Postural Orthostatic Tachycardia Syndrome

Basic Information

- Postural orthostatic tachycardia syndrome is characterized by orthostatic tachycardia in the absence of orthostatic hypotension and additional multisystem manifestations
- Common symptoms include palpitations, lightheadedness, extreme fatigue, exercise intolerance, headache, and mental clouding

Terminology

- Outdated terms for postural orthostatic tachycardia syndrome include Da Costa syndrome,[1] soldier's heart, mitral valve prolapse syndrome,[2] neurocirculatory asthenia, orthostatic tachycardia, and orthostatic intolerance[3]
- Orthostatic hypotension: sustained decrease in systolic blood pressure 20 mm Hg and higher or diastolic blood pressure 10 mm Hg and higher within 3 minutes of standing or on head-up tilt test[4]
- Initial orthostatic hypotension: transient drop in systolic blood pressure of 40 mm Hg or more, or diastolic blood pressure 20 mm Hg or more, which occurs within 15 seconds of standing, with blood pressure recovery within 45 seconds of standing[5,6]
- Peripheral acrocyanosis (postural orthostatic tachycardia syndrome feet): dependent cyanosis characterized by dark red-blue discoloration of the feet
- Orthostatic intolerance: a constellation of symptoms that include frequent, recurrent, or persistent lightheadedness, palpitations, tremulousness, generalized weakness, blurred vision, exercise intolerance, and fatigue on standing. These symptoms can occur with or without orthostatic tachycardia or syncope. Individuals with orthostatic intolerance have 1 or more of these symptoms associated with reduced ability to maintain upright posture

Epidemiology

- Postural orthostatic tachycardia syndrome primarily affects females of childbearing age
  - The female:male ratio is more than 5:1[7]
    - The reason for the strong female predominance in postural orthostatic tachycardia syndrome is not known. However, females also have a higher prevalence of orthostatic intolerance compared to males[8] and a higher prevalence of conditions that often co-occur with postural orthostatic tachycardia syndrome (eg, autoimmune disease, irritable bowel syndrome)

- A large online patient-community survey[7] of self-reported postural orthostatic tachycardia syndrome patients found that most initially present with symptoms in adolescence and early adulthood
  - The most common age of symptom onset was 14 years with a median age of 17 years, and 50% of patients had symptom onset before 18 years of age[7]
- The natural history of postural orthostatic tachycardia syndrome is not clear, but it does not appear to increase the risk of mortality[9]

Quality of Life in Postural Orthostatic Tachycardia Syndrome

- Patients with postural orthostatic tachycardia syndrome are often young females of childbearing age whose work productivity and quality of life are negatively affected[10]
- Functional impairment in patients with postural orthostatic tachycardia syndrome has been reported to be similar to that in chronic obstructive pulmonary disease and congestive heart failure[11]
- Over 25% of postural orthostatic tachycardia syndrome patients are unable to work as a result of their disability[11]
- Postural orthostatic tachycardia syndrome patients describe poorer sleep quality, more daytime sleepiness, less sleep efficiency,[12] greater fatigue, and substandard quality of life compared to healthy subjects[10]

Postural Orthostatic Tachycardia Syndrome Triggers

- Patient-reported survey data show that in approximately 40% of postural orthostatic tachycardia syndrome patients, symptoms began following acute stressors (eg, presumed viral illness [most common], pregnancy, major surgery)
- Symptoms develop more insidiously in the remainder of patients[7]
- Some patients have developed postural orthostatic tachycardia syndrome following infection with the SARS-CoV2 virus.[13] This has been termed *long-COVID postural orthostatic tachycardia syndrome*. The exact mechanisms are uncertain, but they are presumed to be a sequelae of the immune response to the virus
- A small observational study found that about 80% of female patients report an exacerbation of symptoms around menstruation[14]

Etiology and Risk Factors

Etiology

- There is likely a multitude of underlying pathophysiologic mechanisms across the spectrum of postural orthostatic tachycardia syndrome patients
  - Standing tachycardia is a final common pathway of many pathophysiologic processes

- Postural orthostatic tachycardia syndrome should be viewed as a clinical syndrome rather than a single disease
- Many disorders with orthostatic tachycardia have been described

- An overarching schema of different putative mechanisms that could lead to a postural orthostatic tachycardia syndrome presentation is shown in **Figure 1**

