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Evaluating and managing postural tachycardia syndrome

ABSTRACT

Postural tachycardia syndrome (POTS) is a disorder of the autonomic nervous system with many possible causes, characterized by an unexplained increase in heartbeat without change in blood pressure upon standing. Associated cardiac and noncardiac symptoms can severely affect quality of life. Therapy, using a combined approach of diet and lifestyle changes, plus judicious use of medications if needed, can usually improve symptoms and function.

KEY POINTS

Several POTS subtypes have been recognized, including hypovolemic, neuropathic, and hyperadrenergic forms, overlapping with Ehlers-Danlos syndrome, mast cell activation, and autoimmune syndromes.

Treatment should take a graded approach, beginning with increasing salt and water intake, exercise, and compression stockings.

If needed, consider medications to expand blood volume, slow heart rate, or reduce central sympathetic tone.

Certain medications, including venodilators, diuretics, and serotonin-norepinephrine reuptake inhibitors, can exacerbate symptoms and should be avoided.

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Some people, most of them relatively young women, experience lightheadedness, a racing heart, and other symptoms (but not hypotension) when they stand up, in a condition known as postural tachycardia syndrome (POTS).[1] Although not known to shorten life,[1] it can be physically and mentally debilitating.[2,3] Therapy rarely cures it, but a multifaceted approach can substantially improve quality of life.

This review outlines the evaluation and diagnosis of POTS and provides guidance for a therapy regimen.

HOW IS POTS DEFINED?

POTS is a multifactorial syndrome rather than a specific disease. It is characterized by all of the following[1,4–6]:

- An increase in heart rate of ≥ 30 bpm, or ≥ 40 bpm for those under age 19, within 10 minutes of standing from a supine position
- Sustained tachycardia (> 30 seconds)
- Absence of orthostatic hypotension (a fall in blood pressure of ≥ 20/10 mm Hg)
- Frequent and chronic duration (≥ 6 months).

These features are critical to diagnosis. Hemodynamic criteria in isolation may describe postural tachycardia but are not sufficient to diagnose POTS.

The prevalence of POTS is estimated to be between 0.2% and 1.0%,[7] affecting up to 3 million people in the United States. Most cases arise between ages 13 and 50, with a female-to-male ratio of 5:1.[8]

MANY NAMES, SAME CONDITION

In 1871, Da Costa[9] described a condition he called "irritable heart syndrome" that had characteristics similar to those of POTS, including

extreme fatigue and exercise intolerance. Decades later, Lewis[10] and Wood[11] provided more detailed descriptions of the disorder, renaming it "soldier's heart" or "Da Costa syndrome." As other cases were documented, more terms arose, including "effort syndrome" and "mitral valve prolapse syndrome."

In 1982, Rosen and Cryer[12] were the first to use the term "postural tachycardia syndrome" for patients with disabling tachycardia upon standing without orthostatic hypotension. In 1986, Fouad et al[13] described patients with postural tachycardia, orthostatic intolerance, and a small degree of hypotension as having "idiopathic hypovolemia."

In 1993, Schondorf and Low[14] established the current definition of POTS, leading to increased awareness and research efforts to understand its pathophysiology.

MULTIFACTORIAL PATHOPHYSIOLOGY

During the last 2 decades, several often-overlapping forms of POTS have been recognized, all of which share a final common pathway of sustained orthostatic tachycardia.[15–19] In addition, a number of common comorbidities were identified through review of large clinic populations of POTS.[20,21]

POTS is a multifactorial syndrome rather than a specific disease

Hypovolemic POTS

Up to 70% of patients with POTS have hypovolemia. The average plasma volume deficit is about 13%, which typically causes only insignificant changes in heart rate and norepinephrine levels while a patient is supine. However, blood pooling associated with upright posture further compromises cardiac output and consequently increases sympathetic nerve activity. Abnormalities in the renin-angiotensin-aldosterone volume regulation system are also suspected to impair sodium retention, contributing to hypovolemia.[1,22]

Neuropathic POTS

About half of patients with POTS have partial sympathetic denervation (particularly in the lower limbs) and inadequate vasoconstriction upon standing, leading to reduced venous return and stroke volume.[17,23] A compensatory increase in sympathetic tone results in tachycardia to maintain cardiac output and blood pressure.

