

Postural Tachycardia Syndrome: Beyond Orthostatic Intolerance

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Abstract Postural tachycardia syndrome (POTS) is a form of chronic orthostatic intolerance for which the hallmark physiological trait is an excessive increase in heart rate with assumption of upright posture. The orthostatic tachycardia occurs in the absence of orthostatic hypotension and is associated with a >6-month history of symptoms that are relieved by recumbence. The heart rate abnormality and orthostatic symptoms should not be caused by medications that impair autonomic regulation or by debilitating disorders that can cause tachycardia. POTS is a “final common pathway” for a number of overlapping pathophysiologies, including an autonomic neuropathy in the lower body, hypovolemia, elevated

sympathetic tone, mast cell activation, deconditioning, and autoantibodies. Not only may patients be affected by more than one of these pathophysiologies but also the phenotype of POTS has similarities to a number of other disorders, e.g., chronic fatigue syndrome, Ehlers-Danlos syndrome, vasovagal syncope, and inappropriate sinus tachycardia. POTS can be treated with a combination of non-pharmacological approaches, a structured exercise training program, and often some pharmacological support.

Keywords Tachycardia · Orthostatic · Autonomic · Treatment · Non-pharmacological · Medication

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Introduction

Postural tachycardia syndrome (POTS) is a form of chronic orthostatic intolerance in which upright posture is associated with an excessive increase in heart rate (HR) and incapacitating symptoms. An expert consensus statement [1] defines POTS as a HR increment ≥ 30 beats/min within 10 min of standing or head-up-tilt (HUT) which is sustained in the absence of orthostatic hypotension (a drop >20 mmHg in systolic blood pressure (BP) or >10 mmHg in diastolic BP). Children must meet a higher HR threshold ≥ 40 beats/min for a diagnosis due to their greater physiologic orthostatic tachycardia. Patients with POTS experience cardiac and non-cardiac presyncopal symptoms chronically (≥ 6 months). POTS is not considered to be a unique disease but rather the common phenotype of a number of heterogeneous, overlapping pathophysiological processes [2].

POTS is estimated to affect approximately 500,000 [3] to 3,000,000 individuals in the USA, with a female to male ratio of 4–5:1. There is no confirmed explanation for this female predominance in POTS, although lower orthostatic tolerance in

healthy females compared with males has been linked to a smaller upright stroke volume [4]. Patients are often young women of childbearing age whose work productivity and quality of life are negatively affected [5]. Functional impairment in patients with POTS has been reported to be similar to that in chronic obstructive pulmonary disease and congestive heart failure [6]; 25 % are unable to work as a result of their disability [7]. The natural history of POTS is not clear, but it does not appear to increase the risk of mortality [8•].

Hemodynamic Physiology of Standing

With assumption of upright posture, blood shifts from the chest to the lower abdomen, buttocks, and legs and from the vasculature into the interstitial space. The decrease in circulating blood volume stimulates compensatory physiological adjustments that are impaired with hypovolemia and POTS. Normally, standing reduces venous return, causing a transient decline in both cardiac filling and arterial pressure and a decrease in stroke volume. As baroreceptors are unloaded, compensatory sympathetic activation increases HR and vascular tone. With time, venous return and cardiac output are restored. Hence, a normal response to standing is a 10–30 beat/min increase in HR, a negligible change in systolic BP, and a ~5 mmHg increase in diastolic BP [2]. In a condition of resting hypovolemia, the body cannot adequately compensate for the orthostatic decrease in blood volume [9], and upright HR is elevated [4]. Patients with POTS may experience an exaggerated orthostatic shift in plasma volume [10]. Venous return remains decreased, so standing cardiac output and stroke volume are not normalized, and HR is elevated in comparison to healthy control subjects [11–13].

