Review

Orthostatic Intolerance: Potential Pathophysiology and Therapy

Chih-Cherng Lu[1], Ching-Jiunn Tseng[3], Hung-Shang Tang[4], and Che-Se Tung[2]

Departments of [1]Anesthesiology and [2]Physiology
National Defense Medical Center
Taipei, Taiwan, R.O.C.
[3]Department of Medical Education and Research
Kaohsiung Veterans General Hospital
Kaohsiung, Taiwan, R.O.C.
[4]Department of Gastroenterology
Cardinal Tien Hospital
Taipei, Taiwan, R.O.C.

Abstract

Orthostatic intolerance affects an estimated 1 in 500 persons and causes a wide range of disabilities. After essential hypertension, it is the most frequently encountered dysautonomia, accounting for the majority of patients referred to centers specializing in autonomic disorders. Patients are typically young females with symptoms such as dizziness, visual changes, head and neck discomfort, poor concentration, fatigue, palpitations, tremulousness, anxiety, and, in some cases, syncope. Syncope is the most hazardous symptom of orthostatic intolerance, presumably occurring because of impaired cerebral perfusion and in part to compensatory autonomic mechanisms. The etiology of this syndrome is still unclear but is heterogeneous. Orthostatic intolerance used to be characterized by an overall enhancement of noradrenergic tone at rest in some patients and by a patchy dysautonomia of postganglionic sympathetic fibers with a compensatory cardiac sympathetic activation in others. However, recent advances in molecular genetics are improving our understanding of orthostatic intolerance, such as several genetic diseases (such as Ehler-Danlos syndrome and norepinephrine transporter deficiency) presenting with symptoms typical of orthostatic intolerance. Future work will include investigation of genetic functional mutations underlying interindividual differences in autonomic cardiovascular control, body fluid regulation, and vascular regulation in orthostatic intolerance patients. The goal of this review article is to describe recent advances in understanding the pathophysiological mechanisms of orthostatic intolerance and their clinical significance.

Key Words: orthostatic intolerance, autonomic dysfunction

Introduction

One of the major achievements in our understanding of the cardiovascular system has been the recognition of the intimate interaction between the brain and cardiovascular system, largely mediated by autonomic regulation (4, 35, 39). We now recognize that there is a functional dichotomy between severe autonomic disorders (for example, multiple system atrophy or Shy-Drager syndrome), which are devastating in their health effects but which are fortunately relatively rare (7, 28), and the milder disorders like orthostatic intolerance, which is much more common but usually less devastating to health. It is generally accepted that mild autonomic dysfunction is usually a hallmark of orthostatic intolerance. Because upright heart rate is usually greatly increased, the term postural tachycardia syndrome (POTS) is also used (27).

Orthostatic intolerance is common in many

Corresponding author: Dr. Che-Se Tung, Department of Physiology, National Defense Medical Center, 325 Cheng-Kung Road, Sec. 2, Neihu, Taipei 114, Taiwan, R.O.C. Tel: 886-2-8792-3100 ext. 18625, Fax: 886-2-87924823, E-mail: cstung@ndmctsgh.edu.tw
Received: February 20, 2004; Revised; April 10, 2004; Accepted: April 17, 2004.

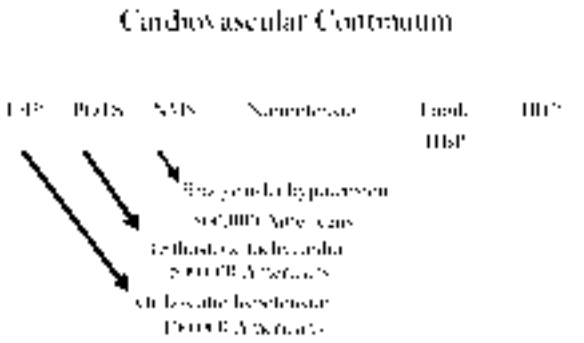

Fig. 1. The spectrum of blood pressure disorders was shown as a cardiovascular continuum. (See description in text) LBP: low blood pressure; POTS: posture tachycardia syndrome; NMS: neural- mediated syncope; HBP: high blood pressure.

Table 1. Names which have been used to describe orthostatic intolerance.

Postural Tachycardia Syndrome, POTS
Effort Syndrome
Hyperdynamic Beta-Adrenergic State
Idiopathic Hypovolemia
Irritable Heart
Mitral Vale Prolapse Syndrome
Neurocirculatory Asthenia
Orthostatic Tachycardia Syndrome
Soldier's Heart Vasoregulatory Asthenia
Chronic Fatigue Syndrome

medical conditions. Specific abnormalities have been described in each of these conditions, and each of which may explain or contribute to orthostatic intolerance. Patients with orthostatic intolerance can be severely impaired by symptoms such as light-headedness, dimming of vision, fatigue, inadequate cerebral perfusion, palpitations, confusion, headache, and nausea, presyncope and occasionally syncope, as well as and signs such as bluish-red decoloration of skin in the lower extremities. Similar orthostatic symptoms of inadequate cerebral perfusion can occur transiently after debilitating illness, substantial weight loss and deconditioning or spaceflight (7-12). It can also occur in otherwise healthy individuals, who may be severely impaired by the associated symptom of orthostatic intolerance. The purpose of the present essay is to succinctly summarize current information regarding the pathophysiologies and therapeutic strategies of orthostatic intolerance.

