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ახალგაზრდა მკვლევარები

Vol. 3 Issue 3, 2025

https://doi.org/10.52340/jr.2025.03.03.15

# Autonomic Dysfunction in Postural Orthostatic Tachycardia Syndrome (POTS): A Neurocardiological Perspective

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## Abstract

Postural Orthostatic Tachycardia Syndrome (POTS) is an autonomic nervous system disorder characterised by an abnormal rise in heart rate, usually about 30 beats per minute or greater, in 10 minutes of standing, and without a decrease in blood pressure. It manifests itself with a variety of symptoms, including palpitations, dizziness, fatigue, gastrointestinal discomfort, and the so-called brain fog, which significantly affects everyday life. Traditionally, POTS has been divided into neuropathic, hypovolemic and hyperadrenergic forms depending on the underlying causes, although recent research indicates that the condition is more complicated. Autoimmune activity, neurohumoral imbalance like the renin-aldosterone paradox, and brain involvement, especially of the autonomic control, are now being identified as important factors. The rise in post-COVID-19 POTS cases highlights the need to understand these mechanisms, with up to 14% of COVID survivors developing POTS-like symptoms. This literature review is a critical analysis of the literature on POTS, autonomic dysfunction, brain-heart axis, and related diagnostic and treatment methods. According to the search of PubMed, Google

Scholar, Scopus, Science Direct, and Web of Science, the publications of 2015-2025, the following key findings can be identified: a repetitive pathophysiology with sympathetic denervation, low blood volume, and excessive sympathetic activity, and neuroimaging showing cerebral hypoperfusion. This reduced blood flow may explain the mental cloudiness patients experience. Diagnosis is suggested to be made using such tools as tilt-table testing, heart rate variability analysis, and triple ECG tests, but there is still no single conclusive test. Lifestyle changes, typically including regular exercise, salt and fluid supplementation, and compression garments, are normally the first line of management and have demonstrated considerable improvement, even remission. Pharmacological therapy, such as beta-blockers, ivabradine, and pyridostigmine, is specific to the symptoms. And more sophisticated interventions, such as vagus nerve stimulation and hybrid ablation, are promising yet needs research. In conclusion, POTS still remains a multifaceted condition that needs personalised care and a multidisciplinary approach. While treatments are improving, more research is needed to refine diagnostic tools, explore novel therapies, and understand long-term outcomes, especially for those whose symptoms emerged after COVID-19.

**Keywords:** *Postural Orthostatic Tachycardia Syndrome, Autonomic Dysfunction, Hypoperfusion, Neurocardiology*

## Introduction

Postural Orthostatic Tachycardia Syndrome (POTS) is a complex autonomic disorder marked by an excessive increase in heart rate upon standing, typically ≥30 beats per minute within 10 minutes, without accompanying orthostatic hypotension (1). This is a condition that manifests through a range of symptoms, including palpitations, dizziness, fatigue, cognitive impairment ("brain fog"), nausea, and visual disturbances, which collectively impair daily functioning and quality of life (1).

Although POTS affects an estimated 1 to 3 million people in the U.S., which is about 0.2–1.0% of the population, research is still limited and mostly based on clinical observations rather than large studies (2). The condition predominantly impacts the female population between the ages of 12 and 50. And it is frequently triggered by factors such as viral infections, surgical procedures, pregnancy, or autoimmune diseases, with infections being the most common out of all (2). COVID-19 has become a known cause of new-onset POTS. Researchers indicate that 2-14 % of COVID-19 survivors develop the condition, and up to 61 % of them experience POTS-like symptoms months after the infection (3–6). These results indicate the post-viral autonomic complications associated with SARS-CoV-2 and indicate a possible major role in the increased prevalence of POTS in the post-pandemic era. POTS can develop either suddenly or gradually and may resolve completely or show recurring episodes (2).

POTS is categorised into subtypes based on underlying mechanisms. Neuropathic POTS is characterised by partial autonomic denervation, leading to impaired vasoconstriction and blood pooling in the lower extremities (7). Hyperadrenergic POTS involves excessive sympathetic nervous system activity,

resulting in elevated norepinephrine levels and potentially increased blood pressure upon standing (8,9). Hypovolemic POTS is marked by reduced blood volume, resulting in decreased venous return and compensatory tachycardia (10). These subtypes often overlap, complicating diagnosis and management.

Yet, this traditional subtype model is being challenged by recent research highlighting a strong autoimmune component. Patients often show autoimmune markers and antibodies targeting autonomic receptors. These findings overlap with other conditions like chronic fatigue syndrome and fibromyalgia, which are increasingly seen as central nervous system (CNS) disorders. Given the similar patterns, there is growing support for viewing POTS as a CNS disorder as well. This tightly integrated framework emphasises how aberrant neural control and cardiovascular feedback underlie POTS, positioning it as a prime target for interventions aimed at restoring ANS-cardiovascular equilibrium (11).

Recent neuroimaging studies have provided growing evidence of central nervous system involvement in POTS and related orthostatic intolerance disorders. For example, brain lesions in autonomic regulatory areas and successful symptom resolution following vagal nerve stimulation highlight the potential role of central autonomic networks (11).

