Reviews

The Postural Tachycardia Syndrome: a Brief Review of Etiology, Diagnosis and Treatment

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"All beginnings are hard..."
The Talmud

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Transient episodes of autonomically-mediated hypotension and bradycardia have become a well recognized cause of recurrent syncope and near syncope[1]. The emergence of tilt table testing as a reliable method for provoking these periods of autonomic decompensation not only provided a useful diagnostic tool but has also allowed for a much better understanding of the pathophysiology of these disorders. In the course of these investigations, it became apparent that these episodic alterations in autonomic tone could result in varying degrees of systemic hypotension that, while not sufficiently large enough to cause complete loss of consciousness, were nevertheless great enough to cause symptoms such as near-syncope, lightheadedness, vertigo, and transient ischemic attacks. At the same time, we and other groups identified a large subgroup of patients who have a less severe form of orthostatic intolerance that is characterized by postural tachycardia, exercise intolerance, disabling fatigue, lightheadedness, dizziness, and blurred vision[2]. Detailed investigations of these patients have revealed that the histories, physical findings, and responses to postural change and head –up tilt were all essentially similar. This disorder has become generally known as the Postural Orthostatic Tachycardia Syndrome. The present paper will review the clinical characteristics of these patients, their responses during head upright tilt table testing, and the various therapies that appear to benefit these patients.

Physiological Aspects

A full description of all the physiologic changes that occur in response to upright posture exceeds the scope of this review. However, briefly, approximately 25% of the body's blood is in the thorax while supine.[1] Almost immediately after assuming upright posture, gravity causes a downward displacement of about 500 ml of blood to the lower extremities and inferior mesenteric area. One-half of the amount is redistributed within seconds after standing and up to 25% of the total blood volume may be involved in the process. This causes a decrease in venous return to heart and stroke volume may fall by 40%. In the normal subject, orthostatic stabilization after standing is achieved in 1 min or less. Immediately after standing there is a slow progressive decline in arterial pressure and cardiac filling, which results in an activation of the high-pressure receptors of the aortic arch and the carotid sinus (as well as low-pressure cardiac and pulmonary receptors). The cardiac mechanoreceptors are

joined by unmyelinated vagal effects from both the atria and ventricles. These cause continuous inhibitory actions on the cardiovascular areas of the brain stem (especially the nucleus tractus solitarii)[3]. The reduced venous return caused by upright posture produces less stretch on these receptors, decreasing their discharge rates. This alteration in input to the medulla results in an increase in sympathetic outflow and there is an increase in systemic vasoconstriction. Simultaneously, the decline in arterial pressure while upright activates the high-pressure receptors in the carotid sinus, which then increase heart rate. Therefore, steady-state adaptation to upright posture causes a 10-15 beats/min increase in heart rate, an increase in diastolic blood pressure of approximately 10 mmHg, with little or no change in systolic blood pressure. More detailed descriptions of the process are available elsewhere[4]. The inability of this complex process to respond adequately (or in a coordinated fashion) can result in a failure to respond normally to sudden changes in posture (and to maintain adequate responses). Failure in this system may manifest itself as hypotension, which, if severe, may cause cerebral hypoperfusion, hypoxia and loss of consciousness.

Historical Aspects and Etiology

Beginning in the nineteenth century, physicians reported patients suffering from a condition characterized by fatigue and poor exercise tolerance that occurred without an obvious cause (such as prolonged bed rest). Some of the first reports were from the American Civil War by DaCosta who used the terms "irritable heart syndrome" and "soldier's heart" to describe the condition[5]. At the time of the First World War there were a number of reports of conditions that were variously labeled as "neurocirculatory asthenia" or "vasoregulatory asthenia" reflecting the idea that these conditions were due to a functional cardiac phenomenon caused by insufficient neural regulation of peripheral blood flow[6]. In 1944 MacLean et al reported on a group of patients with orthostatic tachycardia that was associated with only a mild drop in blood pressure, who complained of palpitations, lightheadedness, weakness, and exercise intolerance[7]. They hypothesized that a potential mechanism for these problems might be a reduction in venous return to the heart from a disturbance at the capillary venous level.