Definition

One way of looking at blood pressure disorders is to examine them in a cardiovascular continuum (Fig. 1). At the right of the spectrum are the patients whose blood pressures are always high and who therefore carry the diagnosis of hypertension. In the middle are the majority of individuals whose blood pressures lie in the normal range. Between this group and the hypertensive group are the labile or borderline hypertensive subjects who may sometimes have normal and sometimes raised blood pressures. The other end of this spectrum, the left side, is not as thoroughly studied in clinical medicine. At the far left are the individuals who always have low blood pressure (LBP) with upright posture. Closest to the normal group are those with neural-mediated syncope (NMS). Patients with orthostatic intolerance or POTS, unlike those with LBP, have tachycardia on standing but without significant low blood pressure on standing.

Perhaps the first clear description of orthostatic intolerance, described as postural tachycardia syndrome, was reported by Rosen and Cryer, and drew the focus of physicians to this disorder (37). For clinical investigation, orthostatic intolerance is defined by the following four criteria: 1) symptoms of sympathetic activation on upright posture; 2) orthostatic tachycardia greater than 30 bpm; 3) change in blood pressure on standing less than 20/10 mmHg; 4) plasma norepinephrine during standing greater than 600 pg/ml. Defined in this way, orthostatic intolerance is best thought of as the "final common pathway" of different genetic and acquired autonomic and cardiovascular entities (35). Because physicians have recognized orthostatic intolerance for many years under a great many clinical circumstances, it has acquired a plethora of names, some of which are shown in Table 1.

One widely used early name for orthostatic intolerance was "effort syndrome." Thomas Lewis studied that in detail in military personnel during World War I. Lewis fully appreciated the nature of the syndrome and its importance and encapsulated this in his writing. Much of the wisdom we had concerning this problem during the twentieth century was an outgrowth of his experience and thought. In 1918, he wrote of this syndrome (25): "We are in the borderland of disease, probably of many diseases, and when we understand this syndrome in all patients, we shall have knowledge which extends throughout the domain of medicine."

Physiology of Upright Posture

In healthy individuals, the cardiovascular effects of upright posture have been clearly defined. On standing, about 300 to 800 ml of blood is forced downward to the abdominal area and lower extremities. Within seconds of this sudden decrease in venous return, pressure receptors in the heart, lungs, carotid

sinus and aortic arch mediate an increase in sympathetic outflow. Through vasoconstriction of capacitance and arteriolar vessels and through increased heart output, a healthy subject is able to reach orthostatic stabilization in 60 seconds or less. This neural-mediated mechanism is the only mechanism by which we can adapt to the first few minutes of an upright position, and it remains the most important mechanism afterward. Additional sequestration of venous blood may take place due to a slow relaxation of the dependent vessels, and transcapillary filtration of fluid into the interstitial spaces in the dependent part as well (2, 3). Both low and high-pressure baroreceptors are activated, leading to sympathetic activation and parasympathetic withdrawal, which together mediate increases in plasma norepinephrine, heart rate and systemic vascular resistance. With longer period of standing, compensatory adjustments are mediated by endocrine and volume control mechanisms.

Norepinephrine and Norepinephrine Transporter

The role of norepinephrine (NE) in evolution has often been described in terms of the "fight and flight reaction." This describes quite well what is observed in animals, but in human subjects, under most daily circumstances, this characterization of sympathetic activity is no longer accurate. As human beings developed upright posture, sympathetic activity and norepinephrine in particular came to have a much more important role in maintenance of blood pressure while standing. It appears likely that under most circumstances more peripheral norepinephrine is released in the cardiovascular system to facilitate maintenance of upright posture than for any other purpose. When a healthy individual stands, many regulatory mechanisms ensure that blood pressure is quite well maintained.

Our understanding of orthostatic intolerance expanded when norepinephrine transporter (NET) deficiency was reported. It has been noted that many patients with orthostatic intolerance have a greater increase in diastolic blood pressure with upright posture than control subjects, but that the increase in heart rate is disproportionately greater. The greater increase in heart rate may be explained by the differences in the synaptic anatomy of the heart and vasculature and the dysfunction of NET. The noradrenergic synaptic clefts are approximately three times narrower in the heart than the vasculature; the removal of NE from the synaptic clefts is far more dependent on NET in the heart. Indeed, NET removes up to 90% of NE in the heart, but perhaps only 60% removal is due to NET in the vasculature. Thus, one would expect a disproportionate effect on heart rate and myocardial contractility as compared with blood pressure if NET were dysfunctional. It is noteworthy that desmethylimipramine (DMI) which blocks NET, elicits a similar hemodynamic profile of orthostatic intolerance when administered to young female patients (1).

Table 2. There are many pathophysiologies in orthostatic intolerance. The left column lists several different categories of orthostatic intolerance and the right column gives examples of specific disorder exemplifying the associated category.

Categories	Examples
Structural	Ehlers-Danlos Syndrome
Hypovolemia (Absolute)	Cl^- channelopathies
Hypovolemia (Orthostatic)	Mastocytosis
Autoimmune	Anti-N_N-α3-subunit
Neuropathic	Neuropathic POTS
Hyperadrenergic ($\uparrow$Release)	Hyperadrenergia
Hyperadrenergic ($\downarrow$Clearance)	NET deficiency

Potential Pathophysiologies

Orthostatic intolerance tends to occur in younger individuals has a predisposition for women, is associated with little or no fall in blood pressure but usually marked tachycardia, may lead to late syncope after standing, and is poorly characterized in terms of pathophysiology. The long-term goal of this study is to find the fundamental causes of orthostatic intolerance and find ways to treat them. Many pathophysiologies may underline orthostatic intolerance. For instance, structural (19, 32, 48), endocrinologic (1, 15), renal (21, 26, 30, 39, 41), immune (32, 50-52), toxic, neuropathic (5, 28, 34, 35) and genetic (24, 40, 41, 44-46) entities have been investigated (Table 2). An overall enhanced noradrenergic tone in response to gravitational stimulus result in a compensatory cardiac sympathetic overactivity. It has been proposed that chronic sympathetic activation may eventually lead to a contraction of vascular space resulting in hypovolemia (15, 20, 49). However, it is hard to determine whether sympathetic hyperactivity is the primary phenomenon leading to hypovolemia, or hypovolemia contributes to reflex hyperadrenergia in orthostatic intolerance patients.