Clinical Presentation of POTS

Diagnostic Criteria

The earliest description of POTS may have come from DaCosta in 1871 [14], who described a syndrome of inappropriate tachycardia and palpitations in Civil War soldiers. This ailment was termed “irritable heart” or “soldier’s heart” [11]. Different nomenclature was used through the years until the “idiopathic postural orthostatic tachycardia syndrome” was defined in 1993 by Schondorf and Low as a symptomatic increase in HR of 30 beats/min or more within 10 min of HUT or standing, or a HR while upright exceeding 120 beats/min, without orthostatic hypotension [15]. In our experience, it is uncommon to diagnose POTS based on the 120 beats/min criterion. POTS was recognized in adolescents by Stewart et al. in 1999 [16]. HUT tests and stand tests are standardized methods to assess an individual’s response to a

change in posture. The patient can be placed securely on a tilt table with continuous or intermittent BP and HR monitoring. Following baseline measurements, the table is inclined to a 70–80° head-up angle for 10 min. A marked rise in HR in POTS is reversed when the tilt table is returned to a flat position. A similar threshold for HR increase is generally used to diagnose POTS with HUT and a standing test, despite the different physiological responses. Active standing engages the “skeletal muscle pump” while the HUT does not. Accordingly, the orthostatic tachycardia is greater with the HUT test in both patients with POTS and control subjects with prolonged tests, but the orthostatic tachycardia is comparable between HUT and active stand for the 10 min used for the POTS criterion [17•].

The orthostatic tachycardia of POTS is exaggerated in the morning compared to the evening. To optimize diagnostic sensitivity, it is recommended that postural testing be performed in the morning [18].

The mere observation of orthostatic tachycardia is not sufficient for a diagnosis of POTS [2] (Table 1). The HR abnormality must be accompanied by chronic (>6 months) orthostatic symptoms that occur in the absence of prolonged bed rest or deconditioning, use of medications that impair autonomic regulation (vasodilators, diuretics, antidepressants, or anxiolytic agents), or other chronic debilitating disorders that might cause tachycardia (such as dehydration, anemia, or hyperthyroidism) [19]. Despite earlier controversy over its existence, the report by Schondorf [15] and the more recent consensus statement [1] have increased awareness of POTS as a syndrome.

Common Clinical Features

Orthostatic Symptoms

Both cardiac symptoms, such as rapid palpitations, lightheadedness, chest discomfort, and dyspnea, and non-cardiac symptoms, such as mental clouding, headache, nausea, tremulousness, generalized weakness, and blurred or tunnel vision, are evident in POTS patients during upright posture [19]. An electrocardiogram (ECG), 24-h Holter monitor, and echocardiogram might be needed to rule out a cardiac etiology

Table 1 Diagnostic criteria for postural tachycardia syndrome

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- Increase in heart rate ≥ 30 bpm within 10 min of upright posture (tilt test or stand) from a supine position
 - Heart rate increase must be >40 bpm in patients <20 years
 - Associated with a constellation of symptoms that are worse with upright posture and that improve with recumbence
 - Chronic symptoms that have lasted for >6 months
 - In the absence of other disorders or medications that are known to predispose to orthostatic tachycardia
-

for the tachycardia in suspected cases of POTS. The tachycardia of POTS is a sinus tachycardia. An ECG should be done to rule out the presence of an accessory bypass tract or any abnormalities of cardiac conduction [11]. Chest pain in POTS is rarely from coronary artery obstruction, but it may be associated with ECG changes when patients are upright [20]. A Holter monitor can supply information on mean HR and its variability during various prescribed or routine activities that precipitate orthostatic symptoms. It might be used to exclude a re-entrant dysrhythmia, especially when the patient reports paroxysmal tachycardia with a sudden onset and offset [19]. It cannot be used to diagnose POTS, since it does not provide information on body position. An echocardiogram may be needed to exclude structural cardiac abnormalities before making a diagnosis of POTS.

Many patients with POTS are diagnosed with migraine headaches. Orthostatic headaches may be related to decreases in spinal venous pressure and volume of cerebrospinal fluid due to an absolute or orthostatic hypovolemia [21].

A dark red-blue discoloration of the legs might occur with standing, extending from the feet to above the knees in ~50 % of patients with POTS. This acrocyanosis in POTS is not due to increased venous compliance [22, 23] but may be caused by a decrease in blood flow to the skin, possibly related to abnormal cutaneous nitric oxide activity [24].

Non-orthostatic Symptoms

In addition to orthostatic symptoms in POTS, patients experience non-specific signs and symptoms that seem unrelated to postural intolerance or excessive tachycardia [25]. These might or might not be associated with the autonomic nervous system and can also occur in individuals without POTS. Autonomic problems in POTS might include gastrointestinal complaints, such as abdominal pain, nausea and irritable bowel syndrome, as well as bladder symptoms and abnormal sudomotor regulation [19, 26]. More generalized complaints in patients with POTS include hypermobile joints, exercise intolerance, migraine headaches, sleep disturbances, and fatigue [19].