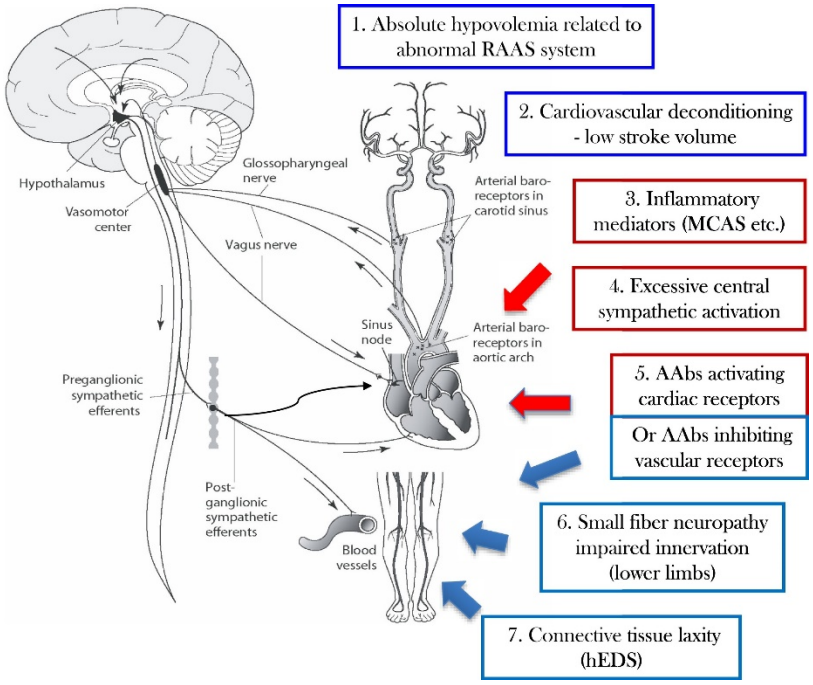

Figure 1. Possible mechanisms leading to postural orthostatic tachycardia syndrome. During upright posture, there is a gravitational shift of plasma volume toward the lower parts of the body that, if unopposed, would result in reduced cardiac preload and a fall in blood pressure. The autonomic baroreflex serves to prevent orthostatic hypotension and preserve cardiac output through sympathetic activation (peripheral vasoconstriction and increased heart rate). In postural orthostatic tachycardia syndrome, excessive orthostatic tachycardia may result from a combination of appropriate autonomic responses to various physiologic changes (shown in blue) or an inappropriate exaggeration of the sympathetic response to orthostatic stress (shown in red). Abnormal cardiovascular physiology could include (1) absolute hypovolemia due to impaired regulation of plasma volume or (2) cardiovascular deconditioning resulting in reduced cardiac mass and low stroke volume. Excessive sympathetic activation may occur in the context of (3) a systemic inflammatory state with increased inflammatory mediators (eg, increased histamine in conditions of mast cell overactivity) or (4) increased sympathetic tone driven by central nervous system (eg, anxiety or chronic pain). Autoantibodies targeting G-protein–coupled autonomic receptors (5) could produce mixed effects by acting as partial agonists that both augment cardiac sympathetic signals and reduce the efficacy of norepinephrine-induced peripheral vasoconstriction. Finally, abnormal peripheral vascular function may result from (6) peripheral small fiber neuropathy causing partial denervation in the lower extremities or (7) tissue laxity resulting in increased dependent venous pooling (which might explain an association of postural orthostatic tachycardia syndrome with hEDS).

AAbs = autoantibodies, hEDS = hypermobile form of Ehlers-Danlos syndrome, MCAS = mast cell activation syndrome, RAAS = renin-angiotensin-aldosterone system.

From Vernino S et al. Postural orthostatic tachycardia syndrome (POTS): State of the science and clinical care from a 2019 National Institutes of Health Expert Consensus Meeting - Part 1. *Auton Neurosci*. 2021;235:102828.

Coexisting Conditions

- Postural orthostatic tachycardia syndrome patients often suffer from coexisting disorders that may contribute to the overall limitations of their functional status and health-related quality of life
- **Table 1** lists the most common self-reported coexisting conditions by postural orthostatic tachycardia syndrome patients in a large patient survey[7]

Table 1. Associated disorders commonly coexisting with postural orthostatic tachycardia syndrome.

Comorbid condition	Prevalence
Chronic migraine/severe headache	40%
Hypermobile Ehlers-Danlos syndrome and hypermobile spectrum	25%
Chronic fatigue syndrome/myalgic encephalomyelitis	21%
Fibromyalgia	20%
Autoimmune disorders	16%
Mast cell activation disorder	9%

Data adapted from Shaw BH et al. The face of postural tachycardia syndrome – insights from a large cross-sectional online community-based survey. *J Intern Med*. 2019;286:438-448.

Chronic Migraines/Headaches

- Headaches are reported in approximately 90% of postural orthostatic tachycardia syndrome patients, and the most common diagnosis is migraine[15]
- Focus treatments on traditional headache management, as the directed treatment of the heart rate and blood pressure in postural orthostatic tachycardia syndrome may not decrease their frequency or severity
- A minority of patients will have headaches that are worse with upright posture. In these cases, consider the diagnosis of spontaneous intracranial hypotension[16]

Ehlers-Danlos Syndrome and Joint Hypermobility Disorders

- Ehlers-Danlos syndrome is a family of heterogeneous disorders associated with inherited abnormalities of collagen

- Key clinical problems include skin hyperextensibility, joint hypermobility, and fragile connective tissues[17]
- Patients with Ehlers-Danlos syndrome, and most commonly those with the hypermobile form of Ehlers-Danlos syndrome (formerly type III), frequently have autonomic symptoms that are also common in patients with postural orthostatic tachycardia syndrome, including lightheadedness, palpitations, chest pains, presyncope, and syncope
    - These symptoms can be triggered by exercise, warm or hot environment, and standing[18,19]
    - Similar to postural orthostatic tachycardia syndrome patients, patients with Ehlers-Danlos syndrome have disturbed sympathetic cardiovascular control on autonomic testing[20]
    - More recent studies of autonomic symptoms/function and quality of life in patients with the hypermobile form of Ehlers-Danlos syndrome confirm a high prevalence of postural orthostatic tachycardia syndrome–like orthostatic symptoms and orthostatic intolerance in these patients
    - Wallman et al.[17] found that about 18% of the postural orthostatic tachycardia syndrome patients in their sample met criteria for Ehlers-Danlos syndrome (versus 0.02% prevalence in the general population and 4% prevalence in their non–postural orthostatic tachycardia syndrome autonomic clinic patients)
    - The reasons for the relationship between postural orthostatic tachycardia syndrome and the hypermobile form of Ehlers-Danlos syndrome are unknown
    - Connective tissue abnormalities in Ehlers-Danlos syndrome could lead to vascular laxity and predispose patients to orthostatic blood pooling in the lower extremities and orthostatic intolerance, although this association has not been proven[20]
    - Alternatively, these patients might have a peripheral neuropathy that could contribute to autonomic impairment[19]

Chronic Fatigue Syndrome/Myalgic Encephalomyelitis

- Chronic fatigue syndrome/myalgic encephalomyelitis is characterized by persistent or relapsing unexplained fatigue, postexertional malaise, unrefreshing sleep, cognitive impairment, and orthostatic intolerance of at least 6 months duration[21]
- Like postural orthostatic tachycardia syndrome, chronic fatigue syndrome/myalgic encephalomyelitis is more commonly diagnosed in females
- Patients with postural orthostatic tachycardia syndrome have a high prevalence of chronic fatigue (48%-77%) and of chronic fatigue syndrome/myalgic encephalomyelitis (17%-23%)[22]

Autoimmune Disorders

- Postural orthostatic tachycardia syndrome patients have a higher than average prevalence of autoimmune disorders[7, 23] including celiac disease,[24] Hashimoto thyroiditis,[25] Sjögren syndrome,[26] and systemic lupus erythematosus[27]
- If a specific autoimmune disorder is found, target therapy toward treatment of that specific autoimmune disorder