In the 1960s, Frolich et al reported two patients who developed a postural tachycardia (with an increase of more than 40 beats/minute on standing without hypotension) who experienced extreme postural anxiety, near syncope, and dizziness[8]. Each patient also had an exaggerated heart rate response to intravenous isoproterenol and both showed symptomatic improvement on beta-blockers. Much later, in 1982, Rosen and Cryer used the term Postural Tachycardia Syndrome to describe a patient who exhibited a greater than 44 beat/minute increase in heart rate upon standing (without orthostatic hypotension) associated with complaints of fatigue, exercise intolerance, and palpitations[9]. Shortly thereafter Fouad et al described patients with orthostatic intolerance who demonstrated postural tachycardia and only a slight degree of hypotension, referring to the condition as "idiopathic hypovolemia"[10]. Streeten et al then reported on a similar group of patients who demonstrated orthostatic tachycardia without hypotension[11]. By using gamma camera counting of sodium pertechnetate Tc 99 mm labeled erythrocytes over the calf areas of patients while supine and upright they showed evidence of extensive gravity dependent venous pooling in the lower extremities. Somewhat later, Streeten then published a report of four similar patients who additionally demonstrated a hypersensitivity to a noradrenalin infusion[12].

Hoeldtke et al have described a total of 13 patients with near syncope, exercise intolerance, fatigue, and cognitive impairment who demonstrated evidence of postural tachycardia[13,14]. Low et al and Schondorf et al have made a comprehensive analysis of 16 patients who suffered from profound fatigue, an inability to exercise, near syncope, dizziness, and bowel hypomotility[15,16]. Many of these patients had been labeled as having psychologic problems such as chronic anxiety or panic attacks. During head upright tilt table testing these patients had markedly abnormal cardiovascular responses, with heart rates that would frequently climb to as high as 120 to 170 beats per minute often within the first two minutes of upright tilt. While some of these patients exhibited a mild reduction in blood pressure, most became hypertensive (with up to a 50 mm/Hg increase in diastolic blood pressure).

These investigators frequently employed the term Postural Orthostatic Tachycardia Syndrome (or POTS) to describe this condition and postulated that it represented an attenuated form of dysautonomia. Khurana described a group of eight patients who had virtually identical symptoms and tilt responses who also had abnormal sudomotor function

with reduced functional activity of the sweat glands of the lower extremities (presumably due to impaired innervation)[2]. Our group reported on 28 patients who presented with extreme fatigue, lightheadedness, orthostatic tachycardia, exercise intolerance, cognitive impairment, and near syncope[2]. During upright tilt table testing each patient demonstrated an increase in heart rate of at least 30 beats/minute (which in each case exceeded 120 beats/minute) within the first 10 minutes of the test. There was a mild fall in systolic blood pressure of approximately 20 mm/Hg during tilt (although no patient's pressure fell below 85-90 mm/Hg). A similar report from Karas et al[17] demonstrated identical findings in a group of 35 adolescent patients, suggesting that there is a large age range affected by the disorder.

Investigators quickly noted that in some patients there was a marked familial predisposition to these disorders, raising suspicions that there was a possible genetic basis to them. This suspicion was recently confirmed by investigators at Vanderbilt, where the exact genetic basis for this disorder was determined in one severely affected family[18]. The defective gene causes a dysfunction in a norepinephrine transporter protein, producing excessive serum norepinephrine levels. Many investigators have postulated that there are multiple genetic forms of the disorder and more detailed investigations are currently in progress.

At the same time, a large number of patients report that symptoms appear after a severe viral infection, suggesting that an immune-mediated mechanism may be involved. This concept was recently confirmed by investigators at the Mayo Clinic, who found that many patients had high serum levels of autoantibodies to peripheral acetylcholine receptors[19]. The levels of these antibodies seemed to vary with the severity of the illness. They may be a considerable degree of overlap between POTS and "inappropriate" sinus tachycardia. Support for this concept has also come from the Mayo Clinic, which reported that radiofrequency ablation had little effect in these disorders, and sometimes made people worse[20].

