HR and BP during orthostasis is provided by subsystems designated “baroreflexes” (pressure reflexes), loosely grouped as arterial and cardiopulmonary baroreflexes, which maintain BP under changing conditions such as orthostasis.¹³

THE NORMAL ORTHOSTATIC RESPONSE AND INITIAL ORTHOSTATIC HYPOTENSION

When supine, blood volume within the central thoracic vasculature is relatively large, although a disproportionate amount (25%–30%) of blood is stored within the splanchnic venous reservoir.¹⁴ Standing transfers >500 mL of central blood caudally, further increasing the volume of the splanchnic pool and filling veins of the lower extremities.¹⁵ An initial period of instability follows, denoted initial orthostatic hypotension¹⁶ (IOH, Fig 1) during which BP can decrease by $\geq 30\%$, reaching its nadir at 10 to 20 seconds after standing. Reflex tachycardia occurs. BP is restored within 30 to 60 seconds. IOH results from the normal delay of arterial baroreflex detection and

response to gravitational blood volume redistribution. Lightheadedness, postural instability, and occasionally brief loss of consciousness occur and are relieved by recumbency, making IOH a form of OI. Thereafter, HR decreases but remains elevated compared with supine, and BP is restored by arterial vasoconstriction, elastic recoil of venous blood in dependent veins, and active venoconstriction in splanchnic veins.¹⁷

After IOH recovery, upright blood volume slowly decreases because of microvascular filtration.¹⁸ Decreased venous return decreases central blood volume and cardiac output (CO) by 20% despite baroreflex mediated vasoconstriction, increased cardiac contractility, and increased HR. Cerebral blood flow velocity (CBFv) decreases by 3% to 12% partly because of reduced cerebral perfusion pressure by 20 mm Hg.¹⁹ Cerebral autoregulation (unchanged cerebral blood flow [CBF] despite changing BP) is blunted during orthostasis. Unless the muscle pump is evoked, standing still places us at risk for decreased CO and CBF.

FIGURE 1
IOH upon standing. There is a short-lived decrease in BP (upper panel) and increase in HR (lower panel). The fall in BP is resolved within ~20 seconds. The patient experienced transient lightheadedness.

OI

Orthostasis means standing up. OI can be defined by the inability to tolerate the upright posture because of signs and symptoms relieved by lying down.²⁰ If symptoms initiate while supine, then there is no OI. Transient OI is commonly experienced during dehydration or infectious disease. Typical signs and symptoms include loss of consciousness or lesser cognitive deficits (memory loss, decreased reasoning and concentration), visual difficulties, lightheadedness, headache, fatigue, either increases (hypertension) or decreases (hypotension) of BP, weakness, nausea and abdominal pain, sweating, tremulousness, and exercise intolerance.²¹ Unless one is in harm's way (eg, standing on a cliff), OI is not lethal. Some OI findings, such as nausea and sweating, pertain directly to autonomic activation. However, loss of consciousness, severe lightheadedness, and neurocognitive loss relate to central nervous system (CNS) dysfunction and oblige recumbence. CNS symptoms are produced by altered brain blood flow perhaps involving the brainstem. CBFv is shown in Fig 2 for 2 common forms of OI, vasovagal syncope (VVS) and postural tachycardia syndrome (POTS).

Cerebral autoregulation may be compromised,²² as in POTS²³ and VVS.²⁴ CBFv may be reduced by hyperventilation and hypocapnic cerebral vasoconstriction. Involuntary postural hyperventilation, mostly hyperpnea, is observed in all VVS patients²⁵ and 50% of POTS patients in my laboratory.²⁶ Trigeminal, sympathetic, or parasympathetic nerve activity may also affect orthostatic CBF.²⁷

ORTHOSTATIC STRESS TESTING AND TOOLS TO STUDY OI

Perhaps the best "test" is medical history, which can often diagnose OI based on symptoms relieved by recumbence. Orthostatic stress tests

