Orthostatic Hypotension, 2001

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Upright posture requires rapid and effective circulatory and neurologic compensations to maintain blood pressure and consciousness. Although it has been recognized over the past 100 years or more that the act of standing may cause hypotension in patients with autonomic dysfunction, only recently several of the pathophysiologic mechanisms resulting in orthostatic intolerance have been discovered. In patients with orthostatic hypotension, failure of reflex vasoconstriction causes pooling of blood in the legs during standing. Not everyone with a postural blood pressure drop requires treatment, nor does everyone with posturally induced symptoms have orthostatic hypotension. This review will discuss current knowledge of a broad, heterogeneous group of disturbances in the autonomic nervous system, each of which is manifested by hypotension, orthostatic intolerance, and often syncope.

Key Words: Primary autonomic disorders, Neurocardiogenic syncope, Postural orthostatic tachycardia

Orthostatic intolerance is the development of symptoms during standing relieved by recumbency. Patients with orthostatic intolerance often complain of exercise intolerance, lightheadedness, palpitations, tiredness, weakness, diminished concentration, tremulousness, nausea, visual changes, discomfort in the head or neck, throbbing of the head, anxiety, chest discomfort, dyspnea, and syncope.

For many years, such patients were felt to have deconditioning and were encouraged to pursue a more vigorous exercise regimen, or they were incorrectly labeled as having panic disorder or chronic anxiety. Clinical examination is often unrevealing because florid autonomic failure is not present; therefore, this disorder is sometimes considered benign.

Orthostatic intolerance has been recognized over the course of the past two centuries. During the United States Civil War, DaCosta described a syndrome in young soldiers he called irritable heart (1), characterized by shortness of breath, palpitations, fatigability, headache, diarrhea, dizziness, disturbed sleep, and sharp or burning chest pain, particularly on exertion. Most patients appeared to be in good physical health. This syndrome was also called soldier’s heart (2), or neurocirculatory asthenia. It was a major incapacitating problem in World Wars I and II, the Vietnam conflict, and Desert Storm. Although, in Desert Storm there is no solid evidence to support this belief (3). The chronic symptoms experienced by veterans after each war were also described in civil populations, disorders such as chronic fatigue syndrome and fibromyalgia have similar reports of complaints (4, 5, 6).

When human beings assume upright posture, the effect of gravity on circulation is increased. Upright posture, a fundamental human characteristic, requires rapid and effective circulatory and neurologic compensations to maintain blood pressure, cerebral blood flow, and consciousness. Several mechanisms compensate for the positioning of the brain well above the neutral cardiac point (roughly at the right atrium level). The presence of large venous reservoirs below the neutral point would cause blood pressure to fall rapidly because of gravitational pooling of blood within the dependent veins with subsequent cerebral ischemia. Once consciousness and postural tone are lost, the ensuing fall would render a person recumbent, causing blood remobilization and restored consciousness. The primary defense against blood pooling is the muscle pump in which contractions of leg muscles propels sequestered venous blood back to the heart. The second line of defense is neurovascular adjustment, which includes rapid changes in selective resistance vessel tone (vasoconstriction) limiting flow to the extremities and splanchnic vascular bed while vasoconstriction enhances venous emptying. Reflex compensatory mechanisms are primarily controlled by the high-pressure arterial baroreceptors and to a lesser degree by low-pressure cardiopulmonary reflexes. The sympathetic efferent pathways are the principal source of both short-and medium-term responses to these positional changes (7). Other mechanisms such as the renin-angiotensin-aldosterone system, and the release of epinephrine and vasopressin also contribute, but their responses are observed later. Disturbances in autonomic function resulting in sympathetic failure may elicit orthostatic (or positional) hypotension with or without loss of consciousness (syncope) (8).

The majority of patients with orthostatic intolerance have a relatively mild disorder, which improves over time. In some patients, symptoms are more severe, the illness duration may be longer, and recovery may not occur. Syncope is an important, common, medical problem elicited by conditions ranging from benign and self-limiting causes to chronic, recurrent, and potentially fatal causes. The relative prevalence of such conditions are

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shown in Fig. 1. These data are similar to those reported in the literature (9). Neurally mediated syncope and postural orthostatic tachycardia syndrome (POTS) are the two most frequent causes of syncope. In patients with severe symptoms of orthostatic intolerance, there is a significant toll on lifestyle and work capacity.

