

# Differential Diagnosis of Vasovagal Syncope: Postural Orthostatic Tachycardia

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Emily M. Garland and Satish R. Raj

## Key Points

- Postural tachycardia syndrome (POTS) is a syndrome in which an excessive increase in heart rate upon assumption of upright posture, in the absence of orthostatic hypotension, is the final common pathway for multiple overlapping pathophysiologies.
- Presyncopal symptoms in POTS may resemble those in vasovagal syncope (VVS).
- In contrast to the immediate increase in heart rate during upright posture in POTS, there is a delayed, albeit abrupt fall in blood pressure and heart rate with standing in VVS.
- Treatment of POTS includes exercise and medications directed at decreasing sympathetic tone or increasing blood volume.

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E.M. Garland, PhD, MSCI

Department of Medicine, Autonomic Dysfunction Center, Vanderbilt University School of Medicine, 1161 21st Avenue South, Nashville, TN 37232-2195, USA  
e-mail: [emily.garland@vanderbilt.edu](mailto:emily.garland@vanderbilt.edu)

S.R. Raj, MD, MSCI (✉)

Division of Clinical Pharmacology, Departments of Medicine and Pharmacology, Autonomic Dysfunction Center, Vanderbilt University School of Medicine, AA3228 Medical Center North, 1161 21st Avenue South, Nashville, TN 37232-2195, USA  
e-mail: [satish.raj@vanderbilt.edu](mailto:satish.raj@vanderbilt.edu)

## 14.1 Introduction

Postural tachycardia syndrome (POTS) was first officially described as a syndrome by Schondorf and Low in 1993 [1] and was most recently defined in 2011 [2]. A diagnosis of POTS is currently based on an increase in heart rate (HR) of  $\geq 30$  bpm, within 10 min of assuming an upright posture (standing or upright tilt), in the absence of orthostatic hypotension [decrease in blood pressure (BP)  $> 20/10$  mmHg]. In young children, a higher HR threshold ( $\geq 40$  bpm) should be used, since healthy younger children have a greater physiological orthostatic tachycardia.

The exact prevalence of POTS is not known, with estimates that range from 500,000 [3] to 3,000,000 patients in the United States, and a female:male ratio of 4–5:1. Because POTS usually presents between 13 and 50 years of age, the impact on productivity at work and lifestyle can be devastating [4–6]. The prognosis for adolescents diagnosed with POTS is more favorable for recovery than for newly diagnosed adults [7, 8], but long-term follow-up data is lacking. Patients with a postviral onset may have a better chance of symptom resolution than patients with more hyperadrenergic features, who may require therapy indefinitely [8].

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## 14.2 Differential Diagnosis of POTS

The evaluation of a patient suspected to have POTS first requires a detailed history and physical examination. Known causes of orthostatic tachycardia must be considered and excluded. These include, but are not limited to, acute dehydration, diabetes mellitus, cardiomyopathy, heavy-metal poisoning, Sjögren's syndrome, systemic lupus erythematosus, deconditioning, inappropriate sinus tachycardia, pheochromocytoma, thyrotoxicosis, or manifestations of a paraneoplastic syndrome [2]. Potentially deleterious medications, such as diuretics, anxiolytics, stimulants, and vasodilators, must be taken into account [2, 9].

The tachycardia of POTS is a sinus tachycardia, and an ECG or Holter monitor should exclude the presence of an accessory bypass tract and arrhythmogenic causes of syncope [7]. Structural problems and cardiomyopathy should be ruled out. The chest pains in POTS are almost never due to coronary artery obstruction, but are sometimes associated with electrocardiographic changes in the inferior leads, particularly when upright [10]. Inappropriate sinus tachycardia (IST) can resemble POTS, though IST patients generally have an elevated resting HR (often  $> 100$  bpm during daytime rest) [11] in contrast to the high normal heart rates seen in POTS. Whereas patients with IST may benefit from sinus node ablation, this procedure is rarely effective for the orthostatic tachycardia of POTS [8]. In addition to a cardiac consult, a neurologist may be asked to evaluate headaches or dizziness. A gastroenterology consultation may be requested if abdominal pain and nausea are present. Blood tests for serum electrolytes, a complete blood count, liver and thyroid functions, a celiac panel, and vitamin B<sub>12</sub> are generally normal, but may be useful to rule out other conditions that cause dizziness, fatigue, and gastrointestinal symptoms.