Symptom Triggers

Patients frequently report symptom onset following acute stressors (e.g., pregnancy, a traumatic event, surgery, or a viral illness) [2, 26]. Symptoms can be exacerbated by simple activities of daily life like standing still, exercise, food or alcohol ingestion, or heat exposure [26].

Psychological Profile in POTS

Patients with POTS commonly present with symptoms of depression and anxiety. Yet a structured evaluation using criteria

from the *Diagnostic and Statistical Manual* (fourth edition, text revision) did not identify a higher incidence of major depressive disorder, anxiety disorders, or substance abuse in POTS patients than the general population [27]. Furthermore, the HR increase in patients is not a response to anxiety [28]. The palpitations, hyperventilation, and tremulousness of POTS can be misinterpreted as symptoms of anxiety. Although many patients with POTS complain of “memory problems” and “mental clouding,” these might actually represent decreased attention and concentration [27]. A comprehensive neuropsychological evaluation of 28 patients in a seated position found deficits in selective attention and cognitive processing, as well as impaired executive functioning. Memory function did not differ from healthy controls [29••].

Disorders Overlapping with POTS

Cardiovascular autonomic function tests [30] to evaluate sympathetic vasoconstriction and cardiac parasympathetic responses should be performed in presumed POTS patients to rule out more severe forms of autonomic failure. Intact vagal function can be demonstrated by a normal sinus arrhythmia ratio in response to deep breathing. A Valsalva maneuver is useful to assess both vagal and sympathetic components of the baroreflex [25]. Patients with POTS often have a vigorous pressor response, with exaggerated BP recovery and overshoot both before and after release [19]. Conversely, patients with impaired vasoconstriction (e.g., patients with partial autonomic neuropathy) can have an impaired Valsalva pressure recovery.

Chronic Fatigue Syndrome

POTS patients describe poorer sleep quality, more daytime sleepiness, greater fatigue, and substandard quality of life compared to healthy subjects [5]. These reports are consistent with a reduction in sleep efficiency determined by actigraphy [31•]. A higher measure for sleep problems is strongly negatively correlated with the RAND-36 physical health composite score and significantly, but to a lesser degree, correlated with the mental health composite score [5]. These data suggest that the impaired health-related quality of life measured in POTS can be attributed significantly to sleep problems [5].

Chronic fatigue syndrome (CFS) is characterized by persistent or relapsing unexplained fatigue and related symptoms of at least 6 months duration. Like POTS, CFS is a clinical syndrome that is more commonly diagnosed in females. For a CFS diagnosis, a patient must meet criteria for physical, mental and post-exertional fatigue, sleep disturbances, pain, neurological or cognitive manifestations (such as confusion, concentration, and memory problems), and symptoms of autonomic, neuroendocrine, or immune disturbances [32]. Patients

with POTS have a high prevalence of chronic fatigue (48–77 %) and of CFS (17–23 %) [8••, 33]. When patients were grouped according to whether or not they met the criteria for CFS [33], fatigue symptoms, orthostatic changes in HR and BP after 10 min, supine and upright plasma norepinephrine, and plasma volume were similar for the two groups. Plasma renin activity and aldosterone tended to be higher in patients with CFS. Autonomic testing indicated a similar autonomic profile but higher sympathetic tone in patients with CFS. Okamoto et al. proposed that CFS is part of the POTS spectrum [33].

Ehlers-Danlos Syndrome

Ehlers-Danlos syndrome (EDS) includes heterogeneous disorders associated with inherited abnormalities of collagen. Patients are characterized by skin hyperextensibility, joint hypermobility, and fragile connective tissue [34•]. Patients with EDS type III (EDS-Hypermobility) frequently have symptoms of autonomic dysregulation that are also common in patients with POTS: palpitations, lightheadedness, chest pain, presyncope, and syncope [35]. In addition, autonomic test results in these patients are consistent with disturbed sympathetic cardiovascular control, similar to POTS. More recent studies of autonomic symptoms/function and quality of life in patients with the hypermobility type of EDS confirm a high prevalence of POTS-like orthostatic symptoms and orthostatic intolerance in these patients. Similar to POTS patients, symptoms can be triggered by exercise, meals, and a hot environment, in addition to standing [36•, 37].

