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Confounders of Vasovagal Syncope: Postural Tachycardia Syndrome

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Abstract

Most patients who present to a cardiologist with syncope will have vasovagal (reflex) syncope. A busy syncope practice will often also see patients with postural tachycardia syndrome, often presenting with severe recurrent presyncope. Recognition of this "syncope confounder" might be difficult without adequate knowledge of their presentation, and this can adversely affect optimal management. Patients with postural tachycardia syndrome exhibit an excessive increase in heart rate ≥ 30 bpm within 10 minutes of standing (in the absence of orthostatic hypotension), in addition to chronic symptoms of orthostatic intolerance. Postural tachycardia syndrome can often be differentiated from vasovagal syncope by its hemodynamic pattern during tilt table test and differing clinical characteristics. This article will briefly review the presentation of postural tachycardia syndrome, its putative pathophysiology and an approach to non-pharmacological and pharmacological management.

Keywords

syncope; vasovagal; postural tachycardia syndrome; treatment; medications; non-pharmacological; postural tachycardia syndrome; vasovagal syncope; autonomic dysfunction; syncope; blood pressure; heart rate

Introduction

While most cases of syncope are due to vasovagal syncope (VVS), more common than syncope is presyncope. Cardiologists working in a syncope clinic or in a tilt table laboratory will realize that a common confounder of vasovagal syncope and presyncope is postural tachycardia syndrome (POTS; primarily presenting with presyncope). Table 1 highlights some contrasting clinical characteristics between these 2 disorders. These disorders can have distinct hemodynamic patterns during tilt table testing. During head up tilt:

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Conflicts of Interest - None

- Patients with VVS will often hold a steady blood pressure (BP) for several minutes (often >10 minutes) post head-up tilt, before they develop symptoms and drop their BP rapidly (Fig. 1a).
- Patients with POTS do not usually drop their BP with head-up tilt. Rather, they classically have an excessive increase in their heart rate (HR) (Fig 1b). This article will review of the presentation, putative pathophysiology, investigation approach and treatment of postural tachycardia syndrome.

Hemodynamic Physiology of Standing: Healthy and POTS

With the assumption of an upright posture, there is a downward shift of ~500 ml of blood to the dependent areas (mainly abdomen and legs). This gravitational shift in blood results in decreased venous return, decreased cardiac output and eventually decreased BP [1] (Fig 2a). This "unloads" the baroreceptors, and triggers a reflex sympathetic activation with a resultant increase in HR and systemic vasoconstriction (countering the initial decline in BP). In a healthy individual, the net effect of assumption of upright posture is an increase in HR of 10-20 bpm, a minimal change in systolic BP, and a ~5 mmHg increase in diastolic BP.

In patients with POTS (Fig 2b), the initial response to upright posture can include a profound drop in stroke volume. With engagement of the baroreflex, there can be a vigorous increase in sympathetic tone and an exaggerated increase in HR. The blood pressure may remain unchanged or even increase if there is excessive sympathetically mediated vasoconstriction. Presyncope can result from the excessive tachycardia and/or the increased sympathoneural tone.

POSTURAL TACHYCARDIA SYNDROME

Patients with POTS demonstrate an excessive increase in HR in response to upright posture (in the absence of orthostatic hypotension) with improvement in symptoms on lying down [1, 2].

It is estimated that there are ~500,000 Americans diagnosed with POTS in the United States [3], with 80-90% female patients [1, 4, 5], often of childbearing age [1, 6].

POTS Diagnostic Criteria (Table 2)

POTS is defined as the presence of symptoms of orthostatic intolerance for >6 months accompanied by a HR increase of ≥30 bpm within 10 min of assuming an upright posture in the absence of orthostatic hypotension (fall in BP >20/10 mmHg). The syndrome must occur in the absence of prolonged bed rest, medications that impair autonomic regulation (e.g. diuretics, vasodilators, diuretics, sympatholytics or certain antidepressants), or any other chronic debilitating disorders that might cause tachycardia (such as dehydration, anemia or hyperthyroidism). Orthostatic tachycardia is necessary, but not sufficient to make the diagnosis of POTS; typical symptoms are also required.

POTS Clinical Features

Symptoms in POTS patients include lightheadedness, shortness of breath, palpitations, tremulousness, chest discomfort, headache, visual disturbances, mental clouding ("brain fog"), and nausea. Only a minority (~30%) of patients with POTS has frank syncope, but daily or almost daily pre-syncope occurs. Chest pains are common, but almost never due to coronary artery obstruction. Most patients complain of significant exercise intolerance and extreme fatigue, even to activities of daily living. Some patients with POTS will also meet diagnostic criteria for chronic fatigue syndrome [7].

