Vanderbilt Autonomic Dysfunction Center

Orthostatic Intolerance/Tachycardia (POTS)

Introduction

When orthostatic symptoms occur in patients, but blood pressure does not fall as much as 20/10 mmHg on assumption of upright posture, the patient has orthostatic intolerance (OI). Additional criteria used for the diagnosis of OI at Vanderbilt’s Autonomic Dysfunction Center include an increase in heart rate of at least 30 beats per minute with standing, and a standing plasma norepinephrine level of at least 600 pg/ml. Because upright heart rate is usually greatly increased, the term Postural Tachycardia Syndrome (POTS) is also used.

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Demographics

Orthostatic intolerance affects an estimated 500,000 Americans and causes a wide range of disabilities. It is a disorder that more frequently affects young women (female-to-male ratio at least 4:1), often less than 35 years of age. Most of these patients experience an excessive heart rate increase when they stand. This heart rate increase is a sign that the cardiovascular system is working hard to maintain blood pressure and blood flow to the brain in the presence of a disordered cardiovascular regulation. Other than essential hypertension, OI is the most common disorder of blood pressure regulation. OI is also the most frequently encountered dysautonomia, accounting for the bulk of patients referred to centers specializing in autonomic disorders.

Symptoms & Signs

Orthostatic intolerance is present when patients experience symptoms such as lightheadedness, palpitations, and tremulousness during standing. Many patients also note other symptoms with
upright posture: visual changes, discomfort in the head or neck, throbbing of the head, poor concentration, tiredness, weakness and occasionally fainting. Patients can be severely impaired by these symptoms and signs, such as a bluish-red discoloration of skin in the lower extremities on standing, which are relieved by lying down. Similar orthostatic symptoms of inadequate cerebral perfusion can occur transiently after serious debilitating illness, substantial weight loss and deconditioning or spaceflight.

Etiology

The etiology of OI is unknown. For many years, such patients were felt to have deconditioning and were encouraged to pursue a more vigorous exercise regimen. However, recently it has become clear that many individuals with these symptoms have a more serious problem than mere deconditioning. The onset of OI is often predated by a recent viral infection. Patients can undergo extensive clinical evaluation without identification of a specific abnormality, and therefore most patients remained undiagnosed. These difficulties are compounded by the heterogeneity of disease states in patients with orthostatic symptoms, spontaneous fluctuations in disease severity, and no uniformity in nomenclature of disease classification. Another problem in the diagnosis of OI is its overlap with other conditions such as Chronic Fatigue Syndrome (CFS), Neurally Mediated Syncope (NMS), physical deconditioning, etc. Improving characterization of the underlying circulatory responses may lead to a clarification of some of those issues, and will facilitate the discovery of the pathophysiology of OI.

Pathophysiology

Patients with OI typically have an exaggerated increase in heart rate on standing, usually greater than 30 beat/minute. The lying (supine) heart rate is usually normal or slightly raised. Blood volume is usually reduced (5-25%). Lying plasma norepinephrine (NE) is high normal, but the standing plasma NE level is usually elevated. Standing plasma NE levels greater than 2000 pg/ml have been encountered and such patients
much be carefully studied to rule out pheochromocytoma.

It is likely that the causes of OI are heterogeneous. Potential pathophysiological mechanisms include a partial autonomic neuropathy, excessive venous pooling, a gravity-dependent fluid shift, diminished plasma volume or red cell mass, cardiac beta-adrenergic hypersensitivity, diminished cardiovagal baroreflex sensitivity, brainstem dysfunction, and enhanced baseline sympathetic activity. It is suggested that the finding of abnormally enhanced sympathetic drive to the cardiovascular system is a final common pathophysiological mechanism in the majority of patients.

A partial dysautonomia could account for the warm dry feet (loss of sudomotor nerve), the gravity-dependent dusky skin (blood suffusion of the skin), the leg vein hyper-responsiveness to norepinephrine, the reduced galvanic responses, abnormal sweating of the extremities, the excessive orthostatic blood pooling, the tachycardia, and the reduced stroke volume seen in OI patients.