Autonomic Dysregulation

Central Autonomic Dysregulation

Several observations support the hypothesis that

a central abnormality in autonomic regulation contributes to orthostatic intolerance. The presence of hypertension and blood pressure liability in some orthostatic intolerance patients is best explained by a central abnormality of autonomic regulation. The fact that patients with orthostatic intolerance have an exaggerated increase in plasma norepinephrine on standing was recognized early. Unfortunately, little has been known about the mechanisms responsible for inappropriate central sympathetic activation.

Partial Autonomic Denervation

We reasoned that a partial dysautonomia could account for the warm dry feet (loss of sudomotor nerve) (13, 28, 38), the gravity-dependent dusky skin (blood suffusion of the skin), the leg vein hyperresponsive to norepinephrine (22, 48), the reduced galvanic responses (16, 17), abnormal sweating of the extremities (16, 49), the excessive orthostatic blood pooling, the tachycardia, and the reduced stroke volume seen in orthostatic intolerance patients. Series of studies support this hypothesis of partial dysautonomia in orthostatic intolerance. This evidence encompassed pressor sensitivity, renin sensitivity (20, 21), and replication of the condition by a rat model (5), and a human model (6, 16).

Beta-Adrenoreceptor Hypersensitivity

Increased sensitivity to infused isoproterenol was considered a hallmark of the "hyperdynamic beta-adrenergic state" syndrome. This finding in orthostatic intolerance patients is especially significant in the presence of increased plasma catecholamines. The opposite result was expected in this situation, i.e., chronic exposure to increased plasma catecholamines was expected to result in beta-adrenoreceptor down regulation and decreased responsiveness to isoproterenol (22, 37). It is noteworthy that not all orthostatic intolerance studies confirm increased beta hypersensitivity.

Hyperadrenergia

For many years, the primary focus of our understanding was based on the assumption that orthostatic intolerance was always due to increased sympathetic nerve activity and consequent release of norepinephrine in a syndrome of hyperadrenergia (19, 22). The hyperadrenergic (elevated plasma norepinephrine) subgroup of orthostatic intolerance displays a clinical spectrum of reduced supine blood volume coupled with dynamic orthostatic hypovolemia, elevated plasma norepinephrine and epinephrine. In some orthostatic intolerance patients, however, there is excessive sympathetic activation continuously, but this presentation tends to be associated with migraine-like headaches and cold, sweaty extremities. Patients with hyperadrenergic orthostatic intolerance may respond to phenobarbital, which has rarely been helpful in orthostatic intolerance patients with partial dysautonomia. The mechanism of hyperadrenergia presumably emanates from the central nervous system, but its actual pathophysiology remains obscure. Some patients with hyperadrenergia also have EKG changes of ST-T depression in inferior leads (II, III, aVF) on standing in the absence of coronary atherosclerosis (Friesinger Syndrome) (14).

Deficiency of Norepinephrine Transporter (NET)

Symptoms of orthostatic intolerance may occur in response to a coding mutation in exon 9 of the NET gene. An Ala457Pro mutation has been reported by Shannon *et al.* (41), which renders the transporter non-functional and presents with altered heart rate regulation and altered norepinephrine metabolism. The heart rate of the proband while supine was about 10 beats per minute faster than the mean value for age-matched normal subjects and increased 25-40 bpm on standing. This change in heart rate was accompanied by an increase in plasma norepinephrine concentration to almost four times its value in the supine position. The genetic defect in the NET protein, which results in decreased NET activity, could explain cardiovascular and endocrine abnormalities such as postural tachycardia and high plasma concentrations of NE in some patients with orthostatic intolerance. It is likely that in the future, other noradrenergic defects will be discovered in patients with orthostatic intolerance.

Hypovolemia

Volume deficits may be of two types. One is orthostatic hypovolemia, which is caused by gravitational stress; and the other is absolute hypovolemia.

Orthostatic Hypovolemia

According to Streeten *et al.* (48, 49), the compression of the lower limb venous system can attenuate orthostatic tachycardia, which supports the importance of lower body venous pooling in orthostatic intolerance patients. Excessive pooling of blood could occur in any of the dependent vascular regions, including muscle, skin, and splanchnic circulations. The rapidity and magnitude of plasma volume shift is remarkable upon standing (3). From a practical standpoint, what this dynamic volume shift means is that the immediate hemodynamic effect of blood pooling is followed by

a subacute depletion of central blood volume over the succeeding half hour. There is a large interindividual variation in normal subjects and patients, ranging from 6% to 28% in a recent study. Some of the orthostatic intolerance patients have had higher filtration rates than normal volunteers (21, 22), and it has been speculated that the rate of this loss might be one of the factors determining orthostatic tolerance.

