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Postural Orthostatic Tachycardia Syndrome (POTS) - A Review of Pathophysiological Mechanisms, Diagnosis and Therapy

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ABSTRACT

Introduction

Postural Orthostatic Tachycardia Syndrome (POTS) is a chronic disorder of the autonomic nervous system. It is characterized by orthostatic tachycardia and orthostatic intolerance upon standing, without low blood pressure. It affects multiple body systems, leading to a wide range of symptoms that contribute to debilitation and reduced functionality. The disorder has

significant functional and economic consequences, although its underlying mechanisms remain only partially understood.
Many POTS patients receive inadequate care due to limited understanding of the etiology of POTS, a lack of evidence-based treatment options, and minimal training among physicians in recognizing and managing POTS.
Aim of the study
The purpose of this review is to provide a comprehensive overview of POTS, including its etiology, associated comorbidities, diagnostic challenges, and approaches to diagnosis, as well as potential pharmacological and non-pharmacological treatment options.
Material and Method
The literature search methodology involved using the keyword "POTS" in combination with terms such as "etiology," "treatment," "diagnosis," "symptoms," "long COVID-19," and "exercise." Searches were conducted in the PubMed and Google Scholar databases, focusing primarily on review articles and clinical trials.
Conclusions
Raising awareness of POTS among physicians is essential for delivering optimal healthcare to patients. Despite the prevalence of POTS and its significant impact on patients' lives, research funding remains disproportionately low. Strengthening research infrastructure is crucial to understand the pathophysiology of POTS and to standardize evaluation tools, outcome measures, and patient care.

Keywords: Postural orthostatic tachycardia syndrome; pathophysiology; diagnosis; non-pharmacological treatment; pharmacological treatment.

1. Introduction

Postural orthostatic tachycardia syndrome (POTS) is a chronic disorder of the autonomic nervous system, the symptoms of which worsen the quality of life of patients and limit the activities of daily life. It was first described in 1982 and then more broadly characterized in 1993. [1] POTS primarily affects young people, especially women aged 15-50. The exact statistics of the incidence of POTS in the European population are not available, but in the population of the United States, the statistics range between 0.2% and 1%, affecting between 500,000 and 3,000,000 people. [2] Symptoms experienced by patients include palpitations, tachycardia, dizziness, presyncope and syncope, as well as fatigue, blurred vision, headaches, sleep problems and gastrointestinal symptoms. [3] The symptoms characteristically appear upon standing and disappear when lying down. [4] The pathophysiology of POTS is multifactorial but poorly understood. Hypotheses considered include the presence of an autoimmune disorder, the occurrence of autonomic neuropathies, hypovolemia, hyperadrenergic states, among others. [5] Treatment of patients with POTS is challenging due to the multisystem nature of this syndrome. The patient's symptoms, their impact on daily life, comorbidities, and medications taken by the patient should be considered when planning appropriate treatment. Several treatment methods reduce symptom severity. Non-pharmacological therapies, primarily involving physical exercise, form the foundation of treatment; however, certain medications may be considered if these are ineffective.

2. Current State of Knowledge

Etiology of POTS

The etiology of POTS is not well understood. The presence of symptoms from various systems suggests a multifactorial and complex pathophysiology of this syndrome. Over the past 30 years, numerous hypotheses have emerged to explain the causes of POTS.

Partial sympathetic denervation

A key mechanism responsible for the occurrence of symptoms such as palpitations and increased heart rate is an imbalance between sympathetic and parasympathetic nervous system activity. [6] It has been shown that partial sympathetic denervation, or reduced sympathetic nerve activity, is observed in half of POTS patients. [7] This is caused by peripheral small fiber neuropathy in the lower limbs. [8, 9] The autonomic nervous system is, among other things, responsible for regulating blood vessel diameter. In POTS patients with reduced sympathetic nerve activity, this regulation is impaired. When standing, blood vessels in the lower limbs do not constrict adequately, causing thoracic hypovolemia and a compensatory increase in heart rate. [10] This produces typical POTS symptoms such as palpitations and shortness of breath. Patients with small fiber neuropathy have shown sympathetic denervation of the heart on cardiac meta-iodobenzylguanidine (MIBG) scans and patchy anhidrosis in the lower limbs on thermoregulatory sweat testing or axon reflex sudomotor testing, indicating a dysfunction in unmyelinated nerve fibers. [11] Some POTS patients show normal norepinephrine release from nerve endings in the upper limbs but reduced release in the lower limbs. Consequently, when maintaining a standing position, there is no adequate increase in peripheral vascular resistance in the lower limbs in response to norepinephrine release. [8, 12] This causes excessive venous pooling in the lower limbs, increased sympathetic activation, and, subsequently, an increased heart rate to maintain proper blood pressure.