Definitions

Combining together the inform data from various investigators, these observations seem to present a fairly consistent picture of this disorder. While a number of different terms have been coined to describe this phenomena, we prefer Postural Orthostatic Tachycardia Syndrome (or POTS) because it is a fairly descriptive term and easy to remember. These patients manifest an orthostatic intolerance in that they develop symptoms while standing that are relieved by recumbency. POTS patients frequently present with complaints of fatigue, exercise intolerance, lightheadedness, nausea, loss of concentration and memory, tremulousness, and recurrent near syncope (and sometimes syncope). These patients may frequently be misdiagnosed as having panic attacks or chronic anxiety. Relatively simple activities such as modest exercise, showering (or sometimes even eating), may intensify these symptoms and profoundly limit even the most basic activities of daily life. Because severe autonomic failure is not present, the general physical exam is often unrevealing and patients are told that "nothing is wrong."

Currently we define POTS as the development of orthostatic symptoms that are associated with at least a 30 beat/minute increase in heart rate or a heart rate of $\geq$120 beats/minute that occurs within the first ten minutes of standing or upright tilt. With respect to age range of patients with POTS (10-60 years) this increase in heart rate exceeds the 99th percentile for control subjects 10-83 years[23]. We have tended to focus on heart rate mainly because it is the earliest, most consistent, and easiest to measure index of orthostatic intolerance. The disadvantage of focusing on the postural tachycardia is that it does not take into account the nonorthostatic symptoms such as the sudden episodes of autonomic decompensation manifested by marked fluctuations in blood pressure, sinus tachycardia, fatigue, and vasomotor symptoms that many patients experience.

Clinical Features

While the etiology of POTS is still unclear, it most likely represents a heterogenous group of disorders with similar clinical characteristics[21]. The largest group of patients appear to have a mild form of idiopathic peripheral autonomic neuropathy (a "partial dysautonomia"), in which an inability to increase peripheral vascular resistance during upright posture results in an excessive compensatory postural tachycardia. Venous pooling appears to be present that results in a reduction in ventricular preload which in turn leads to baroreceptor unloading while upright with a resultant increase in sympathetic outflow[15,16]. Some studies have looked at mean sympathetic nerve activity using microneurography in these patients, as well as heart rate variability indices, and found

that they exhibit an overall enhancement of noradrenergic tone at rest and by a postganglionic sympathetic response to standing (with compensatory cardiac sympathetic over-activity). Interestingly, many of these patients will be noted to develop a bluish discoloration of the lower extremities on prolonged standing.

A second group of patients may have a component of beta-receptor supersensitivity. Some investigators have used the term hyperadrenergic orthostatic intolerance to describe this subset. Many of these patients complain of extreme tremulousness and anxiety in addition to palpitations and tachycardia while standing. They also demonstrate exaggerated responses to low dose isoproterenol infusions while supine (it is not uncommon to see heart rate increases of 30 beats per minute or more in response to a 1 mg/minute isoproterenol infusion). Serum catecholamine levels are quite high (serum norepinephrine levels are often >600 ng/ml). It is unclear whether this supersensitivity is primary in nature or due to a secondary denervation supersensitivity. Indeed, some of these patients appear to display excessive sympathetic activation in some distributions almost all the time. This excessively sympathetic activation is not appropriately attenuated by baroreflex mechanisms[18]. Indeed, recent genetic studies alluded to previously have demonstrated a mutation that results in a deficiency of the norepinephrine transporter that clears it from the synaptic cleft. Impairment of synaptic norepinephrine clearance could potentially produce a state of excessive sympathetic activation in response to physiologic stimuli.

