Orthostatic Hypotension and Autonomic Failure: A Concise Guide to Diagnosis and Management

Blair P. Grubb, Yousuf Kanjwal, Beverly Karabin and Nasar Imran

Electrophysiology Section, Division of Cardiovascular Medicine, Health Science Campus, University of Toledo, Toledo, Ohio U.S.A.

Introduction

One of the most important moments in the ongoing process of human evolution was the adoption of upright posture. While greatly enhancing mobility, it placed an additional burden on a blood pressure control system that had evolved to meet the needs of an animal in the dorsal position, making humans uniquely sensitive to the effect of gravity upon circulation. Indeed the very organ that defines our humanity, the brain, is in a somewhat precarious position in respect to maintenance of cerebral perfusion and oxygenation. In order to maintain homeostasis, the existing systems in the body altered over time to accommodate for both the effect of gravity and subsequent fluid shifts that occurred with activity. Through the actions of sympathetic efferent pathways, the autonomic nervous system plays the principal role in controlling both immediate and intermediate term responses to positional change. While hormonal factors, such as the renin-angiotensin-aldosterone system also play a role, they do so over longer periods of time. Thus, any alteration in autonomic function that impedes sympathetic output may result in orthostatic (or positional) hypotension, which, if sufficiently great, may lead to cerebral hypoperfusion, near syncope, and syncope. The goal of this brief review is to outline the causes, evaluation and management of autonomic nervous system disorders associated with orthostatic hypotension.

Pathophysiology

In a normal individual roughly 25%–30% of the circulating blood volume is in the thoracic cavity while supine.[1] With the assumption of upright posture the effect of gravity will result in displacement of roughly 300–800 ml of blood (or 6–8 ml/kg) to both the abdomen and the dependent extremities.[2] This represents a volume drop of close to 30%, with half of this decline occurring within seconds of standing. The rapid fall in central blood volume results in a concominent fall in venous return to the heart. Since the heart can only pump the blood that it receives the cardiac output can decline by as much as 40%. The reference point from which these changes are determined is referred to as the venous hydrostatic indifference point (HIP), which is defined as the position in the vascular system where pressure is independent of position.[3] The venous HIP lies near the diaphragm while the arterial HIP is around the area of the left ventricle. As opposed to the arterial HIP, the venous HIP is dynamic and affected by factors such as intravascular volume, vascular compliance and muscular activity. While standing, contraction of the leg muscles (in conjunction with the venous valve system) actively propels blood back to the heart, causing the venous HIP to move close to the level of the right atrium. In addition to the aforementioned changes, assumption of upright posture causes a significant increase in transmural capillary pressure of the dependent areas of the body, producing a substantial increase of fluid filtration into tissue spaces. This shift reaches equilibrium after 30 minutes of standing and can result in a net decline of plasma volume of up to 10%.[1]

Successful assumption of upright posture requires the coordinated function of several cardiovascular regulatory mechanisms.[1,4] In normal individuals, orthostatic stability is achieved within sixty seconds of standing. The active processes involved in standing differ somewhat from those seen with the more passive process of upright tilt. Classically there are three phases of the orthostatic response. Phase one consists of

Correspondence: Blair P. Grubb, M.D., Cardiology, Health Science Campus, University of Toledo Medical Center, 3000 Arlington Avenue, Toledo, Ohio 43614.

the initial response seen during the first 30 seconds. Phase two consist of the initial steady state period occurring after 1–2 minutes upright. Phase three represents the response to prolonged orthostatic stress (after approximately five minutes upright).

In the immediate period following head-up tilt, cardiac stroke volume remains constant despite the fall in venous return (felt to occur because of the blood remaining in the pulmonary circulation).[3] Following this there is a gradual decline in both arterial pressure and cardiac filling. The changes result in activation of two types of pressure receptors: high pressure sensitive sites in the carotid sinus and aortic arch and low pressure sensitive areas in the heart and lungs. In the heart there exist mechanoreceptors that are linked by unmyelinated vagal afferents present in both arteries and ventricles. These mechanoreceptors provide a chronic inhibitory effect on the cardiovascular centers of the medulla (most notably the nucleus tractus solitarii) the baroreceptor neurons of the nucleus tractus solitarii stimulate the cardiovagal neurons of the dorsal vagal nucleus and the nucleus ambiguus while at the same time inhibiting the sympathoexcititary neurons found in the rostral ventrolateral medulla. The reduction in venous return and cardiac filling pressures produced by standing cause a reduction in stretch on the receptors in these beds. As firing rates decline the change in medullary input results in an increase in sympathetic outflow. This results in an increase in vascular constriction in both the systemic resistance vessels and the splanchnic capacitance vessels. An additional local axon reflex, (termed the venoarteriolar axon reflex) results in constriction of arterial flow to muscle, skin and adipose tissue. This reflex may account for almost half of the increase in vascular resistance in the limbs seen after standing.[1]