FIGURE 2

Decreased CBFv measured by transcranial Doppler ultrasound occurs during a VVS, (shown in the upper panel) and in POTS (shown in the bottom panel). During VVS, CBF declines gradually at first and then more abruptly as the patient acutely loses consciousness. In POTS, CBF is fairly uniformly reduced; there is no loss of consciousness, although lightheadedness is typical.

supplement history by evoking OI in the laboratory. The predictive value of laboratory-induced OI for real-world OI is unclear, at least for syncope: in >40-year-old adults, tilt tests do not predict VVS.²⁸ Controlled studies have not been performed in younger patients. There is no reference standard for orthostatic testing. Standing without movement may be the most physiologic orthostatic stress but is complicated by muscle pump activity.²⁹ Therefore, tilt tables³⁰ are used to restrict patient movement while passively placing them upright. A recent adult study of POTS³¹ compared the diagnostic accuracy of standing for 10 minutes with 60° upright tilt for ≥10 minutes. Results showed that standing after being supine for 1 hour was at least as good as 10-minute tilt; longer tilts introduced excessive numbers of false positives. Standing HR and BP measurements were taken at 1, 3, 5, and 10 minutes. Thus, standing tests for POTS requires previous supine rest. In our hands, >20 minutes is needed to reach fluid equilibrium. More dramatic results can

be obtained by lower body negative pressure,³² which best simulates hemorrhage but duplicates many OI findings. A combination of lower body negative pressure with upright tilt can evoke OI (usually syncope) in everyone. Tests always include measurements of BP, HR, and heart rhythm and are supplemented in research laboratories by measurements of beat-to-beat CO, CBFv, regional blood flow, blood volume, sympathetic nerve activity, synaptic norepinephrine spillover,³³ and vascular biopsy.³⁴

TYPES OF OH

IOH

Fulfills criteria for OI and has been previously discussed. Treatment options are shown in Table 1.

Orthostatic Hypotension

True orthostatic hypotension (OH) was defined by consensus in 2011 as sustained reduction of systolic BP >20 mm Hg or of diastolic BP >10 mm Hg within 3 minutes of standing

or head-up tilt.³⁵ OH is illustrated in Fig 3. A simple test for OH is to observe BP and HR once a minute during a 3-minute stand.

Nonneurogenic OH is relatively common in the young. It can be caused by drugs or hypovolemia (eg, dehydration, hemorrhage). It is by far the most common form of OH in the young. There is no failure of autonomic function but rather incomplete ANS compensation for excessive nonautonomic stressors.

Neurogenic OH (NOH) signifies serious autonomic illness. It is identified with true autonomic vasoconstrictor failure due to the inadequate release of norepinephrine from sympathetic nerves.³⁵ HR may not increase appropriately with standing. Treatment options are shown in Table 1. NOH is rare in young people but associated with diabetes, amyloidosis, primary autonomic failure and Parkinson's disease in older patients.³⁶ NOH may occur in up to 17% in adults >65 years old.³⁷

FIGURE 3

NOH: mean arterial pressure (MAP, top panel) and HR (bottom panel) are shown during a standing test. The BP begins to decrease immediately upon standing and continues to decrease until the patient is supine. HR increases by only a small amount despite hypotension.

POTS

POTS is defined by chronic day-to-day symptoms of OH plus excessive increase in HR when upright (Fig 4). Hypotension is not in the definition.³⁸ Sinus rhythm is required. POTS is identified with chronic OH³⁹; there must be daily symptoms, and the illness must be present for several months. HR normally increases with standing. Excessive tachycardia was defined in adults by a sustained increase >30 beats per minute or to a HR >120 beats per minute during a 10-minute tilt. Concurrent OH symptoms are necessary. Standardized standing tests are established in adults.³¹ Larger HR increments are observed in healthy young people; the HR increment for POTS has increased to >40 beats per minute in children and teens aged 8 to 19 years.⁴⁰ The number of POTS patients within the United States was estimated at >500 000 in 1999.²⁰ Current estimates are much higher. However, the actual prevalence of POTS is unknown.³⁴

What Causes POTS?

POTS is caused by alterations of the autonomic nervous system, although mild to moderate all-cause hypovolemia mimics POTS.