Hyperadrenergic states

Elevated norepinephrine levels have been found in POTS patients while standing, as well as a correlation between blood norepinephrine levels and symptoms such as an increased heart rate. [13] Patients with this POTS phenotype, known as hyperadrenergic, often experience anxiety, suffer from migraines, and report chest pain. Additionally, when standing for extended periods, increased sweating appears in the lower limbs, which are also cold. It is estimated that about half of POTS patients exhibit excessive orthostatic tachycardia, elevated plasma norepinephrine levels when standing (≥600 pg/ml), an increase in systolic blood pressure by at least 10 mmHg, or symptoms such as palpitations and anxiety upon standing. [14, 15]

Hypovolemia

A significant aspect of POTS pathophysiology is the hypovolemia observed in patients. This may result from inadequate fluid intake and dehydration, blood pooling in the lower limbs, or

increased blood flow through visceral vessels. [16] As a result, less blood returns to the heart in venous return, decreasing cardiac stroke volume during orthostatic stress. Among pediatric POTS patients, a reduced red blood cell volume and an increased risk of POTS occurrence have been shown if daily water intake is less than 800 ml. [17]
The normal response to hypovolemia involves increased renin-angiotensin-aldosterone (RAA) system activity to stimulate sodium and water reabsorption from urine, restoring proper blood volume. However, in POTS patients, circulating angiotensin II levels are consistently elevated. Despite this, blood pressure remains normal, while plasma renin activity and aldosterone are reduced. [18, 19] This suggests that the adrenal glands and vessels do not respond appropriately to high angiotensin II levels. [20] Studies have shown a decrease in heart rate and reduction of symptoms following actions aimed at increasing plasma volume, such as intravenous saline or administration of desmopressin. [21, 22]

Cardiovascular deconditioning
One of the well-described pathophysiological mechanisms of POTS is cardiovascular deconditioning. [23] This significantly contributes to POTS symptoms and is characterized by a reduction in heart size and mass, circulating blood volume, stroke volume, and peak oxygen uptake. [24] Numerous studies have shown that prolonged inactivity, whether due to bed rest or microgravity, can induce a syndrome similar to POTS in previously healthy individuals. [24, 25, 26] This highlights the importance of deconditioning in the development of POTS. The effectiveness of physical training in reducing POTS symptoms in patients confirms the association between POTS and cardiovascular deconditioning, as physical activity helps increase blood volume and improves heart function. [27]

Autoimmune disorders
Autoantibodies have often been detected in POTS patients, suggesting that autoimmune disorders may underlie this syndrome. [28] Antibodies studied include those against acetylcholine receptors (AChR) and alpha-1 and beta-adrenergic receptors. [29, 30] Further research is needed to understand the impact of autoantibodies on the development and course of POTS, as it may open possibilities for immunotherapy targeting these autoantibodies.

Mast cell activation disorder
Another mechanism potentially linked to POTS pathophysiology is mast cell activation disorder (MCAD). [31] Mast cells play an essential role in inflammatory responses and are rich in vasodilatory agents, such as histamine, adenosine, and prostaglandins. In individuals with POTS, mast cell activation occurs due to prolonged standing or physical activity but can also happen after meals. Mast cell degranulation and the release of inflammatory mediators cause vasodilation, leading to compensatory increases in heart rate, hot flashes, dizziness, shortness of breath, headache, excessive urination, and gastrointestinal symptoms (nausea, diarrhea, vomiting, abdominal pain). [31, 32] Diagnosis of this disorder in POTS patients relies on finding elevated levels of histamine metabolites (N-methylhistamine) in urine or increased plasma tryptase during acute MCAD episodes. [31]

Genetic factors and the role of norepinephrine transporter

A hypothesis requiring further investigation is the role of genetic factors in the etiology of POTS. Although it is not a monogenic inheritance, genetic predispositions are suspected due to the higher incidence of POTS among family members - up to 14% of POTS patients have a family member with the syndrome. [3, 33]

