

## Postural Orthostatic Tachycardia Syndrome (POTS): Diagnosis and Management

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### Review Article

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**Abstract:** Postural orthostatic tachycardia syndrome (POTS) is multifactorial clinical syndrome poorly understood but important cause of orthostatic intolerance resulting from cardiovascular autonomic dysfunction. It's defined by an excessive increase in heart rate with assumption of upright posture without orthostatic hypotension. Individuals affected by POTS are mainly young (aged between 15 years and 40 years) and predominantly female. Many overlapping pathophysiologies are behind POTS, including an autonomic neuropathy in the lower body, hypovolemia, hyperadrenergic states, mast cell activation and autoantibodies. Clinically, it's form of chronic orthostatic intolerance associated with a > 6-month history of symptoms (palpitations, dizziness and occasionally syncope) that are relieved by recumbence. POTS have similarities to a number of other disorders, e.g., chronic fatigue syndrome, Ehlers-Danlos Syndrome, vasovagal syncope, and inappropriate sinus tachycardia. We aim in this article to review the characteristics of POTS and outline possible pathophysiological mechanisms of this syndrome, as well as current and investigational treatments.

**Keywords:** Postural orthostatic tachycardia syndrome; autonomic nervous system.

### INTRODUCTION

The first description similar to what is now recognized as POTS was published by Jacob Mendes Da Costa in 1871, during the American Civil War, in which he referred to the disorder as irritable heart syndrome. Known under DaCosta's syndrome or soldier's heart.

This condition was renamed "postural tachycardia syndrome" in 1982 to describe a patient with disabling postural tachycardia without orthostatic hypotension and subsequently recognized as the postural orthostatic tachycardia syndrome, or POTS, by Schondorf and Low in 1993 [1-3]. Though the true prevalence of POTS is unknown, it is estimated that in the USA alone, 500,000 to 3,000,000 individuals report being affected with POTS, occurring most commonly between the ages of 15 to 50 years with a female to male ratio of 4-6:1 [1,4].

POTS is defined as a sustained heart rate increase of 30 bpm or increase of heart rate to 120 bpm within the first minutes of standing upright without significant orthostatic hypotension (OH). It is suspected in the presence of more than 6 months history of symptoms ranging from mild orthostatic dizziness to

marked limitation of activity and multi-systemic signs of autonomic dysfunction [1,5]. It is thought that there is no single mechanism explaining the clinical presentation of POTS and that this syndrome is pathophysiologically complex and heterogenous [1,5,6].

### Normal hemodynamic physiology of standing:

When supine, up to 30% of the blood volume is in the thorax. With assumption of upright posture, 300-800 mL of blood is gravitated downwards from the thorax into the abdomen and lower extremities and from the vasculature into the interstitial space. Most of this pooling into lower limb veins occurs within 10 s. The decrease in circulating blood volume stimulates compensatory physiological adjustments that are impaired with hypovolemia and POTS. This causes a decrease in venous return to the right side of the heart with a subsequent transient decline in both cardiac

filling and arterial pressure and a decrease in stroke volume. Arterial baroreceptors (carotid sinuses and the aortic arch) and cardiopulmonary mechanoreceptors (heart and lung) detect a reduction in pulse pressure and stroke volume. Compensatory sympathetic activation and reduced parasympathetic nervous system output increase HR and vascular tone. 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 [4,7]. In a condition of resting hypovolemia, the body cannot adequately compensate for the orthostatic decrease in blood volume, [8] and upright HR is elevated. [9] 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].

### **Pathophysiology and subtypes of POTS**

POTS is not a disease but rather a clinical syndrome that can result from one or more of heterogeneous and multifactorial underlying disorders when the rise in heart rate remains the “final common pathway”. Its exact mechanisms are not well known, and a number of putative pathophysiologies including autonomic denervation, hypovolemia, hyperadrenergic stimulation, deconditioning, autoimmune, mast cell activation and hypervigilance is thought being behind POTS. Moreover, POTS subtypes often overlap and co-exist in POTS patients, thus that it may be difficult to make the clinical distinction between them in a particular person [4,6,14,15].

### **Neuropathic POTS (Peripheral autonomic denervation)**

Neuropathic POTS was first described when it is believed that impaired sympathetic tone (as measured by norepinephrine spillover) reduces vasoconstriction, leading to venous pooling in the lower limbs and splanchnic beds [15,16]. Sympathetic denervation obstructs compensatory vascular constriction during upright posture, leading to the splanchnic vasculature and lower extremities blood pooling [17,18]. The resulting decrease in venous return leads to the sympathetic activation and tachycardia of POTS [4] but Norepinephrine spillover is not a practical clinical test. Moreover, it was indicated that up to 50% of patients with POTS have a restricted dysautonomic neuropathy of small and distal post ganglionic sudomotor fibers, predominantly of the feet and toes [15]. 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 [4, 19, 20].