Wallman et al. ascertained the prevalence of EDS in their POTS population: 18 % of POTS patients met criteria for EDS, compared to a 0.02 % prevalence in the general population and 4 % prevalence in their autonomic clinic patients without POTS [34•]. Based on experience at his autonomic clinic, Professor Mathias reported that EDS type III is the most common disorder associated with POTS [38].

The exact nature of the relationship between POTS and EDS-Hypermobility is unknown. Connective tissue abnormalities in EDS could lead to vascular laxity and predispose patients to orthostatic blood pooling in the lower extremities and orthostatic intolerance [8••, 35]. Alternatively, these patients might have a peripheral neuropathy that could contribute to autonomic impairment [36•, 37].

Vasovagal Syncope

Vasovagal syncope (VVS) and POTS overlap clinically, and both diagnoses may be appropriate for a given patient [8••]. A HUT test can be helpful in the differential diagnosis. Patients with vasovagal syncope are able to maintain their BP for several minutes following HUT and then experience a rapid drop in BP as stroke volume and cardiac output decrease. Ensuing

cerebral hypoperfusion causes a sudden loss of consciousness [39, 40]. Patients with POTS, on the other hand, have a fairly steady BP when tilted up, but orthostatic tachycardia is enhanced as sympathetic tone increases to compensate for the decrease in circulating blood volume [2]. As the HR rises within the initial 10 min, patients complain of presyncopal symptoms, but they rarely faint. Only 30 % or so of POTS patients actually experience syncope [2].

Inappropriate Sinus Tachycardia

Inappropriate sinus tachycardia (IST) is another disorder having overlapping clinical features with POTS. IST also predominantly affects young women and is characterized by presyncopal symptoms and abnormally high HRs [10]. IST differs from POTS in that the tachycardia can be independent of body position, and resting HR commonly exceeds 100 beats/min, consistent with higher sympathetic tone and decreased parasympathetic tone in IST relative to patients with POTS and healthy controls [41•]. In POTS, the orthostatic change in HR surpasses that in IST. The intrinsic HR does not differ between POTS and IST patients [41•].

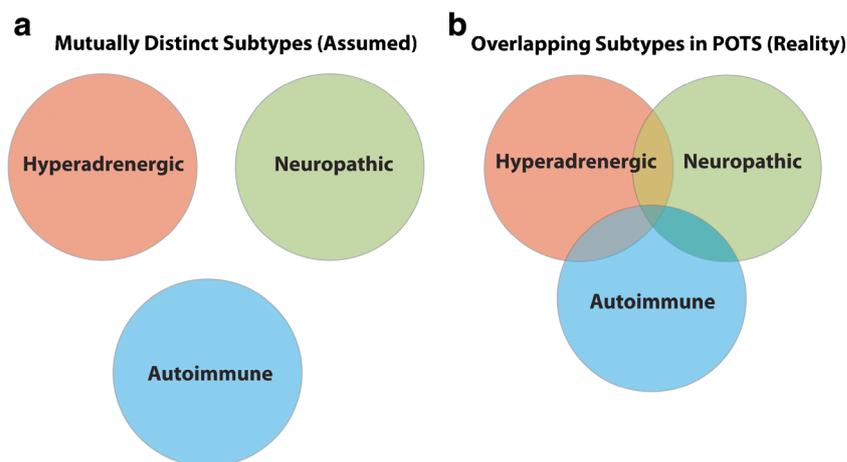
Pathophysiology of POTS

POTS is a “final common pathway” for a number of overlapping pathophysiologies [2]. Although patterns of clinical features have been used to subtype patients, these classifications are mainly descriptive and are not mutually exclusive (see Fig. 1).