Vagal Withdrawal and the Sinus Node

In some mildly ill individuals, POTS is related to loss of parasympathetic slowing of the heart with few peripheral circulatory abnormalities. Upright HRs rarely exceed 120 beats per minute. Often agents that increase cardiac parasympathetic activity such as β -blockers,⁴¹ cardiac glycosides,⁴² acetylcholinesterase inhibitors (pyridostigmine),⁴³ or ivabradine⁴⁴ (not US Food and Drug Administration approved) relieve symptoms.

Others may have excessive β -adrenergic sensitivity of the sinus node. This condition is denoted "inappropriate sinus

tachycardia"⁴⁵ and is regarded as distinct from POTS but less common. Supine HRs >100 beats per minute are observed, symptoms are less severe than in POTS, and β -blocker therapy can be efficacious.

Neuropathic POTS and Hyperadrenergic POTS

The remainder of patients are often partitioned among neuropathic POTS, in which partial dysautonomic adrenergic denervation occurs, and hyperadrenergic POTS, in which sympathetic overactivity prevails.

Neuropathic POTS

As originally described, decreased adrenergic vasoconstriction in the legs causes decreased norepinephrine spillover,⁴⁶ vasodilation,⁴⁷ and increased blood flow even supine.⁴⁸ When upright, redistributive central hypovolemia caused by leg blood pooling leads to reflex tachycardia.⁴⁸ In another neuropathic variant, decreased adrenergic vasoconstriction and redistribution of central blood to the splanchnic vasculature⁴⁹ causes reflex tachycardia. Intense leg vasoconstriction produces acrocyanosis. Autonomic autoimmune neuropathy,⁵⁰ presenting as POTS, causes similar reflex tachycardia. Central hypovolemia produces hyperpnea and hypocapnia in 50% of our patients.²⁶ Treatment with vasoconstrictors (eg, midodrine) and pyridostigmine can help.

Hyperadrenergic POTS

The adrenergic synapse can be altered at presynaptic or postsynaptic levels. Presynaptic abnormalities include increased sympathetic nerve activity even when supine. Although this has been reported,³⁸ the finding is not consistent.⁵¹

Increased synaptic norepinephrine is observed in the norepinephrine transporter (NET) deficiency heterozygote,⁵²

Day-to-Day Symptoms of OI

+

Sustained Excessive Tachycardia

(without Hypotension)

Adults $\Delta >30$ or HR >120 beats per minute
within 10 minutes Adolescent – $\Delta >43$

+

Concurrent Symptoms of OI

during testing

Improved by Recumbence

FIGURE 4

A representative POTS patient's data. HR (top panel) increases excessively without significant change in mean arterial pressure (MAP, bottom panel) change during a tilt test.

and in more prevalent epigenetic NET downregulation⁵³. Presynaptic and postsynaptic adrenergic activity may be enhanced by local chemical milieu, including angiotensin-II excess caused by angiotensin converting enzyme–2⁵³ deficit and nitric oxide deficiency, a hyperadrenergic variant with tachycardia, pallor, vasoconstriction, and absolute hypovolemia. Angiotensin (type 1) receptor blockers have shown benefit. β -blockers may also help.

Distinguishing Among POTS Variants: A Matter of Opinion

Distinguishing among POTS variants may be difficult for the pediatrician (and for the OI expert) despite apparent straightforward differences. Some would say that POTS with increased upright BP is hyperadrenergic; others would say that increased plasma catecholamines (or better, increased norepinephrine spillover) is required. Excessive orthostatic BP is a matter for consensus because

both systolic and diastolic BP normally increase upon standing; how much is too much is unclear. As a heuristic, POTS patients with high supine HR, who are cool to touch and are pasty white in appearance when supine, often have hyperadrenergic POTS. Standing HR is elevated to the 130 to 180 range during quiet standing indicating hyperadrenergic drive; vagal withdrawal alone increases HR to the 100 to 120 range. Those with upright HR <120 beats per minute are more likely neuropathic. Recent (unpublished) work with sympathetic nerve recordings have demonstrated normal sympathetic activity when supine and supranormal activity when upright. This supports adrenergic enhancement (NET deficiency, angiotensin-II excess) in patients with hyperadrenergic POTS. Confusing matters further, neuropathic patients can have increased upright catecholamines even though spillover is decreased in the lower extremities.⁴⁶

Gravitational Deconditioning—Caveat Bedrest!

