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Postural Orthostatic Tachycardia Syndrome: Mechanisms and New Therapies

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Abstract

Postural orthostatic tachycardia syndrome (POTS) is a clinically heterogeneous disorder with multiple contributing pathophysiologic mechanisms manifesting as symptoms of orthostatic intolerance in the setting of orthostatic tachycardia (increase in heart rate by at least 30 beats per minute upon assuming an upright position) without orthostatic hypotension. The three major pathophysiologic mechanisms include partial autonomic neuropathy, hypovolemia, and hyperadrenergic state. Patients often will exhibit overlapping characteristics from more than one of these mechanisms. The approach to the treatment of POTS centers on treating the underlying pathophysiologic mechanism. Stockings, abdominal binders, and vasoconstrictors are used to enhance venous return in partial neuropathic POTS. Exercise and volume expansion are the main treatment strategies for hypovolemic POTS. For hyperadrenergic POTS, beta-blockers and avoidance of norepinephrine-reuptake inhibitors is important. Attempts should be made to discern which pathophysiologic mechanism(s) may be afflicting patients so that treatment regimens can be individualized.

INTRODUCTION

Postural orthostatic tachycardia syndrome (POTS) is a clinically heterogeneous disorder characterized by a constellation of symptoms that include, but are not limited to, palpitations, presyncope, mental clouding, nausea, anxiety, fatigue, blurry vision, and dyspnea, after assuming an upright position (1, 2). These symptoms improve with recumbency, and this phenomenon must persist for at least 3–6 months in the absence of chronic conditions or medications that promote orthostatic intolerance. The severity of the symptoms is highly variable and can run the spectrum of mildly bothersome to outright debilitating (3). Although the exact prevalence of this condition is unknown, POTS has been considered the most common disorder seen in autonomic specialty clinics and is estimated to affect between 0.5–3 million individuals in the United States (4, 5). The majority (>90%) of POTS patients are young, white women of childbearing age (2).

Though the nature and severity of symptoms widely vary among POTS patients, the *sine qua non* of POTS diagnosis rests on a cardinal hemodynamic finding—an increase in heart rate by at least 30 beats per minute (bpm) on assuming an upright position in the absence of orthostatic hypotension—that was first described in 1988 in a subset of patients with orthostatic intolerance undergoing lower-extremity blood plethysmography studies (6). This is a striking hemodynamic finding that is not psychogenic (7). Despite this discovery 30 years ago, an all-inclusive, pathophysiologic mechanism for this rather prevalent syndrome remains elusive (8). The reason behind this will be explored, along with its implications for the treatment and management of this syndrome.

PATHOPHYSIOLOGY

POTS should not be considered a disease but a clinical syndrome or phenotype, with the aforementioned signs (orthostatic tachycardia) and symptoms that worsen and improve with posture change. Thus far, the literature has identified three different pathophysiologic mechanisms that are capable of manifesting the POTS phenotype: (*a*) partial autonomic neuropathy, (*b*) persistent predilection for hypovolemia, and (*c*) central hyperadrenergic state. These three pathophysiologic mechanisms engender somewhat distinct variants of the POTS phenotype that henceforward will be referred to as endophenotypes (4). While many conditions, such as mast cell activation disorders (9), Ehlers-Danlos Syndrome (10, 11), deconditioning (12), and genetic mutations of norepinephrine transporters (13) coexist with POTS, their downstream effects also funnel into these three principal pathophysiologic mechanisms. These three endophenotypes and how they relate to comorbidities commonly observed in POTS are discussed below (**Figure 1**).