Mast Cell Activation Syndrome

- Some postural orthostatic tachycardia syndrome patients have symptoms suggestive of abnormal mast cell activation[7]
- These postural orthostatic tachycardia syndrome patients commonly report episodes of flushing, urticaria, dyspnea, headache, excessive diuresis, and gastrointestinal symptoms (eg, diarrhea, nausea, vomiting)
- To confirm the diagnosis, assess for elevated urine methylhistamine (a histamine metabolite) or urinary 11-β-prostaglandin F_2 (a prostaglandin D_2 metabolite), acute elevations in serum tryptase, or elevation in the levels of other mast cell mediators[28]

Diagnosis

Approach to Diagnosis

Diagnostic Criteria

- Postural orthostatic tachycardia syndrome is a clinical syndrome that requires *both* excessive orthostatic tachycardia and chronic symptoms of orthostatic intolerance (**Figure 2**)[4,9,29]
    - Orthostatic tachycardia is not, by itself, sufficient to make the diagnosis of postural orthostatic tachycardia syndrome
- A diagnosis of postural orthostatic tachycardia syndrome requires the chronic presence of symptoms of orthostatic intolerance (for at least 3 months) accompanied by a heart rate increase of at least 30 beats per minute within 10 minutes of assuming an upright posture in patients 20 years or older
    - Normal physiologic orthostatic tachycardia is higher in children and adolescents and decreases with increasing age, so the threshold for *excessive orthostatic tachycardia* is a heart rate increase of at least 40 beats per minute for those patients aged 12 to 19 years
    - There is not a defined heart rate criterion in North America for patients aged younger than 12 years
- Excessive orthostatic tachycardia should occur in the absence of orthostatic hypotension (a fall in systolic blood pressure 20/10 mm Hg or more)

- The diagnosis requires the absence of prolonged bed rest, medications that impair autonomic regulation (eg, vasodilators, diuretics, antidepressants, anxiolytic agents), or any other disorders that might cause tachycardia (eg, dehydration, anemia, Addison disease, hyperthyroidism) (**Table 2**)

Table 2. Criteria for the postural orthostatic tachycardia syndrome.

• Sustained heart rate increase of 30 beats per minute or higher from supine to standing or head-up tilt within 10 minutes in patients aged 20 years or older
○ In patients aged 12 to 19 years, the heart rate increase must be 40 beats per minute or higher to be considered excessive
• The excessive orthostatic tachycardia must occur in the absence of significant orthostatic hypotension (blood pressure fall 20/10 mm Hg or more)
• Symptoms get worse with standing and better with recumbence
• Symptoms are chronic, lasting 3 or more months
• Absence of other overt cause of orthostatic symptoms or tachycardia (eg, active bleeding, acute dehydration, prolonged bedrest, hyperthyroidism, Addison disease, medications)

Caveats with the Postural Orthostatic Tachycardia Syndrome Hemodynamic Criteria

- While the heart rate criterion must occur in the absence of orthostatic hypotension, the transient orthostatic hypotension seen with initial orthostatic hypotension does not preclude the diagnosis of postural orthostatic tachycardia syndrome if orthostatic tachycardia is sustained
- Patients with postural orthostatic tachycardia syndrome may occasionally have orthostatic hypotension (especially when hypovolemic)
- Orthostatic tachycardia can vary from day to day, and throughout a day,[30] and depends on whether a stand test or a head-up tilt test[31] was used for assessment
  - Heart rate criterion does not need to be met on every assessment to maintain the diagnosis of postural orthostatic tachycardia syndrome
- Assess heart rate frequently (5-10 times), or continuously over the 10-minute upright assessment
- Excessive orthostatic tachycardia must be sustained, meaning that the heart rate above threshold should be seen on at least 2 readings at least 1 minute apart (and not a transient increase in heart rate that rapidly falls below the heart rate threshold)[29]

  - Typically, once the heart rate exceeds the threshold with upright posture, it remains that way for the upright duration
  - In contrast, the heart rate in a disorder such as initial orthostatic hypotension can increase initially and then recover over a few minutes
- Some people have a very low resting heart rate that rises to normal values on standing. Even if these reach the threshold of 30 or more beats per minute,[9] it does not necessarily indicate postural orthostatic tachycardia syndrome. Adjustment should be made for the low resting heart rate in the assessment
- The Canadian Cardiovascular Society proposed a floor resting heart rate of 60 beats per minute for the purpose of the orthostatic tachycardia assessment[29]
  - For example, if an adult had a resting heart rate of 50 beats per minute, an upright heart rate of 81 beats per minute would not be adequate to meet the postural orthostatic tachycardia syndrome heart rate criterion. Rather, they would need to have an upright heart rate 90 beats per minute or higher (based on a floor heart rate of 60 beats per minute + 30 beats per minute = 90 beats per minute)

Workup

- Include a complete history, physical examination, and measurement of orthostatic vital signs at initial evaluation
- Order routine blood tests:
  - CBC
  - Electrolyte levels (Na^+, K^+, and Cl^-)
  - Renal function (creatinine and urea)
  - TSH[32]
- Consider a ferritin level (iron stores) and a morning cortisol level to exclude Addison disease[29]
- Obtain an ECG on all patients
- Refer to a specialist (eg, cardiologist, neurologist) for additional diagnostic workup if necessary:
  - Additional laboratory studies
  - 24-hour Holter monitoring
  - Autonomic testing
  - Echocardiography
  - Tilt-table testing
  - Exercise stress tests[29]