One confounding and alarming issue is the tendency for POTS patients to bedrest. Prolonged bedrest emulates microgravity and has deleterious effects⁵⁴ including OI,⁵⁵ profound reductions in blood volume and cardiac size, redistribution of blood, osteoporosis, skeletal muscle pump atrophy, and more.⁵⁶ Vasoconstriction is impaired.⁵⁷ Bedrest causes a self-perpetuating state of OI, which can emulate or intensify POTS. It is paramount for POTS patient to leave bed and recondition. Well-structured exercise protocols are essential and must accommodate patients who start off bedrested.⁵⁸ Reconditioning invariably improves patient well-being. Recent work supports the idea that POTS patients are also exercise deconditioned compared with matched volunteers.⁵⁹ Although exercise deconditioning may or may not be causal in POTS, it is clear that exercise reconditioning is beneficial and should be advocated for all POTS patients.

What Are POTS Patients Like?

Quality of life can be severely compromised. A few features are common to all variants:

- Females predominate 3:1. Onset is usually from menarche to menopause.
- The onset often follows a flulike illness. Illness may occasionally represent a self-limited autoimmune disease.⁵⁰ The role of immune and epigenetic factors remains ill defined.
- Some patients have an insidious onset over years, sometimes with a past history of VVS.
- Some patients have joint hypermobility syndromes.⁶⁰ Causality is unclear.
- While supine or seated, some patients appear well, others pasty pale.
- Patients are unable to remain upright for long periods of time. Symptoms are similar to the prodrome of VVS.
- BP is typically well maintained and may increase when upright in hyperadrenergic individuals. Prolonged laboratory tilt may provoke VVS.
- Cognitive deficits and exercise intolerance are prominent complaints.⁶¹
- Gastrointestinal symptoms include dysmotility issues.⁶²
- Young women may be underweight, and POTS must be differentiated from eating disorders, which can produce POTS-like OI in early stages.
- Environmental heat reroutes blood to the skin and makes patients worse. Air-conditioning may be required and standing hot showers untenable.
- Schoolwork may be impaired. Home schooling is common. Colleges are often accommodating because of

adaptive scheduling and improved logistics.

- A wide variety of pharmacologic therapies are recommended with variable effects including β blockade, α -1 agonists (midodrine), acetylcholinesterase inhibitors (pyridostigmine), and fludrocortisone acetate (Florinef). Treatment options are shown in Table 1.
- Water ingestion is a useful, short-lived palliation.⁶³ Effects are through TRPV4 receptors in the splanchnic vasculature.⁶⁴ Sixteen ounces of water and waiting 20 to 30 minutes yields benefit for hours.
- Salt and water loading can help but often require Spartan efforts.
- Even when the cause is known (eg, NET deficiency) pharmacologic treatment is rarely curative. Most young people improve over time. In some, POTS persists.

Postural Syncope (VVS, Neurally Mediated Syncope, Neurocardiogenic Syncope, Acute OI)

Syncope (fainting) is defined as “complete loss of consciousness [and postural tone] due to transient global cerebral hypoperfusion characterized by rapid onset, short duration, and spontaneous complete recovery”⁶⁵. This means that people lose consciousness and fall down, and it is caused by critically reduced blood flow (~50%⁶⁶) or oxygen supply to the brain. Other causes of abrupt loss of consciousness such as seizures have neither decreased ictal CBF⁶⁷ nor typically hypotension. BP and CBF determinations during loss of consciousness are infrequently obtained during episodes outside of the laboratory. Apparent loss of consciousness without profoundly decreased cerebral oxygen delivery is not syncope. The lifetime incidence of VVS is ~40%, half presenting during adolescence.^{68–70} The most frequent age for first syncope is 15 years.⁶⁸

What Causes Syncope?