Neuropathic POTS (Partial Autonomic Neuropathy)

There is much evidence in the literature suggesting preferential autonomic neuropathy in certain vascular beds promoting blood stasis in the pelvic, splanchnic, and lower extremities. Stewart et al. (14–17) noted that pediatric patients with POTS had excessive pooling of blood in the lower extremities, primarily due to arteriolar dysregulation rather than inappropriately increased venous capacitance. Jacob et al. (18) demonstrated significantly impaired sympathetic nervous system activity in the lower extremities of POTS patients. Amounts of norepinephrine released at sympathetic nervous system synapses in the lower extremities in response to a cold pressor test, a nitroprusside infusion, and tyramine infusion were markedly lower in POTS patients than in healthy controls. In contrast, the amounts of norepinephrine released in the upper extremities in response to the same stimuli were no different between POTS patients and healthy controls. Another interesting finding is that POTS patients demonstrate an exaggerated

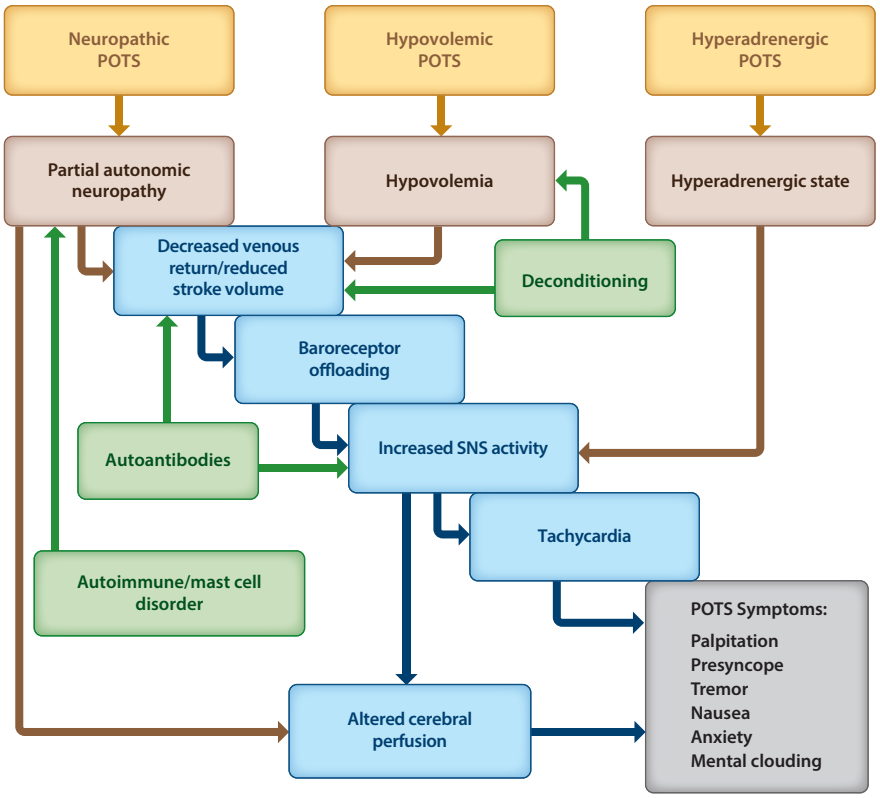

Figure 1

Pathophysiologic mechanisms of postural orthostatic tachycardia syndrome (POTS). Three primary endophenotypes of POTS are listed at the top (*gold boxes*) with their respective pathophysiologic mechanisms below (*brown boxes*) leading to signs and symptoms of POTS (*gray box*). The pathophysiology of neuropathic and hypovolemic POTS converges with decreased venous return and reduced stroke volume (*topmost blue box*) before cascading down toward baroreceptor unloading, increased sympathetic nervous system (SNS) activity, tachycardia, and altered cerebral perfusion (*subsequent blue boxes*). The pathophysiology of hyperadrenergic POTS merges with the cascade at the increased SNS activity phase. Common comorbidities associated with POTS (deconditioning, autoimmune disorders, and autoantibodies; *green boxes*) are depicted entering the cascade at various entry points, all eventually leading to the POTS phenotype (*gray box*).

vasoconstrictive response to locally administered norepinephrine in the lower extremities, suggestive of a functionally denervated or depleted postganglionic state at baseline (19).