Absolute Hypovolemia

Preliminary evidence suggests that some patients with orthostatic intolerance not only start with a lower plasma volume, but also occasionally have physiological fall in plasma volume on standing which is exaggerated by gravity-dependent fluid shift (13). There may be hypovolemia at all times, as in channelopathies and endocrinologic syndromes being elucidated in genetic studies of renal disorders, for instance, Bartter's syndrome, Gitelman syndrome, and defective aldosterone synthesis and pseudohypoaldosteronism type 1 (26, 30, 34). In conditions where baseline blood volume is low, the cardiovascular response to standing is more dramatic; the magnitude of heart rate increase will be amplified by upright posture because pooling of blood on standing worsens the hypovolemia.

Structural Defect

There is an exaggerated venous pooling during upright posture in many orthostatic intolerance patients. Perhaps the best-known examples of structural vascular abnormalities that can induce this phenomenon include absent venous valves, varicose vein and Ehlers-Danlos syndrome (EDS). Julian and Rowe demonstrated that orthostatic intolerance was occasionally due to EDS, a vascular disease caused by a genetic defect, locus at 2q31, in collagen synthase type III collagen (38). This subset of patients have abnormal connective tissue in dependent blood vessels, which permits veins to distend excessively and leads to increased venous pooling and its hemodynamic and symptomatic consequences.

According to Coghlan *et al.* (6), mitral valve prolapse syndrome (MVPS) patients have a similar clinical picture to orthostatic intolerance. Recently, mitral valve prolapse has been classified as an inheritable connective tissue disorder that is regarded as an autosomal dominant disorder with variable penetrance. The mechanisms underlying the condition have been shown to include increased adrenergic activity, disturbances of catecholamine regulation, and hyper-responsiveness to adrenergic stimulation, anomalous beta-adrenergic receptors and dysfunction of the parasympathetic portion of the autonomic nervous system. Since hypovolemia is the common problem for both MVPS and orthostatic intolerance patients, orthostatic emptying of the left ventricle in orthostatic intolerance patients may make the physical findings of MVPS more evident.

Abnormalities of Body Fluid Control

The elucidation of genomic loci involved in body fluid control has been reviewed by Lifton (26). Controlled blood flow within the kidney is essential for the renal regulation of salt and water balance. The kidney filters about 175 liters of plasma per day, including about 25 moles of salt. Only 2% of sodium is reabsorbed *via* the epithelial Na channel (ENaC) in the cortical collecting system, the ENaC in the distal collecting tubule (DCT) is in fact the principal site that determines salt balance. The ENaC is highly regulated by the renin-angiotensin system. Angiotensin II induces secretion of aldosterone from adrenal glomerulosa. Aldosterone binds to the mineralocorticoid receptor in the distal nephron, leading to increased ENaC activity and therefore increased salt reabsorption. Recently, the potential molecular mechanisms underlying primary hypovolemia and abnormal hemodynamic regulation have emerged. The following are well-known genetic mutation related to blood pressure and volume regulation recently reviewed by Lifton (26).

Defective Aldosterone Synthesis

Two enzymes on chromosome 8, aldosterone synthase and 11-beta-hydroxylase, have nearly identical DNA sequences. In glucocorticoid-remediable aldosteronism, one of the progeny chromosomes resulting from unequal crossing over between these two genes, which carries a gene duplication that fuse regulatory sequences of the 11-beta-hydroxylase gene to the coding sequences conferring aldosterone synthase enzymatic activity on the encoded gene product, resulting in hypertension. However, in individuals with two defective copies, the opposite clinical condition emerges, with severely impaired renal salt retention and impaired potassium and hydrogen excretion in the distal nephron. These individuals have severe hypotension and shock due to reduced intravascular volume. Less severely impaired individuals might have the orthostatic intolerance phenotype (12, 26, 36).

Pseudohypoaldosteronism Type 1 (PHA-1)

Patients with PHA-1 exhibit neonatal salt wasting with hypotension in spite of raised aldosterone levels; affected patients have hyperkalemia and metabolic acidosis due to diminished aldosterone-

responsive Na^+ absorption in the renal distal tubule. Mutations in all three subunits of the epithelial sodium channel (α, β, and γENaC) have been identified. A metabolic finding of surviving αENaC (–/–) Tg mice provides further insight into the role of the sodium channel (ENaC) in a defective Na^+ absorption in kidney. The clinical course observed in the αENaC (–/–) Tg mice is similar to that seen in infants with PHA-1. These infants have no apparent problem with clearance of fetal lung liquid in the perinatal period and generally present with clinical symptoms related to metabolic dysfunction only after the first 48 h of life (26, 30).

Gitelman and Bartter Syndromes

The successful emerging of molecular genetics for both Bartter's and Gitelman's syndromes have advanced our understanding of renal physiology and might be implicated in orthostatic intolerance (26, 44-47). These low normal or low blood pressure syndromes are a group of autosomal recessive disorders, and result from inactivating mutations affecting the main cotransporters involved in the absorption of sodium. Gitelman syndrome is due to a loss-of-function mutation in the gene encoding the thiazide-sensitive Na-Cl co-transporter of the DCT. Bartter's syndrome is caused by a renal Na-K-2Cl co-transpoter mutation, in chromosome 16 NKCC2 locus.

Cyclooxygenase-2 and Prostaglandin E Receptor

Cyclooxygenase-2 is physiologically regulated in response to alterations in volume status. The transcriptional regulation of cyclooxygenase-2 expression in response to alterations in the extracellular ionic composition indicates a potentially important role in the modulation of renal regulation of salt and water homeostasis. Non-steroidal anti-inflammatory drugs are potent inhibitors of the cyclooxygenase enzymes, and have been used to eliminate orthostatic hypotension in Shy-Drager Syndrome. Its mechanism was speculated as a result of vasoconstriction mediating by reducing the prostaglandin synthesis (24, 33, 47).