### **Hypovolemia and the Renin-Angiotensin-Aldosterone System in POTS**

Blood volume is reduced in up to 70% of patients with POTS [14,15]. A decrease in oxygenation related to the low red blood cell volume could exacerbate symptoms of orthostatic intolerance [4,21]. Another cohort of patients with POTS might not have a hypovolemia but an exaggerated decrease in volume on standing [10]. Normally, the renin-angiotensin-aldosterone system is fundamental for the regulation of blood volume. It is activated by upright posture and by a reduction in blood volume. Plasma renin activity, angiotensin II and aldosterone would be expected to be elevated in POTS in response to the hypovolemia. [4] Paradoxically, some of these patients have low plasma renin activity and aldosterone levels compared with healthy subjects. This is a low-flow sub type with inappropriately high angiotensin II levels. 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 [14,15].

### **Central Hyperadrenergic POTS**

The elevated sympathetic tone is more common as a secondary mechanism in patients with POTS who have hypovolaemia or peripheral sympathetic denervation, but it can also be the primary underlying problem [22,14]. This manifestation, occurring in up to 50 % of patients, is associated with systolic blood pressure increases of 10 mmHg while standing upright for 10 minutes and plasma norepinephrine levels 600 pg/mL while standing [15]. These patients have tachycardia similar to those of other patients with POTS but tend to have prominent sympathetic activation symptoms, such as palpitations, anxiety, tremor, cold and sweaty extremities. [4; 15] 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: during upright posture, norepinephrine >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 [22]. A spectral analysis index of sympathetic function and plasma norepinephrine are sometimes used as criteria for the “hyperadrenergic subtype” of POTS. [4] This hyperadrenergic state in patients with POTS may also be reflected by is An exaggerated sympathetic vasoconstrictor response during the recovery and overshoot phases of the Valsalva maneuver [4, 22].

### **Norepinephrine Transporter Deficiency**

A very rare form of hyperadrenergic POTS is caused by a loss-of-function mutation in the SLC6A2 gene encoding for the norepinephrine transporter (NET) [21, 23]. NET is a clearance transporter for norepinephrine, and this genetic form of NET deficiency leads to increased synaptic norepinephrine

and overall increased sympathetic activity [14]. Pharmacological blockade of the norepinephrine transporter with atomoxetine further exacerbates the heart rate increases and its symptoms in patients with POTS when upright [24]. Some POTS patients (without a mutation) may have decreased expression of NET protein in their peripheral sympathetic nerves, leading to a functional NET deficiency. [4; 14]

### **Physical deconditioning**

Patients with POTS often have poor exercise tolerance and deconditioning [15]. Fatigue and exercise intolerance with reduced stroke volume and reflex tachycardia are typical manifestations of cardiovascular deconditioning as well as POTS [15,19]. However, it's unclear if deconditioning is a primary problem or secondary to POTS. Indeed; due to their disability, many patients with POTS have restrictions on their activity and can become deconditioned over time. Otherwise, an individual can become physically deconditioned secondary to another illness or bed rest and develop a clinical phenotype that resembles POTS. Despite this, many POTS patients do have cardiovascular deconditioning and do benefit from a program of aerobic exercise and resistance training [13].

### **Mast Cell Activation**

Some POTS patients present with severe flushing in addition to their tachycardia with elevated urine methyl histamine concentrations, without autonomic impairment [14]. 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 is cause or consequence of mast cell degranulation [4]. This diagnosis is most often made with an elevated histamine metabolite (>230 µg methylhistamine/g creatinine) in a 4h urine sample started at the onset of a severe flushing spell [4,14]. This urinary analysis may be negative in these patients, since methylhistamine release is episodic and not constant. Plasma tryptase levels and urinary prostaglandin may also be elevated.

