

# The postural tachycardia syndrome: When to consider it in adolescents

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**ABSTRACT** The postural tachycardia syndrome (POTS) is characterized by symptoms of orthostatic intolerance and an exceedingly high heart rate—but often not orthostatic hypotension—on first standing up. Symptoms can include palpitations, fatigue, nausea, headache, near syncope, and syncope and be severe enough to limit daily functioning. The developmental form of this syndrome affects adolescents, often beginning around 14 years of age after a rapid growth spurt and peaking at about age 16. In general, the younger the patient with POTS, the better the prognosis, and most of those with the developmental form respond to combined physical therapy and pharmacotherapy by their mid-20s.

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Since the mid-1980s, there has been a substantial increase in our understanding of illnesses that result from disturbances in the autonomic nervous system.<sup>1</sup> Attention was initially focused on conditions such as neurocardiogenic (vasovagal) syncope. During the course of these investigations, it became evident that a subgroup of patients suffered from a related (yet distinct) condition characterized by postural tachycardia, fatigue, and exercise intolerance.<sup>2,3</sup> This disorder has now come to be known as the postural tachycardia syndrome (POTS) and is composed of a group of diverse conditions that share similar clinical characteristics. This review outlines the presentation, diagnosis, and management of POTS.

## The defining characteristics of POTS

The principal feature of these conditions is orthostatic intolerance, defined as the provocation of symptoms after assuming upright posture that are relieved by recumbence.<sup>1,2</sup> Patients complain of palpitations, fatigue, lightheadedness, exercise intolerance, nausea, headache, near syncope, and syncope. Symptoms may be severe enough to limit the performance of daily activities such as bathing, housework, and even eating.<sup>4</sup> POTS patients have been reported to suffer from a degree of functional impairment similar to that seen in conditions such as congestive heart failure or chronic obstructive pulmonary disease.<sup>5</sup> All too often these patients are misdiagnosed as having severe anxiety or panic disorder. A system for grading the degree of functional impairment in POTS has been developed<sup>6</sup> (Table 1, page 20).

POTS is currently defined as symptoms of orthostatic intolerance associated with documented heart rate increases of 30 or more beats per minute (or a rate that exceeds 120 beats per minute) that occurs

**Table 1**

Grades of orthostatic intolerance	
Grade 0	Normal orthostatic tolerance
Grade I	<p>Orthostatic symptoms are infrequent or occur only under conditions of increased orthostatic stress.</p> <p>Subject is able to stand &gt; 15 minutes on most occasions.</p> <p>Subject typically has unrestricted activities of daily living.</p>
Grade II	<p>Orthostatic symptoms are frequent, developing at least once a week. Orthostatic symptoms commonly develop with orthostatic stress.</p> <p>Subject is able to stand &gt; 5 minutes on most occasions.</p> <p>Some limitation in activities of daily living is typical.</p>
Grade III	<p>Orthostatic symptoms develop on most occasions and are regularly unmasked by orthostatic stresses.</p> <p>Subject is able to stand &gt; 1 minute on most occasions.</p> <p>Patient is seriously incapacitated, being bed- or wheelchair-bound because of orthostatic intolerance.</p> <p>Syncope/presyncope is common if patient attempts to stand. Symptoms may vary with time and state of hydration and circumstances.</p> <p>Orthostatic stresses include prolonged standing, a meal, exertion, and head stress.</p>

Source: Low PA, Novak V, Novak P, et al. Postural tachycardia syndrome. In: Low PA, ed. *Clinical Autonomic Disorders: Evaluation and Management*. 2nd ed. Philadelphia, Pa: Lippincott-Raven; 1997:681-698.

within the first 10 minutes of standing or upright tilt; it is not associated with other chronic debilitating conditions such as protracted periods of bed rest or the use of medications known to affect vascular or autonomic function.<sup>7</sup> The estimated prevalence of those who are affected by POTS in the United States is at least 500,000.<sup>8</sup> A number of patients with orthostatic intolerance due to POTS will not manifest orthostatic hypotension (defined as a fall of more than 20/10 mm Hg). Instead, they may have no change, a small decline, or even a modest increase in blood pressure on standing.<sup>1</sup> Some investigators have noted that fo-

cus on heart rate ignores many of the additional autonomic symptoms that affect POTS patients, such as disturbances in sweating, temperature regulation, and bowel and bladder function.<sup>1</sup>

**Classifying POTS: A many-faceted syndrome**

As noted, POTS appears to be a diverse group of disorders with similar clinical characteristics. Most investigators classify the syndrome as primary or secondary.<sup>9</sup> The primary forms are not associated with other disease states, while the secondary forms occur in conjunction with a known disease or disorder. Proper management depends on the adequate recognition of the subtype affecting the patient.

