

# Postural orthostatic tachycardia syndrome

## Dental treatment considerations

John K. Brooks, DDS; Laurie A.P. Francis, RDH

**O**rthostatic intolerance (OI) refers to a heterogeneous group of disorders of hemodynamic disturbances, characterized by insufficient cerebral perfusion on standing upright or tilting the head upward.<sup>1</sup> A common form of OI is orthostatic hypotension, the aberrant physiological response to body position in which patients typically experience a pronounced decline in blood pressure on assuming an upright position.

A subset of affected patients may have postural orthostatic tachycardia syndrome (POTS), which is defined as disproportionate increases in cardiac rate of 30 beats per minute within five minutes of moving from a supine to an elevated position, accompanied by at least three orthostatic symptoms.<sup>2,3</sup> A prerequisite for a diagnosis of POTS is that patients must be symptomatic for more than three months.<sup>4</sup> At times, extreme fluctuations of heart rate are evident, and the rate may accelerate to at least 170 bpm within minutes of elevating from a supine position. Systolic and diastolic blood pressure may suddenly attain dangerously high levels and vacillate greatly, while some patients experience hypotensive episodes and others maintain minimal changes in blood pressure.

POTS has been referred to by various names, including neurocirculatory asthenia, mitral valve prolapse (MVP) syndrome, irritable heart, soldier's heart, idiopathic orthostatic intolerance, orthostatic tachycardia syndrome, postural tachycardia syndrome, hyperadrenergic orthostatic tachycardia and hyperadrenergic orthostatic hypotension. Clinicians have estimated that this syndrome may affect at least 500,000 to 1 million Americans.<sup>3,5</sup> There is a decisive 4-6:1 female predilection, with a mean age of 29 years and an age range from 15 to 50 years.<sup>4,6</sup> Although numerous articles have been written about POTS, minimal information is available in the dental literature.

**Background.** Postural orthostatic tachycardia syndrome (POTS) is a chronic, relatively common autonomic disorder typically affecting younger females. It is distinguished by a dramatic increase in heart rate on the assumption of an upright posture from the supine position.

**Methods.** The authors provide an overview of the demographics, clinical assessment, diagnostic features, differential diagnoses, pathogenesis and medical treatment of patients with POTS, with an emphasis on the clinical treatment of the dental patient affected by the syndrome.

**Conclusion.** Patients frequently exhibit symptoms of lightheadedness, fatigue, palpitations and syncope. Patients with POTS may have Ehlers-Danlos syndrome, mitral valve prolapse, chronic fatigue syndrome or, rarely, the Brugada syndrome. Despite widespread dissemination of information regarding POTS in the medical literature, scant information on it has appeared in dental publications.

**Practice Implications.** Dentists need to be familiar with the clinical features of POTS and be prepared to treat patients at risk of developing syncope.

**Key Words.** Postural orthostatic tachycardia syndrome; autonomic disorder; dental treatment.

*JADA* 2006;137:488-93.

Dr. Brooks is a clinical professor, Department of Diagnostic Sciences and Pathology, Baltimore College of Dental Surgery, Dental School, University of Maryland, 666 W. Baltimore St., Baltimore, Md. 21201, e-mail "Oralpath5@aol.com". Address reprint requests to Dr. Brooks. Ms. Francis is in private practice, Mt. Airy, Md.



## CLINICAL FEATURES

Patients diagnosed with POTS exhibit a myriad of clinical manifestations<sup>4,7,8</sup> (Table). Orthostatic symptoms that may occur in at least 75 percent of patients are light-headedness/dizziness, fatigue/weakness, palpitations, exercise intolerance, tremulousness, photosensitivity, shortness of breath and disequilibrium.<sup>4,7,8</sup> Awareness of orthostatic symptoms is significant because they may herald the commencement of syncope or near syncope. Fifty-six percent of subjects, in fact, experience syncope.<sup>7</sup>

Patients also may report experiencing chest discomfort, hyperventilation, chills, sleep disruption, reduced vitality, generalized aching, numbing or tingling sensations, dysphagia, frequent urination and lapses of mental acuity.<sup>6,7,9</sup> About one-third of affected patients report suffering migraine headaches.<sup>10,11</sup>

Various gastrointestinal disturbances associated with POTS are diarrhea (75 percent of patients), bloating (72 percent), abdominal cramps (62 percent), constipation (50 percent), early satiety (46 percent) and vomiting (25 percent), and these constitutional changes are more apparent after meals.<sup>4</sup> Secretomotor symptoms noted are heat intolerance (58 percent), dry eyes (38 percent) and xerostomia (38 percent).<sup>4</sup> Jacob and colleagues<sup>7</sup> reported postprandial flushing in 44 percent of patients. In addition, peripheral appendages may be painful and exhibit pallor, redness, coldness or diaphoresis.

Some women may experience cyclic episodes of POTS, often associated with menstruation, leading to fluid loss and weight fluctuations of up to 5 pounds.<sup>6</sup> Nearly three-fourths of patients report experiencing flare-ups at random times of the day, while others may become symptomatic with sustained standing, exertion, stress and heat exposure.<sup>4</sup> It is of note that some women may become asymptomatic after pregnancy.<sup>3</sup>

## DIAGNOSIS

Paramount to establishing an accurate diagnosis of POTS is taking a comprehensive medical history and conducting a thorough physical examination, including a cardiovascular, pulmonary

and neurological examination, detailing signs and symptoms specifically with regard to frequency of symptoms and stimuli induction. The box provides a summary of the diagnostic features of POTS.

Head-up tilt-table testing is the main method of evaluating OI. After the patient assumes a supine position in the apparatus, the clinician records his or her baseline blood pressure and heart rate. The clinician then varies the table angulation, usually by 30 and 60 degrees. After administering various drugs, he or she then repeats the blood pressure and heart rate evaluations.<sup>12,13</sup> Infusion of isoproterenol, a  $\beta$ -adrenergic agonist, may immediately provoke exaggerated feelings of cardiac awareness or emotional distress; reversal of these affectations is achieved with administration of propranolol, a  $\beta$ -adrenergic receptor antagonist.<sup>14</sup> Additional assessment of autonomic function may reveal decreased sweat output in the extremities following a thermoregulatory sweat test.

TABLE

### Orthostatic symptoms associated with postural orthostatic tachycardia syndrome.\*

CLINICAL FEATURE	REPORTED FREQUENCY (PERCENTAGE OF SUBJECTS)
Lightheadedness/Dizziness	77-100
Fatigue/Weakness	67-94
Palpitations	39-89
Exercise Intolerance	81-83
Tremulousness	50-80
Photosensitivity	78
Shortness of Breath	42-77
Disequilibrium	75
Nausea	50-72
Pallor	71
Clamminess	56-70
Anxiety	56-69
Visual Disturbances	53-61
Chest Discomfort	61
Syncope/Near Syncope	55-56
Flushing	44
Headaches	44

\* Sources: Sandroni and colleagues<sup>4</sup>; Jacob and colleagues<sup>7</sup>; Bonyhay and Freeman.<sup>6</sup>

## BOX

**Diagnostic features of postural orthostatic tachycardia syndrome.****POSITIVE TILT-TABLE TEST RESULTS**

- Cardiac acceleration of at least 30 beats per minute within five minutes
- Heart rate 120 bpm or more within five minutes
- Elevated plasma norepinephrine release with reduced clearance
- Provocation of at least three symptoms of orthostatic intolerance