Vasopressin

Vasopressin increases renal conservation of water by acting through both V_1 and V_2 receptors. V_1 receptor-mediated reduction in inner medullary blood flow contributes to the maximum concentrating capacity of the kidney and also stimulates prostaglandin synthesis. Since prostaglandin E_2 inhibits adenyl cyclase in the collecting duct, stimulation of prostaglandin synthesis by V_1 receptors may restrain V_2 receptor-mediated antidiuresis (18). V_2 receptors mediate the most prominent response to vasopressin. Nephrogenic diabetes insipidus, acquired or genetic, is characterized by the inability of the kidney to concentrate urine in response to vasopressin (18, 47). Ninety percent of these patients carry a mutation in the gene coding for the vasopressin V_2 receptor located on the X chromosome (18, 47).

Aquaporin Water Channel

Aquaporin-2 (AQP-2), the major water channel responsible for water balance is regulated by the binding of vasopressin to V_2 receptors in the medullary collecting duct. Furthermore, mutations of V_2 receptor and AQP-2 water channels have both been shown to be involved in nephrogenic diabetes insipidus. Interestingly, alpha 2-adrenoceptor agonists increase free water clearance secondary to inhibition of vasopressin. The decrease in water reabsorption was found to be associated with a redistribution of AQP-2 away from the luminal membrane of the medullary collecting duct, which indicated that the alpha-2 adrenoceptor regulates water excretion at least in part by its effects on AQP-2 (18, 34). Recently, studies of two unrelated patients with aquaporin-1 deficiency found that they had impaired urinary concentrating ability. One of the two patients had ankle edema. Aquaporins are likely to prove central to the pathophysiology of a variety of clinical conditions from diabetes insipidus to various forms of edema, and it could be a target for therapy in diseases of altered water homeostasis.

Autoimmune

Nearly half of orthostatic intolerance patients appear to have had a viral illness prior to their onset of disease, suggesting that a virus-triggered autoimmune reaction could be involved in the pathophysiology of orthostatic intolerance (22, 50). According to Vernino *et al*., an antibody against the alpha-3 subunit of the nicotinic receptor on autonomic ganglia has been detected in a subgroup of patients with autonomic problems (52), including orthostatic intolerance. About 15 % of a small population of patients with orthostatic intolerance was found to have this antibody in their plasma (50-52). Obviously, an autoimmune response resulting in a neuropathic process cannot be overlooked in the pathophysiology of orthostatic intolerance. This discovery by Vernino *et al*. represents an important achievement and identifies an important direction for future research.

Additionally, estrogen has been suggested to be involved in the mechanism of orthostatic intolerance because of higher prevalence in young females.

Blackstrom *et al*. speculated that estrogen causes neuropsychiatry symptoms, such as irritability, headaches, and anxiety probably from over stimulation of the limbic system by direct excitatory effect on the central nervous system (31). However, currently there is no direct evidence that implicates estrogen as a cause for orthostatic intolerance.

Microgravity and Deconditioning

The mechanisms leading to post flight orthostatic intolerance are not well-understood yet but have been thought to include the following: changes in leg hemodynamic, alteration in baroreceptor reflex gain, decreases in exercise tolerance and aerobic fitness, hypovolemia, and altered sensitivity of beta-adrenergic receptors in the periphery (7, 22). Zhang *et al.* demonstrated changes of structure, function and perivascular innervations of arterial vasculature during simulated weightlessness, suggesting that microgravity-induced changes in the cardiovascular effector apparatus are resulted from structure remodeling and functional adjustment in vascular smooth muscle, which might play an important role in the genesis of post flight orthostatic intolerance (54, 55). The alterations of the gain of vestibular influences on cardiovascular control may also contribute to post flight orthostatic symptoms (53). Hypovolemia in microgravity is probably the result of a new lower set point for total body water on volume receptors (baroreceptors and osmoreceptors) and effector organs (kidneys, hypothalamic thirst centers). Which happens as an early adaptation to space flight, but subsequent alterations in neural controlling mechanisms contribute to orthostatic intolerance (53-55).

The ability to cope with an orthostatic challenge following prolonged bed rest is reduced. Many patients with orthostatic intolerance respond to their illness by reducing their physical activity. When they present to physicians, they therefore present with both orthostatic intolerance and deconditioning (9, 11, 31). Both deconditioning and orthostatic intolerance share many clinical features and their separation can prove challenging and more research is needed to characterize this overlap.

Therapeutic Intervention

The first step in the management of orthostatic intolerance patients is to recognize and remove potential reversible causes. Most of these causes, such as weight loss, chronic debilitating diseases or prolonged immobilization are obvious. Less obvious causes, such as surreptitious drug or diuretic abuse should be evaluated. Fortunately, we are acquiring an armamentarium of treatment strategies that may result in improvement in symptoms in individual patients. These include 1) orthostatic "exercise", 2) water ingestion, 3) salt and /or fludrocortisone, 4) low dose beta-blockade, 5) low dose alpha 2 agonist (clonidine), and 6) low dose alpha-1 agonist (midodrine).

Non-pharmacologic approach which includes fitted stockings or abdominal banding as venous compression has been shown to be acutely effective. Patients should be encouraged to use resistance training, which will eliminate the potential contribution of deconditioning to orthostatic intolerance. This is an effective way of helping orthostatic intolerance patients to understand that they are not alone in facing their illness.