While these patients share a number of characteristics with those who suffer from the partial dysautnomia form of POTS, they more often complain of tremor, migraine headache, and cold, sweaty extremities. Furthermore, detailed studies are presently under way to better understand the differences present in these two groups, and whether other subtypes may also exist. Recent data have suggested that a third group of patients exists, those with Ehlers-Danlos III syndrome (hypermobility syndrome). These patients demonstrate reduced vascular reactivity and failure to vasoconstrict during upright posture.

The term "Secondary POTS" is applied to those patients with a known autonomic disorder with preserved cardiac innervation despite peripheral autonomic denervation. This can be due to diseases such as diabetes, amyloidosis, Sjogren's syndrome or lupus. In occasional patients it may be the presenting sign of more severe disorders such as Pure Autonomic Failure or Multiple Systems Atrophy[22].

Diagnosis and Management

Initially the patient gives a detailed history and undergoes physical examination that includes a careful neurologic examination. Patients should also be evaluated for recognizable causes of orthostatic intolerance such as anemia, dehydration, or any chronic debilitating illness. Drugs that the patient may be taking that could cause or aggravate the problem (such as vasodilators, tricyclic antidepressants, MAO inhibitors or alcohol) should be identified. Heart rate and blood pressure should be measured in the supine, sitting, and standing positions. If cardiac causes are suspected, these should be appropriately evaluated. Sinus tachycardia that is abrupt in onset and termination unrelated to posture suggests possible sinus node re-entry and may require electrophysiologic studies.

Tilt table testing is often useful as a standardized measure of response to postural change[1].

The treatment of these patients can be somewhat of a challenge, as no single approach is uniformly successful. The first step in management of these patients is to rule out any correctable cause that might need special treatment. Conditions such as diabetes, significant weight loss, chronic debilitating disease, or prolonged immobilization are usually self-evident. One should also determine if any medications the patient may be taking could be contributing to the problem, (and in some individuals one must consider whether illicit drug use could potentially play a role). An extremely important part of therapy is educating the patient and his family as to the nature of the disorder and to avoid aggravating factors such as extreme heat, dehydration, and excess alcohol consumption. Next, we try to increase salt and fluid intake. Patients are encouraged to sleep with the head of their beds slightly elevated. Mild aerobic exercise is strongly encouraged, with an eventual goal of performing 20 minutes of aerobic activity at least three times a week. Resistance training to build up the lower extremities can be particularly helpful. Elastic support hose are useful in some patients. The hose should be waist high and provide 30 mm/Hg ankle counter-pressure. Pharmacologic therapy must be tailored to meet the

needs of each individual patient and those needs will change over time. Fludrocortisone is useful in many patients, with the usual dose around 0.2 mg/day. Midodrine is quite useful, due to its peripheral vasoconstrictive action, and is usually given in 5-10 mg doses three times a day. Patients with the b-receptor hypersensitivity form may respond to either b-blocking agents or to clonidine. In patients refractory to other forms of therapy, erythropoietin may be useful. Some groups have reported that phenobarbital may be useful in selected patients. We have found the selective serotonin reuptake inhibitors useful in many patients, the most effective one being venlafaxine[23]. Frequently patients will require a combination of various therapies to be effective. A comprehensive review of potential treatments is beyond the scope of this review and more in-depth discussions of therapy can be found elsewhere[21].

Conclusions

POTS is a potentially recognizable and treatable disorder in which patients present with a marked orthostatic intolerance manifested by postural tachycardia, palpitations, weakness, fatigue, and exercise intolerance. The importance of this disorder goes beyond the number of people it affects, as it may cause substantial disability among young, otherwise healthy, individuals. During passive upright tilt these patients demonstrate a heart rate increase of >30 beats/minute or a peak rate of >120 beats/ minute within the first ten minutes, reproducing the patients symptoms. Some patients may exhibit an exaggerated response to isoproterenol. Therapies directed at correcting autonomic balance can often relieve the severity of the symptoms. Greater efforts will be necessary to better understand this syndrome and its various subtypes and provide therapies that will help this group of highly symptomatic patients return to normal life. Continuing research will help provide greater insight into this and other autonomic disturbances associated with chronic orthostatic intolerance.

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