The most frequently encountered form of POTS is referred to as the partial dysautonomic (PD) form.<sup>2,9</sup> These patients appear to have a mild form of peripheral autonomic neuropathy in which the peripheral vasculature (especially the venous system) cannot initiate or maintain vascular resistance in the face of gravitational stress. This results in a much greater than normal amount of blood pooling in the more dependent areas of the body (legs, lower arms, and lower part of the splenic vasculature).<sup>9</sup>

This tremendous sequestration of blood away from the central vasculature produces a compensatory increase in heart rate and myocardial contractility that tries to maintain a constant degree of cerebral perfusion. This increased heart rate and contractility may at first compensate fully for a given degree of peripheral venous pooling, but over time the amount of pooling may increase and exceed the compensatory effect.<sup>2,3</sup> Affected individuals then depend increasingly on their skeletal muscle pump to maintain adequate blood pressure until the peripheral pooling exceeds its compensatory effects as well, producing an even greater degree of blood pooling.

Interestingly, there is a roughly 5:1 female-to-male ratio in this form of POTS. A number of patients report that symptom onset occurred after an acute febrile illness (presumed to be viral) or after immunization, pregnancy, sepsis, surgery, or trauma. Current thinking is that a number of patients with the PD form of POTS have an autoimmune disorder. A series of studies have found serum autoantibodies to  $\alpha 3$  acetylcholine receptors in the peripheral autonomic ganglia in patients with a postviral cause.<sup>10,11</sup>

A second type of primary PD POTS, labeled devel-

opmental, has recently been elaborated. This form affects adolescents and often begins around 14 years of age (frequently after a period of very rapid growth and development). Symptoms steadily worsen and usually reach their peak around age 16. Orthostatic intolerance and other symptoms (such as headache and nausea) may be of such severity that the patient is functionally disabled. Once this peak is reached, symptoms will slowly fade so that by young adulthood (19-24 years) about 80% are asymptomatic. The cause remains unclear but is currently felt to represent a temporary period of autonomic imbalance that may occur in some rapidly growing adolescents.<sup>9</sup>

Another distant form of primary POTS, termed hyperadrenergic,<sup>9</sup> is far less common than the others. Patients often report a slower, more progressive onset of symptoms over long periods of time. These patients are more likely to report symptoms such as anxiety, tremor, and cold sweaty extremities. More than half experience migraine headaches and a significant increase in urinary output after being upright for even a short time. The major differentiating feature is that many of these patients manifest orthostatic hypertension in addition to orthostatic tachycardia. Many will also have an exaggerated response to intravenous isoproterenol and will have significantly elevated serum norepinephrine levels (above 600 ng/mL). Early observations of a strong familial tendency in hyperadrenergic POTS led to identifying a genetic basis of the disorder. A landmark study by researchers at Vanderbilt identified a single point mutation resulting in a poorly functioning reuptake transporter protein that clears and recycles norepinephrine from the intrasynaptic cleft.<sup>12</sup> This leads to an excessive norepinephrine spill-over in response to a number of sympathetic stimuli, thus producing a relative hyperadrenergic state, (not unlike that seen in pheochromocytoma).<sup>13</sup>

The term secondary POTS designates a wide variety of conditions that result in peripheral autonomic deinnervation or vascular unresponsiveness with relative sparing of cardiac innervation. The most frequently encountered form is associated with chronic diabetes mellitus, but it may also accompany disorders such as sarcoidosis, amyloidosis, systemic lupus erythematosus (SLE), Sjögren's syndrome, alcoholism, chemotherapy, and heavy metal intoxication.