The current paper is a review of the existing concepts concerning this important topic, with clinical relevance for internists and cardiologists. Special emphasis is given to the clinical aspects, pathophysiology, diagnosis, and treatment of the conditions that may elicit orthostatic hypotension.

**Disorders of Orthostatic Control**

The clinical spectrum of dysfunction in orthostatic cardiovascular homeostasis includes usually benign conditions such as neurally mediated syncope, postural tachycardia syndrome, chronic fatigue syndrome, fibromyalgia, and severe forms of primary chronic autonomic failure with multisystemic involvement such as pure autonomic failure, and multiple system atrophy.

**Orthostatic Hypotension**

**Definition.** Orthostatic hypotension has been defined as a fall of more than 20 mmHg in systolic blood pressure within 3 minutes of standing. A lesser drop in blood pressure associated with symptoms may also be important. Some patients may have a slow but steady decline in blood pressure over a longer period of time (10 to 15 minutes) associated with symptoms. The absolute blood pressure drop is not the only factor responsible for symptoms; they also depend on the rate of blood pressure fall and cerebral perfusion autoregulation.

**Etiology.** The neurogenic causes of orthostatic hypotension may be subdivided into primary and secondary causes according to the American Autonomic Society and the American Academy of Neurology classification (10) (Table 1). Primary causes are, for the most part, idiopathic, while secondary causes are associated with a known biochemical or structural anomaly, or are seen as part of a particular disease or syndrome.

**Primary Neurogenic Causes of Autonomic Dysfunction**

Clinical dysautonomic syndromes may be either acute or chronic. The physician is more likely to encounter chronic forms of autonomic failure than their acute counterparts.

**Acute Disorders**

Even though these syndromes are rare, the acute autonomic neuropathies that produce hypotension and syncope are frequently dramatic in presentation. These disorders are sudden in onset, and demonstrate severe and widespread failure of both the sympathetic and parasympathetic systems while leaving the somatic fibers unaffected. Many patients tend to be young and, prior to the illness, healthy (11). A large number of these individuals had a febrile illness before the onset of symptoms, giving rise to the notion that there may be an autoimmune component to the disorder. Patients frequently complain of bowel and bladder dysfunction, and lose their ability to sweat. The long-term prognosis of these patients is variable, with some achieving complete recovery while others experience a chronic debilitating course.

**Chronic Disorders**

**Pure Autonomic Failure.** Pure autonomic failure, or Bradbury-Eggleston syndrome, is a degenerative disorder of the autonomic nervous system presenting in middle to late life, affecting men more than women. In these patients there exists a generalized state of autonomic dysfunction as manifested by orthostatic hypotension and syncope, as well as disturbances in bowel, bladder, thermoregulatory, sudomotor, and sexual function. Patients complain of impotence, dizziness, or faintness on standing, pain in the neck or back of the head relieved by lying down, nocturia, urgency, occasional incontinence, and change in the pattern of sweating. While the cause of pure autonomic failure remains unknown, several investigators have postulated that there is degeneration of the peripheral postganglionic autonomic neurons (11).

**Multiple System Atrophy.** In 1960 Shy and Drager (12) described this complex multisystem disorder as a widespread autonomic failure associated with impairment of several neurologic systems such as cerebellar, extrapyramidal, neuromuscular, or pyramidal. It is manifested by severe orthostatic hypotension, progressive urinary and rectal incontinence, loss of sweating, iris atrophy, external ocular palsy, impotence, rigidity, and tremors. Both muscle fasciculations and distal muscle wasting may occur late in the disorder. The average age of onset is during the sixth decade of life, but some individuals begin to have symptoms earlier. The pathologic hallmark of multiple system atrophy is neuronal loss and gliosis.
within multiple sites in the brain. Multiple system atrophy can appear surprisingly similar to Parkinson disease. An autopsy study recently found that somewhere between 7% and 22% of people thought to have Parkinson’s disease actually had neuropathologic findings diagnostic for multiple system atrophy (11).