**ELECTROCARDIOGRAPHY**

- Usually normal results except for episodes of tachycardia

**ECHOCARDIOGRAPHY**

- Forty-six to 50 percent of patients may have mitral valve prolapse

**LABORATORY STUDIES**

- Normal results for complete blood cell count, electrolytes and urinalysis
- Normal results for thyroid and adrenal gland function tests

**Electrocardiographic studies.** The results of electrocardiographic studies usually are normal, with the exception of the detection of sinus tachycardia with 24-hour Holter monitoring. The results of echocardiographic investigations otherwise are normal, although 46 to 50 percent of patients with POTS may have MVP with detectable valvular pathosis.<sup>7,15,16</sup>

**Differential diagnosis.** Although the development of tachycardia on assuming an upright position is a fundamental diagnostic criterion for POTS, the differential diagnosis is diverse and may involve considerable phenotypic overlap. Orthostatic hypotension is distinguished by a decrease in systolic blood pressure of at least 30 millimeters of mercury or a decrease in diastolic blood pressure of at least 20 mm Hg, without significant alteration of heart rate.<sup>10</sup>

Neurally mediated (vasovagal) syncope is the result of reflex bradycardia and hypotension, triggered by anxiety, shock, overexertion, aortic stenosis, various drugs and alcohol consumption.<sup>17</sup> Chronic fatigue syndrome is noted for its imposing periods of physical and mental exhaustion and headaches; however, a subset of patients may have POTS concurrently.<sup>18</sup> MVP may precipitate fatigue, palpitations, chest pain and orthostatic symptoms. Patients with multiple system atrophy and pure autonomic failure exhibit declines in blood pressure in response to exercise. Panic attacks may initiate episodes of hyperventi-

lation comparable to the response to reduced cerebral blood flow apparent in patients with POTS. The Brugada syndrome, a form of right bundle branch block, is noted for the onset of near syncope, palpitations and potentially lethal ventricular tachydysrhythmia, and it may be distinguished from POTS by the electrocardiographic findings and results of pharmacologic provocation with pilsicainide.<sup>19</sup>

Finally, 75 percent of patients diagnosed with the Ehlers-Danlos syndrome (EDS) manifest symptoms of OI, 58 percent of which are attributable to POTS.<sup>20</sup> Establishment of an accurate diagnosis of POTS often is preceded by a protracted sequence of referrals to various medical disciplines, including psychiatry.

**PATHOGENESIS**

The pathogenesis of POTS is complex and multifactorial. Autonomic dysfunction may account for one-half to two-thirds of cases, resulting from reflex parasympathetic withdrawal concomitant with sympathetic stimulation.<sup>6,21</sup> In an otherwise healthy person, the gravitational effect on achieving an upright posture produces a sudden reduction in venous return of at least 700 milliliters, which is detected by baroreceptors in the lower extremities. This mediates a central nervous system reflex feedback mechanism that promotes a compensatory norepinephrine discharge from cardiovascular postganglionic axons, thereby maintaining control of arterial pressure without any symptoms.<sup>22,23</sup>

Patients with POTS, however, exhibit sympathetic denervation of the legs and manifest exaggerated responses to baroreceptor challenges, leading to vasomotor debility. Thus, prolonged standing may result in marked venous pooling from the thorax into the splanchnic bed and lower extremities, with a vast decline in pulse pressure, often leading to cyanotic skin and swelling.<sup>24</sup> Hence, insufficient venous return enhances sympathovagal activity, with compensatory cardiac acceleration and blood pressure lability.

Another pathophysiological mechanism associated with POTS is  $\beta$ -adrenergic hyperresponsiveness, with substantial elevations of plasma norepinephrine levels, implicated by such symptoms as tachycardia, palpitations, anxiety and tremulousness on achieving an upright posture.<sup>7</sup> A familial predisposition is a salient feature of POTS and is found in at least one-fourth of affected patients.<sup>4,25</sup>

Other studies have pointed to hypovolemia as an underlying cause of POTS.<sup>22,26,27</sup> Interestingly, in approximately 50 percent of cases, the onset of POTS may have been triggered by an antecedent infection, presumably postviral.<sup>4,21</sup> In select cases, an autoimmune-mediated process has led to the production of autoantibodies to ganglionic acetylcholine receptors and facilitates autonomic neuropathy.<sup>28</sup> Singer and colleagues<sup>29</sup> reported a demonstration of an intrinsic sinus node abnormality in a subpopulation of patients with POTS.

### MEDICAL TREATMENT

Treatment of POTS requires a multidisciplinary approach entailing pharmacologic, kinesiological and dietary strategies correlating to the prevailing clinical deficits. Orthostatic hypotension resulting from peripheral adrenergic failure may be ameliorated with various  $\alpha$ -adrenergic agonists, such as fludrocortisone, midodrine, clonidine,  $\alpha$ -methyldopa or phenylpropranolamine.<sup>1,15,30</sup> These sympathomimetics and other pressor agents, including ergotamine, dihydroergotamine and octreotide, may promote vasoconstriction in the extremities and splanchnic bed, thereby reducing venous pooling.<sup>27</sup> Patients who wear elastic support hose may experience an improvement in venous return.<sup>16</sup> In addition, cardiovascular deconditioning through elevation of the patient's bed (a head-up bed) and physical countermeasures, such as flexing and relaxing the muscles in the extremities, may be beneficial.<sup>1,6</sup> A regular mild exercise regimen is expressly advised.<sup>1</sup>

Tachycardia that occurs in response to  $\beta$ -receptor supersensitivity may be treated with the  $\beta$ -adrenergic antagonists propranolol, metoprolol or nadolol,<sup>6,31</sup> although their effectiveness has been challenged.<sup>1</sup> However, practitioners must consider carefully the appropriateness of using  $\beta$ -blockers to treat patients who also are affected with mast cell activation disorders.<sup>30</sup>

When hypovolemia is an etiological factor, patients can maintain homeostasis with ample hydration, high dietary salt intake and use of sodium chloride tablets (in dosages ranging from 10 to 20 grams daily).<sup>6,22</sup> Recombinant erythropoietin may improve intravascular volume by increasing the erythrocyte count,<sup>32</sup> although its efficacy has been questioned.<sup>33</sup> Patients also should avoid ingesting substances that may affect blood pressure, including nitrates, garlic and ginseng, and they should restrict intake of coffee, tea and alcohol.

The clinical course of POTS usually is self-

limited, with repeated instances of remission and relapse. In an 18-month follow-up study, 80 percent of affected patients reported experiencing clinical improvement, yet only 60 percent regained normal or near-normal functionality (that is, daily activities).<sup>4</sup> In severely affected patients, the impaired quality of life may result in undesirable psychosocial consequences, including the inability to work and possible depression.<sup>34</sup>

### DENTAL TREATMENT

When treating a patient with a history of POTS, the dentist should assess his or her blood pressure and heart rate before administering local anesthetic, particularly one containing the vasoconstrictor epinephrine or levonordefrin. Judicious use of local anesthetic is essential for patients whose cardiovascular status is not well-maintained, because excessive dosing may promote a pressor response and perhaps initiate a myocardial ischemic event or dysrhythmia.<sup>35,36</sup> Nevertheless, inadequate anesthesia may promote endogenous release of epinephrine and risk untoward cardiac events in affected patients who may develop tachycardia or elevated blood pressure at the dental visit. Frequent aspiration during nerve blocks and infiltrations and minimal use of intraligamentary injections will diminish inadvertent intravenous deposition of local anesthetic and possible untoward clinical responses.<sup>37</sup> In addition, clinicians should avoid using retraction cord impregnated with epinephrine and select only non-epinephrine-based hemostatic solutions to control localized bleeding.