Hyperadrenergic POTS

Up to 50% of patients with POTS have high norepinephrine levels (≥ 600 pg/mL) when upright. This subtype, hyperadrenergic POTS, is characterized by an increase in systolic blood pressure of at least 10 mm Hg within 10 minutes of standing, with concomitant tachycardia that can be similar to or greater than that seen in nonhyperadrenergic POTS. Patients with hyperadrenergic POTS tend to report more prominent symptoms of sympathetic activation, such as palpitations, anxiety, and tremulousness.[24,25]

Norepinephrine transporter deficiency

The norepinephrine transporter (NET) is on the presynaptic cleft of sympathetic neurons and serves to clear synaptic norepinephrine. NET deficiency leads to a hyperadrenergic state and elevated sympathetic nerve activation.[18] NET deficiency may be induced by common antidepressants (eg, tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors) and attention-deficit disorder medications.[4]

Mast cell activation syndrome

The relationship between mast cell activation syndrome and POTS is poorly understood.[4,26] Mast cell activation syndrome has been described in a subset of patients with POTS who have sinus tachycardia accompanied by severe episodic flushing. Patients with this subtype have a hyperadrenergic response to postural change and elevated urine methylhistamine during flushing episodes.

Patients with mast cell activation syndrome tend to have strong allergic symptoms and may also have severe gastrointestinal problems, food sensitivities, dermatographism, and neuropathy. Diagnosis can be difficult, as the condition is associated with numerous markers with varying sensitivity and specificity.

Autoimmune origin

A significant minority of patients report a viral-like illness before the onset of POTS symptoms, suggesting a possible autoimmune-mediated or inflammatory cause. Also, some autoimmune disorders (eg, Sjögren syndrome) can present with a POTS-like manifestation.

Research into the role of autoantibodies in the pathophysiology of POTS offers the poten-

tial to develop novel therapeutic targets. Autoantibodies that have been reported in POTS include those against M1 to M3 muscarinic receptors (present in over 87% of patients with POTS),[27] cardiac lipid raft-associated proteins,[28] adrenergic G-protein coupled receptors, alpha-1-adrenergic receptors, and beta-1- and beta-2-adrenergic receptors.[29] Although commercial enzyme-linked immunosorbent assays can assess for these antibody fragments, it is not known whether targeting the antibodies improves outcomes. At this time, antibody testing for POTS should be confined to the research setting.

LINKS TO OTHER SYNDROMES

POTS is often associated with other conditions whose symptoms cannot be explained by postural intolerance or tachycardia.

Ehlers-Danlos syndromes are a group of inherited heterogeneous disorders involving joint hypermobility, skin hyperextensibility, and tissue fragility.[30] The hypermobile subtype is most commonly associated with POTS, with patients often having symptoms of autonomic dysregulation and autonomic test abnormalities.[31–33] Patients with POTS may have a history of joint subluxations, joint pain, cervical instability, and spontaneous epidural leaks. The reason for the overlap between the two syndromes is not clear.

Chronic fatigue syndrome is characterized by persistent fatigue that does not resolve with rest and is not necessarily associated with orthostatic changes. More than 75% of patients with POTS report general fatigue as a major complaint, and up to 23% meet the full criteria for chronic fatigue syndrome.[34]

DIAGNOSTIC STRATEGY

A patient presenting with symptoms suggestive of POTS should first undergo a detailed history and physical examination. Other causes of sinus tachycardia should be considered.

Detailed history, symptom review

The history should focus on determining symptom burden, including tachycardia onset, frequency, severity, and triggers; the presence of syncope; and the impact of symptoms on daily function and quality of life.