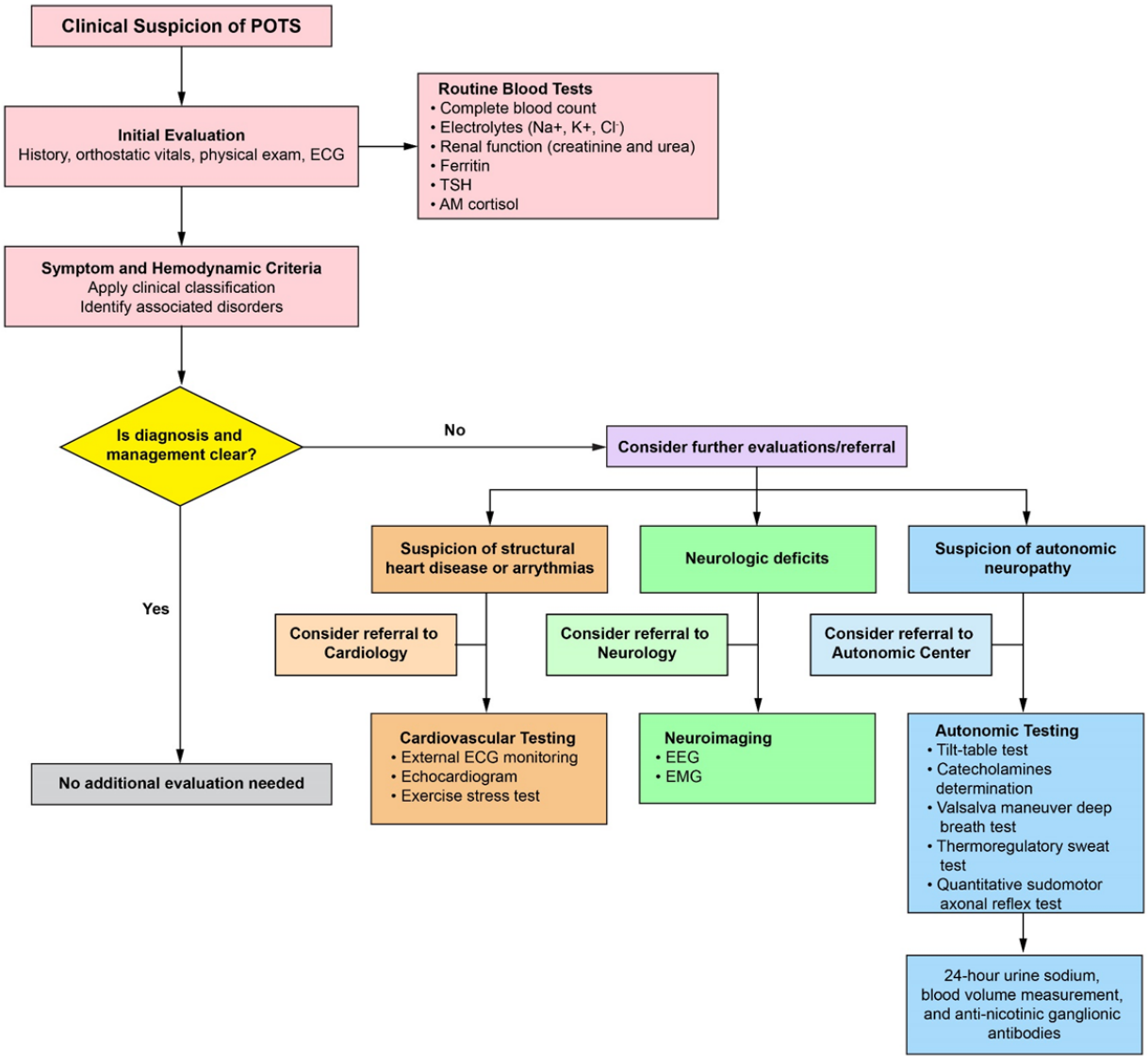

Figure 2. Postural orthostatic tachycardia syndrome diagnostic criteria algorithm. A flow algorithm that includes a diagnostic approach to postural orthostatic tachycardia syndrome, relevant investigations, and indications for referral to a specialist, to help clinicians navigate the diagnosis of postural orthostatic tachycardia syndrome and related disorders of orthostatic intolerance and orthostatic tachycardia.

ECG, electrocardiography; EDS, Ehlers-Danlos syndrome; EEG, electroencephalography; EMG, electromyography; IST, inappropriate sinus tachycardia; MCAS, mast cell activation syndrome; POTS, postural orthostatic tachycardia syndrome.

History

- Evaluate for common symptoms (see Table 2):
  - Palpitations
  - Shortness of breath
  - Tremulousness
  - Chest discomfort
  - Headache
  - Lightheadedness
  - Perceived mental clouding (brain fog)
  - Fatigue[22]
  - Nausea
  - Poor sleep[10]
- Presyncope is common in these patients; however only 20% to 30% of patients lose consciousness and experience frank syncope
- Evaluate for exercise intolerance and ability to complete activities of daily living
- Evaluate for positional changes in symptoms
  - While many symptoms may be worse with upright posture, some symptoms are not necessarily positional (eg, lightheadedness, sleep disturbances, fatigue)
- **Table 3** lists some common symptoms of orthostatic intolerance that are seen in postural orthostatic tachycardia syndrome patients

Table 3. Symptoms associated with postural orthostatic tachycardia syndrome.

Common orthostatic intolerance symptoms
– Light headedness – Palpitation (heart racing) – Dyspnea – Tremulousness – Atypical chest discomfort
Other commonly reported symptoms not necessarily associated with particular postures
– Sleep disturbances – Headaches – Chronic fatigue

– Chronic pain – Exercise intolerance and deconditioning – Perceived cognitive impairment (brain fog) – Peripheral acrocyanosis (postural orthostatic tachycardia syndrome feet) – Frequent nausea – Mild diarrhea/constipation/bloating/unspecific abdominal pain
Debilitating noncardiovascular symptoms seen in some postural orthostatic tachycardia syndrome patients
– Intractable headaches – Severe chronic pain – Joint hypermobility – Gastric emptying problems (too fast or too slow) with intractable nausea and sometimes vomiting – Severe constipation and/or diarrhea – Neurogenic bladder/incontinence/urinary retention – Significant flushing/anaphylaxis symptoms – Severe food intolerances – Paresthesia and numbness

Modified from Raj SR et al. Canadian Cardiovascular Society position statement on postural orthostatic tachycardia syndrome (POTS) and related disorders of chronic orthostatic intolerance. *Can J Cardiol*. 2020;36:357-372.