**Surgical procedures.** Oral and maxillofacial surgical procedures require several modifications. Potential hemodynamic fluctuation during administration of general anesthetic warrants electrocardiographic monitoring and vigilant checking of vital signs. Clinicians can maintain the patient's blood pressure and heart rate with isoflurane titration and improve vascular tone by administering low doses of phenylephrine. Blood expanders, such as crystalloid, also should be on hand during surgical procedures.<sup>38</sup>

**Postoperative care.** Postoperative care should consist of measures to lessen OI, such as providing adequate analgesics to limit the vasopressor response, advising patients to increase fluid levels to avoid dehydration and urging patients to promptly resume their routine physical activities. Because of the potential for impaired mental concentration in patients with POTS, clinicians should provide surgical patients with written postopera-

tive instructions on discharge. Approximately 15 percent of patients with POTS report having drug allergies; consequently, clinicians must conduct a careful pharmacological review before prescribing medications.<sup>39</sup>

**EDS and POTS.** Several dental concerns arise when treating patients who have both EDS and POTS. The intrinsic collagen defects associated with EDS may lead to severe, refractory periodontitis. Oral surgical procedures may be complicated by the inherent capillary fragility, which increases the risk of bleeding. Postsurgical hemorrhage may be significant and require the administration of hemostatic agents, such as desmopressin.<sup>40</sup> Spontaneous rupture of medium and large blood vessels in the cranium, bowel and gravid uterus is of great concern for patients with EDS subtypes IV and VI.<sup>41,42</sup>

Echymosis formation often is seen after surgery and is induced simply by minor trauma. Delayed wound healing may be apparent, and the increased friability of the mucosa requires that sutures remain in place two to three times longer than usual.<sup>43</sup> Hyperextensibility of the joints may lead to recurrent subluxation of the temporomandibular joint and potentiate the need for surgical intervention.<sup>44,45</sup> Orthodontic treatment may lead to rapid tooth movement and increased mobility, typically requiring longer retention on completion of the case.<sup>46</sup>

**Antibiotic prophylaxis.** In light of the finding that approximately one-half of patients with POTS are diagnosed with MVP,<sup>7,15</sup> clinicians must ascertain the need for antibiotic prophylaxis for prevention of bacterial endocarditis in conjunction with invasive dental procedures. The dentist should consult with the patient's physician to determine valvular incompetency and to obtain the results of echocardiographic studies. If cardiac assessment has revealed significant cardiac regurgitation, the patient must comply strictly with the antibiotic regimen for prevention of endocarditis established by the American Heart Association.<sup>47</sup>

Fatigue is a predominant feature of POTS and often is associated with chronic fatigue syndrome.<sup>48</sup> It may influence adherence to a satisfactory oral hygiene regimen. For these patients, it may be prudent for the dentist to consider more frequent recall appointments. To facilitate tolerance of dental treatment and reduce fatigue, dental offices should schedule patients for shorter, morning procedures and advise them to eat only a small breakfast. Orthostatic intolerance may be minimized with earlier appointments, when ambient temperatures

usually are lower. Sleep disturbances commonly affect patients with POTS, and use of hypnotic agents the night before the dental appointment may be advantageous. Patients who feel refreshed are more likely to have improved coping mechanisms.

Another vexing problem is the prevalence of xerostomia, which poses a fundamental risk of developing caries, candidiasis and burning mouth syndrome. Successful treatment outcomes may dictate the use of various sialogogues and fluoride supplements (including rinses, gels and possibly custom fluoride trays). A heightened perception of anxiety is another clinical finding in patients with POTS, and it may become more pronounced among patients with inherent fears of dental procedures. In these situations, clinicians should consider premedication with oral anxiolytics. Because a majority of patients experience photosensitivity<sup>8</sup> and may be bothered by the bright overhead light used in the dental operator, we suggest that they wear darkened eyewear.

Patients with POTS are at an increased risk of developing syncope with prolonged standing. Accordingly, it is preferable for them to complete any insurance forms while sitting. When patients are called to the dental operator, a team member should make an effort to escort them and ensure that they stand up gradually from the seated position. Likewise, at the completion of the dental procedure, a team member should slowly return the supine patient to an upright position and ensure that he or she stands gradually.

The dentist must recognize the onset of a syncopal episode and intervene promptly. He or she should place the patient in a completely recumbent position or elevate the patient's legs slightly above the level of the heart. The dentist or a team member can place a cool, moistened cloth on the patient's forehead and use aromatic ammonia, which may stimulate a return of consciousness. The dentist should contact the patient's physician immediately and ask him or her if the patient should make an appointment for reassessment. Any patient who has experienced loss of consciousness or an altered state of alertness should not leave the dental facility unescorted and transportation must be provided.

## CONCLUSION

Dental health care providers should be familiar with the clinical features of POTS and formulate appropriate treatment planning protocols to mini-

mize exacerbation of the patient's underlying hemodynamic disorder. The medical history should specifically address the signs and symptoms of OI and ascertain whether the patient has various associated conditions, such as EDS, MVP, chronic fatigue syndrome or Brugada syndrome. Routine monitoring of blood pressure and heart rate before and at the end of dental procedures is warranted. Dentists need to be prepared to treat patients at risk of developing syncope. ■