To diagnose pure autonomic failure and multiple system atrophy, thoughtful and careful evaluation should be undertaken. Posture studies with blood pressure and heart rate monitoring with catecholamine levels in the supine and upright position should be done. The definitive diagnosis of hypotension as the cause of orthostatic symptoms is usually made by the demonstration of a decline in systolic blood pressure of 20 mmHg or more and diastolic blood pressure of 10 mmHg after at least 1 minute of standing. The change of heart rate on standing is minimal or absent and will often be fixed; 40–50 beats/min, associated with chronotropic incompetence (13). Orthostatic hypotension is usually accompanied by supine hypertension. Pure autonomic failure patients have greatly reduced levels of catecholamines. These levels are very low while lying down, and increase little on standing. In multiple system atrophy, basal serum norepinephrine concentrations are normal. Other potential evaluations include autonomic function testing, computed tomography, magnetic resonance imaging, positron-emission tomography of the brain, sleep study, and urodynamic testing. A precise diagnosis is essential for the prognosis, which is good in pure autonomic failure and poor in multiple system atrophy.

**Secondary Neurogenic Causes of Autonomic Dysfunction**

Generalized secondary dysfunction of the autonomic nervous system often complicates neurologic disorders and systemic diseases (11). Drugs may cause autonomic dysfunction directly or through a neuropathy, as in alcoholic neuropathy. Chief among these are the peripherally acting vasodilator agents. Beta-blocking agents may also worsen syncope in some patients. Centrally acting agents, such as the tricyclic antidepressants, reserpine, methylomega, and monoamine oxidase (MAO) inhibitors, may also exacerbate otherwise mild hypotension. Over the past decade, a number of enzymatic abnormalities that can result in autonomic disruption have been identified. Among these, the isolated dopamine beta-hydroxylase deficiency syndrome is a condition that is now easily treated by replacement therapy. Additional deficiency syndromes involving nerve growth factor, monoamine oxidase, aromatic L-amino decarboxylase, and...
some sensory neuropeptides may all result in autonomic failure and hypotension.

**Neurally Mediated Syncope**

**Clinical Aspects**

Neurally mediated syncope (vasovagal or neurocardiogenic) is the most common type of syncope. Clinical descriptions of it have been present in the medical literature for a long time. It occurs most frequently in young people and is characterized by premonitory signs and symptoms (lightheadedness, weakness, pallor, diaphoresis, blurred vision, impaired hearing, yawning, hyperventilation, and nausea). If the patient sits or lies down promptly, syncope may be aborted. Onset of vasovagal syncope is usually gradual, but sudden loss of consciousness without warning is sometimes observed. When consciousness returns, the patient may have a persistent sensation of weakness but is not usually confused. Vasovagal syncope may be precipitated by the sight of blood, loss of blood, sudden stressful or painful experiences, surgical manipulation, or trauma. A history of childhood syncope may provide a clue to the cause of vasovagal syncope in adults. Many people who are misdiagnosed with epilepsy may actually have convulsive neurally mediated syncope.

**Pathophysiology**

The pathophysiology of this condition is not completely understood, often resulting in difficult diagnosis and treatment. The precipitating events of syncope trigger a complex hemodynamic response, resulting in marked hypotension, usually with bradycardia and loss of consciousness. Several theories have been proposed to explain these hemodynamic events. The ventricular theory suggests that when baroreceptors detect a fall in blood pressure initiated by excessive venous pooling associated with upright posture, a decrease in ventricular volume results, a reflex increasing the efferent sympathetic traffic. Increased sympathetic tone in a setting of an empty ventricle stimulates ventricular afferents that in turn trigger an increased vagal tone (Bezold-Jarisch reflex) and sympathetic withdrawal, resulting in hypotension and bradycardia just before the syncope. Vasovagal syncope in humans, however, is probably triggered by mechanisms beyond those described by the Bezold-Jarisch reflex. In animal models and in heart transplant patients, neurally mediated hypotension and bradycardia have been observed despite cardiac denervation (14). Although it has been proposed that receptors in other cardiovascular regions may be excited by hypovolemia and trigger neurally mediated syncope, no experimental confirmation is available.

Another important premise of the ventricular theory is the presence of increased sympathetic tone. This idea is not supported by studies in neurally mediated syncope patients, which have shown that muscle sympathetic nerve activity (MSNA) does not increase before syncope. Mosqueda-Garcia et al. (15) found an attenuated sympathetic response to orthostatic stress, characterized by a
significantly blunted increase in MSNA, followed by a progressive decrease and total disappearance before syncope.