Reduced expression of the norepinephrine transporter (NET) has been detected in POTS patients. NET is responsible for the reuptake of extracellular norepinephrine, and NET deficiency results in elevated norepinephrine levels in the bloodstream, contributing to autonomic dysfunction. [34] In one family with familial orthostatic tachycardia, a mutation was found in the NET gene (solute carrier family 6 member 2 gene - SLC6A2). [35, 36] Reduced NET levels have been observed in POTS patients in vein biopsies and leukocyte testing of NET gene expression. [37] Although these mutations are rare, patients using norepinephrine reuptake inhibitors (prescribed for conditions like depression or ADHD) may experience exacerbated POTS symptoms and orthostatic tachycardia. [38] These drugs include serotonin-norepinephrine reuptake inhibitors (SNRIs) like duloxetine and venlafaxine, tricyclic antidepressants, and NET inhibitors like atomoxetine and reboxetine. Extra caution is advised when prescribing these medications to POTS patients.

Impact of sex and menstrual cycle

The prevalence of orthostatic intolerance is notably higher in women compared to men, which may be due to physiological differences, such as lower stroke volume and reduced compliance of the heart walls in women. [23, 39] Hormonal fluctuations also play a significant role in the severity of POTS symptoms, as women report symptom variability throughout the menstrual cycle, with worsening symptoms in the premenstrual or early follicular phase when estrogen and progesterone levels are low. [40] Additionally, POTS is rarely observed in postmenopausal women, suggesting a potential connection between POTS and hormonal changes unique to a woman's reproductive years. [23]

Iron defficiency

Low levels of ferritin and vitamin D have been observed in adolescents with POTS. [41] Iron plays a regulatory role in the synthesis, transport, and signaling of nitric oxide (NO). [42] In cases of iron deficiency, NO synthesis increases, leading to vasodilation, which may contribute to the onset of POTS symptoms in children and adolescents. [43, 44] Additionally, pediatric patients with POTS show a reduced mean corpuscular hemoglobin concentration (MCHC) and an elevated mean corpuscular volume (MCV) compared to control groups, likely indicating decreased iron storage. [45] Further research is needed to clarify the link between low iron and ferritin levels and POTS, given the relative ease of iron supplementation, which could potentially alleviate symptoms in these patients.

The immune system

The role of the immune system in POTS development remains partially understood. Many POTS patients report the onset of symptoms following an acute viral illness, such as infectious mononucleosis. [46, 47, 48] Recently, a link between POTS and COVID-19

infection has been suggested, with POTS symptoms emerging as a possible complication of long COVID. [49, 50, 51, 52] Post-COVID-19 POTS can develop months or even years after initial infection, as seen with other long COVID symptoms, which are characterized by sustained inflammatory responses, including ongoing cytokine production and endothelial cell damage. [53, 54] This persistent inflammation may cause dysregulation of the autonomic nervous system, thereby contributing to POTS.

Additionally, autoimmune reactions, such as the production of antibodies targeting the autonomic nervous system, can be triggered by COVID-19. [55] IgA antibodies, typically involved in mucosal immunity, play a prominent role in these responses and may worsen vascular dysregulation and autonomic dysfunction, aligning with POTS symptomatology. [56, 57, 58]

Diagnostic criteria for POTS

Diagnosing POTS ich challenging due to the lack of a standardized clinical scale to guide diagnosis and treatment adjustments. Since the first POTS definition was established in 1993, [59] diagnostic criteria have evolved slightly and are now recognized by international cardiology, neurology, pediatric, and autonomic nervous system associations. Key diagnostic criteria include:

- Sustained heart rate increase of ≥30 bpm within 10 minutes of standing (or ≥40 bpm in patients aged 12-19);
- Absence of orthostatic hypotension (defined as a drop in blood pressure >20/10 mmHg within 3 minutes of standing);
- Frequent orthostatic intolerance symptoms that resolve upon lying down;
- Symptoms persisting for at least 3 months;
- Exclusion of other conditions causing sinus tachycardia and similar symptoms, such as anxiety disorders, anorexia nervosa, anemia, fever, chronic pain, dehydration, hyperthyroidism, pheochromocytoma, and deconditioning from prolonged bed rest. [15, 60]