### **Autoimmune POTS (Autoantibodies)**

The autoimmune cause of POTS in some patients is suggested since many reports have described the occurrence of POTS following febrile illness, presumably viral and post-vaccine [25-27]. Furthermore, patients with dysautonomia have higher rates of autoimmune disorders such as Hashimoto thyroiditis. Recent evidence has shown the presence of adrenergic and cholinergic receptor antibodies in patients with POTS in patients with cholinergic receptor antibodies, higher titers correlate with the disease severity [25]. Li *et al.* presented evidence from two cohorts of POTS patients for  $\alpha 1$  adrenergic receptor

(AR) autoantibodies acting as partial peripheral receptor antagonists. Activation of these receptors could lead to increased central sympathetic nervous system activity, increased circulating norepinephrine and subsequent exaggerated tachycardia [28]. Fedorowski A *et al.* has shown a strong relationship between adrenergic autoantibodies and POTS which support the concept that allosteric-mediated shifts in the  $\alpha 1$  adrenergic receptor) and  $\beta 1$  adrenergic receptor responsiveness are important in the pathophysiology of postural tachycardia. This model, if validated, would provide concrete support for novel therapeutic approaches against POTS based on immunotherapy [29]. These data suggest an exciting new immune-mediated pathophysiology for Autoimmune POTS patients. However, it remains to be proven and further research is needed to establish clinical significance [4,14].

### **Anxiety and hypervigilance**

Anxiety and somatic vigilance are thought to be the sources of the POTS symptoms since they are significantly higher in patients with POTS. It was attempted to dissect the psychological and physiologic contributions to tachycardia of POTS. Detailed physiologic and psychometric studies showed that although anxiety is commonly present in POTS, the orthostatic tachycardia is due to an underlying physiologic abnormality not to anxiety [15].

### **Expanded pathophysiology of POTS: what's new?**

POTS are a heterogeneous and multifactorial disorder of the autonomic nervous system that can result from multiple overlapping etiologies. Recent studies suggest new potential physiopathological mechanisms of POTS:

#### **Vitamin B1 deficiency**

An increased prevalence of vitamin B12, a vitamin D 25-OH and iron deficiency has been observed in patients with POTS. A small subset of patients with POTS may have vitamin B1 deficiency. Testing for vitamin B1 deficiency and correcting the deficiency is recommended. Further research is necessary to determine the utility and efficacy of vitamin B1 supplementation, as well as other vitamins and supplements commonly used in patients with POTS [30].

#### **Gluten sensitivity**

It was noticed that patients with postural tachycardia syndrome (POTS) were placing themselves on a gluten free diet without medical consultation. POTS patients also had a higher prevalence of self-reported gluten sensitivity (42 vs. 19 %, respectively; odds ratio: 3.1, 95% confidence interval: 2.0–5.0;  $P < 0.0001$ ) compared with age-matched and sex-matched controls. A potential association between gluten-related disorders and POTS is suggested and need to be validated by further prospective studies [31].

### Platelet storage pool deficiency

The data suggest that patients with POTS have significant comorbidities including bleeding symptoms and/or family bleeding histories, and have diminished PL 5HT (serotonin) levels supporting the hypothesis that POTS is a low 5HT level disorder. There was no significant relationship with POTS and d-SPD (delta granule storage pool deficiency). However, these findings establish an additional comorbidity frequently seen in POTS that could explain a number of disparate symptoms often affecting the severity of POTS [32].

### High Serum Resistin levels

Serum resistin levels in children with POTS were significantly higher than those in healthy children and negatively correlated with a change in heart rate from the supine to upright position. These results suggest a protective role of increased resistin in the pathogenesis of POTS [33].

### Epidemiology and natural history of POTS

The prevalence of POTS is approximately 0.2% with up to 3,000,000 Americans are affected with POTS. POTS are also common in patients with chronic fatigue syndrome. Most patients present with POTS between the ages of 15 and 25 years. This demographic is likely to be largely attributable to diagnosis at a relatively young age, but symptoms might also resolve as patients get older. The incidence is higher in women than men with a female to male ratio of 4-6:1 [1, 2, 4, 5, 7]. The chronic and usually systemic symptoms and the frustration caused by the difficulty in obtaining medical help can significantly lower the quality of life. POTS are perceived as a chronic condition with no known mortality, and with eventual improvement. Its course probably varies substantially from patient to patient [1, 3, 4, 15].

### Symptomatology and clinical features of POTS

#### Symptoms

The symptoms associated with POTS are myriad and can be divided into orthostatic and non-orthostatic types. The manifestations of POTS that reflect orthostatic intolerance (POTS in the strict sense) include those of cerebral hypoperfusion and reflex sympathetic activation. Up to one-third of patients may develop secondary orthostatically triggered vasovagal (reflex, neutrally mediated) syncope. The most common symptoms reported in POTS' patients are palpitations, chest discomfort, and shortness of breath, exercise intolerance and dizziness (vertigo) with or without a headache upon standing. [14] There are also many non-specific symptoms such as gastrointestinal symptoms (abdominal pain, nausea, and vomiting) irritable bowel syndrome and Dermatologic symptoms (erythromelalgia, livido reticularis, hives, varicose veins, and Raynaud's phenomenon [34], which often lead to difficulties with diagnosis. For adolescents, it should be noted that POTS symptom presentation may not correlate with the degree of postural tachycardia,

because some adolescents can have postural changes in heart rate normally [35] As in all types of orthostatic intolerance, typical exacerbating factors include heat exposure, physical exertion, heavy meals, prolonged recumbency, menses, and drugs such as diuretics and vasodilators [6; 7] For up to 75% of adolescent patients, POTS symptoms may improve or even disappear by age 21 to 25 years [1].