The extent of partial autonomic neuropathy extends beyond the lower extremities into the pelvic and splanchnic circulation. Both Doppler ultrasound and plethysmography studies have demonstrated abnormally increased blood flow and pooling in the splanchnic and pelvic circulation of POTS patients both at rest and in an upright position (20–24). Other studies have also demonstrated that POTS patients have significantly greater decreases in thoracic and cerebral blood flow when compared to healthy controls during tilt (21, 23, 25–27). Taken altogether, these observations suggest that excessive blood pooling likely occurs below the level of the thorax in POTS patients when assuming an upright position.

The patients with this particular endophenotype of POTS commonly exhibit acrocyanosis, a marked darkening in skin hue with standing. Medow et al. (28) found defective cutaneous vasodilation of the microvasculature mediated by nitric oxide with local heating in POTS patients versus

healthy control subjects. This cutaneous vasodilation is mediated by nitric oxide, as the addition of a nitric oxide synthase inhibitor blunts the vasodilation in both POTS patients and healthy controls to the same degree. Neuronal nitrous oxide synthase, and not endothelial nitrous oxide synthase, was determined to be responsible for causing this phenomenon (29).

A significant proportion of patients with Ehlers-Danlos syndrome exhibit autonomic dysfunction and orthostatic intolerance (11). De Wandele et al. (30) performed autonomic function testing in 39 patients with Ehlers-Danlos syndrome and found that orthostatic intolerance was much more common in this population. This intolerance primarily manifests as excessive orthostatic tachycardia and reduced QSART (cholinergic sympathetic nerve sweat testing) responses when compared to those of healthy controls (30).

Mast cell activation disorders are another condition that frequently coexists with POTS (9). Mast cell degranulation causes a variety of vasoactive substances (histamine, prostaglandins, platelet-activating factor) to be released into the circulation, potentially causing excessive vasodilation and blood pooling in the lower extremities (31). This may also be associated with an inflammatory neuropathy. These patients commonly complain of excessive flushing, abdominal cramping, and diarrhea in addition to the more traditional presyncopal symptoms experienced by POTS patients (9). Evidence of autoantibodies that act as partial alpha-1 antagonists have also been found in POTS patients (32). These could have an effect similar to a partial autonomic neuropathy due to inadequate vasoconstriction in response to alpha-adrenergic stimulation (**Figure 1**).

Hypovolemic POTS

A significant portion of POTS patients suffer from a state of persistent hypovolemia. Studies have shown that some POTS patients have 13–22% less plasma or blood volume than do healthy controls (33–35). Despite these low blood and plasma volumes, plasma renin activity and aldosterone levels are also inappropriately low in POTS patients. This phenomenon has been referred to as the "renin-aldosterone paradox" (34, 35). Additionally, the aldosterone:renin ratio was found to be lower in POTS patients than in healthy control subjects (34).

Further investigations into the renin-angiotensin aldosterone system (RAAS) revealed that plasma angiotensin 2 (Ang-II) levels in some POTS patients are elevated (on the order of 2–3 times higher) when compared to healthy controls (35, 36). Ang-II is the major effector of the RAAS axis, causing systemic vasoconstriction, raising blood pressure, and promoting fluid retention, and it is critical for maintaining fluid balance homeostasis through aldosterone secretion. Despite their high Ang-II levels, POTS patients are paradoxically prone to hypovolemia (37). One explanation would be that POTS patients respond differently to Ang-II. This is supported by the finding that POTS patients have an attenuated hypertensive response to Ang-II versus healthy control subjects after infusion of a standardized dose of Ang-II (38).

Deconditioning is an important comorbidity observed in this endophenotype of POTS patients due to the prevalence of hypovolemia in deconditioned patients. Levine et al. (39) demonstrated that in six previously healthy male astronauts, just 16 days of spaceflight resulted in a decrease in blood volume of nearly 6% (39). Another study in 18 cosmonauts, who had spent several months on a space station, demonstrated that previously healthy individuals can experience moderate hemodynamic changes that almost meet some POTS criteria (average orthostatic heart rate increase by 26 bpm in the absence of orthostatic hypotension), with one individual meeting the orthostatic tachycardia criterion (heart rate increase by 31 bpm), despite undergoing regular cardiovascular exercise during spaceflight (40). Under normal gravitational conditions, two weeks of strict bedrest resulted in a 17% reduction in plasma volume and a near 10% reduction in stroke volume (41). The decrease in stroke volume, as predicted by the Starling