The most striking physical feature of POTS is the severe tachycardia that develops on standing from a supine position. Recent data suggests that there is a significant circadian variability in the orthostatic tachycardia in patients with POTS, with greater orthostatic tachycardia in the morning than in the evening [8]. Another remarkable physical feature of POTS is the dependent acrocyanosis that occurs in close to 50% of patients with POTS (Fig 3) [1]. These patients experience a dark red-blue discoloration of their legs, which are cold to the touch.

POTS Pathophysiology

Tachycardia on standing is a final common pathway of many pathophysiological processes. POTS is a heterogeneous syndrome rather than a single disease. Over the last 20 years, much has been learned about specific sub-types within POTS, although categorizing the individual patient remains difficult. Some pathophysiological phenotypes include the following:

- **Neuropathic POTS** – some patients likely have a form of dysautonomia, with preferential denervation of sympathetic nerves innvervating the lower limbs [2, 9, 10].
- **Chronic Hypovolemia** – Many patients with POTS have a low blood volume when formally assessed [4, 11, 12]. We [4, 13] and others [14] have reported irregularities in the renin-angiotensin-aldosterone system with low aldosterone that may contribute to abnormal renal sodium handling and hypovolemia in POTS.
- **Hyperadrenergic POTS** – Many patients have evidence of a hyperactive sympathetic nervous system, indicated by a standing plasma norepinephrine level >600 pg/ml [6]. In most cases, the hyperadrenergic state is compensatory for another disorder (e.g. hypovolemia, blood pooling). Occasionally, the underlying problem may be excessive sympathetic discharge, with very high levels of upright norepinephrine. Patients can sometimes have large increases in BP on standing.
- **Norepinephrine Reuptake Transporter Deficiency** - A specific genetic abnormality with a loss of function mutation in the norepinephrine transporter has been identified in a kindred with hyperadrenergic POTS [15]. Clearance of synaptic norepinephrine is likely impaired as a result of this mutation. Many psychiatric drugs inhibit the norepinephrine reuptake transporter, recreating an orthostatic tachycardia phenotype in previously unaffected subjects [16, 17].
- **Mast Cell Activation Disorder** - Some POTS patients have mast cell degranulation without an overt trigger. These patients have episodic flushing and abnormal increases in urine methylhistamine (the primary urinary metabolite of histamine) [18].

Investigation of POTS (Table 3)

- **Orthostatic Challenge** – POTS diagnostic criteria require an increase in HR of ≥30 bpm within 10 minutes of upright posture (tilt or standing, even though these are not identical [19].
- **Confirm Sinus Tachycardia** - POTS patients should have only sinus tachycardia. An electrocardiogram should be done routinely to rule out the presence of an accessory bypass tract or any abnormalities of cardiac conduction. A Holter monitor might prove useful to exclude a re-entrant dysrhythmia, especially if the patient gives a history of paroxysmal tachycardia with a sudden onset and offset.
- **Echocardiogram** – Required in individual cases when there is doubt about the structural integrity of the heart.

- **Supine and Upright Plasma Norepinephrine** - The supine norepinephrine is often high normal in patients with POTS, while the upright norepinephrine is usually elevated (>600 pg/ml). This likely reflects the exaggerated sympathoneural tone that is present in many patients while upright.
- **Autonomic Function Tests** – Responses are usually intact or exaggerated to both cardiovagal testing (sinus arrhythmia), and Valsalva BP in Phase II & IV.
- **Blood Volume Assessment** - The blood volume is low in many patients with POTS [4], and this can be assessed in many Nuclear Medicine laboratories.
- **Blood Tests** – complete blood count and electrolyte panel; thyroid function tests, celiac panel with gastrointestinal symptoms, vitamin B_{12} and iron indices.

Non-Pharmacological Treatment of POTS (Table 4)

- **Remove potentially contributory medications** – especially venodilators (such as nitrates), diuretics, and norepinephrine reuptake transporter inhibiting drugs.
- **Reconditioning** – Patients that have been sedentary or in bed for prolonged periods of time require reconditioning.
- **Avoid ablating the sinus node** – While there are anecdotal reports of benefits with sinus node modification, many patients do poorly post-procedure (potentially with a pacemaker). The underlying problem is not in the sinus node.
- **Patient Education** – Patients should learn to avoid aggravating factors such as dehydration (drink 8-10 cups of water/day and consume ~200 mEq Na^+/day), and extreme heat. There are many patient websites, include the Vanderbilt Autonomic Dysfunction site (www.mc.vanderbilt.edu/gcec/adc).
- **Waist High Compression Garments** - 30-40 mmHg of counter-pressure can minimize venous pooling, especially when the patient needs to stand for prolonged periods of time. Unfortunately, they can be hot, itchy and uncomfortable.