TABLE 1

Typical symptoms of postural tachycardia syndrome

Cardiac symptoms
Palpitations
Lightheadedness
Chest discomfort
Dyspnea
Noncardiac symptoms
Mental clouding ("brain fog")
Headache
Nausea
Tremulousness
Blurred or tunnel vision
Sleep disturbances
Fatigue
Presyncope
Gastrointestinal pain, heartburn, diarrhea, constipation

POTS-associated orthostatic intolerance manifests with cardiac and noncardiac symptoms (**Table 1**).

Hypovolemia occurs in up to 70% of patients

Presyncope and its associated symptoms occur in less than one-third of patients with POTS, and syncope is not a principal feature.[4] If syncope is the predominant complaint, alternative causes should be investigated. The usual cause of syncope in the general population is thought to be vasovagal.

In addition to orthostatic intolerance, gastrointestinal disturbances are common in POTS, presenting as abdominal pain, heartburn, irregular bowel movements, diarrhea, or constipation. Symptoms of gastroparesis are less common. Gastrointestinal symptoms tend to be prolonged, lasting hours and occurring multiple times a week. They tend not to improve in the supine position.[35]

POTS-associated symptoms may develop insidiously, but patients often report onset after an acute stressor such as pregnancy, major surgery, or a presumed viral illness.[4] Whether these putative triggers are causative or coincidental is unknown. Symptoms of orthostatic

TABLE 2

Differential diagnosis of postural tachycardia syndrome symptoms

Hyperthyroidism
Infection
Pheochromocytoma
Inappropriate sinus tachycardia
Acute dehydration
Exercise
Physical deconditioning
Panic attacks
Pain
Alcohol
Caffeine
Medication-induced or exacerbated

Information from references 39–41.

intolerance tend to be exacerbated by dehydration, heat, alcohol, exercise, and menstruation.[36,37]

POTS is often associated with Ehlers-Danlos syndrome

Consider the family history: 1 in 8 patients with POTS reports familial orthostatic intolerance,[38] suggesting a genetic role in some patients. Inquire about symptoms or a previous diagnosis of Ehlers-Danlos syndrome and mast cell activation syndrome.

Consider other conditions

Other causes of orthostatic tachycardia are listed in **Table 2**.[39–41] Most can be diagnosed with a careful history, physical examination, and laboratory tests. Two of the more challenging diagnoses are described below.

Pheochromocytoma causes hyperadrenergic symptoms (eg, palpitations, lightheadedness) like those in POTS, but patients with pheochromocytoma typically have these symptoms while supine. Pheochromocytoma is also characterized by plasma norepinephrine levels much higher than in POTS.[4] Plasma metanephrine testing helps diagnose or rule out pheochromocytoma.[5]

Inappropriate sinus tachycardia, like pheochromocytoma, also has clinical features similar to those of POTS, as well as tachycardia present when supine. It involves higher sympathetic tone and lower parasympathetic tone compared with POTS; patients commonly have a daytime resting heart rate of at least 100 bpm or a 24-hour mean heart rate of at least 90 bpm.[1,42] While the intrinsic heart rate is heightened in inappropriate sinus tachycardia, it is not different between POTS patients and healthy individuals.[42,43] Distinguishing POTS from inappropriate sinus tachycardia is further complicated by the broad inclusion criteria of most studies of inappropriate sinus tachycardia, which failed to exclude patients with POTS.[44] The Heart Rhythm Society recently adopted distinct definitions for the 2 conditions.[1]

Physical examination: Focus on vital signs

The most critical component of the physical examination is thorough measurement of orthostatic vital signs (**Figure 1**). Blood pressure and heart rate should be measured while the patient has been supine for at least 5 minutes, and again after being upright for 1, 3, 5, and 10 minutes. These measurements determine if orthostatic hypotension is present and whether the patient meets the heart rate criteria for POTS. Patients with POTS tend to experience greater orthostatic tachycardia in the morning, so evaluation early in the day optimizes diagnostic sensitivity.[5]

Dependent acrocyanosis—dark red-blue discoloration of the lower legs that is cold to the touch—occurs in about half of patients with POTS upon standing.[4] Dependent acrocyanosis is associated with joint hypermobility and Ehlers-Danlos syndrome, so these conditions should also be considered if findings are positive.