curve, was out of proportion to the degree of plasma volume reduction (41). This finding suggests that deconditioning, with its subsequent plasma volume reduction and decreased stroke volume, may play a significant role in the development of a POTS phenotype (42). Given the common overlapping theme of hypovolemia in these two conditions, it is unclear if deconditioning alone can cause hypovolemic POTS or simply unmask it in certain vulnerable individuals, such as those with an inherently dysregulated RAAS axis, since the vast majority of individuals with imposed bedrest do not develop this clinical syndrome.

Regardless, the renin-aldosterone paradox and dysregulation of RAAS play a central role in the pathogenesis of this POTS endophenotype, and clearly would be worsened in the setting of any deconditioning, either voluntary or imposed.

Hyperadrenergic POTS

Hyperadrenergic POTS is an important endophenotype of POTS with the characteristic, neurohormonal hallmark of elevated upright plasma norepinephrine (34, 36). In this endophenotype, the predominant symptom is palpitations due to orthostatic tachycardia that is primarily driven by a hyperadrenergic state.

In healthy subjects, the supine plasma norepinephrine level is approximately 200 pg/ml, and upon standing, it doubles before it plateaus after 7.5 min (43). Supine levels of norepinephrine are similar between healthy controls and POTS patients (34). However, levels of norepinephrine in POTS patients can increase more than threefold, exceeding 800 pg/ml in many cases, while the increase in healthy controls after assuming an upright position is much more modest at approximately 400–500 pg/ml (36, 43). Levels of plasma epinephrine appear to be similar between POTS patients and healthy subjects (34, 36). Although this elevated norepinephrine state may be secondary to partial autonomic neuropathy or hypovolemia, the hallmark of this endophenotype is primary adrenergic excess. This is epitomized by a subset of patients who have adrenergic autoantibodies or dysregulation of norepinephrine metabolism, either of which may serve as the primary driver of an overactive sympathetic nervous system (13, 32).

Higher levels of autoantibodies against beta-1 and beta-2 adrenoreceptors have been detected in POTS patients versus healthy controls in serologic studies (32, 44). The binding of these autoantibodies to the adrenergic receptors is postulated to drive the tachycardia in some POTS patients (32). Fedorowski et al. (44) demonstrated that these autoantibodies, in addition to acting like a direct beta-agonist, can also upregulate sympathetic nervous activity through allosteric interactions with the beta-receptors. This group also demonstrated that autoantibody affinity toward beta-receptors positively correlated with a greater degree of orthostatic tachycardia (44).

Alteration of norepinephrine metabolism, congenital or iatrogenic, is another well-described cause of hyperadrenergic POTS. Shannon et al. (13) discovered a single missense mutation (ALA457Pro) in the norepinephrine transporter gene (*SLC6A2*) that resulted in a 98% loss of function in the transporter and was present in two identical twins with POTS. Each twin had normal levels of supine plasma norepinephrine (269 pg/ml and 199 pg/ml), but standing plasma norepinephrine exceeded 900 pg/ml. One of the twins even became hypertensive with standing (13). Another study demonstrated that epigenetic modification of the *SCL6A2* gene resulting in its downregulation was more prevalent in POTS patients than in healthy controls (45).

Iatrogenic inhibition of the norepinephrine transporter has also been shown to engender a POTS-like state, increase upright heart rate, and exacerbate symptoms in POTS patients (46–49). Administration of reboxetine, a norepinephrine transporter inhibitor, to healthy controls provoked hemodynamic changes consistent with POTS (48). Administration of atomoxetine, a selective norepinephrine reuptake inhibitor (NRI), significantly increased the standing heart rate

(from 105 bpm to 121 bpm) in POTS patients and resulted in greater symptoms of orthostatic intolerance (46). Administration of a selective serotonin reuptake inhibitor (SSRI), sertraline, also appeared to acutely worsen symptoms in POTS patients, possibly due to nonselective inhibition of the norepinephrine transporter (47). Anecdotally, serotonin-norepinephrine reuptake inhibitors (SNRIs) can also worsen tachycardia in POTS.