#### Signs

The cardinal clinical sign in POTS is the presence of an abnormal tachycardia on the assumption of upright posture. Rarer physical signs could be found on patient examination including the acrocyanosis during prolonged standing (40–50%), pupillary dysfunction (1.3%) and signs consistent with a peripheral neuropathy (1.4%). [7]

### Evaluation of suspected POTS

#### Definition

Postural tachycardia syndrome (POTS) is defined as a clinical syndrome that is usually characterized by frequent symptoms that occur with standing such as lightheadedness, palpitations, tremulousness, generalized weakness, blurred vision, exercise intolerance, and fatigue; an increase in heart rate of  $\geq 30$  bpm when moving from a recumbent to a standing position held for more than 30 seconds (or  $\geq 40$  bpm in individuals 12 to 19 years of age); and the absence of orthostatic hypotension ( $>20$  mm Hg drop in systolic blood pressure). The standing (or orthostatic) heart rate of individuals with POTS is often  $\geq 120$  bpm, and undergoes greater increases in the morning than in the evening. The increases in orthostatic heart rate gradually decrease with age and not abruptly at age 20. POTS is a systemic illness, with postural tachycardia one of several criteria. Many patients with POTS faint occasionally, although presyncope is much more common. It is important to note that the diagnoses of POTS and vasovagal syncope are not mutually exclusive [3, 4, 14].

#### Clinical evaluation and diagnosis

The evaluation of a patient suspected of having POTS should include a complete history and physical examination, orthostatic vital signs, and a 12-lead electrocardiogram (ECG) [15].

Selected patients might benefit from a thyroid function test and hematocrit, 24-hour Holter, transthoracic echocardiogram, and exercise stress testing to screen for a potential cardiovascular or systemic etiology [15].

A complete patient history should include assessment of when the symptoms began (cardiac, gastrointestinal, any temperature regulation concerns, or excessive sweating) and symptom progression [1].

The clinical history should focus on defining the chronicity of the condition ( $\geq 6$  months), possible causes of orthostatic tachycardia, modifying factors, impact on daily activities, potential triggers (dehydration, heat, alcohol, and exercise), and detailed family history assessing for the presence of cardiac rhythm disorders or cardiomyopathies [15,35].

Particular attention should be focused on the patient's diet (fluid and caffeine intake), the level of physical activity, sleep pattern, response to previously tried treatments, and the use of medications [1,15].

A thorough physical examination should be undertaken with particular attention to an overall assessment of appearance, color of distal extremities when standing, pupillary size, and any notable changes (including BP measurements) when moving from a sitting to standing position [1].

A full autonomic system review should assess symptoms of autonomic neuropathy. If orthostatic vital signs are normal and the clinical suspicion of POTS is high, a tilt-table test (monitoring for heart rate variability) might be helpful because it can provide vital signs over more prolonged periods than a simple stand test [1, 15].

The tilt table test with heart rate variability is used in diagnosis of suspected POTS. During this test, the adolescent is tilted with the head up around 60 for up to 45 minutes. During the test, patients with POTS will experience an increase in heart rate by at least 40 bpm, but the corresponding blood pressure may remain normal [2,36].

Another measurement used is the stand test, in which the patient's heart rate and blood pressure are measured while supine and then again after standing at 2, 5 and 10 minute intervals, each time observing for puffiness and a purplish discoloration of feet and/or hands. When changes in heart rate and blood pressure are seen in conjunction with a sustained heart rate increase greater than 40 bpm, a diagnosis of POTS is likely [1,2].

For most patients, this minimal approach is sufficient to establish a diagnosis and initiate treatment. However, if the patient's symptoms do not resolve or markedly improve, a more extensive evaluation at a center experienced with the autonomic testing of patients with POTS should be considered.

Autonomic reflexes are usually intact on autonomic nervous system exploration in POTS patients with preserved vagal function, a vigorous pressor response to the Valsalva maneuver, and an exaggerated blood pressure recovery and overshoot both before and after release.