Diagnosing POTS requires a detailed clinical history, symptom assessment, physical examination, and selective testing. History taking focuses on identifying the onset and triggers of symptoms, while evaluation of autonomic involvement helps determine disease extent. A thorough physical exam, especially cardiac, neurological, and dermatologic, is essential. No single test can definitively diagnose POTS; evaluation aims to rule out other conditions and identify coexisting disorders that may affect treatment. Additional testing should be guided by symptom duration, severity, and treatment response. A personalised, mechanism-based approach is recommended for effective diagnosis and management (11).

Given these diagnostic challenges, heterogeneous presentation, and increasing evidence of CNS and autoimmune involvement, there is a critical need to synthesise current knowledge. This review aims to explore evolving perspectives on POTS subtypes, mechanisms, and central regulation, with a focus on neuroimaging and diagnostic implications.

## Methodology

In this review paper, a thorough and systematic methodology was applied to the available body of literature on autonomic dysfunction in Postural Orthostatic Tachycardia Syndrome (POTS), with a focus on its diagnostic, pathophysiological, and management considerations. The search was extended to well-known academic medical and multidisciplinary databases to avoid omission of key articles, including Google Scholar, PubMed, Science Direct, Web of Science, and Scopus. The search was conducted using a combined keyword and subject heading search of: "POTS", "autonomic dysfunction", "neurocardiology", "brain-heart axis", "central autonomic network", "heart rate variability (HRV)", and

"baroreflex". Search results were limited to English language publications, and those published from January 2015 through July 2025.

Studies were included if they focused on POTS or autonomic dysfunction with emphasis on neurocardiological or neurocardiac mechanisms, including the central autonomic network (CAN), heart rate variability (HRV), baroreflex function, or brain-heart activity. Clinical research that contributed to essential medical knowledge on POTS diagnosis, pathophysiology, and treatment options was prioritized. Human studies involving participants of any age and sex were included. The review considered various literature types such as original research including clinical trials, cohort studies, case-control studies and other observational studies, as well as systematic and narrative reviews, meta-analyses, informative case series, and clinical guidelines. Only open access articles or full texts available through institutions with appropriate subscription rights were included.

Exclusion criteria involved studies focused on orthostatic hypotension in isolation, other dysautonomias, or non-autonomic cardiovascular conditions. Animal studies or basic science research without clinical application were excluded. Non-English language studies, non-peer reviewed articles such as blogs and editorials, as well as book chapters or preprints from unverified databases, were also excluded. Case reports were generally excluded unless they provided new information.

While we have set a broad inclusion criteria for this review, not all the included papers have met every individual item within these criteria. However, each paper did fulfil several core aspects of the inclusion framework, and all exclusion criteria were strictly followed. This ensured we included the most relevant studies while still keeping our review rigorous and reliable.

## Discussion

### Pathophysiology of autonomic dysfunction in POTS.

POTS can be broadly divided into several types based on underlying mechanisms.

### Neuropathic POTS

This is a form of sympathetic denervation, particularly of the vasoconstrictor fibers of the lower limbs and the splanchnic circulation. When standing up, approximately 500 ml of blood collects in these areas (12). This pooling reduces the venous return, which causes a reduction in cardiac output and stroke volume. The body responds by activating the baroreceptors that stimulate the sympathetic system to sustain cerebral perfusion. It is mainly neurogenic and is associated with impairment at the peripheral autonomic nerve level (13).

### RAAS and Hypovolemia in POTS

Hypovolemia, which is a low circulating blood volume, causes a decreased venous return in an upright position. This decreases stroke volume and cardiac output, stimulating baroreceptors and raising

sympathetic outflow, leading to compensatory tachycardia. Recent studies have highlighted that there is hormonal imbalance involving the renin-angiotensin-aldosterone system (RAAS), which is autonomous of volume status, in POTS pathophysiology. Observations include low levels of aldosterone despite low renin (14), insufficient rise in renin levels upon standing impairing normal compensation, and high renin but normal or low aldosterone in some cases. Together, these findings are referred to as the renin-aldosterone paradox (12).

Another significant factor is chronic deconditioning. It is associated with reduced left ventricular mass, stroke volume, and blood volume (15). Since cardiac filling is impaired when standing, the stroke volume is decreased, which worsens the orthostatic symptoms.The symptoms may start after the illness and are also enhanced by hypervigilance, leading to inactivity and further deconditioning.It remains unclear whether deconditioning is a primary or secondary process (12).

### Hyperadrenergic POTS

This variant is characterized by excessive sympathetic activation due to primary overactivity or defective norepinephrine (NE) handling. Loss of function single point mutation in norepinephrine transporter(NET) gene SLC6A2 causes defective NE reuptake and high circulating NE levels (15). Secondary hyperadrenergic states can also arise in response to hypovolemia, neuropathy, or autoimmune triggers (12).

### Clinical presentation

POTS commonly presents with orthostatic intolerance, orthostatic tachycardia, palpitations, dizziness, lightheadedness, and (pre-)syncope. Exercise intolerance is also frequent. Other symptoms include dyspnea, chest pain or discomfort, acrocyanosis, Raynaud's phenomenon, venous pooling, and limb edema (8).