IV Saline for POTS—Acute blood volume expansion with intravenous saline 1-2 L is very effective at controlling the heart rate and acutely improving symptoms [20]. Due to vascular access issues, this treatment is not practical on a day to day basis, but can be used as a “rescue medicine” at times of decompensation.

Exercise Training for POTS—Exercise has routinely been recommended as a part of the POTS treatment regimen for many years. Unfortunately, POTS patients report feeling debilitated for days post-exertion, limiting compliance with exercise training. Anecdotally, patients that did exercise seemed to have a better long-term prognosis, but it was not certain if this was a selection bias. Fu et al. have recently demonstrated the dramatic benefits of exercise [21]. They administered a structured 3 month exercise program to 19 patients with POTS, and showed improved quality of life, reduced orthostatic tachycardia, and increased blood volume, stroke volume and LV mass. This study shows that exercise training is an important treatment in this population. Recommendations regarding exercise training for POTS patients are included in Table 5.

Pharmacological Treatment of POTS (Table 6)

Volume Expansion—

- **Fludrocortisone 0.05-0.2 mg daily** – Many patients with POTS are hypovolemic [4], so fludrocortisone (an aldosterone analogue) is often used. Through enhanced renal sodium retention, it should expand the plasma volume (although the

data are poor). Potassium wasting can result in hypokalemia, so serum K^+ should be monitored periodically.

- **Desmopressin 0.2 mg PO PRN (not daily)** – Oral desmopressin promotes renal free water retention, and is often used for enuresis. Desmopressin can acutely lower standing HR in POTS and improve symptoms [22]. Potential side effects include hyponatremia, edema and headache. Serum Na^+ should be monitored periodically during therapy.

Sympatholysis—

- **Propranolol 10-20 mg PO QID** – Many patients report intolerance to beta-blockers when first seen at the Vanderbilt Autonomic Dysfunction Center. The vast majority of POTS patients, however, respond well hemodynamically and symptomatically to low doses of propranolol [5]. Of note, more complete beta-blockade with higher doses of propranolol cause symptoms to worsen. Long acting propranolol was not found to be helpful [14]. This is our 1st line pharmacological agent.
- **Methyldopa 125mg QHS-BID** – Methyldopa is a false neurotransmitter that can lower central sympathetic tone. It is particularly useful in hyperadrenergic patients.
- Clonidine 0.05-0.2 mg PO BID (or a long acting patch) - Alpha 2 adrenergic agonist that acts centrally to decrease sympathetic nervous system tone. It can stabilize HR and BP, but it can also cause drowsiness, fatigue and worsen the mental clouding of some patients.

Vasoconstrictor Therapy—

- **Midodrine 5-10mg PO q4H x3/day** - Since a failure of vascular resistance may be an integral part of neuropathic POTS, vasoconstrictors such as midodrine (alpha-1 agonist) can be employed [23].

Increasing Vagal Tone—

- **Pyridostigmine 30-60 mg PO TID** – Pyridostigmine is a peripheral acetylcholinesterase inhibitor. By increasing synaptic acetylcholine at both the autonomic ganglia and the peripheral muscarinic parasympathetic receptors, pyridostigmine significantly restrains the heart rate in response to standing in patients with POTS [24, 25]. Pyridostigmine is most effective in combination with low dose propranolol. Since pyridostigmine enhances bowel motility, it is often not well tolerated in patients with diarrhea-predominant irritable bowel syndrome symptoms [26].

Vanderbilt Approach to Pharmacotherapy for POTS—In addition to initial non-pharmacological approaches, and strong advice about an exercise regimen, most POTS patients require some pharmacotherapy. We will often start with low-dose propranolol. If the patient has hypovolemia, then we will add in fludrocortisone. As 3rd line therapy, if the patient is very hyperadrenergic, then we might consider a central sympatholytic; otherwise midodrine would be our 3rd line agent.