In our studies of the effect of water on blood pressure in autonomic failure, the large (30 mm Hg) increases in blood pressure observed following water ingestion (29), which was not replicated by the intravenous infusion of comparable volumes of dextrose solution (23). Water ingestion significantly attenuates orthostatic tachycardia and other orthostatic symptoms, and it is indicated in the therapeutic intervention of orthostatic intolerance (42, 43). The fact that acute ingestion of water exerts such profound effects may be exploited in situations where prophylaxis against syncope (29). Other circumstances where acute administration of water might be helpful in astronauts on return from the microgravity environment, as it might attenuate their orthostatic intolerance on return to earth.

Patients may show improvement after acute saline infusion, fludrocortisone and sodium chloride tablets. The most widely used agents are beta-adrenoreceptor antagonists, known to attenuate symptomatic tachycardia on standing. Long-term administration of low doses of alpha-1-adrenoceptor agonists may compensate for the patchy sympathetic denervation and may reduce heart rate responses to standing by activating baroreceptor reflexes without producing baseline hypertension. However, alpha1-adrenoceptor agonists must be used judiciously because enhanced sensitivity of alpha-1 adrenoceptors has been described (4, 22, 28, 37). Other drugs that cause arterial vasoconstriction, including the ergot alkaloid dihydroergotamine and the somatostatin analog octreotide, have been shown to attenuate abnormal hemodynamic responses to upright posture in these patients (17, 22).

A rather attractive potential strategy would be the use of clonidine to stimulate both alpha-2-autoreceptors (which would attenuate NE release) and central alpha-2-adrenoreceptors involved in brainstem cardiovascular regulation, which would have the effect of reducing sympathetic outflow. This approach was found to be of some benefit, but adrenomedullary discharges of epinephrine persisted during stress, and

plasma volume was not expanded (15). Another α-2 agonist prodrug α-methyldopa (125 mg bid) helps in treating some orthostatic intolerance patients, especially those with NET deficiency. Alternative therapeutic interventions with carbidopa that can prevent the conversion of DOPA to DA in the periphery (but not central) are under investigation. Now that many centers are actively pursuing research in the field of orthostatic intolerance, rapid improvements in diagnosis and therapy can be expected. Although current approaches to both diagnosis and treatment leave much to be desired, they are improving.

Conclusion

Orthostatic intolerance is a category of disease complexes, which implies that many pathophysiologies fall under the umbrella of orthostatic intolerance and contribute to orthostatic tachycardia. These pathophysiologies encompass hypovolemia (absolute and/or orthostatic), abnormalities of central autonomic cardiovascular regulation, partial peripheral denervation and others. The rapid pace of gene discovery and implementation of new molecular and genetic approaches have opened up entire new areas of investigation and facilitate the development of new therapeutic strategies.

Acknowledgments

This study was carried out in Tri-Service General Hospital/National Defense Medical Center, Taipei, Taiwan, Republic of China. It was supported in part by the Autonomic Dysfunction Center, Vanderbilt University, Nashville, TN 37232-2195, USA and the National Science Council program, NSC-91-2912-1-016-009-A2, ROC.