A recently identified cause of secondary POTS is the connective tissue disorder known as joint hyper-

mobility syndrome (JHS).<sup>14</sup> This genetic syndrome is due to replacement of certain types of collagen with a more elastic form, resulting in connective tissue fragility, joint hypermobility, and skin with a soft (almost velvety) feel. Patients may experience early varicose veins, easy bruisability, postural acral cyanosis, and diffuse muscle and joint pain. The condition may also cause POTS because the abnormal degree of elasticity of the vasculature (in particular the venous system) does not maintain an adequate degree of vasoconstriction in the face of orthostatic stress, allowing excessive peripheral vascular pooling of blood with subsequent compensatory tachycardia. Recent investigations have reported that as many as 70% of indi-

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*Developmental POTS affects  
adolescents, often beginning around  
age 14, peaking at 16, then  
slowly fading in young adulthood.*

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viduals with JHS may be predisposed to orthostatic intolerance.<sup>14</sup> Some think there may be a connection between JHS and the developmental form of POTS, and this potential relationship is under investigation.

On occasion, POTS may be the presenting form of the more severe autonomic nervous system disorders such as pure autonomic failure and multiple systems atrophy. POTS can also be a paraneoplastic syndrome and occur in association with adenocarcinoma of the breast, lung, pancreas, and ovary. Mayo Clinic studies have demonstrated that the tumors make antibodies against acetylcholine receptors in the autonomic ganglia,<sup>10</sup> much like those seen in postviral syndromes.<sup>15</sup> Current trials are under way to better identify and categorize these antibodies.

### **POTS evaluation and management**

A careful history is the single most important part of the evaluation. When did symptoms begin? Was the onset abrupt or gradual? Were there any associated events such as infection? What symptoms bother the

Table 2

Drugs that can cause or worsen orthostatic intolerance
$\alpha$ -Receptor blockers
Angiotensin-converting-enzyme inhibitors
$\beta$ -Blockers
Bromocriptine
Calcium channel blockers
Diuretics
Ethanol
Ganglionic blocking agents
Hydralazine
Monoamine oxidase inhibitors
Nitrates
Opiates
Phenothiazines
Sildenafil citrate (Viagra)
Tricyclic antidepressants

patient most? Are symptoms other than cardiovascular involved, such as gastrointestinal, thermoregulatory, or sudomotor?

Equally important is the physical examination, which should also include a careful neurologic examination. Heart rate and blood pressure should be measured supine, sitting, upon initial standing, and at intervals of 2, 5, and 10 minutes. Examination of the extremities while upright may reveal a bluish, mottled discoloration (acral cyanosis) that may indicate peripheral venous pooling. As heart rate and blood pressure responses are variable during upright posture, we often perform tilt table testing, as it is a more controlled setting with fewer variables. In select patients, other tests of autonomic function such as thermoregulatory sweat testing, sudomotor axon testing, and cold pressor tests may be useful for evaluating certain symptoms. Specimens for serum levels of dopamine, epinephrine, and norepinephrine should be obtained in the supine and upright positions in patients in whom the hyperadrenergic form of POTS is suggested. More detailed information regarding these disorders can be found elsewhere.

Adequate treatment depends on adequate diagnosis. Any pharmacotherapy that may be exacerbating the patient's condition should be stopped (Table 2), and any condition that may be contributing to POTS should be diagnosed and adequately treated.<sup>16</sup> We encourage all patients to start a reconditioning program

with a goal of at least 20-30 minutes of aerobic activity three or more times a week. We also recommend resistance training of the lower extremities in order to enhance the effectiveness of the peripheral skeletal muscle pump. Patients are also told to drink about 2 L of fluid a day and ingest 2-4 g of salt (except patients with the hyperadrenergic form of POTS). Compression stockings can sometimes be helpful in the PD form of POTS, but to be effective must be waist high and provide at least 30 mm Hg of ankle counterpressure.

While conservative measures alone are effective in treating some patients, others will be so ill that some form of pharmacotherapy will be required. Pharmacotherapy is used to stabilize patients enough for them to pursue reconditioning. It should be noted that the Food and Drug Administration has not approved any drug for treating POTS, and any treatment mentioned in this article is thus off-label. Correctly identifying the subtype is valuable in selecting appropriate pharmacotherapy (Table 3).

- *Therapy for the PD form of POTS* is frequently aimed at increasing peripheral vascular resistance and fluid volume, for which we often use fludrocortisone acetate, 0.1-0.2 mg qd. The drug promotes sodium and fluid retention and also seems to promote vascular constriction. An alternative agent is desmopressin acetate (DDAVP), 0.1-0.2 mg at bedtime. If necessary, we next add a vasoconstrictor such as midodrine HCl (Pro-Amatine), beginning at 5 mg tid. The dose may be progressively increased to 10-15 mg qid if needed. It is often useful to give the first dose of midodrine around 15-20 minutes before getting out of bed in the morning, since symptoms may be worse then. The most common side effects of midodrine are "goose bumps," scalp tingling, and nausea. In patients who cannot tolerate midodrine, an effective substitute can be methylphenidate HCl (Ritalin, Methylin, Concerta, etc.). Some authors have also used yohimbine as successful therapy, again because of its vasoconstrictive effects.