CONCLUSIONS/SUMMARY

POTS is a multisystem disorder of the autonomic nervous system. The hallmark manifestation is symptomatic orthostatic tachycardia, with lightheadedness and presyncope. While it is not primarily a syncopal disorder, a minority of patients can also have VVS.

POTS is associated with substantial functional disability among otherwise healthy people. Patients with POTS demonstrate a heart rate increase of >30 bpm with standing (within 10 minutes), often have high levels of upright plasma norepinephrine, and many patients have a low blood volume. Exercise training has been found to be highly effective at improving the physiology and symptoms in POTS patients. Pharmacological therapies aimed at correcting the hypovolemia and the excess sympathetic tone may also help improve the symptoms.

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Key Points

- Most patients who present to a cardiologist with syncope have vasovagal (reflex) syncope.
- A common confounder of vasovagal syncope and presyncope is postural tachycardia syndrome (POTS), a multisystem disorder of the autonomic nervous system.
- The hallmark manifestation of POTS is symptomatic orthostatic tachycardia, with lightheadedness and presyncope.
- Patients with POTS demonstrate a heart rate increase of >30 bpm with standing (within 10 minutes), often have high levels of upright plasma norepinephrine, and often have a low blood volume.
- Postural tachycardia syndrome can often be differentiated from vasovagal syncope by its hemodynamic pattern during tilt table test and differing clinical characteristics.
- Exercise training has been found to be highly effective at improving the physiology and symptoms in POTS patients. Pharmacological therapies aimed at correcting the hypovolemia and the excess sympathetic tone may also help improve the symptoms.

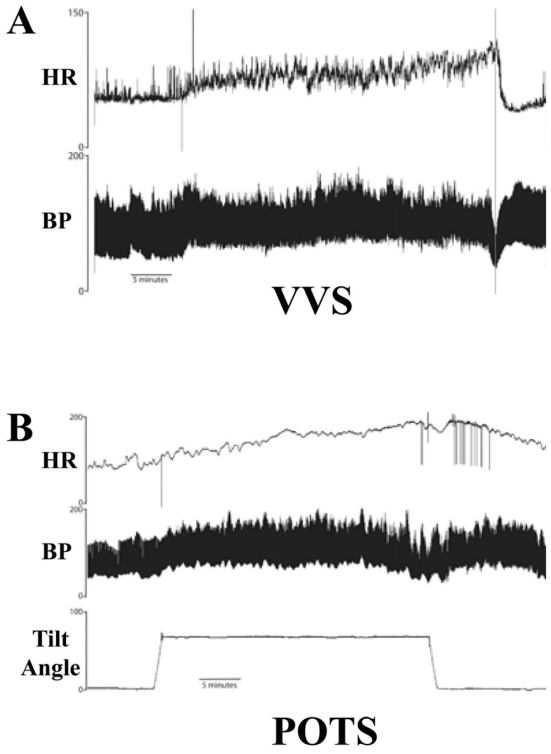

Figure 1. Head-up tilt test traces from a patient with Vasovagal Syncope (VVS; Panel A) and postural tachycardia syndrome (POTS; Panel B)

Panel A: With VVS, the heart rate (HR) and blood pressure (BP) increases a little bit at the onset of tilt, and they are maintained for over 25 minutes before a sudden precipitous drop in BP before the table is returned to the supine position. Panel B: With POTS, the BP often increases a little bit with head-up tilt, and starts to return to baseline when the table returns to the supine position. Traces are reprinted with permission from reference [27].