Laboratory testing for other causes

Laboratory testing is used mainly to detect primary causes of sinus tachycardia. Tests should include:

- Complete blood cell count with hematocrit (for severe anemia)
- Thyroid-stimulating hormone level (for hyperthyroidism)
- Electrolyte panel (for significant electrolyte disturbances).

Evidence is insufficient to support routinely measuring the vitamin B_{12} level, iron indices, and serum markers for celiac disease, although these may be done if the history or

physical examination suggests related problems.[4] Sicca symptoms (severe dry eye or dry mouth) should trigger evaluation for Sjögren syndrome.

Electrocardiography needed

Electrocardiography should be performed to investigate for cardiac conduction abnormalities as well as for resting markers of a supraventricular tachyarrhythmia. Extended ambulatory (Holter) monitoring may be useful to evaluate for a transient reentrant tachyarrhythmia[4]; however, it does not record body position, so it can be difficult to determine if detected episodes of tachycardia are related to posture.

Additional testing for select cases

Further investigation is usually not needed to diagnose POTS but should be considered in some cases. Advanced tests are typically performed at a tertiary care referral center and include:

- Quantitative sensory testing to evaluate for small-fiber neuropathy (ie, Quantitative Sudomotor Axon Reflex Test, or QSART), which occurs in the neuropathic POTS subtype
- Formal autonomic function testing to characterize neurovascular responsiveness
- Supine and standing plasma norepinephrine levels (fractionated catecholamines) to characterize the net activation of the sympathetic nervous system
- Blood volume assessments to assess hypovolemia
- Formal exercise testing to objectively quantify exercise capacity.

GRADED MANAGEMENT

No single universal gold-standard therapy exists for POTS, and management should be individually determined with the primary goals of treating symptoms and restoring function. A graded approach should be used, starting with conservative nonpharmacologic therapies and adding medications as needed.

While the disease course varies substantially from patient to patient, proper management is strongly associated with eventual symptom improvement.[1]