1. Jacob G, Biaggioni I. Idiopathic orthostatic intolerance and postural tachycardia syndromes. *Am J Med Sci* 1999;317(2):88-101.
2. Novak V, Novak P, Opfer-Gehrking TL, O'Brien PC, Low PA. Clinical and laboratory indices that enhance the diagnosis of postural tachycardia syndrome. *Mayo Clin Proc* 1998;73:1141-50.
3. Stewart JM. Chronic orthostatic intolerance and the postural tachycardia syndrome (POTS). *J Pediatr* 2004;145:725-30.
4. Sandroni P, Opfer-Gehrking TL, McPhee BR, Low PA. Postural tachycardia syndrome: clinical features and follow-up study. *Mayo Clin Proc* 1999;74:1106-10.
5. Robertson D. The epidemic of orthostatic tachycardia and orthostatic intolerance. *Am J Med Sci* 1999;317(2):75-7.
6. Low PA, Opfer-Gehrking TL, Textor SC, et al. Postural tachycardia syndrome (POTS). *Neurology* 1995;45(supplement 5):S19-25.
7. Jacob G, Costa F, Shannon JR, et al. The neuropathic postural tachycardia syndrome. *N Engl J Med* 2000;343:1008-14.
8. Bonyhay I, Freeman R. Sympathetic nerve activity in response to hypotensive stress in the postural tachycardia syndrome. *Circulation* 2004;110:3193-8.
9. Karas B, Grubb BP, Boehm K, Kip K. The postural orthostatic tachycardia syndrome: a potentially treatable cause of chronic fatigue, exercise intolerance, and cognitive impairment in adolescents. *Pacing Clin Electrophysiol* 2000;23:344-51.
10. Low PA, Opfer-Gehrking TL, Textor SC, et al. Comparison of the postural tachycardia syndrome (POTS) with orthostatic hypotension due to autonomic failure. *J Auton Nerv Syst* 1994;50(2):181-8.
11. Mokri B, Low PA. Orthostatic headaches without CSF leak in postural tachycardia syndrome. *Neurology* 2003;61:980-2.
12. Benditt DG, Ferguson DW, Grubb BP, et al. Tilt table testing for assessing syncope. *American College of Cardiology. J Am Coll Cardiol* 1996;28:263-75.
13. Grubb BP, Kosinski DJ, Boehm K, Kip K. The postural orthostatic tachycardia syndrome: a neurocardiogenic variant identified during head-up tilt table testing. *Pacing Clin Electrophysiol* 1997;20:2205-12.
14. Frohlich ED, Tarazi RC, Dustan HP. Hyperdynamic  $\beta$ -adrenergic circulatory state: increased  $\beta$ -receptor responsiveness. *Arch Intern Med* 1969;123(1):1-7.
15. Jacob G, Shannon JR, Black B, et al. Effects of volume loading and pressor agents in idiopathic orthostatic tachycardia. *Circulation* 1997;96:575-80.
16. Low PA, Schondorf R, Novak V, Sandroni P, Opfer-Gehrking TL, Novak P. Postural tachycardia syndrome. In: Low PA, ed. *Clinical autonomic disorders: evaluation and management*. 2nd ed. Philadelphia: Lippincott; 1997:681-97.
17. van Lieshout JJ, Wieling W, Karemaker JM, Eckberg DL. The vasovagal response. *Clin Sci (Lond)* 1991;81:575-86.
18. Freeman R, Komaroff AL. Does the chronic fatigue syndrome involve the autonomic nervous system? *Am J Med* 1997;102:357-64.
19. Morishima I, Sone T, Tsuboi H, Mukawa H, Satoda M, Uesugi M. Asymptomatic Brugada syndrome associated with postural orthostatic tachycardia syndrome: does autonomic disorder increase propensity for future arrhythmic events? *Pacing Clin Electrophysiol* 2004;27:537-40.
20. Rowe PC, Barron DF, Calkins H, Maumenee IH, Tong PY, Geraghty MT. Orthostatic intolerance and chronic fatigue syndrome associated with Ehlers-Danlos syndrome. *J Pediatr* 1999;135:494-9.
21. Schondorf R, Low PA. Idiopathic postural orthostatic tachycardia syndrome: an attenuated form of acute pandysautonomia? *Neurology* 1993;43(1):132-7.
22. Rosen SG, Cryer PE. Postural tachycardia syndrome: reversal of sympathetic hyperresponsiveness and clinical improvement during sodium loading. *Am J Med* 1982;72:847-50.
23. Schondorf R, Benoit J, Stein R. Cerebral autoregulation in orthostatic intolerance. *Ann N Y Acad Sci* 2001;940:514-26.
24. Muentner Swift N, Charkoudian N, Dotson RM, Suarez GA, Low PA. Baroreflex control of muscle sympathetic nerve activity in the postural orthostatic tachycardia syndrome. *Am J Physiol Heart Circ Physiol* 2005;289:H1226-33.
25. Robertson D, Flattem N, Tellioglu T, et al. Familial orthostatic tachycardia due to norepinephrine transporter deficiency. *Ann N Y Acad Sci* 2001;940:527-43.
26. Fouad FM, Tadena-Thome L, Bravo EL, Tarazi RC. Idiopathic hypovolemia. *Ann Intern Med* 1986;104:298-303.
27. Hoeldtke RD, Davis KM. The orthostatic tachycardia syndrome: evaluation of autonomic function and treatment with octreotide and ergot alkaloids. *J Clin Endocrinol Metab* 1991;73(1):132-9.
28. Vernino S, Low PA, Fealey RD, Stewart JD, Farrugia G, Lennon VA. Autoantibodies to ganglionic acetylcholine receptors in autoimmune autonomic neuropathies. *N Engl J Med* 2000;343:847-55.
29. Singer W, Shen WK, Opfer-Gehrking TL, McPhee BR, Hilz MJ, Low PA. Evidence of an intrinsic sinus node abnormality in patients with postural tachycardia syndrome. *Mayo Clin Proc* 2002;77:246-52.
30. Shibao C, Arzubiaga C, Roberts LJ 2nd, et al. Hyperadrenergic postural tachycardia syndrome in mast cell activation disorders. *Hypertension* 2005;45:385-90.
31. Miller AJ, Cohen HC, Glick G. Propranolol in the treatment of orthostatic tachycardia associated with orthostatic hypotension. *Am Heart J* 1974;88:493-5.
32. Grubb BP, Kanjwal MY, Kosinski DJ. Review: the postural orthostatic tachycardia syndrome—current concepts in pathophysiology diagnosis and management. *J Interv Card Electrophysiol* 2001;5(1):9-16.
33. Hoeldtke RD, Horvath GG, Bryner KD. Treatment of orthostatic tachycardia with erythropoietin. *Am J Med* 1995;99:525-9.
34. Benrud-Larson LM, Dewar MS, Sandroni P, Rummans TA, Haythornthwaite JA, Low PA. Quality of life in patients with postural tachycardia syndrome. *Mayo Clin Proc* 2002;77:531-7.
35. Nakamura Y, Matsumura K, Miura K, Kurokawa H, Abe I, Takata Y. Cardiovascular and sympathetic responses to dental surgery with local anesthesia. *Hypertens Res* 2001;24:209-14.
36. Montebugnoli L, Prati C. Circulatory dynamics during dental extractions in normal, cardiac and transplant patients. *JADA* 2002;133:468-72.
37. Replogle K, Reader A, Nist R, Beck M, Weaver J, Meyers WJ. Cardiovascular effects of intraosseous injections of 2 percent lidocaine with 1:100,000 epinephrine and 3 percent mepivacaine. *JADA* 1999;130:649-57.
38. Mchaourab A, Mazzeo AJ, May JA, Pagel PS. Perioperative considerations in a patient with orthostatic intolerance syndrome. *Anesthesiology* 2000;93:571-3.
39. Goldstein DS, Holmes C, Frank SM, et al. Cardiac sympathetic dysautonomia in chronic orthostatic intolerance syndromes. *Circulation* 2002;106:2358-65.
40. Cunniff C, Williamson-Kruse L. Ehlers-Danlos syndrome, type VIII presenting with periodontitis and prolonged bleeding time. *Clin Dysmorphol* 1995;4(2):145-9.
41. North KN, Whiteman DA, Pepin MG, Byers PH. Cerebrovascular complications in Ehlers-Danlos syndrome type IV. *Ann Neurol* 1995;38:960-4.
42. De Paepe A, Malfait F. Bleeding and bruising in patients with Ehlers-Danlos syndrome and other collagen vascular disorders. *Br J Haematol* 2004;127:491-500.
43. Syndromes affecting the skin and mucosa. In: Gorlin RJ, Cohen MM, Levin LS, eds. *Syndromes of the head and neck*. 3rd ed. New York: Oxford University Press; 1990:417-517.
44. Sacks H, Zelig D, Schabas G. Recurrent temporomandibular joint subluxation and facial ecchymosis leading to diagnosis of Ehlers-Danlos syndrome: report of surgical management and review of the literature. *J Oral Maxillofac Surg* 1990;48:641-7.
45. McDonald A, Pogrel A. Ehlers-Danlos syndrome: an approach to surgical management of temporomandibular joint dysfunction in two cases. *J Oral Maxillofac Surg* 1996;54:761-5.
46. Norton LA, Assael LA. Orthodontic and temporomandibular joint considerations in treatment of patients with Ehlers-Danlos syndrome. *Am J Orthod Dentofacial Orthop* 1997;111(1):75-84.
47. Dajani AS, Taubert KA, Wilson W, et al. Prevention of bacterial endocarditis: recommendations by the American Heart Association. *JAMA* 1997;277:1794-801.
48. Schondorf R, Benoit J, Wein T, Phaneuf D. Orthostatic intolerance in the chronic fatigue syndrome. *J Auton Nerv Syst* 1999;75(2-3):192-201.