The most common cause for syncope is hypotension. Conceivably, a transient ischemic attack could cause syncope, although this is infrequent. A separate form of cerebral hypoperfusion without hypotension known as cerebral syncope may produce syncope⁷¹ as can hypoxia from high-altitude exposure.⁷² The VVS response can be evoked in most people by sufficiently large orthostatic stressors or by hemorrhage.⁷³ VVS may represent an evolutionary strategy to cope with excessive blood loss.⁷⁴

Orthostatic Hypotension Can Cause Syncope

Syncope may be due to OH. This is ruled out by the 3-minute standing test.

Is It Cardiogenic or Reflex Syncope? What to Do With a First Faint

If syncope is not caused by OH syncope is partitioned among cardiogenic syncope, frequently due to cardiac arrhythmia or other cardiac disease and reflex or neurally mediated syncope. Cardiogenic syncope can be life-threatening and has a poor prognosis unless specific steps are taken to treat cardiac pathophysiology. Cardiogenic syncope is not OI because recumbency does not specifically produce improvement. Reflex syncope has a good prognosis.⁷⁵ Reflex syncope includes VVS and situational syncope, including carotid sinus syncope,⁷⁶ essentially unknown in pediatrics; deglutition,⁷⁷ defecation,⁷⁸ micturition,⁷⁹ and cough⁸⁰ syncope rarely observed in the young; and hair grooming⁸¹ and adolescent stretch⁸² syncope, variants that are particular to adolescence. Fainting during exercise raises a red flag for cardiogenic syncope, and sport activity is curtailed until cardiac evaluation is complete. Nevertheless, the most common cause of exercise-related syncope in the young is VVS.⁸³ Cardiogenic

syncope, although not usually posturally related, cannot be automatically dismissed during a first faint. Therefore, the first and consequent episodes before cardiovascular evaluation should be treated as urgent. If fainting is subsequently found to be noncardiogenic, then urgency is reduced and simple maneuvers (discussed later) often suffice to deal acutely with the circumstance. The initial evaluation of a patient presenting with syncope comprises a detailed history, physical examination, including orthostatic BP measurements, and an electrocardiogram to look for QT prolongation, pre-excitation, and arrhythmia. History is paramount. Historical details that point toward reflex syncope⁶⁹ include a history of similar recurrent episodes, whether episode(s) occur exclusively when upright or with change in position; whether they are related to activity such as urination, defecation, deglutition, hair grooming, or stretch; whether there are predisposing factors such as fear, noxious stimuli, environmental heat, or immobilization; whether they follow exercise; and whether they are preceded by the prodrome of OI (eg, nausea, sweating, pallor). A more gradual onset (many seconds to minutes) favors reflex syncope, as does a postdrome of pallor, fatigue, and confusion. History that favors an increased likelihood of cardiac syncope includes antecedent heart disease, family history of sudden death, known arrhythmia or arrhythmia risk such as long QT syndrome or pre-excitation, an arrhythmogenic medication history, palpitations preceding the episode, and episodes that occur abruptly, during exercise, or when supine.

VVS = Postural Syncope or Emotional Syncope

Postural syncope and emotional stress syncope (eg, “blood phobia”) comprise VVS, which is the largest subgroup

within reflex syncope.⁸⁴ Regional or systemwide loss of sympathetic adrenergic vasoconstriction occurs in all VVS.⁸⁵ Loss of consciousness is most often preceded by a prodrome of OI symptoms, particularly lightheadedness, nausea, sweating, weakness, and visual disturbance (eg, “blackout,” scotomata). VVS patients often have CNS residua after recovery including headache, disorientation, occasional amnesia for the episode, and severe fatigue.⁸⁶ The “postdrome” is more characteristic of VVS than of (brief) cardiogenic syncope. It is best to rest for the remainder of the day because subsequent VVS can be most easily induced on the day of faint.⁸⁶ Until recently, VVS was thought to be caused by C-fiber afferents activated by a hypercontractile underfilled heart akin to the Bezold-Jarisch chemoreflex.⁸⁷ There is evidence to the contrary. Thus, any such stimulus could be short-lived because baroreceptors would be immediately unloaded⁸⁸; few afferent nerves were excited in the original hemorrhaged cat model⁸⁹; VVS can occur in a transplant recipient with denervated ventricles⁹⁰; and the heart before syncope is neither empty nor hypercontractile.⁹¹ To date, the pathophysiology of simple faint remains elusive.⁹²