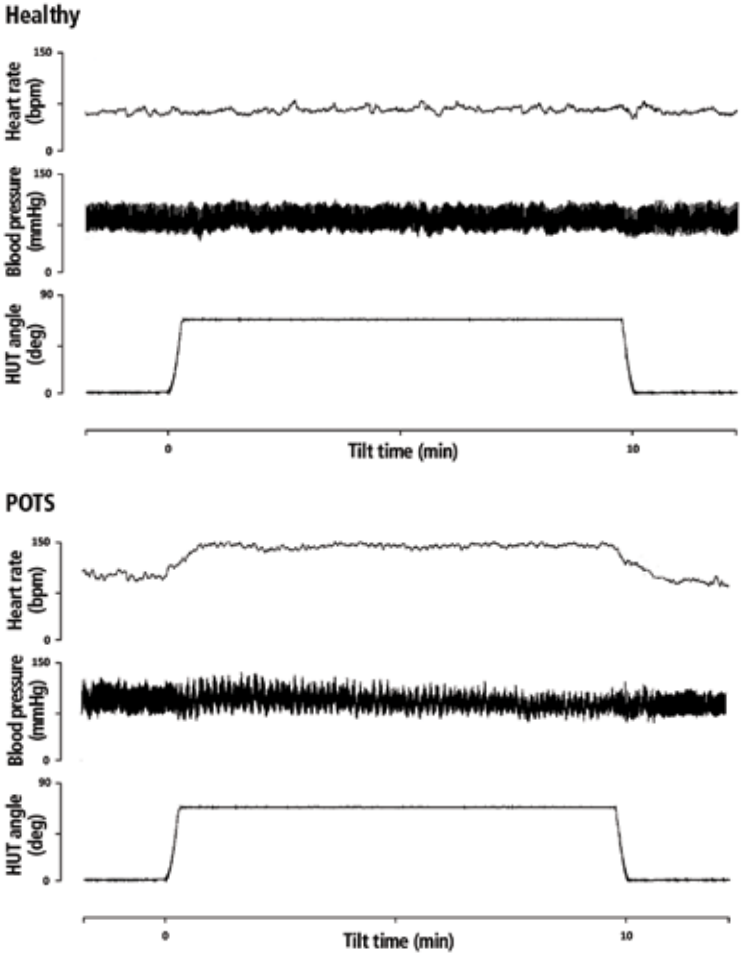

Figure 1. Results of head-up tilt-table (HUT) testing in a healthy person (top) and in a patient with postural tachycardia syndrome (POTS) (bottom). Upon passive head-up tilting, the heart rate increases in POTS by at least 30 bpm but remains largely stable in healthy individuals. Orthostatic hypotension (a fall in blood pressure of ≥ 20/10 mm Hg) does not occur in either patient.

NONPHARMACOLOGIC STEPS FIRST

A multipronged nonpharmacologic approach should be used for all patients before resorting to medications (**Table 3**). In an observational study, most patients reported that such interventions were more helpful than medications.[45] The following elements are recommended:

Education

Patients should be informed of the nature of their condition and referred to appropriate healthcare personnel. POTS is a chronic illness requiring individualized coping strategies,

TABLE 3

Nonpharmacologic treatments for postural tachycardia syndrome

Therapy	Dosage	Pathologic mechanisms addressed	Potential drawbacks	Comments
Exercise	≥ 30 min at least 3 times a week	All	Worsened symptoms at the outset, prolonged fatigue	Gradually progress from non-upright to upright endurance and resistance exercises
Dietary fluid	2–3 L per day	All	Hyponatremia	
Dietary salt	10–12 g per day	All	Difficult to augment sufficiently through diet alone	Supplement with sodium chloride tablets, if necessary
Salt tablets	1 g tablet 3 times daily	Hypovolemia	Poor taste, nausea, dyspepsia	Recommended for use after meals
Acute intravenous normal saline	1 L over 1–3 hours	Hypovolemia	Inconvenient, medical setting required	Heart Rhythm Society Consensus Statement class IIa recommendation (benefit probably exceeds risk)
Chronic intravenous normal saline	1 L every 2 days	Hypovolemia	Access complications and infection with central line	Heart Rhythm Society Consensus Statement class III recommendation (recommends against)

First try nonpharmacologic approaches

intensive physician interaction, and support of a multidisciplinary team. Patients and family members can be reassured that most symptoms improve over time with appropriate diagnosis and treatment.[1] Patients should be advised to avoid aggravating triggers and activities.

Exercise

Exercise programs are encouraged but should be introduced gradually, as physical activity can exacerbate symptoms, especially at the outset. Several studies have reported benefits from a short-term (3-month) program, in which the patient gradually progresses from non-upright exercise (eg, rowing machine, recumbent cycle, swimming) to upright endurance exercises. At the end of these programs, significant cardiac remodeling, improved quality of life, and reduced heart rate responses to standing have been reported, and benefits have been reported to persist in patients who continued exercising after the 3-month study period.[46,47]

Despite the benefits of exercise interventions, compliance is low.[46,47] To prevent early discouragement, patients should be advised that it can take 4 to 6 weeks of continued exercise before benefits appear. Patients are encouraged to exercise every other day for 30 minutes or more. Regimens should primarily focus on aerobic conditioning, but resistance training, concentrating on thigh muscles, can also help. Exercise is a treatment and not a cure, and benefits can rapidly disappear if regular activity (at least 3 times per week) is stopped.[48]

Compression stockings

Compression stockings help reduce peripheral venous pooling and enhance venous return to the heart. Waist-high stockings with compression of at least 30 to 40 mm Hg offer the best results.