It can be argued that recordings of MSNA may not reflect the noradrenergic changes evoked in other relevant regions (ie, heart). During tilt, neurally mediated syncope patients exhibit variable responses in cardiac sympathetic function. While some investigators have found that cardiac sympathetic tone increases before syncope (16, 17), others have found the opposite (18), or even evidence for both increase or decrease (19), depending on the individual subject. Two different patterns may be recognized in the cardiac autonomic changes preceding an occasional vasovagal event. The first pattern is characterized by a progressive increase of cardiac sympathetic modulation that leads to the sudden onset of bradycardia; the second pattern displays a gradual inhibition of sympathetic and a concomitant enhancement of vagal modulation of heart period (18). Currently, it is not clear whether differences in methodology, the selection of patients, or both, may account for these discrepancies.

Mosqueda-Garcia et al. at Vanderbilt University (15) investigated baroreflex sensitivity by stepwise infusions of phenylephrine and sodium nitroprusside. Subjects with recurrent neurally mediated syncope and positive tilt-table tests had reduced cardiac and sympathetic baroreflex responses when compared with controls.

Studies using transcranial Doppler sonography of the middle cerebral artery in patients with neurally mediated syncope during head-up tilt-table testing (HUT) have shown an abnormal cerebral vascular response to orthostatic stress characterized by cerebral vasoconstriction and reduced cerebral blood flow (20). A decrease in cerebral blood flow with head-up tilt has also been shown in patients with POTS suggesting that sympathetically mediated vasoconstriction and hyperventilation causing significant hypocapnia could increase cerebrovascular resistance (21). An accelerated hypersensitivity of cerebral artery response to catecholamine has been proposed as one of the factors inducing syncope (22). In our laboratory, patients with neurally mediated syncope and those with POTS had different patterns in cerebral blood velocity during HUT. Patients with POTS had an earlier decrease and larger oscillations in the middle cerebral artery diastolic velocity than patients with neurally mediated syncope (unpublished observations, Hermosillo, 2001.) These findings support the possibility that abnormalities within the central nervous system may play a pivotal role in the pathogenesis of orthostatic intolerance.

In patients with neurally mediated syncope, the detection of cerebral vasoconstriction by transcranial Doppler sonography before syncope allows the interruption of the test to avoid the risk of asystole. Cerebral monitoring during HUT permits confirmation of chronic orthostatic intolerance in the absence of hypotension.

**Diagnosis**

A careful and concise history and physical examination (which must include neurologic examination) have a far greater diagnostic yield than the mindless ordering of multiple tests. Tilt-table testing, developed in 1986, significantly reduced the number of patients with unexplained syncope, and enabled researchers to study the mechanism of syncope and evaluate the efficacy of different treatments (23, 24). A complete discussion of the therapeutic options is beyond the scope of this review; however, some basic principles will be very briefly outlined (more complete discussions can be found elsewhere).

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where) (7, 8). An algorithm to guide the diagnosis and treatment of patients with neurally mediated syncope and related disorders has been developed (Fig. 3) (25). It is based on a patient’s hemodynamic response to standing, a simple maneuver that should be done as part of the initial evaluation. Assuming the hemodynamic response to standing is normal, the second step is whether treatment will be made empirically, or if HUT will guide therapy. Tilt-table testing offers a great deal of information about a patient’s hemodynamic and autonomic responses to prolonged orthostatic stress. To increase the sensitivity, pharmacologic stimulation with isoproterenol and nitrates is frequently used (17, 23).

**Treatment**

The majority of patients with neurally mediated syncope do not require specific pharmacologic treatment. Teaching the patient ways to avoid syncopal episodes may be effective in preventing recurrence. The assessment of medications and other medical problems that might be contributing to syncope is important. Three agents are widely used to treat these patients: beta-blockers, fludrocortisone, and midodrine. Beta-blockers are thought to blunt the effects of catecholamines. Fludrocortisone results in plasma volume expansion that diminishes the relatively central hypovolemia that occurs with upright posture and reduces the reflex increase in sympathetic drive and the possibility of an intense contraction of a relatively underfilled ventricle. Midodrine is an alpha-1 agonist thought to increase venous vasomotor tone, limiting the venous pooling when upright. Other pharmacologic agents have been used in uncontrolled studies; serotonin reuptake inhibitors, dysopiramide, anticholinergic agents, clonidine, etc. Relatively few patients continue to have recurrent syncope after education, reassurance, and treatment with these agents, alone or in combination. The use of pacemakers should be reserved for patients with prolonged asystole who continue to
have recurrent syncope despite the use of multiple medications (26).