A critical factor in diagnosing POTS is the sustained heart rate increase upon standing, as brief increases due to physiological responses to transient orthostatic hypotension do not constitute POTS. [61] Time also matters; POTS symptoms must be chronic, lasting at least three months, distinguishing it from temporary symptoms during acute infections or fever. [62] Comprehensive differential diagnosis is essential, as other disorders like neurogenic orthostatic hypotension, inappropriate sinus tachycardia, pheochromocytoma, pain, anxiety, anemia, physical exertion, valvular heart disease, cardiac tumors, pulmonary hypertension, and congenital/acquired heart diseases can mimic POTS symptoms. Drugs like tricyclic antidepressants, sympathomimetics, and sudden withdrawal from beta-blockers may also cause sinus tachycardia and must be ruled out. [23] Therefore, eliminating other causes is a primary step in POTS diagnosis. [62]

Diagnostic methods

The standard assessment of a patient presenting symptoms of orthostatic intolerance should begin with a detailed medical history, addressing the circumstances under which symptoms

appear, potential contributing factors, the position the patient is in when symptoms occur, and the position in which symptoms resolve. It is crucial to gather information about any comorbidities and medications the patient is taking, along with additional symptoms. During the physical examination, attention should be given to skin color, temperature, and moisture - for instance, anemia may be suspected in a pale patient with a history of heavy menstrual bleeding, or hyperthyroidism may be suspected if the patient's skin is warm and moist, along with limb tremors.

A simple diagnostic test, feasible even in a primary care physician's office, is the active standing test. For most patients, this test is sufficient for diagnosing POTS, with comparable effectiveness to the tilt-table test. [63] The patient should lie on their back for at least 10 minutes, after which blood pressure and heart rate are measured in the supine position. The patient then stands and remains standing for 10 minutes, with blood pressure and heart rate measured at regular intervals - 1, 3, 5, and then 10 minutes while standing. This test should be conducted in the morning when POTS symptoms tend to be most severe. [23, 62, 64] Additional tests may be performed for differential diagnosis if POTS is suspected. Laboratory tests should include a complete blood count, thyroid function tests, vitamin B12, cortisol, electrolytes, plasma catecholamines, and catecholamine metabolites in the urine. Other additional tests include a 12-lead electrocardiogram, echocardiography, and 24-hour Holter monitoring. [15, 65]

After completing basic tests that rule out diseases mimicking POTS and a positive active standing test, the primary care physician should initiate non-pharmacological treatment based on physical exercise. Specialist consultations are needed if there is suspicion of structural heart disease or arrhythmias, or if first-line interventions are ineffective. [23] Despite clear diagnostic criteria for POTS and an easy diagnostic test that can be conducted in a primary care setting, up to 21% of study participants [46] had to see more than 10 specialists before receiving a correct diagnosis, with an average wait time of 24 months from the first report of POTS symptoms. Importantly, the diagnosis was most often made by a cardiologist (41%) and only by a family physician in 8% of cases. [46]

Common comorbidities in POTS patients

POTS frequently coexists with various other conditions, though statistics on the comorbidity of specific diseases with POTS vary. These can include chronic fatigue, migraines, fibromyalgia, joint hypermobility, among others. [46, 66] The figure below summarizes the most common comorbidities with POTS reported by surveyed patients. [46]