Physical Examination

- Physical examination findings are often normal in a patient with postural orthostatic tachycardia syndrome, aside from orthostatic vital signs
- Assess orthostatic vital signs to evaluate whether excessive tachycardia develops on standing from a supine position
    - Heart rate and blood pressure must be measured after lying supine for 3 to 5 minutes and then again after standing at 1 minute, 3 minutes, 5 minutes, 8 minutes, and 10 minutes
    - There should be a sustained heart rate increase of 30 beats per minute or higher in adults (and 40 beats per minute or higher in patients aged 12-19 years) and the systolic blood pressure should not fall by more than 20 mm Hg
        - In many cases, systolic blood pressure will actually increase with standing
    - Excessive tachycardia must be sustained by the end of the 10 minutes or more (not briefly go up and then come back down while still standing)[29]
- A murmur of mitral valve prolapse may be present on cardiac auscultation, but significant mitral regurgitation is unusual

- Targeted neurologic examination for signs of a peripheral neuropathy if suggestive symptoms are present
- Assess for joint hypermobility syndrome or Ehlers-Danlos syndrome, if suggested by the history
- Evaluate for peripheral acrocyanosis (postural orthostatic tachycardia syndrome feet)
    - Dependent acrocyanosis occurs in 40% to 50% of patients with postural orthostatic tachycardia syndrome (**Figure 3**), characterized by dark red-blue discoloration from the feet to above the knees (in some cases), and is cool to the touch

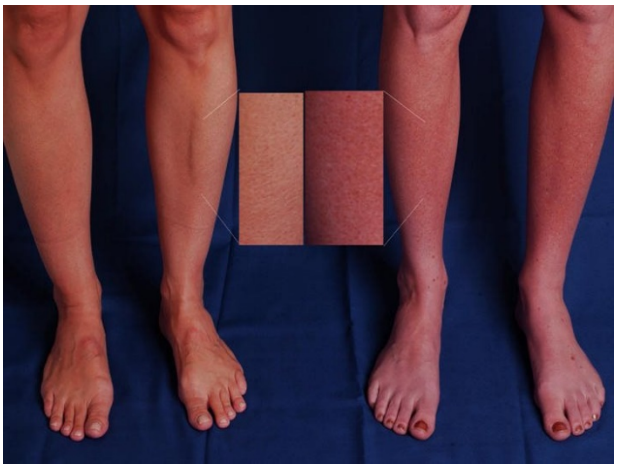

Figure 3. Acrocyanosis in postural orthostatic tachycardia syndrome. One of the more striking physical features in postural orthostatic tachycardia syndrome is the gross change in dependent skin color that can occur with standing. The panel shows the legs of 2 people who have been standing for 5 minutes. The patient with postural orthostatic tachycardia syndrome (right) has significant dark-red mottling of her legs extending up to the knees while standing, while the healthy person (left) does not have a similar discoloration.

Reproduced with permission from Raj SR. The postural tachycardia syndrome (POTS): pathophysiology, diagnosis & management. *Indian Pacing Electrophysiol J*. 2006;6:84-99.

Laboratory Tests

- In the initial evaluation for selected patients with postural orthostatic tachycardia syndrome, potential secondary causes of orthostatic tachycardia may be identified with a basic set of routine blood tests, including:
    - CBC
    - Electrolyte levels (Na+, K+, and Cl−)
    - Renal function (creatinine and urea)
    - Ferritin level
    - TSH level
    - A morning cortisol measurement to assess for adrenal failure[29]

- If there is a suggestion of an autoimmune disorder in the medical history, then targeted further testing would be appropriate

- Further testing under guidance of specialty physicians may include:
  - Assessment of plasma norepinephrine levels in both a supine and standing position (10 minutes in each position before blood sampling from an indwelling IV catheter)
    - The supine norepinephrine level is often high-normal in patients with postural orthostatic tachycardia syndrome, while the upright norepinephrine level is often elevated (more than 600 pg/mL), a reflection of the exaggerated neural sympathetic tone that is present in these patients while upright[33]
  - In evaluating for mast cell activation disorder for patients with episodic flushing coexistent with tachycardia, consider ordering the following tests as close to the episode as possible:
    - 4-hour urinary methylhistamine or prostaglandin $F_{2\alpha}$
    - Serum tryptase levels
  - Assessment of sodium intake through measurement of 24-hour urine for sodium and creatinine levels
    - Although there is slight day-to-day variability, the amount of sodium excreted in the urine is close to the amount of sodium ingested
  - There are some data suggesting that postural orthostatic tachycardia syndrome patients with low urinary sodium excretion are most responsive to increases in dietary sodium[34]

Diagnostic Procedures

ECG

- Postural orthostatic tachycardia syndrome patients should have only sinus tachycardia
- Order an ECG routinely to rule out the presence of an accessory bypass tract or any abnormalities of cardiac conduction[9,29]
  - A Holter monitor[9] may be prescribed to evaluate for presence of a re-entrant dysrhythmia, especially if the patient gives a history of paroxysmal tachycardia with a sudden onset and sudden offset
- If there is concern about underlying structural heart disease or accessory pathways, conduct further cardiac testing under the supervision of a cardiologist
  - Postural orthostatic tachycardia syndrome patients should not have structural heart disease
    - If structural heart disease cannot be ruled out clinically, then echocardiography might be warranted

Other Diagnostic Tools

- Further diagnostic testing is generally managed by specialty physicians or centers that focus on autonomic or neurologic disorders

Autonomic Testing

- **Head-up Tilt Table Test**
  - Head-up tilt table test is a common test for autonomic functioning as a standardized method to assess the response to upright posture[35]
  - The patient is positioned supine on a tilt table; following baseline measurements of blood pressure and heart rate, the patient is inclined to a 70° head-up angle
  - Blood pressure and heart rate are ideally measured continuously with a beat-to-beat blood pressure monitor
  - A similar threshold is used to diagnose orthostatic tachycardia (an increase of more than 30 beats per minute in adults) with the tilt test as with the active stand test
- **Autonomic Cardiovascular Reflex Testing**
  - Test results of cardiovascular autonomic nervous system function typically show intact or exaggerated autonomic reflex responses
  - Patients with postural orthostatic tachycardia syndrome often have preserved cardiovagal function as reflected by sinus arrhythmia ratio in response to deep breathing
  - Patients with postural orthostatic tachycardia syndrome often have a vigorous pressor response to the Valsalva maneuver, with an exaggerated blood pressure recovery before release and exaggerated blood pressure overshoot after release, although this response can vary
    - The vigor of the heart rate and blood pressure responses may be useful to guide initial therapies, according to clinical experience
      - Patients with a blunted blood pressure recovery may benefit more from a pressor medication (eg, midodrine)
      - Patients with a vigorous blood pressure recovery may be more hyperadrenergic and may respond to central sympatholytic medications