The hyperadrenergic subgroup of OI is characterized by a clinical spectrum including attenuated plasma renin activity and aldosterone, reduced supine blood volume coupled with dynamic orthostatic hypovolemia, elevated plasma norepinephrine and epinephrine, impaired clearance of norepinephrine from the circulation and evidence of partial dysautonomia. When the upright posture is assumed, there is a loss of plasma volume from the blood into the surrounding tissue. In normal subjects, about 14% of the plasma volume may leave the blood within 30 minutes of standing. This loss of plasma volume into interstitial tissues is greatly enhanced in patients with OI; occasional patients will lose more than twice this amount of fluid. It is little wonder such patients with supine hypovolemia to begin with develop symptoms in a setting of this excessive dynamic orthostatic hypovolemia. Normal subjects reduce urinary sodium excretion on assumption of upright posture, but patients with OI do so ineffectively. This probably contributes to the severity of their hypovolemia. In patients with florid symptoms of orthostatic intolerance in a setting of hypovolemia and
increased plasma norepinephrine, several interesting findings emerge. The plasma renin activity and aldosterone are generally slightly reduced in proportion to the degree of the hypovolemia. This suggests that the reduced renin level may be responsible for the hypovolemia. It is possible that impaired sympathetic innervation of the juxtaglomerular apparatus in the kidney may underlie this renin deficit.

OI is significantly overrepresented in young women, and the severity of orthostatic symptoms sometimes shows a cyclical change. The exact reasons for this is unknown. Possible reasons for these cyclical changes include an estrogen-dependent change of the plasma volume or a direct estrogen receptor-mediated modulation of vascular reactivity.

Our understanding of orthostatic intolerance was greatly expanded in 2000 when norepinephrine transporter (NET) deficiency was reported. In a proband with significant orthostatic symptoms and tachycardia, we found disproportionately elevated plasma norepinephrine with standing, impaired systemic and local clearance of infused tritiated norepinephrine, impaired tyramine responsiveness, and a dissociation between stimulated plasma NE and DHPG (an intraneuronal metabolite of NE) elevation. Studies of NET gene structure in the proband revealed a coding mutation which converts a highly conserved transmembrane domain Ala residue to Pro. Analysis of the protein produced by the mutant cDNA in transfected cells demonstrated greater than 98% reduction in activity relative to normal. Studies of the proband and her family revealed correlations of plasma NE, DHPG/NE, and heart rate with the mutant allele. These results represent the first identification of a specific genetic defect in OI and the first disease linked to a coding alteration in a Na$^+$/Cl$^-$ dependent neurotransmitter transporter. Identification of this mechanism may facilitate our understanding of genetic causes of OI and lead to the development of more effective therapeutic modalities.

Long-Term Outlook for Patients
The majority of patients with OI have a relatively mild disorder which improves over succeeding weeks and months. Most patients will eventually be free of symptoms. However, in some patients, the symptoms are more severe, the duration of the illness may be longer, and the expected recovery may not occur. Overall, on follow-up, the majority of patients with OI have improved. More than half of the patients remained on treatment. Those patients with antecedent events, such as a viral infection, appeared to do better overall than those who developed the condition spontaneously.

Uncertainties

We need to understand more about where normal ends and where OI begins. We need to know the interrelationships of OI and deconditioning. Both OI and deconditioning share many clinical features and their separation can prove challenging. Perhaps more challenging is the fact that many patients with OI respond to their illness by reducing their physical activity. When they present to physicians, they therefore present with both OI and deconditioning.

Prospectus

Orthostatic intolerance takes a significant toll on lifestyle and work capacity. OI is a category of diseases, which implies that various other diseases fall under the umbrella of OI and contribute to orthostatic tachycardia. These encompass absolute and orthostatic hypovolemia, hyperadrenergic (central autonomic dysregulation or NET deficiency), neuropathic, autoimmune reaction and cardiovascular diseases. It is unlikely that all patients with OI employ precisely the same mechanisms, and a clearer understanding of the pathophysiology in individual patients will be helpful toward developing therapeutic strategies.

Therapy

In individual patients, different therapeutic regimens may result in improvement of symptoms. These include:
(1) orthostatic “exercise”
(2) water
(3) salt and/or fludrocortisone
(4) low dose beta blockade
(5) low dose alpha 2 agonist (clonidine)
(6) low dose alpha-1 agonist (midodrine).

Participate in Research Protocols

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