### 14.3 Clinical Characteristics of POTS

POTS is a chronic condition with symptoms of orthostatic intolerance persisting at least 6 months. Symptoms improve with recumbence [9], and can also be triggered by exercise, heat, or sometimes by food [12]. Patients complain of both cardiac symptoms (palpitations, lightheadedness, chest discomfort, shortness of breath) and noncardiac symptoms (mental clouding, headache, nausea, tremulousness, blurred vision) [9]. Acrocyanosis is apparent in the legs and feet of approximately 50 % of patients. Gastrointestinal complaints are fairly common [12]. Sudomotor testing may be abnormal [12]. Some patients meet the diagnostic criteria for chronic fatigue syndrome [13]. Exercise intolerance exacerbates deconditioning, and the activities of daily life are limited [9, 14].

Significant diurnal variability has recently been reported for the orthostatic tachycardia of POTS [15], with an exaggerated orthostatic tachycardia in the morning compared to that in the evening. The standing HR decreases by late-morning [16]. It is therefore recommended that postural testing be performed in the morning to optimize diagnostic sensitivity for POTS [9].

Patients with POTS frequently have hyperextensible joints [17]. Wallman et al. [18] reported an 18 % prevalence of Ehlers–Danlos syndrome in their POTS population, compared with a 0.02 % prevalence cited for the general population, and 4 % prevalence in their autonomic clinic patients without POTS.

Most patients with POTS complain of fatigue. The prevalence of chronic fatigue in POTS patients has been reported as 48–77 % and of chronic fatigue syndrome (CFS) is 17–23 % [13]. Bagai et al. reported that compared to healthy subjects, POTS patients describe poorer sleep quality, more daytime sleepiness, and greater fatigue [6]. By actigraphy, POTS patients have diminished sleep efficiency [19].

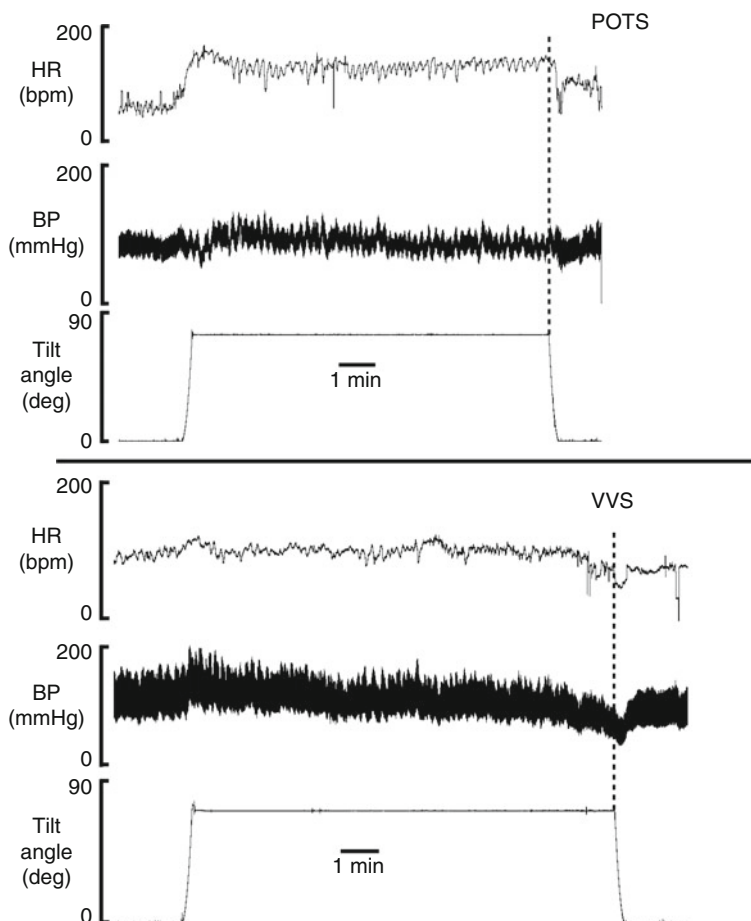
The quality of life for patients with POTS is comparable to chronic obstructive pulmonary disease or congestive heart failure [20], likely due to exercise intolerance, fatigue, and orthostatic symptoms [6, 20]. Physical health domains are primarily affected, while mental health domains are relatively preserved.