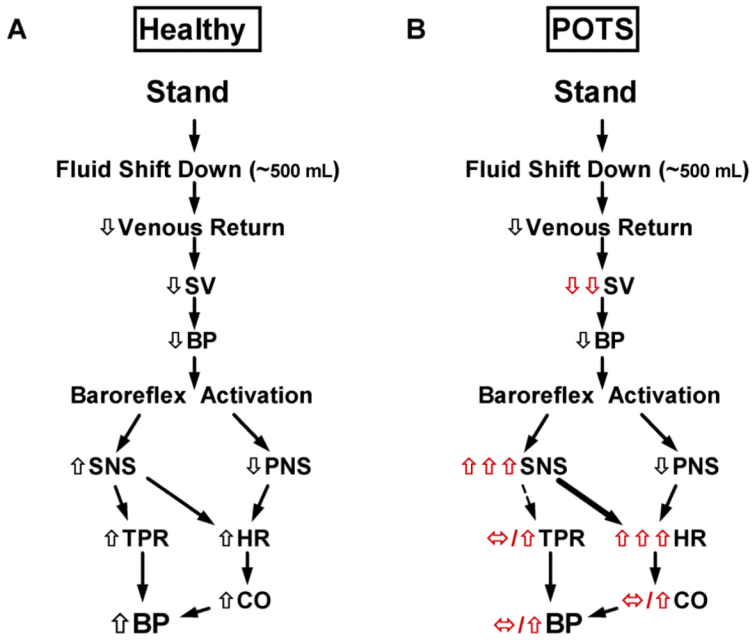

Figure 2. Physiology of Standing in a Healthy Individual and Patient with POTS

Panel A: With the assumption of an upright posture in a healthy individual, there is a downward shift of ~500 ml of blood with a decrease in venous return, stroke volume (SV) and eventually blood pressure (BP) [1]. This "unloads" the baroreceptors, and triggers reflex sympathetic nervous system (SNS) activation with a resultant increase in heart rate (HR) and systemic vasoconstriction (countering the initial decline in BP). In a healthy individual, the net effect of assumption of upright posture is an increase in HR of 10-20 bpm, a minimal change in systolic BP, and a ~5 mmHg increase in diastolic BP. Panel B: In patients with POTS, the initial response to upright posture can include a profound drop in SV. With engagement of the baroreflex, there can be a vigorous increase in SNS tone and an exaggerated increase in HR. The BP may remain unchanged or even increase if there is excessive SNS mediated vasoconstriction. Presyncope can result from the excessive HR increase and/or the increased SNS tone. CO – cardiac output; PNS – parasympathetic nervous system; TPR – total peripheral resistance.

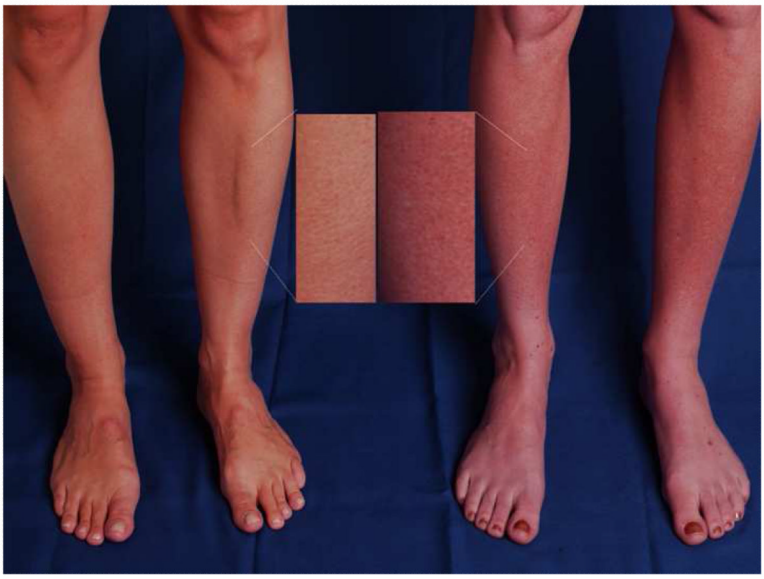

Figure 3. Acrocyanosis in Postural Tachycardia Syndrome (POTS)

A striking physical feature in POTS is the gross change in leg skin color that can occur with standing. The panel shows the legs of a healthy subject (Left Panel) and a POTS patient (Right Panel) who have each been standing for 5 minutes. The POTS patient (Right Panel) has significant dark red mottling of her legs extending up to the knees while standing, while the healthy subject does not have a similar discoloration. Figures are reprinted with permission from reference [1].

Table 1

Clinical Comparison of Vasovagal Syncope and Postural Tachycardia Syndrome

Features	Vasovagal Syncope	Postural Tachycardia Syndrome
Typical age	Any age; 1st episode usually in 2nd/3rd decade	13-50 years
Gender (% Female)	60%	85%
Symptoms with Body Position Change	After prolonged sitting or standing	Immediately with sitting or standing
Syncope	+++	+/−
Presyncope	+	++++
Orthostatic Hypotension	+/− (usually only at time of faint)	+/−
Hemodynamic Pattern with Head Up Tilt	Sudden drop in BP & HR	Early increase in HR≥30bpm

BP - blood pressure; HR - heart rate.