Neurological and cognitive symptoms such as headache or migraine, mental clouding ("brain fog"), cognitive impairment, concentration problems, anxiety, tremulousness, light and sound sensitivity, blurred or tunnel vision, regional neuropathic pain, sleep disorders, and involuntary movements are also reported (8).

Additional features include chronic fatigue, fever, muscle pain, nausea, dysmotility, weight loss, shortness of breath, bladder dysfunction, petechiae, rashes, and erythema (8,16).

### Investigative tools & biomarkers

### Diagnostic criteria

A rise in heart rate of at least 30 bpm in 10 minutes in adults and at least 40 bpm in children aged 12 to 19 years after standing, with no large reduction in blood pressure during the first 3 minutes of standing (no fall of 20 mmHg systolic or 10 mmHg diastolic), and symptoms of orthostatic intolerance

present for at least 6 months. Other causes of increased heart rate, such as stress, dietary factors, medications, or other medical conditions, should be ruled out (15). Refer to Figure 1 for key diagnostic criteria of POTS.

### Clinical evaluation

A thorough physical examination is essential, with careful cardiac, dermatological, and neurological assessment. Laboratory studies may include CBC, thyroid cascade, AM cortisol, plasma and urinary metanephrines, vitamin B12, celiac testing, ANA, Sjögren antibody testing, supine and standing catecholamines, and antiphospholipid antibodies (2).

Cardiologic testing includes ECG, echocardiography, and 24-hour Holter monitoring (2). Other assessments involve GI and genitourinary evaluations, including 24-hour urine collection, and sleep studies (2). Tilt-table testing (TTT) remains the gold standard, along with head-up tilt tests (HUT) (2).

Neurological assessment may involve brain MRI and magnetic resonance spectroscopy (11). Patients with POTS often show a higher prevalence of non-specific autoimmune markers such as ANA, ganglionic N-type and P/Q-type acetylcholine receptor antibodies, alpha-1, beta-1, and beta-2 adrenergic antibodies, and opioid-like antibodies (11).

Some studies have also found elevated autoantibodies against G-protein-coupled receptors. Additionally, there were increases in several cytokine and chemokine biomarkers (IL1β, IL21, TNFα, INFγ, CD30) and decreases in CD40L and RANTES (17). A summary of the diagnostic steps is outlined in Table 1.

### Management Strategies in POTS

A The treatment of POTS is a combination of non-drug and drug interventions, depending on an individual. No drugs are approved by FDA and treatment is symptomatic and aimed at increasing the quality of life (12). It is frequently required to have a team of doctors, nurses, psychologists, and physiotherapists, particularly in post-COVID-19 POTS, where cognitive and emotional problems may be more severe (5,6,18).

### Non-Pharmacological Treatments

### Exercise Programs

Formal exercise programs, structured and semi-supervised, are regarded as one of the initial treatment lines of POTS (Wheatley-Guy et al., 2023). Such programs are especially helpful when the level and the pace of each session are adjusted to the ability of the patient. The purpose of exercise is to improve fitness, decrease orthostatic symptoms, and increase exercise tolerance compared with usual care. This leads to the expansion of blood volume and assists in reducing symptoms (6).

The structured protocols are one of the most common, and they start with horizontal activities, including rowing, swimming, or recumbent bike. These assist in averting the development of upright intolerance. As the patients get stronger and more capable of tolerating activity, they are gradually transferred to upright activities such as walking on a treadmill, jogging, or upright cycling. The programs typically consist of some combination of endurance (aerobic) exercise and lower body and core resistance training. Strength training may also be done at home using floor mats, resistance bands, or Pilates-based exercises in case one does not have access to a gym (10).

These exercise programs have been proved to be effective as studies have shown that after three months of training, patients experienced an 8 percent increase in physical fitness, 12 percent increase in cardiac size, 8 percent increase in cardiac mass and 6 percent increase in blood volume. By the end of three months, about 53 percent of patients in clinical trials and 71 percent in community registries no longer fit the diagnostic criteria of POTS, which means that many of them improved and even went into remission (10). Exercise is initially intolerable to some patients but most patients improve with time (10).

### Compression Therapy

Compression therapy is used to decrease pooling of blood in the lower body and to support circulation, compression stockings or abdominal binders are used often. The use abdomen-high compression garments or abdominal binders is more effective than the knee- or thigh-high options for reducing venous pooling and preventing orthostatic intolerance (10). It is also possible to use these garments to help patients tolerate exercise more easily by reducing blood pooling during exercise (10).

### Salt, Fluids, Lifestyle, and Education

The management of lifestyle is a significant part of POTS treatment. It includes educational, psychological support, and the information about how to prevent triggers such as exposure to high humidity. It is typically advised that patients take up to 10 grams of salt daily (as long as it does not lead to complications) and up to 3 liters of water daily to help increase the volume of plasma and blood (10). They are combined with exercise and compression to sustain blood pressure and improve day to day functioning (10).

The intake of high salt is generally recommended, and tablets are not recommended (10). The ability to consume more salt and fluids should be monitored individually (5,10).