However, in some studies, the analysis of the different autonomic tests had shown vagale hyperactivity in 63% of POTS patients on deep breathing, in 93% on hand grip and in 100% on orthostatic test, an increased alpha central sympathetic activity in 76% of the cases and high "β" central sympathetic activity in 83% of cases [37, 38].

An expanded approach to the evaluation could include a thermoregulatory sweat test to detect autonomic neuropathy (which manifests as abnormal patterns of body sweating), supine and upright plasma epinephrine and norepinephrine level tests, a 24-hour urine sample to assess sodium intake, and a psychological assessment [1,15]. Nevertheless, these tests should not be performed routinely as there is no evidence that they improve the care or the process of care in the majority of patients.

Other recommendations include screening for ferritin, Vitamin D, and Vitamin B12 levels, because low levels are common in the adolescent population [1, 39].

Diagnostic testing for other underlying or contributing conditions such as an autoimmune disease, Ehlers-Danlos syndrome, or mast cell disorders should be considered [1].

### **Comorbidities and disorders overlapping with POTS**

#### **Anxiety and panic disorder**

Because some of the physical symptoms of POTS, such as tachycardia and palpitations, may mimic symptoms of anxiety or panic disorder, patients can be misdiagnosed. Research has reported that POTS patients are similarly or even less likely to suffer from anxiety or panic disorder than the general public. In the adolescent population, one key consideration in diagnosing POTS is the determination of whether or not the postural tachycardia and its associated symptoms interrupt the adolescent's normal activities (school and sports) or if the symptoms are related to discomfort (dizziness, pain) [1,35,40]. Grubb reported that about 25% of patients with POTS cannot attend school or work [17].

#### **Visceral pain and dysmotility**

A percentage of patients with POTS experience visceral symptoms referred to the upper or lower gastrointestinal tract, bladder, and other organs. These symptoms are similar to those typically reported by patients with functional motility disorders. The underlying pathophysiology of these disorders includes mucosal inflammation, visceral hypersensitivity, secondary visceromotor dysfunction, and in most cases, behavioral amplification. Although these symptoms may be more frequently reported in patients with neuropathic POTS, they should not necessarily be considered a manifestation of a primary

underlying autonomic disorder (dysautonomia) because these are disorders of visceral sensitivity mediated by visceral afferents and not due to primary involvement of the enteric nervous system or efferent parasympathetic or sympathetic output via the vagus, pelvic, or splanchnic nerves [6,41].

#### **Headache and other neurologic conditions**

Chronic headache, including migraine, is a common comorbidity in patients with POTS. Orthostatic headaches also occur in patients with POTS, even in the absence of intracranial hypovolemia or cerebrospinal fluid leak. The relationship between POTS and orthostatic headache is uncertain because treatment of orthostatic tachycardia with volume expansion is only partially effective in these patients. Orthostatic tachycardia has also been reported in patients with type I Chiari malformation, in some cases associated with syringomyelia. However, a direct relationship between incidental type I Chiari malformation and orthostatic intolerance has not been convincingly demonstrated. POTS has also been shown in patients with a remote history of traumatic head injury, but this does not necessarily implicate direct damage of central autonomic areas as the primary cause of orthostatic intolerance [6,42,43].

#### **Chronic Fatigue Syndrome (CFS)**

POTS patients describe poorer sleep quality, more daytime sleepiness, greater fatigue, and substandard quality of life compared to healthy subjects. These reports are consistent with a reduction in sleep efficiency determined by actigraphy. Like POTS, CFS is a clinical syndrome that is more commonly diagnosed in females. It is characterized by persistent or relapsing unexplained fatigue and related symptoms of at least six months duration. For a CFS diagnosis, a patient must meet criteria for physical, mental and post-exertional fatigue, sleep disturbances, pain, neurological or cognitive manifestations. Patients with POTS have a high prevalence of chronic fatigue (48-77%) and of CFS (17-23%). Fatigue symptoms, orthostatic changes in HR and BP after 10 minutes, supine and upright plasma norepinephrine, and plasma volume were similar for the two groups (with Vs without criteria of CFS). 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. Moreover, CFS is proposed as part of the POTS spectrum [4,6,15,44].

#### **Basic cellular matrix and connective tissue diseases:**

POTS may overlap with many disorders like diseases of the basic cellular matrix and connective tissue such as Raynaud phenomenon. In the literature, association of POTS with cellular matrix protein disorders as Marfan Syndrome, Ehlers –Danlos Syndrome and Homocystinuria, which is phenotypically

similar to the basic cellular matrix disorders has been reported [40,45].