Blood Volume Assessment

- The blood volume is low in many patients with postural orthostatic tachycardia syndrome[36]
- Blood volume can be objectively assessed with nuclear medicine tests to directly measure either the plasma volume or the red cell volume (or mass)
- This knowledge may help to focus the treatment plan

Neuropsychological Evaluation

- Patients with postural orthostatic tachycardia syndrome may present with symptoms of depression, anxiety, and memory deficits
- Consider referring for formal neuropsychological testing to evaluate for deficits in cognition, memory, or executive functioning if patients have such complaints
    - Raj et al. demonstrated that postural orthostatic tachycardia syndrome patients did not have a higher rate of anxiety disorders, major depressive disorder, or substance abuse than the general population[37]
    - Arnold et al.[38] performed a comprehensive neuropsychological evaluation of 28 postural orthostatic tachycardia syndrome patients and found impaired executive functioning and deficits in selective attention and cognitive processing, but no difference in memory function, compared to healthy controls

Differential Diagnosis

Table 4. Differential diagnosis: postural orthostatic tachycardia syndrome.

Condition	Description	Differentiated by
Orthostatic hypotension	Sustained decrease in systolic blood pressure 20 mm Hg or more, or in diastolic blood pressure 10 mm Hg or more, within 3 minutes of standing or on head-up tilt test[4]	Orthostatic hypertension patients are often older, and they may have signs of a neurodegenerative disease; POTS patients have tachycardia in the absence of hypotension
Initial orthostatic hypotension	Transient drop in systolic blood pressure of 40 mm Hg or more, or in diastolic blood pressure 20 mm Hg or more, that occurs within 15 seconds of standing, with blood pressure recovery within 45 seconds of standing; there can be a reflex tachycardia[5,6]	POTS symptoms do not get better with continued standing
Vasovagal syncope	A form of reflex (or neurally mediated) fainting preceded by sustained upright posture (standing or sitting with the legs down) Can be triggered by pain, emotional distress, severe anxiety Usually characterized by hypotension Heart rate can be low, normal, or elevated	POTS patients often feel faint, but only a minority have true syncope

Inappropriate sinus tachycardia	Characterized by symptomatic resting sinus tachycardia without an obvious other cause.[39] The criteria require a supine daytime resting heart rate 100 beats per minute or more, or a 24-hour mean heart rate 90 beats per minute or more.[9] There may be excessive orthostatic tachycardia, although it is not required for diagnosis	POTS associated with tachycardia upright, but often normal heart rate while supine
Pheochromocytoma	Paroxysms of hyperadrenergic symptoms caused by elevated epinephrine and norepinephrine secretion from an adrenal tumor. Patients with either POTS or pheochromocytoma can have very high heart rate while upright, but patients with pheochromocytoma are more likely than POTS patients to have symptoms while lying down	Supine plasma norepinephrine (and normetanephrine) levels are usually higher in patients with pheochromocytoma
PSWT[29]	If a patient has typical symptoms of orthostatic intolerance, but does not exhibit excessive orthostatic tachycardia, they are said to have PSWT	No excessive orthostatic tachycardia
Postural tachycardia owing to an underlying medical condition or PTOC	Patients meet diagnostic criteria for POTS but have acute or chronic medical conditions or a medication that could exacerbate orthostatic tachycardia. If the contributary condition resolves, they can be reassessed to see if they meet POTS criteria	Comorbid condition, potentially treatable, that could underlie or exacerbate orthostatic tachycardia

POTS, postural orthostatic tachycardia syndrome; PSWT, postural symptoms without tachycardia; PTOC, postural tachycardia of other cause.

Treatment

Nondrug and Supportive Care

- Focus initial treatment efforts on identifying and treating any reversible causes
- Withdraw potentially contributory medications, especially vasodilators, diuretics, and drugs that inhibit the norepinephrine transporter, such as:
    - Atomoxetine
    - Duloxetine
    - Reboxetine
    - Stimulants

  - Venlafaxine
- Treatment modalities include increased water and salt intake, use of compression stockings, exercise, and possible use of IV saline infusion
- Optimize treatment for any chronic disease that is present
- Focus patient education on avoidance of aggravating factors (eg, dehydration, extreme heat)

Table 5. Nonpharmacologic treatment modalities for postural orthostatic tachycardia syndrome.

Therapy	Dosage	Comments
Water	3 L/day	Can be a challenge in patients with gastroparesis
Increase dietary salt	10-12 g NaCl/day (2 teaspoons)	To help to retain more fluid; can cause nausea (especially on an empty stomach)
Waist-high compression garments/abdominal binder	30-40 mm Hg counter-pressure; abdominal binder or waist-high Triathlon tights	Works to enhance venous return when upright; abdominal compression is more important than leg compression
Exercise	30 minutes x 4 days per week; primarily aerobic reconditioning	Non-upright (eg, rowing, recumbent cycle); often feels worse before improvement
Acute IV saline	1 L normal saline over 1-3 hours IV	Effective at acute heart rate control; inconvenient; medical setting needed

NaCl, sodium chloride; POTS, postural orthostatic tachycardia syndrome.

Increase Dietary Salt and Water Intake

- Both the Heart Rhythm Society[9] and the Canadian Cardiovascular Society[29] recommend that postural orthostatic tachycardia syndrome patients ingest a significant amount of water and sodium. However, there are no data on the long-term efficacy of this approach
- 3L of water per day is recommended and 10g NaCl (approximately 2 teaspoons of salt per day)

- Recent data suggest that high dietary sodium (compared to low dietary sodium) increases plasma volume, reduces standing plasma norepinephrine, and reduces standing tachycardia in postural orthostatic tachycardia syndrome patients[40]
- Dietary salt intake does not have a major effect on serum sodium levels (because it leads to a plasma volume expansion, which normalizes the serum concentration)

Waist-High Compression Stockings

- Use of high-waist compression stockings targeting abdomen and thighs, or an abdominal binder, can provide hemodynamic support for patients with postural orthostatic tachycardia syndrome and is recommended by subject matter experts[29]
- In a proof-of-concept study, external compression from the abdomen to the legs decreased the drop in stroke volume and reduced the heart rate with head-up tilt[41]