Following head up right tilt there also seems to be activation of the high pressure receptors located within the carotid sinus.[4] The carotid sinus area include a collection of nerve endings and baroreceptors that are found within the enlarged area of the internal carotid artery adjacent to it's take off from the common carotid artery. Stretch on the arterial wall generates afferent impulses from mechanoreceptors that travel through the sensory fibers of the carotid sinus nerve (that travels with the glossopharyngeal nerve).[5] These afferent nerves lead to the medulla, terminating the nucleus tractus solitarii, close to the dorsal and ambiguous nuclei.[5] The initial rise in heart rate seen with upright tilt is felt to be a product of the decline in carotid artery pressure. The gradual rise in diastolic pressure observed during a tilt appears to be related to an increase in peripheral vascular resistance.[3]

The initial responses seen with standing differ somewhat from those noted during upright tilt. The more active process of standing produces contractions of the leg and abdomen muscles, causing compression of their resistance and capacitance vessels with elevation of peripheral vascular resistance.[6] This increase is great enough to cause a brief rise in right atrial pressure and cardiac output, producing activation of low-pressure cardiac receptors. This increase in neural output to the brainstem elicits a decrease in peripheral vascular resistance (which can fall by as much as 40%). This can permit a fall in mean arterial pressure of as much as 20 mmHg (for as much as 6 to 8 seconds). This drop is then compensated for by the same mechanisms that are brought into play during upright tilt. These initial steady state alterations provoked by upright posture result in an increase in heart rate (approximately 10–15 beats/minute) an increase of diastolic BP as well as a unchanged or slightly diminished systolic SP. Compared to the supine position, at this point in standing there is 30% less blood in the thoracic cavity, the cardiac output has declined by 30%, and the heart rate has increased by 10–15 beats/minute.

The continuation of upright posture results in activation a number of neurohormonal changes, which vary in intensity on the volume status of the patient.[6] The more pronounced the volume depletion the greater the degree of activation of the renin-angiotensin-aldosterone system (as well as vasopressin). Nonetheless the principal mechanism by which the body compensates for prolonged orthostatic stress relies on the arterial baroreceptor (in particular the carotid sinus) effects on peripheral vascular resistance. During upright posture about 5% of the body's blood volume is in the capillary system, 8% is within the heart, 12% in the pulmonary circulation, 15% in the arterial system and 60% in the venous system. A failure of any component of this complex system can result in a failure of the normal compensatory responses to either an initial or prolonged orthostatic challenge, with subsequent hypotension, cerebral hypoperfusion and ultimately syncope. The term dysautonomia refers to any disturbance in autonomic function that adversely affects health.[7]

These conditions can range from those resulting in relatively benign transient alterations of autonomic tone in otherwise normal individuals to potentially disabling or lethal neurodegenerative disorders.

Disturbances of Orthostatic Control

Over the last several decades a group of disturbances of autonomic disorders of orthostatic control have been identified. While similar in nature each appears to be a unique condition. A basic system of organization is presented in Figure 1. With regards to any system of classifications it should be kept in mind that when we observe the apparent chaos of nature we attempt to organize it into a rational system that conforms to both our knowledge and our expectations at that time.[8] Therefore any system of classification is somewhat arbitrary, subject to discussion, and in a continuous state of development and revision.[7] The system presented here has proven both clinically useful and follows the basic guidelines established by the American Autonomic Society.[9] The reflex syncopes (such as neurocardiogenic syncope and carotid sinus sensitivity) and postural tachycardia syndromes are discussed in detail elsewhere.[10,11]

To some extent, all autonomic disorders can be thought of as being either primary or secondary in nature.[12] The primary forms are often idiopathic and can be subdivided into acute and chronic forms the secondary forms are those that are seen in association with other disease processes (such as diabetes, amyloidosis), use of medications (antihypertensive, antidepressant, and chemotherapeutic agents) or exposure to toxic compounds (such as alcohol or heavy metals). Indeed orthostatic hypotension may occur in association with any condition that causes a significant decline in blood or extracellular fluid volume, or in conditions that make a person bedridden or immobile for an extended period of time. However, orthostatic hypotension is one of the principal clinical manifestations of autonomic neurocirculatory dysfunction and in the absence of any other identifiable causes is considered a form of autonomic failure.