Postural VVS

Postural syncope is acute OI. Approximately two-thirds of patients are female. Teenage boys tend to be tall, thin, and rapidly growing.⁸⁴

The most common variant of postural faint occurs episodically in otherwise healthy young patients. Between episodes most VVS fainters are well. However, at times episodes of syncope or presyncope (aborted syncope) may become chronic, as in some patients with the chronic fatigue syndrome.⁹³

In classic form, postural faint often comprises 3 upright stages (Fig 5), which closely emulate the circulatory

changes that occur during progressive hemorrhage.

Stage 1. After IOH, hemodynamic equilibrium is reestablished. BP stabilizes, and HR increases. Restabilization distinguishes VVS from true OH in which BP falls early and remains low. BP and sympathetic activity are often oscillatory with a 10-second period. Sympathetic activity, compensatory vasoconstriction, and HR are typically increased compared with healthy subjects.⁹⁴ Oscillations, often referred to as Mayer waves⁹⁵, represent the delay between sensing and compensating for a change in BP.⁹⁶ This requires intact autonomic reflexes, which are enhanced during central blood volume unloading during standing.

Stage 2. Thereafter, BP slowly declines as HR reflexively increases. The decrease in BP is attributed to a reduction in CO⁹⁷ despite increased vasoconstriction and sympathetic activity.⁹⁸ Prodromal OI symptoms (presyncope) often begin at this point. When combined with tachycardia, a diagnosis of POTS may be entertained in the laboratory setting. However, the HR is rarely >120 beats per minute, and a history of episodic faints interspersed with periods free of OI symptoms distinguishes postural syncope from POTS, in which OI is chronic. Medical history is paramount. Hyperpnea and hypocapnia are also observed and contribute to reduced CBFv.²⁵

Recent explanations offered for the early phases of postural VVS include reduced tyrosine hydroxylase and norepinephrine synthesis in patients with low resting BP, excess NET,⁹⁹ or selective deficit of splanchnic blood vessel vasoconstriction.⁴⁹ Postural VVS is uncommon in patients with vasoconstricted hyperadrenergic POTS.

Most POTS patients have day-to-day symptoms but do not faint, whereas most fainters faint episodically but do not have daily symptoms. This distinction

FIGURE 5

A representative VVS patient's data during a tilt test. HR (top panel) increases until late into the course when it falls abruptly. Mean arterial pressure (MAP, bottom panel) initially stabilizes, then slowly decreases, and finally falls abruptly along with HR. SNA, sympathetic nervous activity; TPR, total peripheral resistance.

has blurred over time; some POTS patients have fainted, typically not concurrently with POTS, and some fainters have daily symptoms that are recognizably presyncopal. Nevertheless, loss of consciousness in POTS is relatively uncommon outside of the laboratory.

Stage 3. Brain blood flow, vasoconstriction, BP, and HR fall precipitously, in that order,¹⁰⁰ causing loss of consciousness. Recent data suggest loss of cardiovagal and sympathetic baroreflex integrity and loss of cerebral autoregulation with entrainment by hyperpnea driven pulmonary reflexes.^{24,101}

In some patients, an abrupt fall in BP and HR is absent (no stage 3). Instead, BP falls steadily while HR continues to rise. This is often called vasodepressor syncope, which in our experience is caused by decreased peripheral resistance and maintained CO. In still other patients, the slow fall in BP is abbreviated or absent (no stage 2, Fig 6) giving rise to convulsive syncope.¹⁰² Episodes occur abruptly, without warning (no prodrome) and in association with asystole or severe bradycardia. Brief, clonic jerks occur with convulsive syncope but generalized tonic-clonic seizures, typical of epilepsy, are uncommon. EEG shows slowing rather

than spikes and findings resolve once supine. Asystole also occurs with phobic VVS. Recently, studies of adults aged >40 years show improvement in asystolic or severely bradycardic VVS with cardiac pacing.¹⁰³ Other forms of VVS do not. There is no controlled data for the pediatric age group. In adults, tilt table induced asystole is unrelated to real-world asystole in older patients²⁸; this has not been ascertained in younger patients.