Overlapping Pathophysiology and Clinical Heterogeneity

POTS patients will sometimes manifest features from more than one of the three major POTS endophenotypes (4). This is likely due to the contribution of multiple pathophysiologic mechanisms to their unique phenotype, resulting in the clinical heterogeneity seen in this syndrome. An all-unifying pathophysiologic mechanism does not exist. POTS may simply be a final common pathway for several interrelated pathophysiologic mechanisms (50).

TREATMENT APPROACHES: INDIVIDUALIZING TREATMENT AND TARGETING PATHOPHYSIOLOGIC MECHANISMS

Over the past 10 years, our knowledge of the treatment of POTS has been advanced considerably by mainly small, but thoughtfully designed, prospective studies. Treatment should be individualized, targeting the underlying pathophysiologic mechanism or mechanisms that affect each patient with POTS. Treatments can be broadly categorized as nonpharmacologic or pharmacologic interventions (**Table 1**).

Treatment for Partial Autonomic Neuropathy

Interventions to treat the neuropathic POTS endophenotype promote venous return by either applying external compression (wearing compression stockings, voluntary muscle contractions, etc.) or enhancing vasoconstriction in the vascular beds of the lower extremities.

Nonpharmacologic interventions. Several nonpharmacologic strategies can be employed to improve venous pooling in the splanchnic, pelvic, and lower extremity circulation (51). Graded compression garments and abdominal binders have improved symptoms of orthostatic intolerance in conditions associated with excessive blood pooling (52, 53). The combination of abdominal binders and lower extremity compression stockings is thought to be more effective than lower extremity compression alone due to the disproportionally greater volume in the splanchnic circulation than in the legs (51). In a study of patients with autonomic failure, abdominal compression of 40 mmHg was as effective as midodrine (53).

Other nonpharmacologic interventions include lower extremity strength training to promote skeletal muscle hypertrophy, which can augment venous blood return, and also performing certain maneuvers (leg crossing, muscle tensing, and muscle pumping) when it is inconvenient to sit or lie down (51).

Pharmacologic interventions. Midodrine, an orally active alpha-1 agonist, is the mainstay of pharmacologic treatment for neuropathic POTS. Administration of 5–10 mg doses acutely reduced both supine and upright heart rate (from 108 bpm to 95 bpm) in 13 patients with POTS. Moreover, this dose did not cause hypertension nor significantly elevate blood pressure in this patient population (54). Time to peak concentration is 1 h after administration, and pharmacologic effects last 4–5 h (55). Midodrine should be administered only in the daytime, and redosed every

Table 1 Interventions for POTS endophenotypes

Endophenotype	Intervention	Dose (70) and/or notes	Pharmacologic or nonpharmacologic
Neuropathic POTS	Stockings (52)	Pantyhose style; target is 30–40 mm Hg	Nonpharmacologic
	Abdominal compression (53)	None	Nonpharmacologic
	Lower extremity maneuvers to augment venous blood return (51)	Leg crossing, muscle tensing, tiptoeing	Nonpharmacologic
	Midodrine (54)	2.5–15 mg orally q4h (t.i.d.) Lasts 4–5 h per dose	Pharmacologic
	Octreotide (59)	50–100 mcg subcutaneously t.i.d. Needs to be refrigerated and injected	Pharmacologic
Hypovolemic POTS	Exercise (42)	Primarily nonupright aerobic training with some leg resistance	Nonpharmacologic
	Fluid hydration (51)	Target 3 L per day	Nonpharmacologic
	High-sodium diet (66)	Target 8–10 g NaCl per day Measuring out teaspoons of NaCl can help	Nonpharmacologic
	Fludrocortisone (67)	0.1–0.2 mg orally once daily Monitor for hypokalemia	Pharmacologic
	Desmopressin (69)	0.2 mg orally as needed Monitor for hyponatremia	Pharmacologic
Hyperadrenergic POTS	Avoiding NRIs, SSRIs, or SNRIs (46, 47, 49)	These drugs can worsen tachycardia and/or symptoms in some patients	Nonpharmacologic
	Propranolol (78)	10–20 mg orally q.i.d. Higher doses can be less effective; maybe more effective in those with higher upright heart rates	Pharmacologic
	Bisoprolol (77)	2.5–5 mg orally once daily (77)	Pharmacologic
	Metoprolol (79)	0.5–1 mg/kg orally b.i.d. (79)	Pharmacologic
	Pyridostigmine (80)	30–60 mg orally t.i.d. Side effects: flatulence, diarrhea, cramping	Pharmacologic
	Methyldopa (70)	125–250 mg orally at bedtime or b.i.d. Start at 125 mg at bedtime and titrate slowly	Pharmacologic
	Ivabradine (83)	2.5 mg orally once daily or b.i.d., up to 10 mg orally b.i.d.	Pharmacologic