Neuropathic POTS

Neuropathic POTS was first described when activation of the sympathetic nervous system increased norepinephrine spillover in the lower limbs of some patients to a lesser extent than in healthy controls, despite similar responses in the arms [42]. Sympathetic denervation obstructs compensatory vascular constriction during upright posture, allowing blood to pool in the splanchnic vasculature and lower extremities [7, 8••, 43]. The resulting decrease in venous return leads to the sympathetic activation and tachycardia of POTS. Norepinephrine spillover is not a practical clinical test. A thermoregulatory sweat test or a Quantitative Sudomotor Axon Reflex Test (QSART), quantitative sensory testing, or a skin biopsy can also be used to determine whether an autonomic neuropathy exists [25, 44••].

Fig. 1 Many patients think about the different subgroups of POTS as distinct and mutually exclusive groups (Panel **a**). While the subgroups are useful pathophysiological concepts, in clinical practice, the subtype labels are often used to describe individual test findings, and the same patient can fit into more than one overlapping subtype (Panel **b**)



Hypovolemia and the Renin-Angiotensin-Aldosterone System in POTS

One of the more consistent findings in patients with POTS is a deficit in total blood, plasma, and red cell volume [13, 45, 46]. Lin has proposed that a decrease in oxygenation related to the low red blood cell volume could exacerbate symptoms of orthostatic intolerance [47]. Another cohort of patients with POTS might not have a hypovolemia but an exaggerated decrease in volume on standing [10].

The renin-angiotensin-aldosterone system is fundamental for the regulation of blood volume [48]. It is activated by upright posture [49] and by a reduction in blood volume [46]. Plasma renin activity, angiotensin II, and aldosterone would be expected to be elevated in POTS in response to the hypovolemia. Some POTS patients with hypovolemia, however, have inappropriately low standing plasma renin activity and aldosterone compared with normovolemic controls [12, 46]. Circulating angiotensin II levels have been reported to be elevated but without a parallel increase in its metabolite angiotensin (1–7) [50, 51]. These paradoxical findings suggest that POTS patients might have decreased angiotensin II metabolism and that dysregulation by the renin-angiotensin-aldosterone system might contribute to hypovolemia in POTS [50, 51].

Central Hyperadrenergic POTS

Although the elevated sympathetic tone in POTS is often secondary to another pathophysiological mechanism, such as neuropathy or hypovolemia, it can also be the primary underlying problem [19]. Furlan et al. reported increased sympathetic tone in patients with POTS [52]. Resting sympathetic nerve activity, measured by microneurography, is elevated. A spectral analysis index of sympathetic function and plasma norepinephrine are sometimes higher at supine rest and increase more with HUT in POTS [52, 53]. Plasma norepinephrine levels should be determined in patients with POTS while in steady state in the supine

and upright positions (at least 10 min in each position). When measured during upright posture, norepinephrine is elevated in many patients with POTS (>3.55 nmol/L (600 pg/mL) and sometimes >5.91 nmol/L (1000 pg/mL)), consistent with the sympathetic neuronal activation elicited by standing in these patients [19]. This is sometimes used as a criterion for the “hyperadrenergic subtype” of POTS.

An exaggerated sympathetic vasoconstrictor response during the recovery and overshoot phases of the Valsalva maneuver may also reflect a hyperadrenergic state in patients with POTS [2, 19]. These patients may have orthostatic hypertension (increase in systolic blood pressure >10 mmHg on standing) and complain of tremor, anxiety, and cold, sweaty extremities [7, 25].

Norepinephrine Transporter Deficiency

A very rare form of hyperadrenergic POTS is caused by a loss-of-function mutation in the gene for the norepinephrine transporter (NET) [54]. NET is a clearance transporter for norepinephrine, and this genetic form of NET deficiency leads to increased synaptic norepinephrine. The mutation has been identified in one kindred thus far. Lambert et al. have reported that some POTS patients may have decreased expression of NET protein, leading to a functional NET deficiency [55].

Mast Cell Activation

Some POTS patients present with severe flushing in addition to their tachycardia and have an associated mast cell activation disorder. These patients often have a hyperadrenergic phenotype, with both orthostatic tachycardia and hypertension in the upright position, as well as dyspnea, headache, lightheadedness, chest discomfort, and gastrointestinal symptoms. It is unknown whether sympathetic stimulation in these patients induces mast cell degranulation or whether primary mast cell activation causes release of vasodilators and compensatory sympathetic activation

[56]. This diagnosis is most often made with an elevated histamine metabolite ($>230 \mu\text{g}$ methylhistamine/g creatinine) in a 4-h urine sample started at the onset of a severe flushing spell. In this manner, we get a urine sample that is enriched for methylhistamine. In our experience, a 24-h urine sample is usually negative in these patients, since methylhistamine release is episodic and not constant. Plasma tryptase levels and urinary prostaglandin D2 may also be elevated.