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### 14.4 Comparison of Vasovagal Syncope and POTS

Considerable clinical overlap exists between vasovagal syncope (VVS) and POTS. VVS can be diagnosed at any age, though the first fainting episode usually occurs in the second and third decades, also the period during which POTS is often diagnosed. The female predominance is somewhat less in VVS than POTS (60 % vs. 85 %). Many patients with POTS do not have frank syncope, though presyncope may occur daily [9, 21]. Though VVS may also occur with pain, anxiety, and exercise, head-up tilt table testing can be used in the clinic to differentiate between POTS and VVS. In addition to a syncope outcome, the hemodynamic response to upright posture differs between the two disorders.

A series of physiological adaptations occur with standing to maintain BP and cerebral perfusion [5]. The characteristic hemodynamic patterns of VVS and



**Fig. 14.1** Traces from head-up tilt table tests for a patient with POTS (*top*) and with VVS (*bottom*). For POTS, there is an early and sustained increase in heart rate and a slight increase in blood pressure with tilt. For VVS, heart rate and blood pressure increase slightly at the tilt onset, but are maintained at levels close to the baseline, until abrupt falls just before the tilt table is lowered

POTS result from failures of these physiologic compensatory mechanisms (Fig. 14.1). In patients with POTS, venous return remains inadequate in the face of enhanced plasma volume shifts from the vascular space to the interstitial space, sympathetic tone increases vigorously, and orthostatic tachycardia is exaggerated with BP unchanged (or even increased) [5]. Patients may complain of symptoms throughout the tilt test, but do not faint. On the other hand, in VVS, upright posture is associated with a generally delayed but abrupt decrease in stroke volume and cardiac output with bradycardia and hypotension [22], and resultant cerebral hypoperfusion leading to a sudden loss of consciousness [23] (Fig. 14.1).

## 14.5 Pathophysiological Mechanisms in POTS

POTS is not a single disease. POTS should be considered as a “final common pathway” for a number of overlapping pathophysiological processes. Thus, POTS is a heterogeneous syndrome with multiple contributing causes.

### Hyperadrenergic POTS

Many POTS patients have excess sympathoneural tone. While supine plasma norepinephrine (NE) is often normal in POTS, a significantly increased upright plasma NE ( $>3.55$  nmol/L and sometimes  $>5.91$  nmol/L) can be seen in many POTS patients [4]. Patients have an exaggerated sympathetic pressor response during the recovery and overshoot phases of the Valsalva maneuver [5, 9]. These hyperadrenergic patients may increase their BP with standing and complain of tremor, anxiety, and cold, sweaty extremities [8]. Yet, the correlation between hyperadrenergic symptoms and a high plasma NE remains to be established [12].

Though elevated sympathetic tone is usually secondary to another pathophysiological mechanism in POTS, it may also be the primary problem. Shannon et al. [24] reported a family with a loss-of-function genetic mutation causing NE transporter (NET) deficiency and POTS in the proband. NET is a clearance transporter, which leads to increased synaptic NE when defective. While this mutation is not common, many drugs act through NET blockade and can worsen tachycardia in POTS [25].