Abbreviations: b.i.d., twice daily; NRI, norepinephrine reuptake inhibitor; POTS, postural orthostatic tachycardia syndrome; q4h, every four hours; q.i.d., four times daily; SNRI, selective norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; t.i.d., three times daily.

4–5 h during periods of the day when the patient is upright. Not surprisingly, midodrine has been shown to be more effective in treating neuropathic POTS than hyperadrenergic POTS (56).

Other vasoconstrictors that have been studied in neuropathic POTS patients include octreotide and droxidopa. Droxidopa is an orally active, synthetic prodrug of norepinephrine that reaches peak plasma concentration in 2 h (57). It has not been well studied prospectively, and a retrospective analysis demonstrated only modest improvement in symptoms (58). Octreotide, a subcutaneously injectable somatostatin analog that causes vasoconstriction in the splanchnic vascular bed, has also been studied in POTS patients (59). While it can reduce orthostatic tachycardia in

POTS patients to a similar extent as midodrine, it lacks a widely available oral dosage form and must be administered subcutaneously (60, 61).

Treatment for Hypovolemic POTS

A persistently hypovolemic state exists in hypovolemic POTS; therefore, treatment centers on augmenting plasma volume. Both nonpharmacologic and pharmacologic interventions exist, and exercise has been shown to be the most enduring solution to augment plasma volume.

Nonpharmacologic interventions. The mainstay of nonpharmacologic treatment of hypovolemic POTS is aerobic reconditioning training (42, 51). POTS patients who participated and completed 3 months of exercise training garnered a significant reduction in orthostatic tachycardia and experienced significant increases in blood volume (42). In fact, 50–70% of POTS patients who complete 3 months of endurance training exhibit hemodynamic changes that no longer meet criteria for POTS (42, 62, 63). Exercise is the only intervention that has been shown to improve the aldosterone:renin ratio and increase plasma and blood volumes chronically (64). Unfortunately, only 41% of POTS patients in the community setting are able to complete a standardized 3-month program involving mild–moderate intensity endurance training 3–5 times per week at 30–45 min per session (63). As adherence is a significant issue with this intervention, it is paramount that patients start out with a recumbent or semi-recumbent form of exercise (rowing, swimming, or recumbent biking) (65).

It is important that POTS patients be very vigilant with regard to oral fluid intake. We often advise POTS patients to drink up to 3 L of water daily to stay adequately hydrated (51). This is difficult, if not impossible, for some patients to accomplish, but the clinician must be a source of encouragement and positive reinforcement for the patient during this process. One small prospective study demonstrated that, in POTS patients, six consecutive days of a low-sodium diet (10 mEq/day) resulted in significantly greater orthostatic tachycardia than six consecutive days of a high-sodium diet (300 mEq/day), highlighting the importance of sodium intake (66). Thus, salt intake should be increased gradually in POTS patients, up to 10 g NaCl daily. Salt tablets should be avoided if possible, as the acutely increased osmotic load can cause gastrointestinal symptoms (51). Acute infusions of normal saline have been shown to afford rapid relief in patients with POTS crisis (8, 54), but this approach is not sustainable in the long-term due to the potential for vascular access complications (67).