Education is an important element of this strategy. Patients tend to stick to the treatment plan more when they understand what to expect and why each intervention is needed, though the symptoms can worsen at first (5,18). It is especially important because lifestyle changes and physical activity can be difficult to maintain without enough support and knowledge (5,19).

## Psychological and Cognitive Support

Patients with POTS, including post-COVID-19 POTS, commonly experience cognitive problems, which are commonly referred to as brain fog. Such issues may include memory, attention, and mental clarity, and they are considered key characteristics of the syndrome (5,6). There is also depression and anxiety, a feeling of loss of control, alteration of self-identity, and frustration due to lack of understanding. Such emotional issues may significantly affect everyday life and the quality of life in general (19).

This once more explains the necessity of a multidisciplinary team (5,18). Pharmacological treatments for orthostatic intolerance, such as propranolol, bisoprolol, and pyridostigmine, have been showing a low depression scores even in those patients who are not on any antidepressants, showing us how physical symptom relief can improve emotional well-being (20).

## Pharmacological Treatments

Pharmacologic therapy is usually started when non-drug measures do not adequately control the symptoms. The treatment used is individualized and only based on the patient's specific presentation and tolerance (5,6,18,20,21). Pharmacological options are listed in Table 2.

Most of the expert consensus guidelines recommend starting with non-drug interventions such as exercise, hydration, and salt, adding medications only when needed (5,6).

## Procedural Interventions

### Neuromodulation

Non-invasive transcutaneous vagus nerve stimulation (tVNS) was tested in a randomised controlled trial in patients having POTS. The results found during the study showed a substantial decrease in postural tachycardias, an increased HRV, and substantially decreased inflammatory markers and autoantibodies (22). It was found that there were no side effects related to the use of the device reported during the study, and the compliance was high during the two months of the study, which suggests both safety and possible efficacy (22).

### Ablation

Hybrid sinus node-sparing ablation has been showing promising results in severe cases that fail to respond to conventional therapies. The procedure itself eliminated all the symptoms and the need to use medications in a multicenter study of patients with drug-resistant POTS. It was reported that pericarditis was the most common complication, with 47 per cent of patients experiencing it, and but all of them were resolved. The Prophylactic use of acetylsalicylic acid and colchicine reduced the risk

of pericarditis by a great margin without increasing other complications such as pneumothorax (1.9%) and sinus arrest that needed pacemaker implantation (1.9%) (23,24).

## Safety, Side Effects, and Risks

Non-pharmacological measures such as salt and fluid intake, use of compression garments, and exercise do not have any major risks and no major risks have been reported in recent guidelines. However, such measures are not easy to all patients at first and they can feel more tired or their symptoms can get worse at first. Most of them improve as they progress (5,10).

Salt tablets should be avoided because they are more likely to cause nausea, vomiting and dehydration all of which may lead to a reduction in plasma volume which is counterproductive (10). Drugs that reduce the heart rate, such as beta-blockers and ivabradine, can be used to manage the symptoms but frequent monitoring is necessary, especially in patients that have comorbidities (5).

The IVIG treatment applied in patients with an autoimmune cause of POTS had not shown any meaningful advantage as compared to volume expansion alone as of yet. Although the adverse events were mostly mild and most of them were reported to be comparable to those of the control group that was administered albumin, the findings indicate that a significant part of the improvement can be explained by the very process of volume loading (25).

tVNS neuromodulation in controlled trials did not show any device-related side effects (22). And hybrid ablation, despite some specific risks, such as pericarditis, proved to be ultimately safe when prophylactic measures were taken (23,24).

## Patient Outcomes and Prognosis

The symptoms of POTS usually start to improve in a few months after lifestyle changes and exercise programs are initiated. The long-term benefits are preserved through the further adherence to these interventions (10). Patients with post-COVID-19 POTS might have more severe cognitive and psychological symptoms and need a powerful multidisciplinary approach. The prognosis of such patients is still unclear in the long term (5). Table 3 summarizes treatment interventions, their possible side effects, and patient outcomes in POTS.

## Recent Insights into POTS

Recent research supports that POTS is associated with a high level of autonomic dysfunction, with a decreased respiratory sinus arrhythmia and an elevated heart rate response to standing, which implies a decreased parasympathetic and an enhanced sympathetic activity (26,27).

Further advanced analyses also show that POTS mainly influences the baroreflex (BR) system, leading to more sympathetic compensation, but the cerebral autoregulation (CA) is relatively intact (28). New brain Single Photon Emission Computed Tomography (SPECT) scans have shown that most POTS patients who have cognitive symptoms have abnormal cerebral blood flow, particularly in the lateral prefrontal and sensorimotor cortices, even when they are lying down. This hypoperfusion is related with both autonomic and gastric symptoms, which leads to a decrease in the quality of life (29).

Also, POTS patients have been found to have impaired renin activity, not the aldosterone level, and the renin levels are not linked to blood pressure control. This implies a distinct neurohumoral imbalance that can be used in the future to develop therapeutic approaches (30). There are also two different hemodynamic profiles: increased venous pooling and hyperadrenergic response, according to the changes in heart rate and stroke volume during the tilt test. Such patterns can show various therapeutic outcomes (31).