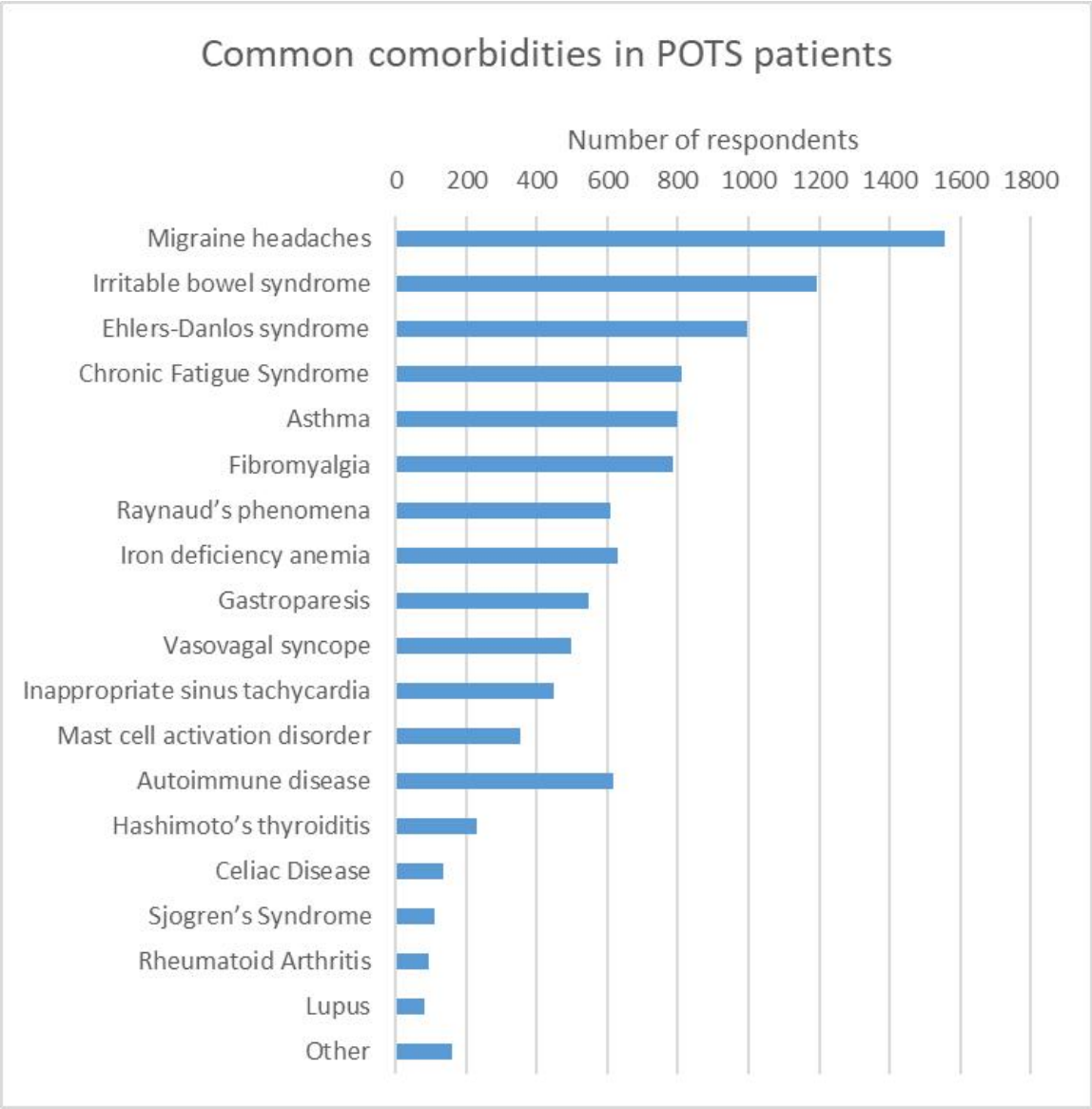

Figure 1 *Common comorbidities in POTS patients. 3933 respondents took part in the survey. [46]*

Non-pharmacological treatment

Effective treatment of POTS is challenging due to the multisystem nature of its symptoms. Given the heterogeneous etiology of POTS, causal treatment is not possible, and symptomatic treatment remains the primary approach. Treatment should begin with educating patients about situations that may trigger symptoms and should be avoided if possible. Patients should avoid prolonged lying down, as it contributes to deconditioning. Additionally, they should avoid high-temperature and humid environments. When rising from a sitting or lying position, particularly in the morning, they should take extra care due to the risk of falling.

Instead of large meals, especially those rich in fats and complex carbohydrates, patients with POTS are advised to eat small, frequent meals to avoid postprandial symptom exacerbation due to increased blood flow to the intestines. [23] Patients should avoid prolonged standing

whenever possible and use counter-maneuvers, such as crossing legs, tensing muscles, squatting, or standing on tiptoes if prodromal symptoms appear. [67, 68, 69]
Exercise is the cornerstone of conservative treatment. Patients with POTS should exercise for at least three months to observe symptom improvement, which occurs in most patients who adhere to the plan. [27] At the beginning, upright exercises should be avoided, with a preference for seated activities like swimming, rowing ergometer, or recumbent cycling. Over time, as physical condition improves, exercise intensity and frequency can increase, and standing exercises, such as resistance training, can be added to strengthen muscles. [27, 70, 71]
This training method significantly improves patients' physical fitness and increases blood volume and cardiac stroke volume. [72, 73] It also improves circulation regulation through the autonomic nervous system and the function of arterial-cardiac baroreceptors. [74]
Initially, patients may feel discouraged by fatigue in the first few weeks, but they should not give up on exercise as it is essential for symptom improvement, and doctors should encourage adherence to the training regimen. While exercise does not eliminate all POTS symptoms, it is recommended as a long-term part of patients' lives. [23, 71]
To counteract blood pooling in the lower limbs and splanchnic vessels due to gravity, compression garments are recommended, especially for patients with low blood pressure. Compression stockings extending to the upper thighs are advised, as well as abdominal binders to reduce blood pooling in abdominal vessels. [75, 76] Additionally, patients should drink at least 2.5–3 liters of water daily to increase blood volume. A salt intake of up to 10 grams per day is permissible if it does not lead to adverse effects such as hypertension or peripheral edema and is tolerated by the patient. [15, 77]
Non-pharmacological treatment should be the primary approach in POTS therapy due to its low invasiveness and associated benefits. However, it is essential to recognize that patients often abandon these treatments due to the lengthy wait for symptom relief or due to side effects like frequent urination or sensations of heat and itching from tight compression garments.