Pharmacologic interventions. Augmenting plasma volume can also be accomplished with a number of pharmacologic agents. Fludrocortisone, a synthetic aldosterone analog that causes sodium retention, is considered the mainstay pharmacologic agent for volume expansion in patients with orthostatic intolerance and hypotension (68). However, its use in POTS is not well studied. Doses should be titrated slowly (up to a daily dose of 0.2 mg) with serum potassium measurements one week after every dose increase.

Agents that antagonize aldosterone, such as spironolactone, should be discontinued before initiating fludrocortisone (3). Drosperinone is a progesterone agent in some oral contraceptives that is also a spironolactone analogue, and this should be avoided in POTS patients.

Desmopressin (DDAVP), an orally available synthetic analog of arginine vasopressin, is another volume expansion agent used in POTS patients. The short-term administration of oral DDAVP and water to POTS patients resulted in standing heart rates significantly lower than that after placebo administration (69). Patients also noted significant improvements in overall symptoms, specifically symptoms related to vision, tremulousness, and palpitations (69). DDAVP doses of

0.1–0.2 mg taken once daily are typical for POTS patients. Patients should be cautioned about the danger of hyponatremia when taking DDAVP and increase their daily intake of salt to mitigate this risk (70). DDAVP can also be used intermittently as a "special event" drug, allowing for optimized blood volume during specific preplanned events (e.g., going to a movie or a wedding).

A less studied and less commonly used agent for volume expansion is erythropoietin. Erythropoietin does not appear to improve the orthostatic tachycardia of POTS (71, 72), but it did improve symptoms, at the expense of elevating blood pressure, in one study of treatment-refractory POTS patients (72). Lack of strong data and the high expense of erythropoietin limit its routine use in the treatment of POTS.

Although midodrine does not directly expand plasma volume, it has been shown to be quite efficacious in treating hypovolemic POTS. Higher levels of plasma copeptin, a peptide fragment of arginine vasopressin, which is a neurohormonal marker for relative hypovolemia, has been shown to positively correlate with treatment response to midodrine in POTS patients (73).

Treatment for Hyperadrenergic POTS

As mentioned previously, a state of hyperadrenergic POTS can be provoked with certain medications. In addition to curbing the sympathetic nervous system with pharmacologic agents, it is important to recognize that certain classes of drugs can worsen or even precipitate this condition and discontinue them whenever possible.

Nonpharmacologic interventions. Withdrawing medications that can worsen POTS symptoms is the key nonpharmacologic strategy for patients with hyperadrenergic POTS. Two classes of antidepressants in particular, SSRIs and SNRIs, have been shown to worsen symptoms in POTS patients, perhaps by altering norepinephrine metabolism (46, 47). Given the high incidence of polypharmacy in POTS patients (10), coupled with the perception of increased depression in POTS patients (74), antidepressant use is likely high in this patient population. However, the benefits and risks of all psychoactive agents that may augment sympathetic autonomic tone must be carefully considered in patients with POTS, especially in light of studies that suggest the true prevalence of psychiatric disorders in this patient population may be no different than in the general population (75). Therefore, we advocate the discontinuation of SSRIs, SNRIs and NRIs for patients in whom demonstrable benefits do not clearly outweigh the risks of these agents.

The potentially detrimental effects of SSRIs and SNRIs are also important to keep in mind during a therapeutic trial of any drug for POTS as an SSRI or SNRI may unknowingly and concomitantly be initiated by another prescriber for clinically significant major depressive disorder. In this instance, the patient may report feeling worse at follow-up, but the source of this complaint must be carefully assessed to avoid falsely attributing treatment failure to the trial agent, which may turn out to be an efficacious and valuable intervention while the culprit may be the SSRI or SNRI.