To achieve a reliable diagnosis and its management, especially for post-COVID POTS, a detailed autonomic testing, like beat-to-beat hemodynamic monitoring and sudomotor assessment, is reccomended (27). A new triple analysis of 24-hour ECG recordings, including the evaluation of heart rate variability (HRV), awakening heart rate increase, and heart rate spikes, has been demonstrated to be effective in the detection of autonomic dysfunction in POTS, which is not observed in other manifestations of long COVID (26).

The stimulation of the tragus nerve has become a promising intervention, which reduces the symptoms of POTS in post-COVID patients and indicates a possible non-pharmacological treatment of autonomic imbalance (32). The use of Physical therapists designed at home, remotely administered exercise programs have proven to be safe and easily accessible, especially to patients with severe orthostatic intolerance (33).

Although these findings are encouraging, there are still a number of limitations and gaps that have to be filled in order to enhance diagnosis and treatment strategies.

## Limitations

In spite of all the advances, this literature identifies some significant gaps for clinical practice and research, particularly the absence objective measures of the diagnosis and differentiation of the subtypes (neuropathic, hypovolemic, and hyperadrenergic) are available, and the existing diagnostic criteria are primarily based on non-specific symptoms and changes in heart rate during orthostatic challenge (11,15).

Biomarkers like Cytokines (IL-1beta and TNFalpha) and autoantibodies (against adrenergic and GPCR receptors) are spotted relatively frequently, but they are not very specific and cannot be used to diagnose POTS reliably (11,17). It also remains unclear is whether deconditioning is the cause of POTS or merely accompanies it (12).

Another problem is that there are no FDA-approved drugs against POTS. Physicians use off-label medications and non-pharmacological interventions, and the majority of the studies are of a relatively small size and not of high-quality randomized controlled trials (RCTs). Due to which, there is weak evidence supporting the effectiveness of most of the current recommendations, and immunological treatments such as IVIG have shown no added benefit over volume expansion alone (25).

The image is even more cloudy in the case of the vagus nerve, and more recent approaches, including transcutaneous vagus nerve stimulation (tVNS) or tragus nerve stimulation, are promising, but are only supported by early or single-study evidence (22,32).

The other issue is that POTS has numerous manifestations, and the symptoms, causes, and response to treatment are not uniform. Recent research also indicates that there are well defined hemodynamic patterns like venous pooling vs hyperadrenergic, but no consistent method of determining which of these a patient presents with, leaving treatment extremely individualized and frequently trial-and-error (31).

We also do not quite understand the prognosis of POTS, particularly in the increasing number of individuals who acquire it following COVID-19. There are no long-term data of safety and efficacy for procedures as the hybrid ablation, and have side effects, such as pericarditis (24). Recently studies have shown new observations like the renin-aldosterone paradox and low cerebral blood flows seen in SPECT tied to "brain fog" (29,30). However, turning these finds into clinically usable diagnostic tools or can be used for targeted therapies remain a huge challenge. The reason is that more sophisticated methods, such as triple ECG tests or quantitative autonomic testing, are not very widespread or universal yet (26,27).

These limitations demonstrate the complicated nature of POTS and reveal the essential need of further investigation in this aspect for improving people's life and help them manage this disorder in their day to day life .

## Conclusion

This research paper gives a good understanding of Autonomic Dysfunction in Postural Orthostatic Tachycardia Syndrome (POTS). The causes of predisposing to the diagnosis of a person with POTS are numerous etiological factors. It is categorically categorized under a number of types and they include Neuropathic, Hypovolemic and Hyperadrenergic POTS. POTS is presented clinically and depends on the pathophysiology that occurs in a person.

POTS has clinical manifestation which depends on the pathophysiological mechanism in a particular patient. POTS is not curable although symptomatic treatment may help to relieve patients of their symptoms that include non-pharmacological and pharmacological treatment depending on the etiology of a case. Non drug intervention involves several exercises, increasing the intake of salt and fluid to enhance blood pressure, application of compression therapy which is defined according to the fitness

and pre-existing conditions of the individual.Recent research indicates a correlation between post COVID 19 POTS patients and problems with memory, attention, brain fog, depression, anxiety and general decline in quality of life. Pharmacological intervention is applied when non-drug techniques are ineffective. This is individualised in relation to etiology factors and severity of symptoms of an individual. According to studies, physical symptoms are better improved with the use of medication to control orthostatic intolerance with the use of propranolol, bisoprolol and pyridostigmine. There are non-drug and drug resistant POTS cases where other invasive procedures assist in the treatment of these cases such as neuromodulation, ablation and so on.

To examine efficacy and safety of interventions in POTS, further large scale RCTs should be carried out. Considering the limited evidence, longitudinal studies may be carried out to determine the efficacy of immunologic treatment, e.g., IVIG, compared to that of the volume expansion. More studies need to be done to study pathophysiology and disease courses in POTS in the post-COVID 19 patients. The connection between such a procedure as hybrid ablation and pericarditis can be explored through the cohort studies. Triple ECG examinations or quantitative autonomic testing in large scale studies can prove useful as a single primary modality in diagnostic POTS. The future study of POTS seems promising in terms of new treatment and improved patient outcomes in those people diagnosed with POTS.