Diet

Increased fluid and salt intake is advisable for patients with suspected hypovolemia. At least 2 to 3 L of water accompanied by 10 to 12 g of daily sodium intake is recommended.[1] This can usually be accomplished with diet and salt added to food, but salt tablets can be used if the patient prefers. The resultant plasma volume expansion may help reduce the reflex tachycardia upon standing.[49]

Check medications

The clinician should review—and perhaps discontinue—medications the patient is already taking that may exacerbate tachycardia or related symptoms (**Table 4**).[50] Venodilators decrease preload, thereby reducing cardiac output and blood pressure, which triggers compensatory tachycardia. Diuretics can reduce effective blood volume and lower preload, leading to worsened symptoms mediated by hypovolemia.

Rescue therapy with saline infusion

Intravenous saline infusion can augment blood volume in patients who are clinically decompensated and present with severe symptoms.[1] Intermittent infusion of 1 L of normal saline has been found to significantly reduce orthostatic tachycardia and related symptoms in patients with POTS, contributing to improved quality of life.[51,52]

Chronic saline infusions are not recommended for long-term care because of the risk of access complications and infection.[1] Moak et al[53] reported a high rate of bacteremia in a cohort of children with POTS with regular saline infusions, most of whom had a central line. On the other hand, Ruzieh et al[54] reported significantly improved symptoms with regular saline infusions without a high rate of complications, but patients in this study received infusions for only a few months and through a peripheral intravenous catheter.

DRUG THERAPY

Drug therapy for POTS should be used only if nonpharmacologic interventions do not adequately relieve symptoms. Given the heterogeneity of POTS, treatment should be tailored to the patient's underlying pathophysiology, key clinical features, and comorbidities. These considerations should guide the initial selection of medications, with adjustments as needed to alleviate adverse effects (**Table 5**).

No medications are approved by the US Food and Drug Administration (FDA) or Health Canada specifically for treating POTS, making all pharmacologic recommendations off-label. Although the drugs discussed below have been evaluated for POTS in controlled laboratory settings, they have yet to be tested in robust clinical trials.

TABLE 4

Medications that can exacerbate postural tachycardia syndrome

Antidepressants (serotonin-norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, and tricyclic antidepressants at higher doses)
Antipsychotic agents (phenothiazines)
Anxiolytic agents
Attention deficit medications
Diuretics
Venodilators and vasodilators
Stimulants (including caffeine, nicotine)

Blood volume expansion

Several drugs expand blood volume, which may reduce orthostatic tachycardia.

Fludrocortisone is a synthetic aldosterone analogue that enhances sodium and water retention. Although one observational study found that it normalizes hemodynamic changes in response to orthostatic stress, no high-level evidence exists for its effectiveness for POTS.[55] It is generally well tolerated, although possible adverse effects include hyperkalemia, hypertension, fatigue, nausea, headache, and edema.[5,56]

Long-term use of saline infusion is not recommended

Desmopressin is a synthetic version of a natural antidiuretic hormone that increases kidney-mediated free-water reabsorption without sodium retention. It significantly reduces upright heart rate in patients with POTS and improves symptom burden. Although potential adverse effects include edema and headache, hyponatremia is the primary concern with daily use, especially with the increased water intake advised for POTS.[57] Patients should be advised to use desmopressin no more than once a week for the acute improvement of symptoms. Intermittent monitoring of serum sodium levels is recommended for safety.