Pharmacologic interventions. The fundamental pharmacologic approach to hyperadrenergic POTS treatment is suppression of the sympathetic nervous system or augmentation of parasympathetic nervous activity. The mainstay of sympathetic nervous system suppression is beta-blockers. Those investigated in prospective studies include metoprolol, propranolol, and bisoprolol (76–79). Raj et al. (78) demonstrated that the use of propranolol (instant release) at a 20 mg dose significantly reduced orthostatic tachycardia, and improved symptoms compared to placebo up to 4 h after administration. In contrast, Fu et al. (64) showed that the long-acting, once-daily formulation of propranolol did not improve quality of life at one month. Zhao et al. (79) demonstrated that

POTS patients with low copeptin levels were far more likely to respond to metoprolol than those with high levels of copeptin, presumably due to a greater contribution of the hyperadrenergic endophenotype to their syndrome.

Working on the other limb of the autonomic nervous system spectrum, pyridostigmine has been shown to improve orthostatic tachycardia in POTS patients. Pyridostigmine enhances cholinergic activity at both the ganglionic nicotinic and the postganglionic muscarinic acetylcholine receptors, with a likely net increase in parasympathetic nervous system tone (3). In a study of 17 POTS patients, symptoms and standing heart rate were significantly reduced after pyridostigmine administration versus placebo in the acute setting (80). Supine and upright blood pressures were no different between the group that received pyridostigmine and the placebo group. Further studies have also demonstrated long-term benefits with using pyridostigmine in POTS patients (81, 82). The main limitation of pyridostigmine's use is adverse gastrointestinal effects, which can include diarrhea, cramping, nausea, vomiting, and flatulence (70). Pyridostigmine is usually well tolerated in patients prone to constipation. A large randomized prospective study demonstrated that propranolol, bisoprolol, propranolol + pyridostigmine, and bisoprolol + pyridostigmine all resulted in improvements in the Orthostatic Intolerance questionnaire, Beck depression inventory, and the physical component of the SF-36 (77).

Ivabradine could treat POTS via a novel mechanism, selectively inhibiting the I_f sodium channel, thereby reducing heart rate without affecting the sympathetic nervous system (83). Small case series have shown that ivabradine reduces upright heart rate and improves symptoms associated with orthostatic intolerance (83, 84). In these studies, doses were initiated at 2.5 mg orally once or twice daily, and titrated up to 10 mg twice daily based on response or side effects with response rates between 60% and 78% (83, 84). However, in the absence of a prospective comparator study, ivabradine should not be considered a first-line therapy drug (85).

Central-acting sympatholytic agents, such as clonidine and methyldopa, have also been used in POTS patients and likely work by decreasing central sympathetic nerve traffic. They have not been well studied in this population, but a small prospective study of patients who failed beta-blockers demonstrated reductions in upright norepinephrine levels and increased plasma volume by 12% on doses of clonidine 0.3–0.4 mg/day (86). Their use in POTS patients is primarily limited by fatigue and brain fog (70). Oral clonidine has a short half-life and can cause a rapid onset–rapid offset phenomenon in some patients. Methyldopa has a longer half-life than oral clonidine and is often better tolerated by POTS patients.

Modafinil, an agent that is used to treat narcolepsy and promote wakefulness, can sometimes help with fatigue in POTS patients. Kpaeyeh et al. (87) demonstrated that modafinil 100 mg did not significantly increase the acute supine or upright heart rate in POTS patients compared to placebo.

CONCLUSION

POTS continues to pose challenges, from both a diagnostic and a therapeutic standpoint, for clinicians across multiple specialties (cardiology, neurology, autonomic specialists) who care for these patients. Patients often report significant delays in diagnosis, exceeding five years between the onset of symptoms and eventual diagnosis in many cases. Many also report encountering initial skepticism during presentation, being given an incorrect psychiatric diagnosis, and having seen more than ten doctors before the correct diagnosis was made (2). Improving clinician awareness can help improve all of these shortcomings (4).

The clinically heterogeneous nature of POTS makes management inherently difficult. In certain cases, it may be possible to recognize key endophenotypes (13, 73, 79). In other more

heterogeneous cases, attempts should be made to discern and possibly quantify a degree of contribution from each endophenotype to a patient's presentation, thus making it easier to formulate treatment strategies. Throughout the entire process, clinicians must demonstrate utmost patience and professionalism, show empathy but be firm, and work together with the patient to manage this enigmatic and difficult condition (88).

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