Table 2

Diagnostic Criteria for Postural Tachycardia Syndrome

- HR increase ≥30 bpm from lying to standing
- Absence of significant drop in BP with standing
- Positional symptoms
  - Many symptoms are worse with upright posture and improve on lying down
  - Some symptoms can be non-positional (e.g. fatigue, headache)
- Chronic symptoms
  - Duration ≥6 months
- Absence of other overt cause for tachycardia
  - E,g, acute blood loss, prolonged bedrest, hyperthyroidism, tachycardia promoting medications

Table 3

Diagnostic Tests in Postural Tachycardia Syndrome (POTS)

Diagnostic Test	Comments
Orthostatic challenge	Increase in HR ≥30bpm within 10 minutes of upright posture required for diagnosis
Electrocardiogram/Cardiac Monitoring	Rule out any abnormal cardiac conduction; Confirm sinus (and not ectopic) tachycardia
Echocardiogram	Rule out structural heart abnormalities
Supine and upright plasma NE	Plasma NE ≥600pg/ml suggestive of a hyperadrenergic response
Autonomic Function Test	Intact (and sometimes vigorous) HR & BP recovery with Valsalva
Blood Volume Assessment	A significant proportion of POTS patients have low blood volume
Other blood test: hemogram, electrolytes, thyroid function, celiac panel, Vitamin B12 and serum iron panel	To rule other medical conditions that can promote sinus tachycardia

HR – heart rate; NE – norepinephrine; BP – blood pressure

Table 4

Non-Pharmacological Treatment for POTS

Measures	Mechanism	Comments
Exercise training	Blood volume expansion and reverses cardiac deconditioning	Improves quality of life & physiology (if patient can complete exercise program)
Physical Maneuvers		
Squatting	Enhances venous return	May prevent syncope
- Sit with feet folded up	Prevents blood pooling	May prevent syncope
Waist high compression garments	Prevents blood pooling	start with 30-40 mmHg pressure for compression garments; can be uncomfortable (hot & itchy) and fashion tragedy
Aggressive fluid intake	Blood volume expansion	8 – 10 cups of water/day
Increased sodium intake	Blood volume expansion	Up to 200 mEq Na^+/day
Saline IV 1-2L PRN	Blood volume expansion	“Rescue” therapy for decompensation

Table 5

Fu/Levine Exercise Training Protocol for POTS Patients

Initial Exercise Training
Avoid upright exercises
Recommend using a rowing machine, recumbent cycle or swimming.
Intensity: target heart rate equivalent to 75-80% of maximum steady state.
Duration: 3-4 sessions/week for 30-45 minutes/session.
Exercise Training Months 2-3
Can begin upright exercise using upright bike, walking, treadmill or jogging
Intensity: gradually increase intensity to maximal steady state 1/week and then 2/week.
Duration: Increase as patient becomes fit with goal of 5 to 6 hours per week.
Resistance Training
Focus on lower body
Start 1/week for 15-20 minutes/session
Gradually increase to 2/week for 45 min/session
Long Term Exercise Training
Patients encouraged to continue exercise indefinitely

Recommendations adapted from reference [14].

Table 6

Pharmacological Treatment for POTS

Drug	Dose	Mechanism	Adverse effects	Comments
Propranolol	10-20 mg PO QID	Beta- adrenergic receptor antagonist	Bradycardia, hypotension and bronchospasm	Attenuates symptomatic tachycardia on standing; low doses can help; high doses not tolerated
Pyridostigmine	30-60 mg PO TID	Acetylcholinesterase inhibitor	Abdominal cramping: diarrhea; increased sweating	Attenuates tachycardia and improve symptoms; can be combined with propranolol
Fludrocortisone	0.05–0.2 mg PO daily	Blood volume expansion; synthetic aldosterone	Hypertension, fluid retention and hypokalemia	Most effective when combined with increased dietary salt & water
Midodrine	2.5- 10 mg PO q4h x3/day	Vasoconstriction; Alpha-1 adrenergic receptor agonist	Scalp itch, Piloerection, urinary retention and hypertension	Can improve venous return and decrease reflex tachycardia
Desmopressin (DDAVP)	0.2 mg PO occasionally	Acute blood volume expansion	Water retention; hyponatremia	Follow serum [Na^+] carefully
Methyldopa	125 mg PO QHS or BID	Central Sympatholytic False neurotransmitter	Sedation and hypotension.	Reduce plasma norepinephrine
Clonidine	0.05-0.2 mg BID (or use a long acting patch)	Central Sympatholytic Alpha-2 receptor agonist	Worsens fatigue; sedation & hypotension.	Reduce plasma norepinephrine

PO – per os; QID – 4 times per day; TID – 3 times per day; BID – twice per day; QHS – at bedtime;