Physical Deconditioning

Fatigue and exercise intolerance with reduced stroke volume and reflex tachycardia are typical manifestations of cardiovascular deconditioning as well as POTS [13, 25]. Due to their disability, many patients with POTS have restrictions on their activity and can become deconditioned over time. Alternatively, an individual can become physically deconditioned secondary to another illness or bed rest and develop a clinical phenotype that resembles POTS. Although it may not be clear if deconditioning is a primary problem or secondary to POTS, many patients with POTS do have cardiovascular deconditioning and do benefit from a program of aerobic exercise and resistance training [13].

Autoimmune/Autoantibodies

A significant minority of POTS patients are diagnosed following a virus-like syndrome. This suggests an autoimmune cause for POTS in some patients. It is noteworthy that the prototypical POTS patient (woman of childbearing age) is of the same demographic as a typical patient with an autoimmune disorder. A low titer of an antibody to the ganglionic acetylcholine receptor (nAChR) was reported in 15 % of adult POTS patients evaluated at the Mayo Clinic between 1993 and 2003 [26]. However, this has not been consistent with our clinical practice, where this antibody is rarely seen in POTS patients.

Recently, Li et al. [57•] presented evidence from two cohorts of POTS patients for $\alpha 1$ adrenergic receptor (AR) autoantibodies acting as partial peripheral receptor antagonists. Compensatory sympathetic activation to maintain adequate vasoconstriction could then induce tachycardia via β -ARs. $\beta 1$ -AR- and $\beta 2$ -AR-activating autoantibodies could also contribute to the tachycardia. These data suggest an exciting new pathophysiology for some patients with POTS. However, only a small number of patients were studied, and further research is needed to establish clinical significance.

Treatment of POTS

A detailed history and physical exam are a requisite initial step in the evaluation of a patient with POTS. The history should determine whether the POTS can be traced back to a particular

illness or trauma, the frequency of symptoms, symptom triggers, the severity of the orthostatic intolerance, associated illnesses, and the impact of POTS on daily functions and quality of life. Family history should also be queried. The answers to these questions help direct the management and treatment of the patient (Table 2).

Non-pharmacological Treatment of POTS

Patients are encouraged to increase their blood volume by drinking 2–3 L/day of water and ingesting $>200 \text{ mEq}$ sodium/day (Heart Rhythm Society (HRS) 2015 Statement Class IIb recommendation) [8•]. Intravenous saline (1–2 L) can quickly expand blood volume and lessen tachycardia in POTS patients [58]. IV saline for an acute clinical decompensation in POTS is a HRS Class IIa recommendation, but chronic regular saline infusions are not recommended (HRS Class III) due to concerns about complications related to long-term venous access [8•].

Non-pharmacologic approaches to counteract the inadequate physiological response to upright posture can be beneficial in POTS. Abdominal compression with elastic waist-high support hose and abdominal binders can help decrease splanchnic-mesenteric venous pooling during standing [43]. The increase in venous return and stroke volume can decrease the orthostatic tachycardia [19, 59].

Exercise in POTS

Excessive tachycardia in POTS occurs during exercise as well as during standing [60, 61], and patients experience significant exercise intolerance [9, 19]. As patients find it difficult to exercise, they can become increasingly deconditioned. The three-month Dallas Program, which involves aerobic exercise coupled with resistance training, improves orthostatic and exercise tachycardia, symptoms, and quality of life [13, 62, 63]. Improvement is related to an increase in the size of the heart and increased blood volume [13]. The improved stroke volume decreases tachycardia.

The challenge with an exercise program in POTS is the marked exercise intolerance and debilitating post-exercise fatigue. The Dallas Program focuses on starting with seated or supine exercises (e.g., rowing machine, recumbent cycle, or swimming) three times per week. Patients must be informed that it can take 5–6 weeks before they notice any improvement, and in the interim, the patients may transiently feel worse. A structured and progressive exercise program is a HRS Class IIa recommendation [8•].