EDS includes heterogeneous disorders associated with inherited abnormalities of collagen. Patients are characterized by skin hyper-extensibility, 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. In addition, autonomic test results in these patients are consistent with disturbed sympathetic cardiovascular control, similar to POTS. More recent studies confirm a high prevalence of POTS-like orthostatic symptoms and orthostatic intolerance in patients with the hypermobility type of EDS. The exact nature of the relationship between POTS and EDS-Hypermobility is unknown. However, it's believed that connective tissue abnormalities in EDS could lead to vascular laxity and predispose patients to orthostatic blood pooling in the lower extremities and orthostatic intolerance. Alternatively, these patients might have a peripheral neuropathy that could contribute to autonomic impairment [2,4,6].

#### **Vasovagal Syncope (VVS)**

Vasovagal syncope and POTS overlap clinically, and both diagnoses may be appropriate for a given patient. A head upright tilt table test (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. 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. As the HR rises within the initial 10 minutes, patients complain of pre-syncopal symptoms, but they rarely faint. Only 30% or so of POTS patients actually experience syncope [4,15].

#### **Inappropriate Sinus Tachycardia (IST)**

IST is another disorder having overlapping clinical features with POTS. IST also predominantly affects young women and is characterized by pre-syncopal symptoms and abnormally high HRs. 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. In POTS, the orthostatic change in HR surpasses that in IST. The intrinsic HR does not differ between POTS & IST patients [4,10,46].

### **POTS and sleep disorder**

Patients with POTS commonly complain of symptoms including higher subjective daytime sleepiness, fatigue, worse sleep and the diminished quality of life. Up to 2011, there were no published data on the quality of sleep or sleep disturbances in patients with POTS [47]. Several studies have attempted to quantify the nature of sleep complaints in POTS patients and found that these patients have poor sleep quality, excessive sleepiness, excessive fatigue, and a high proportion of diminished quality of life due to sleep problems [47,48]. A combination of factors such as body fatigue, chronic pain, and other somatic symptoms common in POTS patients might be the underlying reason for sleep-related symptoms in POTS. [48] Although, almost all POTS patients reported sleep troubles, there is major discrepancy between the high percentage of symptoms and small percentage of patients seeking medical assistance for better sleep quality. Further objective evidences are needed to elucidate the mechanism or the prevalence of sleep-related symptoms in POTS, as well as the effect on patient quality of life to develop optimal treatments [49].

### **POTS and Exercise**

#### **Exercise performance in POTS after physical training**

Patients with the Postural Orthostatic Tachycardia Syndrome have exercise intolerance. During acute exercise, POTS patients have an excessive increase in heart rate and reduced stroke volume for each level of absolute workload; however, when expressed at relative workload, there is no difference in the heart rate response between patients and healthy individuals. Exercise performance is improved after short-term (3 months) exercise training. Specifically, stroke volume is greater and heart rate is lower at any given VO<sub>2</sub> during exercise after training versus before training [50,51]. An evidence-based approach to manage a patient with POTS with a “reconditioning” program of endurance and strength training is necessary [51].

#### **Cardiac responses to exercise distinguish POTS variants**

A disease model of high, normal, and low-flow POTS was proposed based on measurements of limb blood flow at rest. They reported that high-flow POTS was characterized by inadequate peripheral vasoconstriction in both the supine and upright positions which exaggerated cardiac output as in other high-output states. The hypothesis that there were high limb blood flow which ought to be high cardiac output, and this condition would persist during exercise was demonstrated and labeled it hyperkinetic circulation. Also, it exists a subset of patients with POTS who exhibit a relatively low cardiac output and hypokinetic responses during exercise and must therefore regulate systemic arterial pressure primarily by vasoconstriction

in order to maintain adequate muscle perfusion during exercise as a compensatory mechanism. The physical exercise extended the “low-flow”, “normal-flow”, and “high-flow” classification of POTS based on supine calf blood flow measurements to upright exercise. This classification by cardiovascular response to exercise would allow one to tailor non pharmacologic, and perhaps pharmacologic, management since exercise in an essential part of any rehabilitation program for POTS [52].

### **Management of POTS**

The treatment of POTS is difficult; there are no therapies that are uniformly successful, and combinations of approaches are often needed. Few treatments have been tested with the usual rigor of randomized clinical trials. Therefore, both non-pharmacological and pharmacological interventions are useful in the management of POTS. However, the evidence base for many of these interventions is poor, and none of the pharmacological treatments that might help are licensed for use in POTS.