# Postural orthostatic tachycardia syndrome

## Dental treatment considerations

John K. Brooks, DDS; Laurie A.P. Francis, RDH

**O**rthostatic intolerance (OI) refers to a heterogeneous group of disorders of hemodynamic disturbances, characterized by insufficient cerebral perfusion on standing upright or tilting the head upward.<sup>1</sup> A common form of OI is orthostatic hypotension, the aberrant physiological response to body position in which patients typically experience a pronounced decline in blood pressure on assuming an upright position.

A subset of affected patients may have postural orthostatic tachycardia syndrome (POTS), which is defined as disproportionate increases in cardiac rate of 30 beats per minute within five minutes of moving from a supine to an elevated position, accompanied by at least three orthostatic symptoms.<sup>2,3</sup> A prerequisite for a diagnosis of POTS is that patients must be symptomatic for more than three months.<sup>4</sup> At times, extreme fluctuations of heart rate are evident, and the rate may accelerate to at least 170 bpm within minutes of elevating from a supine position. Systolic and diastolic blood pressure may suddenly attain dangerously high levels and vacillate greatly, while some patients experience hypotensive episodes and others maintain minimal changes in blood pressure.

POTS has been referred to by various names, including neurocirculatory asthenia, mitral valve prolapse (MVP) syndrome, irritable heart, soldier's heart, idiopathic orthostatic intolerance, orthostatic tachycardia syndrome, postural tachycardia syndrome, hyperadrenergic orthostatic tachycardia and hyperadrenergic orthostatic hypotension. Clinicians have estimated that this syndrome may affect at least 500,000 to 1 million Americans.<sup>3,5</sup> There is a decisive 4-6:1 female predilection, with a mean age of 29 years and an age range from 15 to 50 years.<sup>4,6</sup> Although numerous articles have been written about POTS, minimal information is available in the dental literature.

**Background.** Postural orthostatic tachycardia syndrome (POTS) is a chronic, relatively common autonomic disorder typically affecting younger females. It is distinguished by a dramatic increase in heart rate on the assumption of an upright posture from the supine position.

**Methods.** The authors provide an overview of the demographics, clinical assessment, diagnostic features, differential diagnoses, pathogenesis and medical treatment of patients with POTS, with an emphasis on the clinical treatment of the dental patient affected by the syndrome.

**Conclusion.** Patients frequently exhibit symptoms of lightheadedness, fatigue, palpitations and syncope. Patients with POTS may have Ehlers-Danlos syndrome, mitral valve prolapse, chronic fatigue syndrome or, rarely, the Brugada syndrome. Despite widespread dissemination of information regarding POTS in the medical literature, scant information on it has appeared in dental publications.

**Practice Implications.** Dentists need to be familiar with the clinical features of POTS and be prepared to treat patients at risk of developing syncope.

**Key Words.** Postural orthostatic tachycardia syndrome; autonomic disorder; dental treatment.

*JADA* 2006;137:488-93.

Dr. Brooks is a clinical professor, Department of Diagnostic Sciences and Pathology, Baltimore College of Dental Surgery, Dental School, University of Maryland, 666 W. Baltimore St., Baltimore, Md. 21201, e-mail "Oralpath5@aol.com". Address reprint requests to Dr. Brooks. Ms. Francis is in private practice, Mt. Airy, Md.



## CLINICAL FEATURES

Patients diagnosed with POTS exhibit a myriad of clinical manifestations<sup>4,7,8</sup> (Table). Orthostatic symptoms that may occur in at least 75 percent of patients are light-headedness/dizziness, fatigue/weakness, palpitations, exercise intolerance, tremulousness, photosensitivity, shortness of breath and disequilibrium.<sup>4,7,8</sup> Awareness of orthostatic symptoms is significant because they may herald the commencement of syncope or near syncope. Fifty-six percent of subjects, in fact, experience syncope.<sup>7</sup>

Patients also may report experiencing chest discomfort, hyperventilation, chills, sleep disruption, reduced vitality, generalized aching, numbing or tingling sensations, dysphagia, frequent urination and lapses of mental acuity.<sup>6,7,9</sup> About one-third of affected patients report suffering migraine headaches.<sup>10,11</sup>

Various gastrointestinal disturbances associated with POTS are diarrhea (75 percent of patients), bloating (72 percent), abdominal cramps (62 percent), constipation (50 percent), early satiety (46 percent) and vomiting (25 percent), and these constitutional changes are more apparent after meals.<sup>4</sup> Secretomotor symptoms noted are heat intolerance (58 percent), dry eyes (38 percent) and xerostomia (38 percent).<sup>4</sup> Jacob and colleagues<sup>7</sup> reported postprandial flushing in 44 percent of patients. In addition, peripheral appendages may be painful and exhibit pallor, redness, coldness or diaphoresis.

Some women may experience cyclic episodes of POTS, often associated with menstruation, leading to fluid loss and weight fluctuations of up to 5 pounds.<sup>6</sup> Nearly three-fourths of patients report experiencing flare-ups at random times of the day, while others may become symptomatic with sustained standing, exertion, stress and heat exposure.<sup>4</sup> It is of note that some women may become asymptomatic after pregnancy.<sup>3</sup>

## DIAGNOSIS

Paramount to establishing an accurate diagnosis of POTS is taking a comprehensive medical history and conducting a thorough physical examination, including a cardiovascular, pulmonary

TABLE

### Orthostatic symptoms associated with postural orthostatic tachycardia syndrome.\*

CLINICAL FEATURE	REPORTED FREQUENCY (PERCENTAGE OF SUBJECTS)
Lightheadedness/Dizziness	77-100
Fatigue/Weakness	67-94
Palpitations	39-89
Exercise Intolerance	81-88
Tremulousness	50-80
Photosensitivity	78
Shortness of Breath	42-77
Disequilibrium	75
Nausea	50-72
Pallor	71
Clamminess	56-70
Anxiety	56-69
Visual Disturbances	53-61
Chest Discomfort	61
Syncope/Near Syncope	55-56
Flushing	44
Headaches	44

\* Sources: Sandroni and colleagues<sup>4</sup>; Jacob and colleagues<sup>7</sup>; Bonyhay and Freeman.<sup>8</sup>

and neurological examination, detailing signs and symptoms specifically with regard to frequency of symptoms and stimuli induction. The box provides a summary of the diagnostic features of POTS.

Head-up tilt-table testing is the main method of evaluating OI. After the patient assumes a supine position in the apparatus, the clinician records his or her baseline blood pressure and heart rate. The clinician then varies the table angulation, usually by 30 and 60 degrees. After administering various drugs, he or she then repeats the blood pressure and heart rate evaluations.<sup>12,13</sup> Infusion of isoproterenol, a  $\beta$ -adrenergic agonist, may immediately provoke exaggerated feelings of cardiac awareness or emotional distress; reversal of these affectations is achieved with administration of propranolol, a  $\beta$ -adrenergic receptor antagonist.<sup>14</sup> Additional assessment of autonomic function may reveal decreased sweat output in the extremities following a thermoregulatory sweat test.