If the combination of a volume expander and vasoconstrictor is not effective, we add either a serotonin reuptake inhibitor (SSRI) or a norepinephrine inhibitor, although SSRIs appear to be more effective in treating neurocardiogenic syncope than POTS. The norepinephrine reuptake inhibitor that we usually use is the extended formulation of bupropion (Wellbutrin XL) starting at 150 mg qd and increasing to 300 mg

Table 3

Therapeutic options in POTS			
Treatment	Application	Effective in	Problems
Reconditioning	Aerobic exercise 20 min 3 times/wk	PD, H	If too vigorous may worsen symptoms
Hydration	2 L qd	PD	Edema
Salt	2-4 g/d	PD	Edema
Bupropion (Wellbutrin XL)	150-300 mg qd	PD, H	Tremor, agitation, insomnia
Clonidine HCl (Catapres)	0.1-0.3 mg bid; 0.1-0.3 mg patch/wk	H	Dry mouth, blurred vision
Desmopressin acetate (DDAVP)	0.1-0.2 mg qhs	PD	Hyponatremia, headache
Duloxetine HCl (Cymbalta)	20-30 mg qd	PD, H	Nausea, sleep disturbance
Erythropoietin (Epogen, Procrit)	10,000-20,000 U SC/wk	PD	Pain at injection site, expensive
Escitalopram oxalate (Lexapro)	10 mg qd	PD, H	Tremor, agitation, sexual problems
Fludrocortisone acetate	0.1-0.2 mg qd	PD	Hypokalemia, hypomagnesemia, edema
Labetalol HCl (Trandate, Normodyne)	100-200 mg bid	H	Fatigue
Methylphenidate (Ritalin, Methylin, Concerta, etc.)	5-10 mg tid	PD	Anorexia, insomnia, dependency
Midodrine (ProAmatine)	5-10 mg tid	PD	Nausea, itching scalp, supine hypertension
Octreotide acetate (Sandostatin)	50-200 µg SC tid	PD	Nausea, diarrhea, gallstones
Pyridostigmine bromide (Mestinon)	30-60 mg qd	PD	Nausea, diarrhea
Venlafaxine HCl (Effexor)	75 mg qd or bid	PD, H	Nausea, anorexia, tremor

**Key:** H = hyperadrenergic; PD = partial dysautonomic; POTS = postural tachycardia syndrome; SC = subcutaneous.

**Note:** The Food and Drug Administration has not approved any drug for treating POTS.

qd if needed. If an SSRI is used, those with combined serotonin and norepinephrine reuptake inhibition (duloxetine HCl [Cymbalta] and venlafaxine HCl [Effexor]) appear to be most useful.

A promising new therapy is pyridostigmine bromide (Mestinon). This acetylcholinesterase inhibitor appears to enhance neural transmission at the ganglionic junction of sympathetic and parasympathetic nerves. Pyridostigmine has thus far proven useful in patients with postviral POTS and those who develop

POTS secondary to an autoimmune process such as SLE. Current protocols use a starting dose of 30 mg bid and titrate to 50-90 mg tid if needed.

In quite debilitated patients in whom other therapies have either been ineffective or poorly tolerated, we use erythropoietin (Epogen, Procrit). Although originally developed to treat anemia, it was found to be a potent vasoconstrictor, a property useful in treating orthostatic disorders. Erythropoietin is given subcutaneously, usually starting at a dosage of 10,000

units a week. Complete blood cell counts must be monitored monthly to assure that the hematocrit does not exceed 50 mL/dL.

Because of its potent vasoconstrictive effects, the somatostatic analog octreotide acetate (Sandostatin) can be used to treat the PD form of POTS. It is also given subcutaneously, usually starting at 50 µg bid-tid, (dosages as high as 100-200 µg per day may sometimes be needed). A recent report found that plasma exchange produced dramatic clinical success in a patient with severe autonomic failure and high circulating acetylcholine receptor antibody levels.<sup>17</sup> Further studies will be necessary to better evaluate this promising form of therapy.