#### **Non-pharmacological**

Non pharmacologic treatments should be attempted first with all patients. These include avoiding situations and medications that worsen orthostatic symptoms such as norepinephrine transport inhibitors, increasing blood volume with enhanced salt and fluid intake, reducing venous pooling with compression garments, and limiting deconditioning [1,7].

#### **Water and salt**

Given Blood volume is low in many patients with POTS and the tachycardic response to upright posture correlates with the severity of hypovolaemia. Patients are advised to increase their fluid intake (up to 3 L/day) and dietary salt intake (8–10 g/day) [14,15].

#### **Exercise**

An exercise programme with regular aerobic exercise and lower limb resistance training may aid blood volume expansion and reverse deconditioning [7]. Patients should engage in a regular (every other day for 30 min in each session) structured, graduated, and supervised exercise program featuring aerobic reconditioning with some resistance training for the thighs. Initially, exercise should be restricted to non-upright exercises including the use of rowing machines, recumbent cycles, and swimming to minimize orthostatic stress on the heart. Rowing may not be tolerated in patients with Ehlers-Danlos syndrome due to risk of joint dislocation and swimming may be safer [14, 15].

#### **Elastic support hosiery**

Waist high support hosiery may improve symptoms by minimising venous pooling in the abdomen, pelvis and legs during orthostasis. The stockings should be fitted to provide 30–40 mmHg of

compression; although this may be uncomfortable, poorly tolerated and not aesthetically pleasing but if there is symptom improvement, most people can manage to be compliant [7,14].

### **Pharmacological treatment**

If non pharmacologic approaches are not completely effective, Pharmacologic therapies may be targeted at specific problems.

### **Fludrocortisone**

Fludrocortisone is a potent mineralocorticoid that might be useful for boosting sodium retention and Expanding the plasma volume, although these pharmacodynamic effects might last only 1–2 days, and its effectiveness has not been tested in randomized clinical trials [39].

### **Midodrine**

Midodrine is an alpha-1 adrenoceptor agonist and causes peripheral arterial and venous constriction. Midodrine (5-10mg) improved symptoms and reduced resting and upright heart rate significantly. Midodrine has a rapid onset with only brief effects and should be administered 3 times daily. Although it has not yet been assessed in a clinical trial, this approach is recommended as rescue therapy for patients who are clinically decompensated and whose symptoms have worsened significantly [1,7,14,15].

### **Beta-blockers (Propranolol)**

It is another useful first-line medication in many patients who report symptoms from the tachycardia that occurs with standing. A low dose of 10–20 mg up to four times a day is recommended. Higher doses are typically not tolerated due to excessive fatigue. One study reported that low doses of propranolol—but not higher doses—significantly improved POTS symptoms. The overall goal should be to ‘take the edge off’ of the orthostatic tachycardia and not to normalize the heart rate [7,14].

### **Ivabradine**

It is a selective If channel blocker that lowers the heart rate, with little effect on blood pressure. There are no randomized studies on its use in POTS. Recently, in one cohort, nearly 78% of patients with POTS using ivabradine reported a significant improvement in symptoms with no major adverse effects reported [14,15,53].

### **Pyridostigmine**

It is an acetylcholinesterase inhibitor, which increases the concentration of acetylcholine at post-ganglionic muscarinic and nicotinic receptors, leading to a net increase in parasympathetic tone is typically used to treat myasthenia gravis, but it may also be useful in POTS. It decreases the heart rate in response to standing and reduces the symptom burden in patients with POTS. Its use is limited by adverse effects such as

diarrhea, abdominal pain and cramps, nausea, and increased urinary urgency and frequency [14,15].

### **Desmopressin**

It increases renal-free water retention and typically used to treat nocturnal enuresis Desmopressin lowers standing heart rates in patients with POTS, while improving symptoms. The dose is typically 0.2 mg/day orally and may be reserved for special occasions. Its use must be carefully monitored, with serum sodium monitoring every 1–2 weeks, due to the side effect of hyponatraemia [1,14].

### **Central sympatholytic agents**

Clonidine (alpha-2 Agonist) and methyldopa may help patients with hyperadrenergic POTS. Both these medications reduce sympathetic outflow and may help to stabilise heart rate and blood pressure in some patients with POTS Methyldopa is sometimes better tolerated given its longer half-life; however, both medications have the side effects of sedation and worsening fatigue [7,14,15].