## BOX

**Diagnostic features of postural orthostatic tachycardia syndrome.****POSITIVE TILT-TABLE TEST RESULTS**

- <sup>19a</sup> Cardiac acceleration of at least 30 beats per minute within five minutes
- <sup>19b</sup> Heart rate 120 bpm or more within five minutes
- <sup>19c</sup> Elevated plasma norepinephrine release with reduced clearance
- <sup>19d</sup> Provocation of at least three symptoms of orthostatic intolerance

**ELECTROCARDIOGRAPHY**

- <sup>19e</sup> Usually normal results except for episodes of tachycardia

**ECHOCARDIOGRAPHY**

- <sup>19f</sup> Forty-six to 50 percent of patients may have mitral valve prolapse

**LABORATORY STUDIES**

- <sup>19g</sup> Normal results for complete blood cell count, electrolytes and urinalysis
- <sup>19h</sup> Normal results for thyroid and adrenal gland function tests

**Electrocardiographic studies.** The results of electrocardiographic studies usually are normal, with the exception of the detection of sinus tachycardia with 24-hour Holter monitoring. The results of echocardiographic investigations otherwise are normal, although 46 to 50 percent of patients with POTS may have MVP with detectable valvular pathosis.<sup>7,15,16</sup>

**Differential diagnosis.** Although the development of tachycardia on assuming an upright position is a fundamental diagnostic criterion for POTS, the differential diagnosis is diverse and may involve considerable phenotypic overlap. Orthostatic hypotension is distinguished by a decrease in systolic blood pressure of at least 30 millimeters of mercury or a decrease in diastolic blood pressure of at least 20 mm Hg, without significant alteration of heart rate.<sup>10</sup>

Neurally mediated (vasovagal) syncope is the result of reflex bradycardia and hypotension, triggered by anxiety, shock, overexertion, aortic stenosis, various drugs and alcohol consumption.<sup>17</sup> Chronic fatigue syndrome is noted for its imposing periods of physical and mental exhaustion and headaches; however, a subset of patients may have POTS concurrently.<sup>18</sup> MVP may precipitate fatigue, palpitations, chest pain and orthostatic symptoms. Patients with multiple system atrophy and pure autonomic failure exhibit declines in blood pressure in response to exercise. Panic attacks may initiate episodes of hyperventi-

lation comparable to the response to reduced cerebral blood flow apparent in patients with POTS. The Brugada syndrome, a form of right bundle branch block, is noted for the onset of near syncope, palpitations and potentially lethal ventricular tachydysrhythmia, and it may be distinguished from POTS by the electrocardiographic findings and results of pharmacologic provocation with pilsicainide.<sup>19</sup>

Finally, 75 percent of patients diagnosed with the Ehlers-Danlos syndrome (EDS) manifest symptoms of OI, 58 percent of which are attributable to POTS.<sup>20</sup> Establishment of an accurate diagnosis of POTS often is preceded by a protracted sequence of referrals to various medical disciplines, including psychiatry.

**PATHOGENESIS**

The pathogenesis of POTS is complex and multifactorial. Autonomic dysfunction may account for one-half to two-thirds of cases, resulting from reflex parasympathetic withdrawal concomitant with sympathetic stimulation.<sup>6,21</sup> In an otherwise healthy person, the gravitational effect on achieving an upright posture produces a sudden reduction in venous return of at least 700 milliliters, which is detected by baroreceptors in the lower extremities. This mediates a central nervous system reflex feedback mechanism that promotes a compensatory norepinephrine discharge from cardiovascular postganglionic axons, thereby maintaining control of arterial pressure without any symptoms.<sup>22,23</sup>

Patients with POTS, however, exhibit sympathetic denervation of the legs and manifest exaggerated responses to baroreceptor challenges, leading to vasomotor debility. Thus, prolonged standing may result in marked venous pooling from the thorax into the splanchnic bed and lower extremities, with a vast decline in pulse pressure, often leading to cyanotic skin and swelling.<sup>24</sup> Hence, insufficient venous return enhances sympathovagal activity, with compensatory cardiac acceleration and blood pressure lability.

Another pathophysiological mechanism associated with POTS is  $\beta$ -adrenergic hyperresponsiveness, with substantial elevations of plasma norepinephrine levels, implicated by such symptoms as tachycardia, palpitations, anxiety and tremulousness on achieving an upright posture.<sup>7</sup> A familial predisposition is a salient feature of POTS and is found in at least one-fourth of affected patients.<sup>4,25</sup>

Other studies have pointed to hypovolemia as an underlying cause of POTS.<sup>22,26,27</sup> Interestingly, in approximately 50 percent of cases, the onset of POTS may have been triggered by an antecedent infection, presumably postviral.<sup>4,21</sup> In select cases, an autoimmune-mediated process has led to the production of autoantibodies to ganglionic acetylcholine receptors and facilitates autonomic neuropathy.<sup>28</sup> Singer and colleagues<sup>29</sup> reported a demonstration of an intrinsic sinus node abnormality in a subpopulation of patients with POTS.

### MEDICAL TREATMENT

Treatment of POTS requires a multidisciplinary approach entailing pharmacologic, kinesiological and dietary strategies correlating to the prevailing clinical deficits. Orthostatic hypotension resulting from peripheral adrenergic failure may be ameliorated with various  $\alpha$ -adrenergic agonists, such as fludrocortisone, midodrine, clonidine,  $\alpha$ -methyldopa or phenylpropanolamine.<sup>1,15,30</sup> These sympathomimetics and other pressor agents, including ergotamine, dihydroergotamine and octreotide, may promote vasoconstriction in the extremities and splanchnic bed, thereby reducing venous pooling.<sup>27</sup> Patients who wear elastic support hose may experience an improvement in venous return.<sup>16</sup> In addition, cardiovascular deconditioning through elevation of the patient's bed (a head-up bed) and physical countermeasures, such as flexing and relaxing the muscles in the extremities, may be beneficial.<sup>1,6</sup> A regular mild exercise regimen is expressly advised.<sup>1</sup>

Tachycardia that occurs in response to  $\beta$ -receptor supersensitivity may be treated with the  $\beta$ -adrenergic antagonists propranolol, metoprolol or nadolol,<sup>6,31</sup> although their effectiveness has been challenged.<sup>1</sup> However, practitioners must consider carefully the appropriateness of using  $\beta$ -blockers to treat patients who also are affected with mast cell activation disorders.<sup>30</sup>

When hypovolemia is an etiological factor, patients can maintain homeostasis with ample hydration, high dietary salt intake and use of sodium chloride tablets (in dosages ranging from 10 to 20 grams daily).<sup>6,22</sup> Recombinant erythropoietin may improve intravascular volume by increasing the erythrocyte count,<sup>32</sup> although its efficacy has been questioned.<sup>33</sup> Patients also should avoid ingesting substances that may affect blood pressure, including nitrates, garlic and ginseng, and they should restrict intake of coffee, tea and alcohol.

The clinical course of POTS usually is self-

limited, with repeated instances of remission and relapse. In an 18-month follow-up study, 80 percent of affected patients reported experiencing clinical improvement, yet only 60 percent regained normal or near-normal functionality (that is, daily activities).<sup>4</sup> In severely affected patients, the impaired quality of life may result in undesirable psychosocial consequences, including the inability to work and possible depression.<sup>34</sup>

### DENTAL TREATMENT

When treating a patient with a history of POTS, the dentist should assess his or her blood pressure and heart rate before administering local anesthetic, particularly one containing the vasoconstrictor epinephrine or levonordefrin. Judicious use of local anesthetic is essential for patients whose cardiovascular status is not well-maintained, because excessive dosing may promote a pressor response and perhaps initiate a myocardial ischemic event or dysrhythmia.<sup>35,36</sup> Nevertheless, inadequate anesthesia may promote endogenous release of epinephrine and risk untoward cardiac events in affected patients who may develop tachycardia or elevated blood pressure at the dental visit. Frequent aspiration during nerve blocks and infiltrations and minimal use of intraligamentary injections will diminish inadvertent intravenous deposition of local anesthetic and possible untoward clinical responses.<sup>37</sup> In addition, clinicians should avoid using retraction cord impregnated with epinephrine and select only non-epinephrine-based hemostatic solutions to control localized bleeding.