Erythropoietin replacement has been suggested for treating POTS to address the significant deficit in red blood cell volume. Although erythropoietin therapy has a direct vasoconstrictive effect and largely improves red blood cell volume in patients with POTS, it does not expand plasma volume, so ortho-

TABLE 5

Pharmacologic treatments for postural tachycardia syndrome

Therapy	Dosage	Pathologic mechanism addressed	Potential drawbacks	Comments
Blood volume expanders				
Fludrocortisone	0.05–0.1 mg twice daily	Hypovolemia	Hypokalemia, hypertension, fatigue, headache, fluid retention, edema	
Desmopressin	0.1–0.2 mg 3 times daily	Hypovolemia	Hyponatremia, headache, edema	Only for occasional use; must monitor blood sodium
Erythropoietin	2,000–3,000 IU subcutaneously 1–3 times per week	Hypovolemia	High cost, requires injection, risk of vascular complications	Reserved for patients with symptoms refractory to more common treatments
Heart rate-lowering agents				
Propranolol	10–20 mg 3–4 times daily	All	Hypotension, fatigue, drowsiness, wheezing	Not well tolerated at higher dosages
Ivabradine	5–7.5 mg twice daily	All	Palpitations, headache, dizziness, constipation	
Central nervous system sympatholytics				
Clonidine	0.05–0.2 mg twice daily	Hyperadrenergic	Mental clouding, fatigue, drowsiness, constipation	Can be associated with rebound hypertension and tachycardia
Methyldopa	125 mg once or twice daily	Hyperadrenergic	Hypotension, fatigue, headache, drowsiness, constipation	Rare lupus-like syndrome reported
Other drugs				
Midodrine	5–15 mg every 4 hours, 3 times daily only	Neuropathic	Hypertension, goose bumps, urinary retention	Not recommended for use within 4-5 hours of sleep
Pyridostigmine	30–60 mg 3 times daily	All	Abdominal cramping, diarrhea, increased sweating	May increase gastrointestinal motility
Droxidopa	100–600 mg 3 times daily	All	Nausea, palpitations, urinary symptoms	May worsen tachycardia
Modafinil	100–200 mg twice daily	"Brain fog"	Headache, dizziness, anxiety, insomnia	May improve cognitive symptoms

static tachycardia is not itself reduced.[22] Nevertheless, it may significantly improve POTS symptoms refractory to more common methods of treatment, and it should be reserved for such cases. In addition to the lack of effect on orthostatic tachycardia, drawbacks to using erythropoietin include its high cost, the need for subcutaneous administration, and the risk of life-threatening complications such as myocardial infarction and stroke.[58,59]

Heart rate-lowering agents

Propranolol, a nonselective beta-adrenergic antagonist, can significantly reduce standing heart rate and improve symptoms at low dosages (10–20 mg). Higher dosages can further restrain orthostatic tachycardia but are not as well tolerated, mainly due to hypotension and worsening of existing symptoms such as fatigue.[60] Regular-acting propranolol works for about 4 to 5 hours per dose, so full-day coverage often requires dosing 4 times per day.

Ivabradine is a selective blocker of the "funny" (I_f) channel that reduces the sinus node firing rate without affecting blood pressure, so it slows heart rate without causing supine hypertension or orthostatic hypotension.

A retrospective case series found that 60% of patients with POTS treated with ivabradine reported symptomatic improvement, and all patients experienced reduced tachycardia with continued use.[61] Ivabradine has not been compared with placebo or propranolol in a randomized controlled trial, and it has not been well studied in pregnancy and so should be avoided because of potential teratogenic effects.

When prescribing ivabradine for women of childbearing age, a negative pregnancy test may be documented prior to initiation of therapy, and the use of highly effective methods of contraception is recommended. Ivabradine should be avoided in women contemplating pregnancy. Insurance coverage can limit access to ivabradine in the United States.

Central nervous system sympatholytics

Patients with prominent hyperadrenergic features may benefit from central sympatholytic agents. However, these drugs may not be well tolerated in patients with neuropathic POTS because of the effects of reduced systemic vascular resistance[5] and the possible exacerbation of drowsiness, fatigue, and mental clouding.[4] Patients can be extremely sensitive to these medications, so they should initially be prescribed at the lowest dose, then gradually increased as tolerated.