Exercise Training Program

- Exercise training has been repeatedly shown to improve symptoms in patients with postural orthostatic tachycardia syndrome[42-44]
- One study found that 3 months of exercise training decreased orthostatic tachycardia, decreased symptom burden, and improved quality of life[45]
- Non-upright exercises are strongly recommended:
    - Rowing machines
    - Recumbent cycles
    - Swimming
- Exercise should be performed regularly (every other day; 4 per week) for 30 minutes duration each session[46]
- Counsel patients that they may feel worse initially and may require a graded approach to exercise therapy (for up to 6 weeks); however, sustained exercise often leads to symptom improvements

Acute Blood Volume Expansion

- IV saline provides some patients with symptomatic relief and control of heart rate[47]
- While IV saline can be used in an acute or emergent setting, it is not a practical plan for long-term management. The primary concern is long-term IV access and the complications of central catheters
- Both the Heart Rhythm Society[9] and Canadian Cardiovascular Society[29] have made regular and repeated saline infusions a class III recommendation (recommendation against routine use)

Drug Therapy

Pharmacologic Treatment of Postural Orthostatic Tachycardia Syndrome

- There are no FDA-approved medications for the treatment of postural orthostatic tachycardia syndrome; thus, all medications that are used for this disorder are off-label
- No pharmacologic agents have been tested in randomized clinical trials lasting longer than 1 month. A summary of pharmacologic approaches to treating postural orthostatic tachycardia syndrome is shown in **Table 6**[48]

Table 6. Pharmacologic treatments for postural orthostatic tachycardia syndrome.

Therapy	Dosage	Comments
Propranolol	10-20 mg PO 4 times a day	Nonselective β-blocker; use in low doses; can worsen fatigue or hypotension
Ivabradine	2.5-7.5 mg PO 2 times a day	I_{funny} (I_f) channel blocker; can cause visual disturbance or fatigue; can be expensive
Midodrine	2.5-15 mg PO 3 times a day	α-1 adrenergic receptor agonist; can cause piloerection, worsen headaches, or rarely urinary retention
Pyridostigmine	30-60 mg PO 3 times a day	Peripheral acetylcholinesterase inhibitor; can increase colonic motility with cramping and diarrhea; can worsen bladder irritability (but may be helpful in patients with constipation)
Methyldopa	125-250 mg PO 2 times a day	False neurotransmitter; decreases central sympathetic nervous system traffic; can cause hypotension and drowsiness

Clonidine	0.05-0.2 mg PO 2 to 3 times a day, *or* 0.1-0.3 mg/24-hours transdermal patch every 7 days	Agonist of presynaptic α-2 receptor; decreases central sympathetic nervous system traffic; can worsen mental clouding, fatigue, or drowsiness. Abrupt cessation can lead to rebound hypertension
Fludrocortisone	0.05-0.2 mg PO daily (can split dose)	Blood volume expansion; can cause hypokalemia (check K^+); worsen headaches, hypertension, osteoporosis, edema
DDAVP	0.1-0.2 mg PO daily or nightly	Blood volume expansion; can cause hyponatremia (check Na^+); can worsen headache or edema
Modafinil	100-200 mg PO up to 2 times a day	Mild stimulant; may reduce mental clouding; mild increase in heart rate

DDAVP, desmopressin; PO, by mouth; POTS, postural orthostatic tachycardia syndrome.

Propranolol

- Propranolol can be a useful first line medication in many patients who are symptomatic from the tachycardia that occurs with standing
- It may be particularly useful in those with very high standing heart rates
- Experts in the field recommend 10 to 20 mg up to 4 times a day[49]
- Goal of treatment is to improve excessive tachycardia but not normalize it completely
  - Complete normalization of heart rate will usually cause intolerable symptoms
- Higher doses cause excessive fatigue and are typically not tolerated
  - While small doses of propranolol (20 mg) can lead to significant symptomatic improvement in postural orthostatic tachycardia syndrome patients, higher doses (80 mg) can aggravate symptoms[49]

Ivabradine

- Ivabradine[50] has recently been approved by the FDA for treatment of heart failure. It is a I_{funny} (I_f) channel blocker that lowers the heart rate, with little effect on blood pressure
- One nonrandomized case series found that 60% of patients with postural orthostatic tachycardia syndrome reported relief on this medication[51]
- Recently, a small randomized trial of ivabradine was performed in 22 patients with hyperadrenergic postural orthostatic tachycardia syndrome.[52] Ivabradine improved symptoms more than placebo in this cohort, providing the first high-quality evidence for ivabradine in this group
- The starting dose is often 5 mg twice daily with up- or down-titration to 7.5 mg or 2.5 mg per dose[29]
- It is fairly well tolerated, although some patients describe visual alterations or fatigue
- Ivabradine is associated with fetal toxicity; thus, females with reproductive potential must use effective contraception

Midodrine

- Midodrine is a prodrug that is converted to desglymidodrine, a selective α1-adrenergic agonist, and acts as both a vasoconstrictor and venoconstrictor
- Midodrine may be particularly helpful in patients with very soft blood pressures, where a decrease in peripheral venoconstriction or vasoconstriction may be present
- Midodrine has a half-life of about 4 hours
  - Peak concentrations are reached in 1 to 2 hours[53]
- Typical dose is 2.5 to 15 mg every 4 hours, up to 3 times a day[29]
- Common adverse effects include piloerection, scalp tingling, urinary retention, and headache

Pyridostigmine

- Pyridostigmine is an acetylcholinesterase inhibitor, which increases levels of acetylcholine at postganglionic muscarinic and nicotinic receptors, leading to a net increase in parasympathetic tone
- It can decrease the heart rate in response to standing and reduce symptom burden in patients with postural orthostatic tachycardia syndrome[54]
- When used in clinic outpatients, the majority of postural orthostatic tachycardia syndrome patients reported improvement, but approximately 20% of patients had to stop medication owing to adverse effects of diarrhea and abdominal cramping[29,55]
- Typical dose is 30 to 60 mg 3 times a day