## Reference


1. Zhao S, Tran VH. Postural Orthostatic Tachycardia Syndrome. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 Jul 11]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK541074/

2. Sebastian SA, Co EL, Panthangi V, Jain E, Ishak A, Shah Y, et al. Postural Orthostatic Tachycardia Syndrome (POTS): An Update for Clinical Practice. Curr Probl Cardiol. 2022 Dec 1;47(12):101384.

3. Blitshteyn S, Whitelaw S. Postural orthostatic tachycardia syndrome (POTS) and other autonomic disorders after COVID-19 infection: a case series of 20 patients. Immunol Res. 2021 Mar 30;69:205–11.

4. Chadda K, Blakey E, Huang C, Jeevaratnam K. Long COVID-19 and Postural Orthostatic Tachycardia Syndrome- Is Dysautonomia to Be Blamed? Front Cardiovasc Med [Internet]. 2022 Mar 9;9. Available from: https://consensus.app/papers/long-covid19-and-postural-orthostatic-tachycardia-huang-jeevaratnam/0aba90553c8e57168029102aeffe515d/

5. Ormiston C, Świątkiewicz I, Taub P. Postural orthostatic tachycardia syndrome as a sequela of COVID-19. Heart Rhythm. 2022 Jul 1;19:1880–9.

6. Park JH, Park S, Kim NH, Lee Y, Chang Y, Song TJ. Postural Orthostatic Tachycardia Syndrome

Associated with COVID-19: A Narrative Review. Medicina (Mex) [Internet]. 2024 Aug 1;60. Available from: https://consensus.app/papers/postural-orthostatic-tachycardia-syndrome-associated-lee-park/3531433b417b518a8179d53dd29bf6ee/

7. Mar PL, Raj SR. Postural Orthostatic Tachycardia Syndrome: Mechanisms and New Therapies. Annu Rev Med. 2020 Jan 27;71(1):235–48.

8. Fedorowski A. Postural orthostatic tachycardia syndrome: clinical presentation, aetiology and management. J Intern Med. 2019 Apr 1;285(4):352–66.

9. Wang E, Ganti T, Vaou E, Hohler A. The relationship between mast cell activation syndrome, postural tachycardia syndrome, and Ehlers-Danlos syndrome. Allergy Asthma Proc. 2021 May 1;42(3):243–6.

10. Fu Q, Levine BD. Exercise and Non-Pharmacological Treatment of POTS. Auton Neurosci Basic Clin. 2018 Dec;215:20–7.

11. Blitshteyn S. Is postural orthostatic tachycardia syndrome (POTS) a central nervous system disorder? J Neurol. 2022 Feb;269(2):725–32.

12. Ghazal M, Akkawi AR, Fancher A, Oundo E, Tanzeem H, Sajjad L, et al. Pathophysiology and management of postural orthostatic tachycardia syndrome (POTS): A literature review. Curr Probl Cardiol. 2025 Mar 1;50(3):102977.

13. Mar PL, Raj SR. Postural Orthostatic Tachycardia Syndrome: Mechanisms and New Therapies. Annu Rev Med. 2020 Jan 27;71(Volume 71, 2020):235–48.

14. Mar PL, Raj SR. Postural Orthostatic Tachycardia Syndrome: Mechanisms and New Therapies. Vol. 71, Annual Review of Medicine. Annual Reviews; 2020. p. 235–48.

15. Arnold AC, Ng J, Raj SR. Postural tachycardia syndrome – Diagnosis, physiology, and prognosis. Auton Neurosci. 2018 Dec;215:3–11.

16. Olshansky B, Cannom D, Fedorowski A, Stewart J, Gibbons C, Sutton R, et al. Postural Orthostatic Tachycardia Syndrome (POTS): A critical assessment. Prog Cardiovasc Dis. 2020 May;63(3):263–70.

17. Gunning WT, Stepkowski SM, Kramer PM, Karabin BL, Grubb BP. Inflammatory Biomarkers in Postural Orthostatic Tachycardia Syndrome with Elevated G-Protein-Coupled Receptor Autoantibodies. J Clin Med. 2021 Feb 6;10(4):623.

18. Wheatley-Guy C, Shea M, Parks J, Scales R, Goodman B, Butterfield R, et al. Semi-supervised exercise training program more effective for individuals with postural orthostatic tachycardia syndrome in randomized controlled trial. Clin Auton Res. 2023 Aug 20;33:659–72.

19. Waterman S, Opie M, Waterman D, Langdon D. Experiences of living with postural tachycardia syndrome. Chronic Illn. 2021 Nov 17;19:184–96.

20. Moon J, Kim DY, Lee WJ, Lee H, Lim JA, Kim TJ, et al. Efficacy of Propranolol, Bisoprolol, and Pyridostigmine for Postural Tachycardia Syndrome: a Randomized Clinical Trial. Neurotherapeutics. 2018 Mar 2;15:785–95.