- *The hyperadrenergic form of POTS* responds best to agents that block norepinephrine release or its effects. The most frequently used agent is clonidine HCl (Catapres), in pill or patch form. The oral dose is 0.1 mg qd or bid, titrated upward. The patch form is useful in that it provides a continuous and constant level of the drug for up to 1 week at a time. The combined  $\alpha_1/\beta$ -blocker labetalol HCl (Trandate, Normodyne) is useful in some patients, as  $\beta$ -blockade alone may worsen symptoms (due to unopposed  $\alpha$ -receptor stimulation). Starting dosages of 100-200 mg bid are used, with a maximum dosage of 400 mg bid. Methyldopa may also be useful in occasional patients. In addition, the SSRIs and norepinephrine reuptake inhibitors are helpful in select patients. The interested reader is directed to more in-depth discussions of the topic.

- *Treatment in patients with secondary POTS* is first aimed at correcting or stabilizing the underlying disorder as much as possible. Patients such as those with diabetes or JHS tend to behave and respond to treatment as do those with the PD form of POTS. Those with paraneoplastic POTS may respond well to therapy with pyridostigmine, and symptoms often abate with treatment of the malignancy.

Some patients suffering from POTS may be extremely debilitated by the disorder, to such an extent that they are unable to continue normal employment or educational activities, and many will become understandably depressed. They often need the help of social workers, psychologists, and legal aid to address the scope of problems brought on by their illness. As with many chronic illnesses, the attitude of the treating physician is critical. Hope is a powerful medicine that should be encouraged.

### The relatively uncertain prognosis of POTS

At the present time, only limited information is available on the prognosis of patients with POTS. Studies are under way analyzing the outcome of patients and of specific subgroups. About half the patients with postviral POTS make a reasonable recovery after 2-5 years, with recovery defined as the relative absence of orthostatic symptoms along with the ability to perform activities of daily living with little or no restriction. Nonetheless, some patients do not recover, and others worsen over time.

For the most part, the younger the patient, the better the prognosis. Roughly three fourths of adolescents with the developmental form of POTS will display a significant recovery by their mid-20s. In general, about 90% of patients will respond to a combination of physical therapy and pharmacotherapy. Most patients with the hyperadrenergic form of POTS require therapy indefinitely. The outcome of those with the secondary form of POTS usually depends on the prognosis of the causative disorder.

### Conclusion

The postural tachycardia syndrome represents a heterogeneous group of various disorders with similar clinical characteristics that occur as a result of a disturbance in normal autonomic control. Adequate treatment often depends on determining the subtype and instituting a complete treatment program. ■

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## SELF-EXAMINATION

1. All of the following except \_\_\_\_\_ are common symptoms in the postural tachycardia syndrome (POTS).
  - a) fatigue
  - b) exercise intolerance
  - c) anorexia
  - d) headaches
  - e) near syncope
2. Which of these drug classes is not likely to cause or

worsen orthostatic intolerance in patients with POTS?

- a) tricyclic antidepressants
- b)  $\beta$ -blockers
- c) diuretics
- d) combined serotonin and norepinephrine reuptake inhibitors
- e) monoamine oxidase inhibitors

3. POTS may be secondary to any of the following except \_\_\_\_\_.

- a) diabetes
- b) systemic lupus erythematosus
- c) lymphoma
- d) alcoholism
- e) heavy metal intoxication

4. Which of these statements about POTS is false?

- a) A defining characteristic of POTS is symptoms of orthostatic intolerance associated with heart rate increases of 30 or more beats per minute.
- b) Not all POTS patients have orthostatic hypotension.
- c) Other autonomic symptoms in patients with POTS include disturbances in sweating, temperature regulation, and bowel and bladder function.
- d) POTS frequently occurs in patients after febrile, presumably viral illnesses, immunization, sepsis, or trauma.
- e) The male-female ratio of POTS is 5:1.

5. Common elements of treatment for POTS include all of the following except \_\_\_\_\_.

- a) aerobic exercise (20 min at least 3 days weekly)
- b) hydration (1 L of water daily)
- c) erythropoietin
- d) sodium nitrate (2-4 g/day)
- e) bupropion (extended-release form)

*Answers at end of reference list.*

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■ **Answers:** 1)c, 2)d, 3)c, 4)e, 5)b