Furlan et al. [26] evaluated the sympathetic tone in patients with POTS using microneurographic recording from the peroneal sympathetic nerve, plasma norepinephrine, and spectral analysis of BP and HR variabilities. Sympathetic drive to vessels and the heart was enhanced in the supine position. During upright tilt, however, the increase in sympathetic drive to vessels was blunted in patients, whereas sympathetic modulation of HR was maintained or enhanced. These results might indicate a central nervous system cause of a hyperadrenergic state in some patients with POTS [26].

### Hypovolemic POTS

Blood volume is frequently low in patients with POTS [27–29]. Raj et al. reported significant deficits in total blood, plasma, and red cell volume in POTS when patients were controlled for sodium intake and withdrawn from medications prior to testing [27]. Chronic hypovolemia could contribute to a hyperadrenergic state. An expected compensatory response for hypovolemia is activation of the renin–angiotensin–aldosterone system to promote sodium and volume retention, but some POTS patients with hypovolemia have inappropriately low standing plasma renin activity and aldosterone compared with the controls [4, 30]. These can be accompanied by high circulating angiotensin II levels [31] without a parallel increase in its

metabolite, angiotensin (1–7), suggesting that angiotensin-converting enzyme 2 abnormalities might contribute to the plasma volume deficit in POTS [9, 32].

## Neuropathic POTS

Up to 50 % of POTS patients may have a preferential denervation of sympathetic nerves in the lower limbs [33], as first shown by diminished NE spillover [34]. The inability of the peripheral vasculature to maintain sufficient constriction during upright posture allows blood pooling in the splanchnic vasculature [35, 36] and lower extremities [8]. A partial dysautonomia in POTS has also been indicated by impaired sudomotor function [37], excessive venous pooling in standing patients [38], and reduced intraepidermal nerve fiber density [33].

## Mast Cell Activation Disorder

Some POTS patients report severe flushing in association with their tachycardia and may have a mast cell activation disorder. These patients often have a hyperadrenergic appearance, with orthostatic tachycardia and hypertension, as well as dramatic BP overshoots in phase 4 of the Valsalva maneuver. It has not been determined whether the sympathetic activation induces mast cell degranulation or if mast cell activation causes the release of vasoactive mediators and sympathetic activation compensates for the ensuing vasodilation [39]. Measuring urinary methylhistamine levels around a spell can make the diagnosis.

## Autoantibodies

A diagnosis of POTS following a virus-like syndrome in some patients has stimulated a quest for autoantibodies that affect autonomic functions in POTS. Rare cases are associated with a low titer of an antibody targeting the ganglionic acetylcholine receptor [12]. Recently, Li et al. found evidence of functional autoantibodies to  $\alpha$ -adrenergic receptors (AR) and  $\beta$ -AR in POTS patients, with much lower activity in the control subjects [40]. This is an emerging area of POTS research.

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## 14.6 Treatment of POTS

### Nonpharmacological Treatment of POTS

The initial step in the care and treatment of patients with POTS is education about behaviors and medications that can precipitate symptoms. Patients must be examined for any existing illnesses, which could be causing their POTS. Medications that might contribute to POTS should be discontinued or reduced.

Patients should be advised to avoid extreme heat and activities that lead to dehydration. In an effort to increase intravascular volume, they should be encouraged to drink water 2–3 L/day, while increasing their sodium intake to >200 mEq/day. Intravenous saline (1–2 L) can quickly expand blood volume and curb tachycardia in POTS patients [41], but this treatment is associated with an increased risk of vascular access complications (including infections) when used chronically.

Venous pooling as a result of upright posture in POTS appears to occur primarily in the splanchnic region [36], and abdominal compression to inhibit pooling may improve stroke volume and cardiac output. Elastic waist-high support hose or body-shaper garments may be effective at increasing venous return.