**Surgical procedures.** Oral and maxillofacial surgical procedures require several modifications. Potential hemodynamic fluctuation during administration of general anesthetic warrants electrocardiographic monitoring and vigilant checking of vital signs. Clinicians can maintain the patient's blood pressure and heart rate with isoflurane titration and improve vascular tone by administering low doses of phenylephrine. Blood expanders, such as crystalloid, also should be on hand during surgical procedures.<sup>38</sup>

**Postoperative care.** Postoperative care should consist of measures to lessen OI, such as providing adequate analgesics to limit the vasopressor response, advising patients to increase fluid levels to avoid dehydration and urging patients to promptly resume their routine physical activities. Because of the potential for impaired mental concentration in patients with POTS, clinicians should provide surgical patients with written postopera-

tive instructions on discharge. Approximately 15 percent of patients with POTS report having drug allergies; consequently, clinicians must conduct a careful pharmacological review before prescribing medications.<sup>39</sup>

**EDS and POTS.** Several dental concerns arise when treating patients who have both EDS and POTS. The intrinsic collagen defects associated with EDS may lead to severe, refractory periodontitis. Oral surgical procedures may be complicated by the inherent capillary fragility, which increases the risk of bleeding. Postsurgical hemorrhage may be significant and require the administration of hemostatic agents, such as desmopressin.<sup>40</sup> Spontaneous rupture of medium and large blood vessels in the cranium, bowel and gravid uterus is of great concern for patients with EDS subtypes IV and VI.<sup>41,42</sup>

Echymosis formation often is seen after surgery and is induced simply by minor trauma. Delayed wound healing may be apparent, and the increased friability of the mucosa requires that sutures remain in place two to three times longer than usual.<sup>43</sup> Hyperextensibility of the joints may lead to recurrent subluxation of the temporomandibular joint and potentiate the need for surgical intervention.<sup>44,45</sup> Orthodontic treatment may lead to rapid tooth movement and increased mobility, typically requiring longer retention on completion of the case.<sup>46</sup>

**Antibiotic prophylaxis.** In light of the finding that approximately one-half of patients with POTS are diagnosed with MVP,<sup>7,15</sup> clinicians must ascertain the need for antibiotic prophylaxis for prevention of bacterial endocarditis in conjunction with invasive dental procedures. The dentist should consult with the patient's physician to determine valvular incompetency and to obtain the results of echocardiographic studies. If cardiac assessment has revealed significant cardiac regurgitation, the patient must comply strictly with the antibiotic regimen for prevention of endocarditis established by the American Heart Association.<sup>47</sup>

Fatigue is a predominant feature of POTS and often is associated with chronic fatigue syndrome.<sup>48</sup> It may influence adherence to a satisfactory oral hygiene regimen. For these patients, it may be prudent for the dentist to consider more frequent recall appointments. To facilitate tolerance of dental treatment and reduce fatigue, dental offices should schedule patients for shorter, morning procedures and advise them to eat only a small breakfast. Orthostatic intolerance may be minimized with earlier appointments, when ambient temperatures

usually are lower. Sleep disturbances commonly affect patients with POTS, and use of hypnotic agents the night before the dental appointment may be advantageous. Patients who feel refreshed are more likely to have improved coping mechanisms.

Another vexing problem is the prevalence of xerostomia, which poses a fundamental risk of developing caries, candidiasis and burning mouth syndrome. Successful treatment outcomes may dictate the use of various sialogogues and fluoride supplements (including rinses, gels and possibly custom fluoride trays). A heightened perception of anxiety is another clinical finding in patients with POTS, and it may become more pronounced among patients with inherent fears of dental procedures. In these situations, clinicians should consider premedication with oral anxiolytics. Because a majority of patients experience photosensitivity<sup>8</sup> and may be bothered by the bright overhead light used in the dental operator, we suggest that they wear darkened eyewear.

Patients with POTS are at an increased risk of developing syncope with prolonged standing. Accordingly, it is preferable for them to complete any insurance forms while sitting. When patients are called to the dental operator, a team member should make an effort to escort them and ensure that they stand up gradually from the seated position. Likewise, at the completion of the dental procedure, a team member should slowly return the supine patient to an upright position and ensure that he or she stands gradually.

The dentist must recognize the onset of a syncope episode and intervene promptly. He or she should place the patient in a completely recumbent position or elevate the patient's legs slightly above the level of the heart. The dentist or a team member can place a cool, moistened cloth on the patient's forehead and use aromatic ammonia, which may stimulate a return of consciousness. The dentist should contact the patient's physician immediately and ask him or her if the patient should make an appointment for reassessment. Any patient who has experienced loss of consciousness or an altered state of alertness should not leave the dental facility unescorted and transportation must be provided.

## CONCLUSION

Dental health care providers should be familiar with the clinical features of POTS and formulate appropriate treatment planning protocols to mini-

mize exacerbation of the patient's underlying hemodynamic disorder. The medical history should specifically address the signs and symptoms of OI and ascertain whether the patient has various associated conditions, such as EDS, MVP, chronic fatigue syndrome or Brugada syndrome. Routine monitoring of blood pressure and heart rate before and at the end of dental procedures is warranted. Dentists need to be prepared to treat patients at risk of developing syncope. ■