Pharmacological Treatment of POTS

The US Food and Drug Administration has not approved any drugs for the treatment of POTS. Although the successful off-

Table 2 Treatments for postural tachycardia syndrome

Treatment	Dose	HRS class	Comments
Non-pharmacological treatments			
Oral water	2–3 L/day	I Ib	
High-sodium diet	>200 mEq/day	I Ib	Best if done with diet, but NaCl supplements can be used
IV saline—ACUTE	1–2 L	I Ia	Can be used at times of clinical decompensation to avoid hospital admission
IV saline—CHRONIC	1–2 L daily-weekly	I III	Not recommended due to risks of vascular access complications
Waist-high compression stockings	30–40 mmHg		Lower abdomen is major site of blood pooling when upright. If used, stockings should be pantyhose style
Abdominal binders or corset-like garments			If leg compression is not tolerated, abdomen/pelvis only alternatives might be an option
Exercise training program	Every other day × 30+ minutes	I Ia	Focus on aerobic reconditioning starting with seated/supine exercises; benefits can take 4–6 weeks to manifest
Impedance threshold breathing device	7 cm H ₂ O		Breathing through this when feeling unwell can acutely increase stroke volume and decrease heart rate
Pharmacological treatments			
Propranolol	10–20 mg PO QID	I Ib	Useful to decrease the heart rate in POTS and improve symptoms acutely
Alpha methyl dopa	125–250 mg PO BID	I Ib	Sometimes needed with prominent hyperadrenergic features; can cause profound fatigue, drowsiness or mental clouding if too much is given
Pyridostigmine	30–60 mg PO TID	I Ib	May restrain heart rate by increasing parasympathetic tone; diarrhea can be a limiting side effect
Midodrine	2.5–10 mg PO Q4h × 3	I Ib	Vasoconstrictor and venoconstrictor; may improve venous return and decrease reflex tachycardia
Octreotide	12.5–50 mcg SQ BID		Injectable splanchnic vasoconstrictor; may use a long-acting preparation once dose has been stabilized
Ivabradine	5–7.5 mg BID		Funny channel blocker that has shown benefit in IST patients, and in case reports in POTS patients
Fludrocortisone	0.05–0.2 mg PO daily	I Ib	Mineralocorticoid that enhances renal sodium reabsorption in the short term
DDAVP (desmopressin)	0.2 mg PO per dose		Encourages renal free water retention and acute blood volume expansion; hyponatremia can result if given in excess
Sertraline	50 mg daily		Sertraline does not have any significant negative hemodynamic effects in POTS; it may be helpful in coping with chronic illness
SNRI/NETi medications		I III	Drugs that block the norepinephrine transporter can worsen tachycardia and symptoms in POTS patients
Modafinil	50–200 mg PO BID		This has anecdotally been reported to help with the fatigue and “brain fog” in POTS; it has only minimal heart rate increase in most patients

HRS Class refers to the class of Recommendation from the Heart Rhythm Society Statement on postural tachycardia syndrome. Class I Ia and I Ib is a favorable recommendation, but in the absence of high-level evidence. Class III is a negative recommendation cautioning against the use of a treatment *IV* intravenous, *PO* oral administration, *SQ* subcutaneous administration, *BID* twice daily, *TID* 3 times daily, *QID* 4 times daily, *SNRI* serotonin-norepinephrine reuptake inhibitor, *NETi* norepinephrine transporter inhibitor

label use of different medications might be expected to be influenced by the POTS subtype, Thieben et al. did not find this to be true with a variety of medications [26].

After the initiation of non-pharmacological treatments, our approach is to decrease the influence of sympathetic tone on the heart. The non-selective β -AR antagonist propranolol acutely restrains orthostatic tachycardia and symptoms at doses that appear to be low enough (10–20 mg) to avoid the side effect of significant fatigue [64]. The decrease in standing HR was verified in a four-week trial of long-acting propranolol although quality of life was not improved [62]. Propranolol is a HRS Class I Ib recommendation [8••]. Central sympatholytics (e.g., clonidine and methyl dopa) can also be used to

decrease sympathetic tone in patients with prominent hyperadrenergic features, but might produce drowsiness and worsening of the mental clouding [19] (HRS Class I Ib) [8••].