Clonidine, an alpha-2-adrenergic agonist, decreases central sympathetic tone. In hyperadrenergic patients, clonidine can stabilize heart rate and blood pressure, thereby reducing orthostatic symptoms.[62]

Methyldopa has effects similar to those of clonidine but is easier to titrate owing to its longer half-life.[63] Methyldopa is typically started at 125 mg at bedtime and increased to 125 mg twice daily, if tolerated.

Other agents

Midodrine is a prodrug. The active form, an alpha-1-adrenergic agonist, constricts peripheral veins and arteries to increase vascular resistance and venous return, thereby reducing orthostatic tachycardia.[52] It is most useful in patients with impaired peripheral vasoconstriction (eg, neuropathic POTS) and may be less effective in those with hyperadrenergic POTS.[64] Major limitations of midodrine include worsening supine hypertension and possible urinary retention.[39]

Because of midodrine's short half-life, frequent dosing is required during daytime hours (eg, 8 AM, noon, and 4 PM), but it should not be taken within 4 to 5 hours of sleep because of the risk of supine hypertension. Midodrine is typically started at 2.5 to 5 mg per dose and can be titrated up to 15 mg per dose.

Midodrine is an FDA pregnancy category C drug (adverse effects in pregnancy seen in animal models, but evidence lacking in humans). While ideally it should be avoided, we have used it safely in pregnant women with disabling POTS symptoms.

Pyridostigmine, an acetylcholinesterase inhibitor, increases cardiovagal tone and possibly sympathetic tone. It has been reported to significantly reduce standing heart rate and improve symptom burden in patients with POTS.[65] However, pyridostigmine increases gastrointestinal mobility, leading to severe adverse effects in over 20% of patients, including abdominal cramps, nausea, and diarrhea.[66]

Droxidopa, a synthetic amino acid precursor of norepinephrine, improves dizziness and fatigue in POTS with minimal effects on blood pressure.[67]

Modafinil, a psychostimulant, may improve POTS-associated cognitive symptoms.[4] It also raises upright blood pressure without significantly worsening standing heart rate or acute orthostatic symptoms.[68]

POTS rarely resolves without ongoing treatment

EFFECTS OF COMORBID DISORDERS ON MANAGEMENT

Ehlers-Danlos syndrome

Pharmacologic approaches to POTS should not be altered based on the presence of Ehlers-Danlos syndrome, but because many of these patients are prone to joint dislocation, exercise prescriptions may need adjusting.

A medical genetics consult is recommended for patients with Ehlers-Danlos syndrome. Although the hypermobile type (the form most commonly associated with POTS) is not associated with aortopathy, it can be confused with classical and vascular Ehlers-Danlos syndromes, which require serial aortic screening.[30]

Mast cell activation syndrome

Consultation with an allergist or immunologist may help patients with severe symptoms.

Autoantibodies and autoimmunity

Treatment of the underlying disorder is recommended and can result in significantly improved POTS symptoms.

SPECIALTY CARE REFERRAL

POTS can be challenging to manage. Given the range of physiologic, emotional, and functional distress patients experience, it often requires significant physician time and multidisciplinary care. Patients with continued severe or debilitating symptoms may benefit from referral to a tertiary-care center with experience in autonomic nervous system disorders.

PROGNOSIS

Limited data are available on the long-term prognosis of POTS, and more studies are needed in pediatric and adult populations. No deaths have been reported in the handful of published cases of POTS in patients older than 50.[1] Some pediatric studies suggest that some teenagers "outgrow" their POTS. However, these data are not robust, and an alternative explanation is that as they get older, they see adult physicians for their POTS symptoms and so are lost to study follow-up.[6,44,69]

We have not often seen POTS simply resolve without ongoing treatment. However, in our experience, most patients have improved symptoms and function with multimodal treatment (ie, exercise, salt, water, stockings, and some medications) and time.

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