How Can VVS Be Treated (Table 1)?

- VVS is not deadly unless one is in harm's way.
- To date, no single pharmacologic intervention has proven effective above the placebo effect in large clinical trials.^{104,105} Placebo exerts 30% to 40% benefit in these studies. Treatment options are shown in Table 1.
- Iron and even ferritin deficiency aggravates VVS.¹⁰⁶
- Trained athletes have increased risk of VVS compared with untrained persons.¹⁰⁷
- Salt and water supplementation can be helpful, but a large amount of salt is needed¹⁰⁸.

FIGURE 6

Asystolic postural VVS during a tilt test. HR (electrocardiogram, top panel) rapidly transits to asystole from a preceding sinus tachycardia. BP (bottom panel) falls in concert. There was no prodrome, although careful scrutiny shows a small decrease in BP before asystole supervenes.

- Currently, compensatory physical maneuvers (countermeasures) are recommended treatment.⁵
- The fainting prodrome must be recognized for countermeasures to be effective. First faints are rarely countered because patients do not understand what's happening.
- Countermeasures: immediate lying down or squatting cause postural VVS to cease; with prolonged prodrome counterpressure such as leg crossing, buttocks clenching, or fist clenching may be effective.^{109–111}
- Once supine, the patient should not immediately stand. Instead, I suggest a 16-oz bottle of water and remaining supine for >20 minutes after the episode.
- If there is no prodrome or if there is abrupt onset with injury, consider asystolic vasovagal faint or an arrhythmia and evaluate by loop recording electrocardiography.^{112,113} Twenty-four hour Holter monitoring is inadequate for arrhythmia determination.⁸⁴
- If total loss of consciousness is not transient, then it is not a faint; it is

TABLE 1 Treatment Options

Orthostatic syndrome	Defect/pathophysiology	Treatment
Initial OH	Rapid redistribution of blood to dependent body	Physical counter-maneuvers: sit down, isometric exercise (exercise pressor reflex) Infrequently supportive medication such as midodrine or fludrocortisone
Neurogenic OH	Systemically defective or absent adrenergic vasoconstriction; autonomic failure frequent parasympathetic dysfunction	Physical counter-maneuvers: lie down, sit down, squat, clench buttocks, leg crossing, support garment Droxidopa, ^{118,119} salt and water loading, fludrocortisone, midodrine, atomoxetine + yohimbine; if secondary (eg, diabetes) treat underlying disorder Rapid water ingestion palliation
Nonneurogenic OH	Loss of blood volume, vasodilator drugs	Correct problem
Neuropathic POTS	Loss of regional vasoconstrictive ability	Physical counter-maneuvers, salt and water loading, midodrine, Mestinon, exercise Rapid water ingestion palliation
Hyperadrenergic POTS	Adrenergic potentiation	Physical counter-maneuvers β -blockers, AT1RB (angiotensin-II type 1 receptor blocker), ivabradine? fludrocortisone, exercise
Postural VVA	? Loss of regional vasoconstrictive ability ? Acute reversible baroreflex dysfunction	Physical counter-maneuvers Salt and water Acute water ingestion Selective serotonin reuptake inhibitor; Midodrine Rapid water ingestion palliation

coma. VVS is <2 minutes of total loss of consciousness, as a matter of consensus. Rarely, fainting promotes an underlying seizure disorder via cerebral ischemia.