21. Xu B, Gao Y, Zhang QY, Li XY, Liu X, Du J, et al. Establishment and validation of a multivariate predictive model for the efficacy of oral rehydration salts in children with postural tachycardia syndrome. eBioMedicine [Internet]. 2024 Jan 2;100. Available from: https://consensus.app/papers/establishment-and-validation-of-a-multivariate-zhang-xu/bfe4d25cfc5f58b69ddf5bd37bcd5935/

22. Stavrakis S, Chakraborty P, Farhat K, Whyte S, Morris L, Asad ZUA, et al. Noninvasive Vagus Nerve Stimulation in Postural Tachycardia Syndrome: A Randomized Clinical Trial. JACC Clin Electrophysiol [Internet]. 2023 Nov 1; Available from: https://consensus.app/papers/noninvasive-vagus-nerve-stimulation-in-postural-morris-yu/ae53e675d5f65e82b5038c5d0be91c16/

23. De Asmundis C, Chierchia G, Lakkireddy D, Romeya A, Okum E, Gandhi G, et al. Sinus node sparing novel hybrid approach for treatment of inappropriate sinus tachycardia/postural sinus tachycardia: multicenter experience. J Interv Card Electrophysiol. 2021 Aug 23;63:531–44.

24. De Asmundis C, Marcon L, Pannone L, Della Rocca D, Lakkireddy D, Beaver T, et al. Pericarditis prophylactic therapy after sinus node–sparing hybrid ablation for inappropriate sinus tachycardia/postural orthostatic sinus tachycardia. Heart Rhythm O2. 2024 Jan 1;5:137–44.

25. Vernino S, Hopkins S, Bryarly M, Hernandez R, Salter A. Randomized controlled trial of intravenous immunoglobulin for autoimmune postural orthostatic tachycardia syndrome (iSTAND). Clin Auton Res Off J Clin Auton Res Soc [Internet]. 2024 Feb 4; Available from: https://consensus.app/papers/randomized-controlled-trial-of-intravenous-salter-hopkins/f358d8be6ad1567e98c42f334ea6afb0/

26. Hupin D, Pichot V, Back M, Bonnier N, Reistam U, Runold M, et al. Diagnostic value of 24-h ECG recording in Long COVID patients with postural orthostatic tachycardia syndrome. Europace [Internet]. 2023 May 24;25. Available from: https://consensus.app/papers/diagnostic-value-of-24h-ecg-recording-in-long-covid-bruchfeldt-hupin/7b2588fe287c57c69dddad57a05d4903/

27. Seeley MC, Gallagher C, Ong E, Langdon A, Chieng J, Bailey D, et al. High incidence of autonomic dysfunction and postural orthostatic tachycardia syndrome in patients with long-COVID: Implications for management and healthcare planning. Am J Med [Internet]. 2023 Jun 1; Available from: https://consensus.app/papers/high-incidence-of-autonomic-dysfunction-and-postural-langdon-gallagher/8d732a37540b58f5b996734802e43c5f/

28. Yeh S, Lung CW, Jan YK, Lee LL, Wang YC, Liau B. The relationship between cardiovagal baroreflex and cerebral autoregulation in postural orthostatic tachycardia disorder using advanced cross-correlation function. Sci Rep [Internet]. 2024 Oct 24;14. Available from: https://consensus.app/papers/the-relationship-between-cardiovagal-baroreflex-and-wang-liau/4f359459bf225fd4ba51ac3304c42c47/

29. Seeley MC, O'Brien H, Wilson G, Coat C, Smith T, Hickson K, et al. Novel brain SPECT imaging unravels abnormal cerebral perfusion in patients with postural orthostatic tachycardia syndrome and cognitive dysfunction. Sci Rep [Internet]. 2025 Jan 28;15. Available from: https://consensus.app/papers/novel-brain-spect-imaging-unravels-abnormal-cerebral-obrien-lau/c08b6692b0555dde9d470da1eec13f83/

30. Spahic J, Mattisson I, Hamrefors V, Johansson M, Ricci F, Nilsson J, et al. Evidence for Impaired Renin Activity in Postural Orthostatic Tachycardia Syndrome. J Clin Med [Internet]. 2023 Jul 1;12. Available from: https://consensus.app/papers/evidence-for-impaired-renin-activity-in-postural-spahic-mattisson/733b2d6d6b6658649bc0cfde463e5106/

31. Van Campen C, Rowe P, Visser F. Two Different Hemodynamic Responses in ME/CFS Patients with Postural Orthostatic Tachycardia Syndrome During Head-Up Tilt Testing. J Clin Med [Internet]. 2024 Dec 1;13. Available from: https://consensus.app/papers/two-different-hemodynamic-responses-in-mecfs-patients-visser-rowe/0f6cf5a32c2e59a9866bbacf8b307d32/

32. Wang Z, Zhu T, Li X, Lai X, Chen M. Tragus Nerve Stimulation Attenuates Postural Orthostatic Tachycardia Syndrome in Post COVID-19 Infection. Clin Cardiol [Internet]. 2025 Feb 27;48. Available from: https://consensus.app/papers/tragus-nerve-stimulation-attenuates-postural-wang-zhu/5f5131bc86ad58c7bea1e95b6f8ff5bb/