Central Sympatholytic Medications

- Central sympatholytic medications are often useful and well tolerated in postural orthostatic tachycardia syndrome patients with severe hyperadrenergic features, but may not be as well tolerated in hyperadrenergic symptoms at doses of 125 mg to 250 mg PO twice a day[56]
  - Starting dose is recommended to be 125 mg at bedtime and with slow increase by 125 mg per increment
  - Avoid use for patients with active liver disease
- Clonidine is an α-2 agonist that acts centrally to decrease sympathetic nervous system tone
  - Clonidine, at doses of 0.05 mg to 0.2 mg PO 2 to 3 times daily, can stabilize heart rate and blood pressure in patients with grossly excessive sympathetic nervous system tone
  - Clonidine may also be administered via transdermal patch, which may be advantageous owing to continuous medication release, at doses of 0.1 to 0.3 mg/24 hours applied every 7 days
  - Clonidine has a short half-life, and it can cause drowsiness and fatigue and worsen the mental clouding of some postural orthostatic tachycardia syndrome patients. Abrupt discontinuation of clonidine may precipitate withdrawal symptoms

Fludrocortisone

- Fludrocortisone (an aldosterone analogue) can be added for patients with hypovolemia who do not respond to augmentation of salt and water intake
- Through enhanced sodium retention, it theoretically expands the plasma volume, although there is a paucity of data regarding the exact mechanisms of action
- Adverse effects can include hypokalemia, hypomagnesemia, worsening migraine headaches, acne, and fluid retention with edema, although it is usually well tolerated in most individuals
- Doses of up to 0.2 mg/day have a low incidence of hypokalemia and are unlikely to suppress the hypothalamic-pituitary-adrenal axis[57]

Desmopressin

- Oral vasopressin is a volume-expanding agent that may be helpful for short-term use by causing the kidney to retain free water but not sodium
- There is evidence that oral vasopressin 0.2 mg PO and 500 mL water can acutely lower orthostatic tachycardia and improve symptoms[58]
- Check serum sodium at least weekly to monitor for potential adverse effects, including edema, headache, and hyponatremia
- Excessive use is strongly discouraged

Modafinil

- Modafinil is a stimulant (with unclear mechanism) that some postural orthostatic tachycardia syndrome patients have used improve alertness at a dose of 100 mg twice daily
- Modafinil can increase sympathetic activation,[59] but it seems to increase heart rate only modestly in postural orthostatic tachycardia syndrome patients[60]
- Caution is advised as it may aggravate the orthostatic tachycardia[8]

Treatment Procedures

- Procedural treatments for postural orthostatic tachycardia syndrome are all considered class III (do not routinely recommend) by both the Heart Rhythm Society and the Canadian Cardiovascular Society[9,29]
- Radiofrequency modification of the sinus node can lower or eliminate the tachycardia, but they often do not improve symptoms
    - This is an area of ongoing procedural research

Persistent or Recurrent Disease

- Postural orthostatic tachycardia syndrome is a chronic condition that can be treated but not typically cured
- The clinical course can wax and wane with improvements followed by setbacks due to various stressors

Admission Criteria

- The management of postural orthostatic tachycardia syndrome is a long-term endeavor that is usually best managed in an outpatient setting
- Admission is driven by associated clinical problems that justify it, and not because of a diagnosis of postural orthostatic tachycardia syndrome

Special Considerations

POTS Plus

- Patients with postural orthostatic tachycardia syndrome may have a combination of orthostatic and/or nonorthostatic symptoms
  - Patients may have variable improvement of orthostatic symptoms and nonorthostatic symptoms during their postural orthostatic tachycardia syndrome treatment
  - In some cases, persistent severe nonorthostatic symptoms may reflect another underlying problem
  - The terms *POTS plus* can be used to reflect the added complexity from these symptoms or significant coexisting conditions

Follow-up

Monitoring

- Specialists with experience with autonomic dysfunction should follow postural orthostatic tachycardia syndrome patients regularly on an outpatient basis, as treatments will sometimes need adjustment
- Monitor orthostatic vital signs and other associated symptoms for improvement

Prognosis

- Robust data are lacking regarding the long-term prognosis in postural orthostatic tachycardia syndrome
- Very few adult patients are cured, but many experience improvement in their symptoms and daily function with treatment
- There is a suggestion that children with postural orthostatic tachycardia syndrome may have significant improvement or abatement of symptoms once they reach adulthood, but the data are quite poor

Referral

- Postural orthostatic tachycardia syndrome patients have a multisystem illness and often require the expertise of a myriad of specialists
- The primary postural orthostatic tachycardia syndrome specialists often have initial training in neurology, cardiology, or internal medicine, but their interest and expertise in the management of postural orthostatic tachycardia syndrome is more important than their primary Medical Board certification
- Refer to a cardiologist if there is concern about structural heart disease or arrhythmia

- Refer to a neurologist if patient presents with neurologic deficits or for management of complicated headaches or migraine
- Refer to a gastroenterologist if there are significant gastrointestinal motility issues
- Refer to an allergist or immunologist for signs of mast cell activation syndrome, multiple allergies, or signs such as dermographism
- Refer to a geneticist if there is concern about coexistent Ehlers-Danlos syndrome
- Consider a physiotherapist to help with the exercise program or joint stabilization

Summary

Key Points

- The cardinal feature of postural orthostatic tachycardia syndrome is excessive orthostatic tachycardia
- Postural orthostatic tachycardia syndrome is a chronic multisystem disorder with many different potential manifestations
- The typical patient with postural orthostatic tachycardia syndrome is a female of childbearing age
- Postural orthostatic tachycardia syndrome is associated with poor quality of life and significant functional disability
- Postural orthostatic tachycardia syndrome patients often have neurocognitive complaints (brain fog), but do not seem to have a higher rate of anxiety or depression than the general population
- Patients with postural orthostatic tachycardia syndrome often feel faint, and 20% to 30% will experience syncope
- While postural orthostatic tachycardia syndrome cannot be cured, it can be treated
- Treatment begins with nonpharmacologic approaches to increase blood volume (augmented dietary salt and water), aerobic exercise training (non-upright at least initially), and lower-body compression garments
- Many patients with postural orthostatic tachycardia syndrome will require medications in addition to the nonpharmacologic approaches. However, there are no FDA-approved pharmacologic treatments for postural orthostatic tachycardia syndrome

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