- Very frequent or extremely prolonged syncope can point to psychogenic syncope or conversion responses. These are easily distinguished from true syncope in the laboratory because there is no hypotension or reduced CBF. However, attacks may be real to the patient. Some patients may have had bona fide VVS interspersed with more frequent psychogenic episodes as learned or conditioned responses. One school of thought suggests that such patients actually experience the symptoms of true VVS without the signs.

Postural Hyperpnea

Standing causes an increase in tidal volume, which is accentuated by

increased central blood volume unloading.¹¹⁴ Marked involuntary hyperpneic hypocapnia precedes VVS in association with hypotension and in 50% of POTS patients without hypotension^{25,26,115} and reduces CBF. CO₂ administration relieves hyperventilation, but paper bag rebreathing promotes hypoxia.¹¹⁶

Postural hyperpnea occurs without POTS where it has been regarded as part of a psychogenic hyperventilation syndrome.¹¹⁷ In our hands, postural hyperpnea occurs during normoxic aerobic physical activities, particularly in athletic young women in whom it can be associated with variable changes in BP, increased HR, vasoconstriction, sympathetic activation, and decreased CO, CO₂ and CBF as a result of hypocapnia. It is provoked by upright tilt and relieved by administering CO₂. Hypocapnia, sympathetic activation, and anxiety occur in order. The patient experiences marked dyspnea, chest

pain, limb tingling, and numbness. Cardiopulmonary evaluations are normal.

SUMMARY

- OI is defined by symptoms and signs when upright relieved by recumbence.
- OH is a form of OI, but neurogenic OH is rare in childhood
- Initial OH is a common form of OI in the young.
- Postural tachycardia syndrome is a form of chronic OI that can result from a partial denervated circulatory system, a hyperadrenergic state, or chronic bed rest.
- It is essential to distinguish reflex syncope from cardiogenic syncope.
- Postural VVS is the most common form of OI, occurring ≥ 1 times in 40% of the populace throughout life. The most common age of onset is age 15 years.
- Physical countermeasures can defend against OI. Lying down aborts VVS. Do not constrain a VVS patient in the upright position.
- Postural hyperpnea may be a separate OI syndrome distinct from anxiety disorders.

FUTURE RESEARCH

OI is common at all ages. Neither VVS nor POTS is completely understood in terms of molecular and genetic/epigenetic mechanisms. However, progress has been made recently in the study of neurovascular signaling molecules and in potential related genetic and epigenetic disorders. In addition to determining basic mechanisms, it will be important to define physiologic correlates of common symptoms, including postural lightheadedness, exercise intolerance, and memory and concentration problems when upright.

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RIDING INTO OLDER AGE: *A good friend of mine loves to ride his classic Harley-Davidson motorcycle. Each weekend, as long as the weather is nice, he and his wife cruise the back roads of Vermont. I am always a bit mystified by his passion as he tends to see the children who have been most seriously injured in motor vehicle, snowboarding, or other traumatic accidents. Now I have a new concern. As reported in The New York Times (Safe Travels: February 8, 2013), older motorcycle riders have a much higher risk of accidents than younger riders and my friend is 60 years old. Researchers examined data from the National Electronic Injury Surveillance System-All Injury Program to assess emergency department-treated injuries resulting from motorcycle crashes between the years 2001 and 2008. The frequency, types, and severity of injuries among those aged 20–39 years, 40–59 years, and 60+ years were compared. While during this time span, the number of injuries increased in all groups, the greatest rate of increase occurred in adults ≥ 60 years of age. Adults 40–59 years had twice and adults ≥ 60 years had three times the rate of hospitalization as adults 20–39 years of age. Moreover, middle-age and older adults were more likely to have severe injuries, such as fractures and internal organ damage including brain damage, than younger adults. Why adult riders are more accident prone is not known. Possibilities include a decline in vision and reaction time or that older riders tend to ride bigger motorcycles which may be harder to keep upright. The increased risk of severe injury may simply be due to a normal aging process; bones are more brittle and there is less muscle mass. With more than 25% of all adults over the age of 50 riding motorcycles, the implications are enormous. As for my friend, he is fit and cautious but I still tell him to keep it slow and steady.*

Noted by WVR, MD