**Postural Tachycardia Syndrome**

**Clinical Aspects**

Postural tachycardia syndrome is a disabling chronic disorder that primarily affects young women. This disorder is characterized by tachycardia and symptoms of cerebral hypoperfusion and sympathetic activation. The main complaints are lightheadedness, blurred vision, palpitations, nausea, and fatigue. These symptoms become manifest with upright posture and are relieved by sitting or lying down; they are aggravated by body warming, stress, a meal, and exertion. Half of patients have an antecedent of a presumed viral illness. Postural tachycardia syndrome has a cyclical nature of the symptoms. Some females will have more symptoms at certain stages of their menstrual cycle. These patients have large fluctuations in their weight. Some patients have episodic symptoms at rest usually early in the morning. The heart rate alterations are typically a sinus tachycardia, although a bradycardia with marked sinus arrhythmia may coexist. Pulse pressure may be excessively reduced. Another clinical sign is the development of acral coldness. With continued standing there may be venous prominence resulting in blueness and even swelling of the feet. Some patients with postural tachycardia syndrome develop symptoms, despite a hypertensive response to standing, when diastolic blood pressure may increase by up to 50 mmHg (27). There is a danger of misdiagnosing the condition as inappropriate sinus tachycardia. In these cases, radiofrequency modification of the sinus node can make symptoms worse.

**Pathophysiology**

Patients with postural tachycardia syndrome frequently have high plasma norepinephrine concentrations of at least 600 pg/mL on standing, suggesting a primary hyperadrenergic condition (28). Excessive pooling of the blood in the legs while standing has been reported, suggesting that denervation of the legs is part of the syndrome (29). Plasma volume is generally normal in postural tachycardia syndrome, although some patients with hypovolemia have been described (30).

Different mechanisms have been considered to account for the symptoms and the hemodynamic profile of
postural tachycardia syndrome patients. These include the presence of a mild form of partial dysautonomia resulting in dysregulation of autonomic control of the cardiovascular system (31), the development of a compensatory hyperadrenergic response to a reduced plasma volume or excessive venous pooling in the lower extremities (28), or sympathetic dysfunction emanating from the central nervous system (32).

Recent data from Vanderbilt University suggest that postural tachycardia syndrome is a disorder with discordant cardiac and vascular sympathetic control. Furlan et al. (33) have combined tilt testing, microneurographic recordings, and spectral analysis of cardiovascular variability to provide a moment-by-moment characterization of hemodynamics, sympathetic traffic, and symptoms in patients with postural tachycardia syndrome. In postural tachycardia syndrome there are faster heart rates and increased sympathetic traffic to muscle blood vessels (muscle sympathetic nerve activity, MSNA), during supine rest. On upright tilt, blood pressure does not change. The changes in central venous pressure with upright tilt are similar to the changes in control subjects, but there is an exaggerated tachycardic response and a blunted increase in MSNA in postural tachycardia syndrome patients compared with normal subjects. The potentiated chronotropic response is accompanied by an attenuated sympathetic (presumed vasoconstrictor) response, thus ruling out hypovolemia alone as an explanation. Increases in norepinephrine and the ratio of low-frequency to high-frequency components (LF/HF) of normal ECG R-R intervals are preserved in postural tachycardia syndrome, suggesting that any blunting of autonomic function is selective for sympathetic efferent traffic to muscle blood vessels, perhaps for the lower extremities only (33). These responses occur in the absence of impaired baroreflex gain.