### **Droxidopa**

Recently, FDA has approved Droxidopa for treatment of neurogenic orthostatic hypotension (NOH). It’s hypothesized that Droxidopa would be a safe alternative treatment for patients with refractory POTS through its vasoconstrictive activity. Droxidopa, a norepinephrine pro-drug, increases the amount of synaptic Norepinephrine that can bind to both alpha-2 and alpha-1 receptors, and therefore improves both sympathetic splanchnic arterial and venous vasoconstriction in POTS and may represent an ideal drug to improve the orthostatic response in POTS. In recent study, symptoms of dizziness, syncope and fatigue were reported less after treatment by Droxidopa; 75.7%, 51.4% and 40.5%, respectively among pots patients. Droxidopa appears to improve some symptoms of orthostatic intolerance in patients with POTS and further assessment in large clinical trials is needed to evaluate its efficacy [54].

### **Modafinil**

It has been occasionally used to increase concentration and alertness in patients with POTS. Given that it is a stimulant, this medication may potentially worsen tachycardia, although in a recent study the pro-tachycardia effects were minimal [14,15].

### **Acute intravenous infusion**

Acute blood volume expansion through 2 L intravenous saline can give symptom relief and can control heart rate [35]. While this can be used in an emergency setting for short clinical decompensation, it is not a practical plan for long-term management. The primary concern is long-term intravenous access and the complications of central catheters [14].

Thus, no one treatment is uniformly effective. It's recommended that all patients with POTS are provided with education about situations that may exacerbate symptoms, are advised to increase salt and fluid intake, and are provided with an exercise plan. If there is no improvement, then medications can be added. While there is no set protocol for first-line medications, we often start with low dose of propranolol [15].

#### Invasive interventions

Radiofrequency sinus node modification for the sinus tachycardia of POTS is not recommended, because it often worsens symptoms and occasionally results in the patient requiring a pacemaker. Although a number of patients with POTS have been found to have herniation of their cerebellar tonsils (Chiari I), there is no association between cerebellar tonsil herniation and POTS. Nonetheless, a number of neurosurgical centers decompress the cerebellar tonsils in an effort to "cure" POTS. This approach should not be offered until prospective controlled data have demonstrated its efficacy [15].

#### Predictors for Therapeutic Response to Treatment in POTS patients

##### BMI

Recently, it was shown in one cohort, that BMI is associated with the therapeutic response to oral rehydration solution (ORS) in children with POTS. Indeed, The BMI was correlated negatively with Delta HR in the POTS group ( $n = 54$ ,  $r = -0.766$ ,  $p < 0.01$ ) and with the decrease in symptom scores after treatment in POTS patients ( $n = 54$ ,  $r = -0.28$ ,  $p < 0.05$ ). A cutoff value of the BMI of  $18.02 \text{ kg/m}^2$  had high sensitivity (92 %) and high specificity (82.8 %) with area under the ROC curve at 92.3 % for predicting the effect of ORS treatment for POTS. [55]

##### Electrocardiography-Derived Predictors

Corrected QT interval dispersion (QTcd) might be useful for predicting the effectiveness of physical treatment for POTS patients. Baseline QTcd was positively correlated with the HR elevation from supine to upright seen in children with POTS ( $r = 0.348$ ;  $P = .003$ ). Receiver operating characteristic curve analysis demonstrated an area under the curve of 0.73, and using 43.0 msec as a cutoff of QTcd yielded a sensitivity of 90% and a specificity of 60%. [56]

##### Hemocytometric Measures

Mean corpuscular hemoglobin concentration (MCHC) could be used to predict the effectiveness of oral rehydration solution for treating POTS in children. Indeed, in POTS children, responders to ORS had baseline lower MCV (mean corpuscular volume) and higher MCHC than non-responders. The receiver operating characteristic curve for the predictive value of MCHC showed that area under the curve was 0.73; with

a cutoff value for MCHC of 347.5 g/L yielding a sensitivity of 68.8% and a specificity of 63.2%. [57]

##### Baroreflex sensitivity

Baroreflex sensitivity (BRS) is a useful index to predict the short-term outcome of POTS patients. BRS was positively correlated with HR change in POTS Group ( $r = 0.304$ ,  $P < 0.05$ ). Area under curve (AUC) was 0.855 (95% of confidence interval  $0.735 \pm 0.975$ ), and BRS of 17.01 ms/mmHg as a cut-off value yielded the predictive sensitivity of 85.7% and specificity of 87.5% [58].

#### CONCLUSION

Postural orthostatic tachycardia syndrome is a chronic, potentially disabling condition with no clear pathologic substrate and multiple interacting pathophysiologic mechanisms. The hallmark physiological trait is an excessive increase in Heart rate upon assumption of the upright posture, in the absence of orthostatic hypotension. A complete clinical evaluation and diagnostic testing can provide the basis for a comprehensive management plan to enable the patient to live as normally as possible.

##### Conflict of interest

The authors have no conflict of interest to declare.

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