Patients with POTS complain of significant exercise intolerance [9, 42]. Deconditioning contributes to the limited ability to exercise, which then exacerbates the deconditioning. A 3-month aerobic exercise program coupled with resistance training improves orthostatic tachycardia, symptoms, and quality of life [28, 43].

Raj et al. found that POTS patients were mildly depressed, which may reflect unhappiness about living with a chronic illness [44]. Behavioral approaches, such as yoga and biofeedback, to help patients cope with their disorder can be important components of the treatment of POTS [7].

## Pharmacological Treatment of POTS

Randomized placebo-controlled trials are lacking for this patient population [9, 14, 42]. Given the heterogeneity of POTS, the success of a medication may be influenced by the POTS subtype, though Thieben et al. reported no difference in the symptomatic improvement of different subtypes of POTS to a variety of medications [12].

A hyperadrenergic phenotype with POTS might respond better to agents that decrease sympathetic tone. Low doses (10–20 mg) of the nonselective  $\beta$ -AR antagonist propranolol can acutely control HR and orthostatic symptoms without causing fatigue [45]. A 4-week trial of long-acting propranolol decreased standing HR without improving the quality of life [28]. Central sympatholytics (e.g., clonidine and methyl dopa) can decrease the sympathetic nervous system tone, but need to be used carefully to avoid undesirable side effects such as drowsiness and worsening of the mental clouding [9]. Pyridostigmine can also restrain HR in POTS [46]. It inhibits acetylcholinesterase and raises parasympathetic tone by increasing the availability of acetylcholine at both the autonomic ganglia and the peripheral muscarinic receptors. It has led to long-term symptom improvement in approximately 50 % of patients with POTS, though increased gut motility may lead to discontinuation in 20 % of patients [47].

Ivabradine is a novel agent approved for the treatment of angina in many parts of the world, but not yet in the United States. It slows HR by inhibiting the pacemaker funny channel current in the sinoatrial node and does not affect BP. A retrospective case series found decreased tachycardia in 60 % of POTS patients [48].

Midodrine, an  $\alpha$ 1-AR agonist, can be used to increase peripheral resistance by stimulating vasoconstriction. It not only improves the symptoms and orthostatic

tachycardia, but can also be associated with the unpleasant sensations of scalp-tingling and goose bumps [41].

Fludrocortisone, an aldosterone analog, increases sodium reabsorption in the distal tubules of the kidney, and should thereby increase sodium retention and volume expansion. Fludrocortisone also stimulates potassium excretion, making it necessary to monitor potassium levels, and it can also worsen migraine headaches [9, 21].

The vasopressin analog, desmopressin (DDAVP), can also increase volume and reduce tachycardia and symptoms [49]. It can lead to hyponatremia, as only free water is retained. Erythropoietin may also be used to increase blood volume, via increasing red cell mass, and may cause vasoconstriction as well [8], but its side effects, cost, and need for injection make it a less attractive option [7].

NET inhibitors, or serotonin-norepinephrine reuptake inhibitors (SNRIs), may worsen tachycardia in POTS [25]. In contrast, selective serotonin reuptake inhibitors (SSRIs) such as sertraline do not worsen tachycardia or orthostatic symptoms in POTS patients [50]. Studies on its benefit related to coping with the POTS syndrome have not been conducted.

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### Conclusion

POTS is a heterogeneous disorder, related to multiple, overlapping pathophysiological mechanisms. The hallmark clinical trait is an excessive increase in HR upon assumption of the upright posture, in the absence of orthostatic hypotension. Unlike VVS patients, POTS patients do not generally faint, though a number of cardiac and noncardiac symptoms may be triggered within a few minutes of standing and persist until recumbence in POTS. Presyncopal symptoms in VVS may resemble those in POTS, but their appearance is delayed in VVS (often for several minutes after standing), and they are associated with an abrupt fall in BP and HR. Exercise training is an important therapeutic strategy in POTS. Pharmacological treatments are second-line approaches that often target specific pathophysiological features.

**Conflicts of Interest** None

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