To test the hypothesis that postural tachycardia syndrome is caused by partial dysautonomia which results in dysregulation of autonomic control of the cardiovascular system, Jacob et al. (34) measured the spillover of norepinephrine (the rate of entry of norepinephrine into the venous circulation) in the arms and legs of patients with postural tachycardia syndrome and in normal subjects before and after exposure to several stimulators of sympathetic activation. At rest, plasma norepinephrine concentration in the femoral vein was lower in patients with postural tachycardia syndrome than in the normal subjects. Norepinephrine spillover in the arms increased to a similar extent in the two groups in response to each of the stimulators of sympathetic activation, the increases in the legs were smaller in the patients with postural tachycardia syndrome. They concluded that postural tachycardia syndrome results from partial sympathetic denervation, especially in the legs. The reduced clearance of norepinephrine in the legs, without a similar reduction in the arms, may result from impairment of norepinephrine-uptake mechanisms caused by isolated damage to nerve terminals in the legs. Changes in capillary permeability in the limbs may also contribute to the observed alterations in norepinephrine spillover and clearance (34).

**Diagnosis**

There is a sustained increase of heart rate of at least 30 beats/min, without fall in systolic/diastolic blood pressure >20/10 mmHg, within 5 minutes of standing. Considering the age range of most patients with postural tachycardia syndrome (15–50 years), an increment of 30 bpm exceeds the ninetieth percentile for female control subjects from 10 to 83 years but is more stringent in terms of the absolute orthostatic heart rate. Some patients might have a heart rate increment of 30 bpm with a standing heart rate below 120 bpm, a criterion that was previously accepted (35).

**Prognosis**

Limited information is available on prognosis. The variability in severity and the number of confounding variables are factors that render prognostication difficult. Sandroni et al. (36) reported that in the majority of patients postural tachycardia syndrome is self-resolving, especially in those with a triggering event (postviral). On follow-up, orthostatic tolerance improved in 80% of patients, 60% were functionally normal, and 90% were able to return to work.

Shannon et al. (37) found a deficiency in norepinephrine transport in the proband and several members of a family with postural tachycardia syndrome. This deficiency was the result of a functional mutation in the gene encoding the norepinephrine transporter. In many patients with orthostatic intolerance, the disproportionately greater increase in heart rate than in diastolic pressure in the upright posture may be explained by a deficiency of the norepinephrine transporter. The noradrenergic synapic clefts in the heart are approximately three times as narrow as the synaptic clefts in the vasculature, making the removal of norepinephrine from the synapses in the heart far more dependent on the activity of the norepinephrine transporter than is removal from synapses in the vascular beds (37). Therefore, genetic or acquired deficits in norepinephrine inactivation may underlie hyperadrenergic states that lead to orthostatic intolerance.

**Treatment**

The dysautonomia associated with postural tachycardia syndrome suggests that its treatment should be similar to that of pure autonomic failure, which results from nearly complete peripheral autonomic neuropathy. Autonomic failure is treated by increasing blood volume through greater intake of fluids and sodium, administration of the mineralocorticoids such as fludrocortisone (38), and by minimizing orthostatic pooling of the blood in the lower limbs by compression pantyhose to increase extravascular hydrostatic pressure or with short-acting vasoconstrictors to increase intravascular pressure (25). Beta-blockers with weak penetration in the central nervous system can also be used (39). The treatment of these patients is uncertain, because there is no single approach that is always effective.
Conclusions

Disorders of cardiovascular autonomic function are common. It is conceivable that their natural history comprises transitions from one hemodynamic profile to another. The heterogeneity of hemodynamic profiles of orthostatic intolerance requires an individualized therapeutic approach.

References


A historic editorial describing the functional disorders of the heart.


A description of unexplained symptoms among veterans after each war.


A report of tilt study in chronic fatigue syndrome, describing the hemodynamic response with hypotension and bradycardia.


Two different patterns may be recognized in the cardiac autonomic changes preceding an occasional vasovagal event.


Subjects with fibromyalgia have decreased 24-hour heart rate variability, suggesting a decreased parasympathetic activity.


This excellent book comprehensively covers all key human autonomic disorders.


This chapter focuses on autonomic dysfunction as a cause of orthostatic hypotension leading to syncope.


A classification of the disorders of orthostatic control.


A recent classification of the disorders of orthostatic control.


Classification of autonomic disorders, their clinical aspects, diagnosis, and potential management options.


The original description of Multiple System Atrophy.
A comprehensive algorithm to help in the diagnosis and treatment of patients with neurally mediated syncope.


Symptoms of postural tachycardia syndrome may be triggered by cerebral vasoconstriction.