References

1. Ali, Y.S., Daamen, N., Jacob, G., Jordan, J., Shannon, J.R., Biaggioni, I. and Robertson, D. Orthostatic intolerance: a disorder of young women. *Obstet. Gynecol. Surv*. 55: 251-259, 2000.
2. Auklanz, K. and Reed, R.K. Interstitial-lymphatic mechanisms in the control of extracelullar fluid volume. *Physiol. Rev*. 73: 1-78, 1993.
3. Auklanz, K. Why don't our feet swell in the upright position? *News Physiol. Sci*. 92: 214-219, 1994.
4. Biaggioni, I. and Robertson, D. Orthostatic intolerance syndrome, vasoregulatory asthenia and other hyperadrenergic states. In Robertson, D., Biaggioni, I. eds, Disorders of the Autonomic Nervous System. *Vanderbilt University, Harwood Academic Publishers*.1995, pp. 185-271.
5. Carson, R.P., Appalsamy, M., Diedrich, A., Davis, T.L. and Robertson, D. Animal model of neuropathic tachycardia syndrome. *Hypertension* 37: 1357-1361, 2001.
6 Coghlan, H.C., Phares, P., Cowley, M., Copley, D. and James, T.N. Dysautonomia in mitral valve prolapse. *Am. J. Med*. 67: 235-244, 1979.
7. Convertino, V.A. Aerobic fitness, endurance training, and orthostatic intolerance. *Exerc. Sport. Sci. Rev*. 15: 223-259, 1987.
8. Convertino, V.A. Clinical aspects of the control of plasma volume at microgravity and during return to one gravity. *Med. Sci. Sports Exerc*. 28: S45-S52, 1996.
9. Convertino, V.A., Doerr, D.F. and Stein, S.L. Changes in size and compliance of the calf after 30 days of simulated microgravity. *J. Appl. Physiol*. 66: 1509-1512, 1989.
10. Cornish, K.G., Hughes, K., Dreessen, A. and Olguin, M. Head-out immersion in the non-human primate: a model of cardiovascular deconditioning during microgravity. *Aviat. Space. Environ. Med*. 70: 773-779, 1999.
11. Ertl, A.C., Diedrich, A. and Biaggioni, I. Baroreflex dysfunction induced by microgravity: potential relevance to postflight orthostatic intolerance. *Clin. Auton. Res*. 10: 269-277, 2000.
12. Ertl, A.C., Diedrich, A., Biaggioni, I., Levine, B.D., Robertson, R.M., Cox, J.F., Zuckerman, J.H., Pawelczyk, J.A., Ray, C.A., Buckey, J.C. Jr., Lane, L.D., Shiavi, R., Gaffney, F.A., Costa, F., Holt, C., Blomqvist, C.G., Eckberg, D.L., Baisch, F.J. and Robertson, D. Human muscle sympathetic nerve activity and plasma noradrenaline kinetics in space. *J. Physiol*. 538: 321-329, 2002.
13. Fouad, F.M., Tadena-Thome, L., Bravo, E.L. and Tarazi, R.C. Idiopathic hypovolemia. *Ann. Intern. Med*. 104: 298-303, 1986.
14. Friesinger, G.C. and Ryan, T.J. Coronary heart disease. Stable and unstable syndromes. *Cardiol. Clin*. 17: 93-122, 1999.
15. Gaffney, F.A., Lane, L.B., Pettinger, W. and Blomqvist, C.G. Effects of long-term clonidine administration on the hemodynamic and neuroendocrine postural responses of patients with dysautonomia. *Chest* 83: 436-438, 1983.
16. Hoeldtke, R.D., Davis, K.M., Hshieh, P.B., Gaspar, S. R. and Dworkin, G.E. Autonomic surface potential analysis: assessment of reproducibility and sensitivity. *Muscle Nerve* 15: 926-931, 1992.
17. Hoeldtke, R.D., Dworkin, G.E., Gaspar, S.R. and Israel, B.C. Sympathotonic orthostatic hypotension: a report of four cases. *Neurology* 39: 34-40, 1989.
18. Ishikawa, S., Saito, T., Fukagawa, A., Higashiyama, M., Nakamura, T., Kusaka, I., Nagasaka, S., Honda, K. and Saito, T. Close association of urinary excretion of aquaporin-2 with appropriate and inappropriate arginine vasopressin-dependent antidiuresis in hyponatremia in elderly subjects. *J. Clin. Endocrinol. Metab*. 86: 1665-1671, 2001.
19. Jacob, G. and Biaggioni, I. Idiopathic orthostatic intolerance and postural tachycardia syndromes. *Am. J. Med. Sci*. 317: 88-101, 1999.
20. Jacob, G., Robertson, D., Mosqueda-Garcia, R., Ertl, A.C., Robertson, R.M. and Biaggioni, I. Hypovolemia in syncope and orthostatic intolerance role of the renin- angiotensin system. *Am. J. Med*. 103: 128-133, 1997.
21. Jacob, G., Biaggioni, I., Mosqueda-Garcia, R., Ertl, A., Robertson, R.M. and Robertson, D. Hypereninemic hypovolemia: an etiology of orthostatic intolerance. *Clin. Auton. Res*. 5: 319-325, 1995.
22. Jordan, J., Shannon, J. and Robertson, D. The physiological conundrum of hyperadrenergic orthostatic intolerance. *Chinese J. Physiol.* 40: 1-8, 1997.
23. Jordan, J., Shannon, J.R., Black, B.K., Ali, Y., Farley, M., Costa, F., Diedrich. A., Robertson, R.M., Biagionni, I. and Robertson, D. The pressor response to water drinking in humans: a sympathetic reflex? *Circulation* 101: 504-509, 2000.
24. Kim, J.S., Chae, H.D., Choi, S.Y. and Kim, K.T. Transcriptional enhancement of tyrosine hydroxylase by prostaglandin E2 in SK-N-BE(2) *C cells. Brain Res. Mol. Brain. Res*. 39: 177-184, 1996.
25. Lewis, T. The soldier's heart and the effort syndrome. Hoeber, New York, USA (1919).
26. Lifton, R.P., Gharavi, A.G. and Geller, D.S. Molecular mechanisms of human hypertension. *Cell* 104: 545-556, 2001.
27. Low, P.A., Opfer-Gehrking, T.L., Textor, S.C., Benarroch, E.E., Shen, W.K., Schondorf, R., Suarez, G.A. and Rummans, T.A.