1. Jacob G, Biaggioni I. Idiopathic orthostatic intolerance and postural tachycardia syndromes. *Am J Med Sci* 1999;317(2):88-101.
2. Novak V, Novak P, Opfer-Gehrking TL, O'Brien PC, Low PA. Clinical and laboratory indices that enhance the diagnosis of postural tachycardia syndrome. *Mayo Clin Proc* 1998;73:1141-50.
3. Stewart JM. Chronic orthostatic intolerance and the postural tachycardia syndrome (POTS). *J Pediatr* 2004;146:725-30.
4. Sandroni P, Opfer-Gehrking TL, McPhee BR, Low PA. Postural tachycardia syndrome: clinical features and follow-up study. *Mayo Clin Proc* 1999;74:1106-10.
5. Robertson D. The epidemic of orthostatic tachycardia and orthostatic intolerance. *Am J Med Sci* 1999;317(2):75-7.
6. Low PA, Opfer-Gehrking TL, Textor SC, et al. Postural tachycardia syndrome (POTS). *Neurology* 1995;45(supplement 5):S19-25.
7. Jacob G, Costa F, Shannon JR, et al. The neuropathic postural tachycardia syndrome. *N Engl J Med* 2000;343:1008-14.
8. Bonyhay I, Freeman R. Sympathetic nerve activity in response to hypotensive stress in the postural tachycardia syndrome. *Circulation* 2004;110:3193-8.
9. Karas B, Grubb BP, Boehm K, Kip K. The postural orthostatic tachycardia syndrome: a potentially treatable cause of chronic fatigue, exercise intolerance, and cognitive impairment in adolescents. *Pacing Clin Electrophysiol* 2000;23:344-51.
10. Low PA, Opfer-Gehrking TL, Textor SC, et al. Comparison of the postural tachycardia syndrome (POTS) with orthostatic hypotension due to autonomic failure. *J Auton Nerv Syst* 1994;50(2):181-8.
11. Mokri B, Low PA. Orthostatic headaches without CSF leak in postural tachycardia syndrome. *Neurology* 2003;61:980-2.
12. Benditt DG, Ferguson DW, Grubb BP, et al. Tilt table testing for assessing syncope. American College of Cardiology. *J Am Coll Cardiol* 1996;28:263-75.
13. Grubb BP, Kosinski DJ, Boehm K, Kip K. The postural orthostatic tachycardia syndrome: a neurocardiogenic variant identified during head-up tilt table testing. *Pacing Clin Electrophysiol* 1997;20:2205-12.
14. Frohlich ED, Tarazi RC, Dustan HP. Hyperdynamic  $\beta$ -adrenergic circulatory state: increased  $\beta$ -receptor responsiveness. *Arch Intern Med* 1969;123(1):1-7.
15. Jacob G, Shannon JR, Black B, et al. Effects of volume loading and pressor agents in idiopathic orthostatic tachycardia. *Circulation* 1997;96:575-80.
16. Low PA, Schondorf R, Novak V, Sandroni P, Opfer-Gehrking TL, Novak P. Postural tachycardia syndrome. In: Low PA, ed. *Clinical autonomic disorders: evaluation and management*. 2nd ed. Philadelphia: Lippincott; 1997:681-97.
17. van Lieshout JJ, Wieling W, Karemaker JM, Eckberg DL. The vagal response. *Clin Sci (Lond)* 1991;81:575-86.
18. Freeman R, Komaroff AL. Does the chronic fatigue syndrome involve the autonomic nervous system? *Am J Med* 1997;102:357-64.
19. Morishima I, Sone T, Tsuboi H, Mukawa H, Satoda M, Uesugi M. Asymptomatic Brugada syndrome associated with postural orthostatic tachycardia syndrome: does autonomic disorder increase propensity for future arrhythmic events? *Pacing Clin Electrophysiol* 2004;27:537-40.
20. Rowe PC, Barron DF, Calkins H, Maumenee IH, Tong PY, Geraghty MT. Orthostatic intolerance and chronic fatigue syndrome associated with Ehlers-Danlos syndrome. *J Pediatr* 1999;135:494-9.
21. Schondorf R, Low PA. Idiopathic postural orthostatic tachycardia syndrome: an attenuated form of acute pandysautonomia? *Neurology* 1993;43(1):132-7.
22. Rosen SG, Cryer PE. Postural tachycardia syndrome: reversal of sympathetic hyperresponsiveness and clinical improvement during sodium loading. *Am J Med* 1982;72:847-50.
23. Schondorf R, Benoit J, Stein R. Cerebral autoregulation in orthostatic intolerance. *Ann N Y Acad Sci* 2001;940:514-26.
24. Muenster Swift N, Charkoudian N, Dotson RM, Suarez GA, Low PA. Baroreflex control of muscle sympathetic nerve activity in the postural orthostatic tachycardia syndrome. *Am J Physiol Heart Circ Physiol* 2005;289:H1226-33.
25. Robertson D, Flatter N, Tellioglu T, et al. Familial orthostatic tachycardia due to norepinephrine transporter deficiency. *Ann N Y Acad Sci* 2001;940:527-43.
26. Fouad FM, Tadana-Thome L, Bravo EL, Tarazi RC. Idiopathic hypovolemia. *Ann Intern Med* 1986;104:298-303.
27. Hoeldtke RD, Davis KM. The orthostatic tachycardia syndrome: evaluation of autonomic function and treatment with octreotide and ergot alkaloids. *J Clin Endocrinol Metab* 1991;73(1):132-9.
28. Vernino S, Low PA, Fealey RD, Stewart JD, Farrugia G, Lennon VA. Autoantibodies to ganglionic acetylcholine receptors in autoimmune autonomic neuropathies. *N Engl J Med* 2000;343:847-55.
29. Singer W, Shen WK, Opfer-Gehrking TL, McPhee BR, Hilz MJ, Low PA. Evidence of an intrinsic sinus node abnormality in patients with postural tachycardia syndrome. *Mayo Clin Proc* 2002;77:246-52.
30. Shibao C, Arzubiaga C, Roberts LJ 2nd, et al. Hyperadrenergic postural tachycardia syndrome in mast cell activation disorders. *Hypertension* 2005;45:385-90.
31. Miller AJ, Cohen HC, Glick G. Propranolol in the treatment of orthostatic tachycardia associated with orthostatic hypotension. *Am Heart J* 1974;88:493-5.
32. Grubb BP, Kanjwal MY, Kosinski DJ. Review: the postural orthostatic tachycardia syndrome—current concepts in pathophysiology diagnosis and management. *J Interv Card Electrophysiol* 2001;5(1):9-16.
33. Hoeldtke RD, Horvath GG, Bryner KD. Treatment of orthostatic tachycardia with erythropoietin. *Am J Med* 1995;99:525-9.
34. Benrud-Larson LM, Dewar MS, Sandroni P, Rummans TA, Haythornthwaite JA, Low PA. Quality of life in patients with postural tachycardia syndrome. *Mayo Clin Proc* 2002;77:531-7.
35. Nakamura Y, Matsumura K, Miura K, Kurokawa H, Abe I, Takata Y. Cardiovascular and sympathetic responses to dental surgery with local anesthesia. *Hypertens Res* 2001;24:209-14.
36. Montebugnoli L, Prati C. Circulatory dynamics during dental extractions in normal, cardiac and transplant patients. *JADA* 2002;133:468-72.
37. Replogle K, Reader A, Nist R, Beck M, Weaver J, Meyers WJ. Cardiovascular effects of intraosseous injections of 2 percent lidocaine with 1:100,000 epinephrine and 3 percent mepivacaine. *JADA* 1999;130:649-57.
38. Mchaourab A, Mazzeo AJ, May JA, Pagel PS. Perioperative considerations in a patient with orthostatic intolerance syndrome. *Anesthesiology* 2000;93:571-3.
39. Goldstein DS, Holmes C, Frank SM, et al. Cardiac sympathetic dysautonomia in chronic orthostatic intolerance syndromes. *Circulation* 2002;106:2358-65.
40. Cunniff C, Williamson-Kruse L, Ehlers-Danlos syndrome, type VIII presenting with periodontitis and prolonged bleeding time. *Clin Dysmorphol* 1995;4(2):145-9.
41. North KN, Whiteman DA, Pepin MG, Byers PH. Cerebrovascular complications in Ehlers-Danlos syndrome type IV. *Ann Neurol* 1995;38:960-4.
42. De Paeppe A, Malfait F. Bleeding and bruising in patients with Ehlers-Danlos syndrome and other collagen vascular disorders. *Br J Haematol* 2004;127:491-500.
43. Syndromes affecting the skin and mucosa. In: Gorlin RJ, Cohen MM, Levin LS, eds. *Syndromes of the head and neck*. 3rd ed. New York: Oxford University Press; 1990:417-517.
44. Sacks H, Zelig D, Schabes G. Recurrent temporomandibular joint subluxation and facial ecchymosis leading to diagnosis of Ehlers-Danlos syndrome: report of surgical management and review of the literature. *J Oral Maxillofac Surg* 1990;48:641-7.
45. McDonald A, Pogrel A. Ehlers-Danlos syndrome: an approach to surgical management of temporomandibular joint dysfunction in two cases. *J Oral Maxillofac Surg* 1996;54:761-5.
46. Norton LA, Assael LA. Orthodontic and temporomandibular joint considerations in treatment of patients with Ehlers-Danlos syndrome. *Am J Orthod Dentofacial Orthop* 1997;111(1):75-84.
47. Dajani AS, Taubert KA, Wilson W, et al. Prevention of bacterial endocarditis: recommendations by the American Heart Association. *JAMA* 1997;277:1794-801.
48. Schondorf R, Benoit J, Wein T, Phaneuf D. Orthostatic intolerance in the chronic fatigue syndrome. *J Auton Nerv Syst* 1999;75(2-3):192-201.