Increasing parasympathetic tone with pyridostigmine can also curtail HR in POTS [65] (HRS Class I Ib) [8••]. This agent inhibits acetylcholinesterase, thereby increasing the availability of acetylcholine at both the autonomic ganglia and the peripheral muscarinic receptors. Pyridostigmine ameliorates symptoms in patients with POTS, although nausea, vomiting, and diarrhea from gut activity may lead to discontinuation in 20 % of patients [66].

Midodrine, a pro-drug of an α 1-AR agonist, can increase peripheral resistance in POTS by stimulating vasoconstriction.

Improvement in symptoms and orthostatic tachycardia can be associated with scalp tingling and goosebumps [58], and midodrine can cause urinary retention [67]. Midodrine is a HRS Class IIb recommendation in POTS [8••].

The somatostatin analog octreotide is a vasoconstrictor that mainly affects the splanchnic circulation. This effect during standing helps to maintain venous return in POTS and inhibits the compensatory increase in HR following acute and chronic administration [68, 69]. However, octreotide is only available in an injectable form, and this likely limits its use and patient acceptability.

Ivabradine is a cardioselective agent that slows HR via inhibition of the funny channel current (I_f) in the cardiac sinoatrial node but does not affect BP. Ivabradine is approved for the treatment of heart failure (USA and Europe) and angina (Europe). A retrospective case series found decreased tachycardia and symptoms in POTS patients [70].

Another approach that can be combined with vasoactive medication is administration of medications to expand blood volume. Fludrocortisone is a synthetic corticosteroid that preferentially binds to the mineralocorticoid receptor and acutely increases sodium reabsorption in the distal tubules of the kidney. Fludrocortisone also stimulates potassium excretion, making it necessary to watch for hypokalemia, and it can also worsen migraine headaches [19, 71]. Fludrocortisone is a HRS Class IIb recommendation [8••].

Two other agents used to increase blood volume are the vasopressin analog, desmopressin (DDAVP), and erythropoietin. Although DDAVP reduces tachycardia and symptoms [71, 72], it can lead to hyponatremia. We have been cautious about the regular use of DDAVP, but we have successfully used this as an “occasional use” medication. With this approach, we have not seen hyponatremia.

Erythropoietin increases red cell mass and may also stimulate vasoconstriction [7]. Potential adverse effects include vascular complications (myocardial infarction and stroke). This, combined with its high cost and the need for injection, makes it a less attractive option [11].

Norepinephrine transporter (NET) inhibitors, or serotonin-norepinephrine reuptake inhibitors (SNRIs), can exacerbate tachycardia in POTS [73••]. The HRS cautions against their use in POTS (HRS Class III) [8••]. Selective serotonin reuptake inhibitors (SSRIs), on the other hand, do not aggravate orthostatic tachycardia or symptoms in POTS patients [74••]. Whether they have any clinical benefit in POTS has yet to be studied.

The Vanderbilt Approach to the Treatment of POTS

We will typically start with non-pharmacological approaches. These routinely include increased dietary salt and water intake and the use of compression stockings if tolerated. We

routinely encourage our patients to engage in a structured exercise program.

Many of our patients will also require adjunct medications. We find that low-dose propranolol is effective and well tolerated in most patients. As needed, we will then add midodrine and/or fludrocortisone. Other medications are used less commonly and based on individual patient characteristics.

Conclusions

POTS is a disabling disorder, related to multiple, overlapping pathophysiological mechanisms. The hallmark physiological trait is an excessive increase in HR upon assumption of the upright posture, in the absence of orthostatic hypotension. POTS is not a single disease. A number of non-specific symptoms that are both associated with and independent of upright posture create a clinical phenotype that overlaps with other disorders like CFS. POTS can be treated with a combination of non-pharmacological approaches, a structured exercise training program, and often some pharmacological support.

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Compliance with Ethics Guidelines

Conflict of Interest Emily M. Garland and Jorge E. Celedonio report grants from National Institutes of Health, during the conduct of the study. Satish R. Raj reports grants from National Institutes of Health, during the conduct of the study; grants from Medtronic; personal fees from Lundbeck Pharmaceuticals; personal fees from GE Healthcare; and personal fees from Medicolegal Consulting, outside the submitted work.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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