Postural tachycardia syndrome (POTS). *Neurology* 45: S19-S25, 1995.
28. Low, P.A., Opfer-Gehrking, T.L., McPhee, B.R., Fealey, R.D., Benarroch, E.E., Willner, C.L., Suarez, G.A., Proper, C.J., Felten, J.A. and Huck, C.A. Prospective evaluation of clinical characteristics of orthostatic hypotension. *Mayo Clin. Proc*. 70: 617-622, 1995.
29. Lu, C.C., Diedrich, A., Tung, C.S. Paranjape, S., Parris, P. Byrne, D. and Robertson, D. Water ingestion as prophylaxis against syncope. *Circulation* 108: 2660-2665, 2003.
30. Luft, F.C., Fineberg, N.S. and Weinberger, M.H. The influence of age on renal function and renin and aldosterone responses to sodium-volume expansion and contraction in normotensive and mildly hypertensive humans. *Am. J. Hypertens*. 5: 520-528, 1992.
31. Millet, C., Custaud, M.A., Allevard, A.M., Gharib, C., Gauquelin-Koch, G. and Fortrat, J.O. Adaptations to a 7-day head-down bed rest with thigh cuffs. *Med. Sci. Sports Exerc.* 32: 1748-1756, 2000.
32. Monos, E., Berczi, V. and Nadasy, G. Local control of veins: biomechanical, metabolic, and humoral aspects. *Physiol. Rev*. 75: 611-666, 1995.
33. Negishi, M., Irie, A., Sugimoto, Y., Namba, T. and Ichikawa, A. Selective coupling of prostaglandin E receptor EP3D to Gi and Gs through interaction of alpha-carboxylic acid of agonist and arginine residue of seventh transmembrane domain. *J. Biol. Chem.* 270: 122-127, 1995.
34. Raymond, J.R. Hereditary and acquired defects in signaling through the hormone-receptor-G protein complex. *Am. J. Physiol*. 266: F 163-F174, 1994.
35. Robertson, D., Shannon, J.R., Biaggioni, I., Ertl, A.C., Diedrich, A., Carson, R., Furlan, R., Jacob, G. and Jordan, J. Orthostatic intolerance and the postural tachycardia syndrome: genetic and environment pathophysiologies. *Neurolab Autonomic Team. Pflugers Arch.* 441: R48-R51, 2000.
36. Robertson, D., Convertino, V.A. and Vernikos, J. The sympathetic nervous system and the physiologic consequences of spaceflight: a hypothesis. *Am. J. Med. Sci*. 308: 126-132, 1994.
37. Rosen, S.G. and Cryer, P.E. Postural tachycardia syndrome. Reversal of sympathetic hyperresponsiveness and clinical improvement during sodium loading. *Am. J. Med. Sci*. 72: 847-850, 1982.
38. Rowe, P.C., Barron, D.F., Calkins, H., Maumenee, I.H., Tong, P.Y. and Geraghty, M.T. Orthostatic intolerance and chronic fatigue syndrome associated with Ehlers-Danlos syndrome. *J. Pediatr*. 135: 94-99, 1999.
39. Rowell, L.B. Circulation: Regulation during Physical Stress. *New York: Oxford*. 1986, pp. 41-43.
40. Schroeder, C., Tank, J., Boschmann, M., Diedrich, A., Sharma, A.M., Biaggioni, I., Luft, F.C. and Jordan, J. Selective norepinephrine reuptake inhibition as a human model of orthostatic intolerance. *Circulation* 105: 347-353, 2002.
41. Shannon, J.R., Flattem, N.L., Jordan, J., Jacob, G., Black, B.K., Biaggioni, I., Blakely, R.D. and Robertson, D. Orthostatic intolerance and tachycardia associated with norepinephrine-transporter deficiency. *N. Engl. J. Med*. 342: 541-549, 2000.
42. Shannon, J.R., Jordan, J. and Robertson, D. Blood pressure in autonomic failure: drinks, meals and other ordeals. *Clin. Sci. (Lond)* 94: 5-11, 1998.
43. Shannon, J.R., Diedrich, A., Biaggioni, I., Tank, J., Robertson, R.M., Robertson, D. and Jordan, J. Water drinking as a treatment for orthostatic syndromes. *Am. J. Med*. 112: 355-360, 2002.
44. Simon, D.B., Karet, F.E., Hamdan, J.M., DiPietro, A., Sanjad, S.A. and Lifton, R.P. Bartter's syndrome, hypokalaemic alkalosis with hypercalciuria, is caused by mutations in the Na-K-2Cl cotransporter NKCC2. *Nat. Genet*. 13: 183-188, 1996.
45. Simon, D.B. and Lifton, R.P. The molecular basis of inherited hypokalemic alkalosis: Bartter's and Gitelman's syndromes. *Am. J. Physiol.* 271: F961-F966, 1996.
46. Simon, D.B. and Lifton, R.P. Mutations in Na (K)Cl transporters in Gitelman's and Bartter's syndromes. *Curr. Opin. Cell Biol*. 10: 450-454, 1998.
47. Sonnenburg, W.K. and Smith, W.L. Regulation of cyclic AMP metabolism in rabbit cortical collecting tubule cells by prostaglandins. *J. Biol. Chem*. 263: 6155-6160, 1988.
48. Streeten, D.H. and Scullard, T.F. Excessive gravitational blood pooling caused by impaired venous tone is the predominant non-cardiac mechanism of orthostatic intolerance. *Clin. Sci. (Colch*) 90: 277-285, 1996.
49. Streeten, D.H. and Anderson, G.H. Jr. Delayed orthostatic intolerance. *Arch. Intern. Med*. 152: 1066-1072, 1992.
50. Tellioglu, T. and Robertson, D. Orthostatic intolerance in Behcet's disease. *Auton. Neurosci*. 89: 96-99, 2001.
51. Vernino, S., Low, P.A., Fealey, R.D., Stewart, J.M., Farrugia, G. and Lennon, V.A. Autoantibodies to ganglionic acetylcholine receptors in autoimmune autonomic neuropathies. *N. Engl. J. Med*. 343: 847-855, 2001.
52. Xu, W., Gelber, S. Orr-Urtreger, A., Armstrong, D., Lewis, R.A., Ou, C.N., Patrick, J., Role, L., DeBiasi, M. and Beaudet, A.L. Megacystis, mydriasis, and ion channel defect in mice lacking the alpha3 neuronal nicotinic acetylcholine receptor. *Proc. Natl. Acad. Sci.* USA. 96: 5746-5751, 1999.
53. Yates, B.J. and Kerman, I.A. Post-spaceflight orthostatic intolerance: possible relationship to microgravity-induced plasticity in the vestibular system. *Brain Res. Rev*. 28: 73-82, 1998.
54. Zhang, R., Zuckerman, J.H., Pawelczyk, J.A. and Levine, B.D. Effects of head-down-tilt bed rest on cerebral hemodynamics during orthostatic stress. *J. Appl. Physiol*. 83: 2139-2145, 1997.
55. Zhang, L.F., Yu, Z.B., Ma, J. and Mao, Q.W. Peripheral effector mechanism hypothesis of postflight cardiovascular dysfunction. *Aviat. Space Environ. Med*. 72: 567-575, 2001.