33. Trimble KZ, Switzer J, Blitshteyn S. Exercise in Postural Orthostatic Tachycardia Syndrome: Focus on Individualized Exercise Approach. J Clin Med [Internet]. 2024 Nov 1;13. Available from: https://consensus.app/papers/exercise-in-postural-orthostatic-tachycardia-syndrome-switzer-blitshteyn/4e5df57e9f6e5f6191345a5b253a3ef5/

## Tables and Figures

**Figure 1.** Diagnostic criteria for Postural Orthostatic Tachycardia Syndrome (POTS)

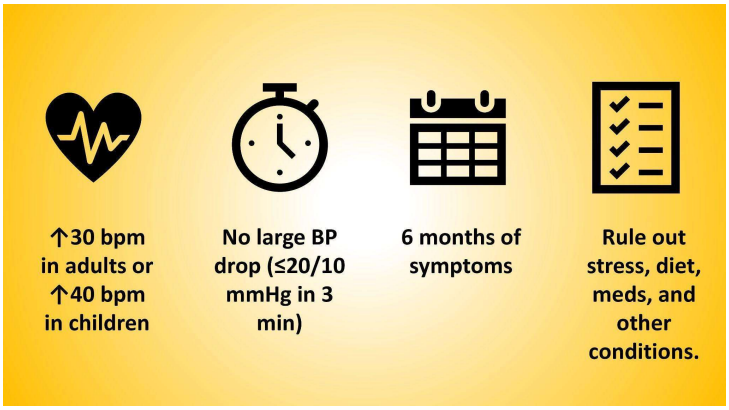


**Table 1.** Recommended Diagnostic Workup for Postural Orthostatic Tachycardia Syndrome (POTS)

| Component | Details | Reference(s) |
|---|---|---|
| **Diagnostic Criteria** | - HR increase ≥30 bpm in adults or ≥40 bpm in adolescents (12–19) within 10 minutes of standing<br>- No orthostatic hypotension (BP drop <20/10 mmHg)<br>- Symptoms present ≥6 months<br>- Rule out secondary causes (e.g., medications, anxiety, anemia, etc.) | (15) |
| **Laboratory Tests** | CBC, thyroid cascade, AM cortisol, plasma and urinary metanephrines, vitamin B12, celiac panel, ANA, Sjögren antibodies, catecholamines, antiphospholipid antibodies. | (2) |
| **Cardiology Workup** | ECG, echocardiography, 24-hour Holter monitoring. | (2) |

| | | |
|---|---|---|
| **Neurological Testing** | Brain MRI and magnetic resonance spectroscopy | (11) |
| **Other Assessments** | GI and genitourinary evaluations (including 24-hour urine collection), sleep studies. | (2) |
| **Autonomic Testing** | Tilt-table test (TTT), head-up tilt test (HUT) is considered the gold standard. | (2) |
| **Biomarkers** | - Non-specific autoimmune markers: ANA, ganglionic AChR antibodies, α1/β1/β2 adrenergic antibodies, opioid-like antibodies<br>- Cytokines: ↑ IL-1β, IL-21, TNF-α, IFN-γ, CD30; ↓ CD40L, RANTES<br>- GPCR autoantibodies also reported in some studies | (11,17) |

**Table 2.** Pharmacological Treatments for POTS

| Medication Type | Examples | Effects | Reference(s) |
|---|---|---|---|
| **Beta-blockers** | Propranolol, Bisoprolol | Lower heart rate and improve symptoms, often effective at low doses. | (20) |
| **Cholinesterase inhibitors** | Pyridostigmine | Reduce tachycardia and improve symptoms. | (20) |
| **Heart rate modulators** | Ivabradine | Used selectively for heart rate control. | (5) |
| **Volume expanders** | Oral rehydration salts. | May help especially in pediatric patients | (21) |

**Table 3.** Summary of Treatment Interventions, Side Effects, and Patient Outcomes in POTS

| Intervention | Side Effects | Patient Outcomes | Reference(s) |
|---|---|---|---|
| **Lifestyle + exercise + compression** | Generally safe; avoid salt tablets; early fatigue common | Significant improvement, possible remission. | (5,10) |
| **Pharmacologic treatments** | Need monitoring for tolerance and comorbidities | Improves orthostatic symptoms, lowers depression. | (20,21) |
| **tVNS (neuromodulation)** | None reported | Reduced tachycardia, improved HRV. | (22) |
| **Hybrid ablation** | Pericarditis (resolved), rare pneumothorax/pace maker | Complete symptom resolution, stable rhythm | (23,24) |
| **IVIG (immunotherapy)** | Mild, similar to control group | No added benefit over volume expansion | (25) |


## Acknowledgements

We affirm that all authors contributed equally to the conception, writing, and refinement of this narrative review. The order of authorship is non-hierarchical and was determined arbitrarily.

We wish that our work will be useful to the readers and contribute, even in a small way, to the general knowledge of this area.


## Conflict of Interest

The authors declare no conflicts of interest related to this work.


## Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.