Pharmacological treatment

When non-pharmacological treatment is ineffective or insufficiently effective, the addition of medications should be considered, primarily aimed at reducing heart rate, increasing peripheral vascular resistance, and addressing hypovolemia. Currently, no medication is officially approved for the treatment of POTS, so pharmacological therapy should be used with caution. [78, 79] Additionally, attention should be paid to other medications the patient is taking, as these may trigger or worsen symptoms. Patients should avoid medications that increase heart rate or cause hypovolemia.

Table 1. Drugs used in POTS treatment

Therapy	Dose	Comments
Heart rate controlling agents		

Therapy	Dose	Comments
Propranolol	10-20 mg orally up to 4 times daily	Other beta blockers can also be used, such as bisoprolol, metoprolol, atenolol. especially recommended in POTS with hr > 120/min while standing [15, 79-81]
Ivabradine	2.5-7.5 mg orally twice daily	An alternative to beta-blockers when they are not well tolerated. Can be effective in patients with low blood pressure [82-85]
Verapamil	40-80 mg orally twice or 3 times daily	Blocks calcium channels. Causes negative chronotrophic effect. Can be effective in patients with lower blood pressure, experiencing chest pain and migraine, but evidence of efficacy in POTS is very limited [86]
Pyridostigmine	30-60 mg orally up to 3 times daily	Inhibitor of acetylcholinesterase. May cause abdominal cramping, muscle cramps and diarrhea, which may be beneficial for patients with constipation. Little to no effect on blood pressure [15, 87, 88]
Vasoactive agents and blood volume expanders		
Midodrine	2.5-10 mg orally 3 times daily	An alpha1-adrenergic agonist. May be effective for patients with low blood pressure and hypovolaemia. The first dose should be taken 15-30 minutes before getting out of bed in the morning, and the last dose should be administered no later than 4 p.m. to reduce the risk of supine hypertension as a possible side effect [15, 67, 77, 89-91]
Clonidine	0.2-0.6 mg orally twice daily	An alpha2-adrenergic agonist. Recommended for patients with hyperadrenergic POTS. Possible side effects are brain fog, hypotension and fatigue [15, 92]

Therapy	Dose	Comments
Fludrocortisone	0.1-0.2 mg daily	Mineralocorticoid that increases blood volume by promoting sodium reabsorption. Side effects include supine hypertension and hypokalaemia. It may be effective for patients with hypovolaemia and low blood pressure [15, 93]
Desmopressin	0.1-0.4 mg twice daily	An analogue of vasopressin. Expands blood volume by increasing water reabsorption. Limited evidence is available, and the effectiveness remains unclear [94]
Physiological saline	1-2 L intravenous infusion	Only for acute, decompensated POTS as an in-hospital treatment to relieve short-term symptoms [15, 95, 96]

3. Conclusions

POTS is a chronic autonomic nervous system disorder primarily affecting young women. It is characterized by an excessive increase in heart rate upon standing, often accompanied by pre-syncopal symptoms and orthostatic intolerance. While the exact cause remains unknown, it's believed to involve multiple pathophysiological factors. Common symptoms include dizziness, lightheadedness, fatigue, palpitations, chest pain, and difficulty concentrating. The condition can significantly impact quality of life, leading to limitations in daily activities, work, and social life. Diagnosis typically involves a detailed medical history, physical examination, and specific tests like tilt-table testing or head-up tilt testing. Treatment often focuses on lifestyle modifications, including a regular exercise program, increased fluid and salt intake, and avoiding triggers like heat and dehydration. In some cases, medications may be used to manage specific symptoms. While research has made progress in understanding POTS, further studies are needed to explore the underlying mechanisms, identify more effective treatments, and improve long-term outcomes for patients.

DISCLOSURE

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