Primary Autonomic Failure: Chronic

Bradbury and Eggleston made the initial reports of chronic autonomic failure in 1925.[13] They employed the term "idiopathic orthostatic

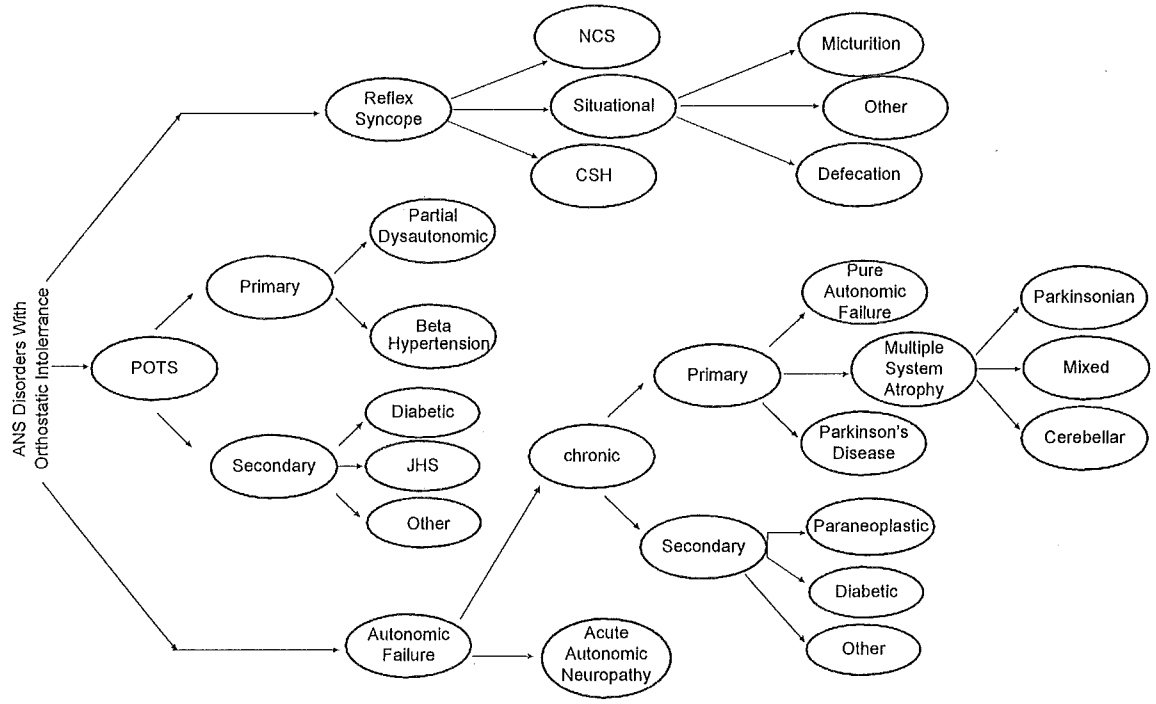

Figure 1. Autonomic disorders associated with orthostatic intolerance.
Abbreviations: ANS, autonomic nervous system; NCS, neurocardiogenic syncope; CSH, carotid sinus hypersensitivity; JHS, joint hypermobility sydrome; POST, postural tachycardia syndrome.

hypotension" because of its apparent lack of effect on other organ systems. However, the term was found to be inadequate to describe the fact that these patients seem to have a generalized state of autonomic failure manifested by disturbed bladder, bowel, sudomotor and sexual function that occurs in the absence of somatic nerve involvement. The condition is now referred to as "Pure Autonomic Failure (PAF)".[14] Symptoms of PAF usually begin in middle age, with the majority of cases being diagnosed between 50 and 70 years of age. PAF is more common among men than women, with reported ratio of 2:1. The disease is frequently quite slow and insidious in onset, most often starting with vague complaints of orthostatic weakness, fatigue, dizziness, and lightheadedness (symptoms often dismissed by physicians as insignificant).[15] Orthostatic hypotension is often the most debilitating symptom of PAF and while it may not be the earliest symptom it is usually the one that prompts the patient to seek medical attention. Men often relate that erectile dysfunction and diminished libido are the earliest symptoms, while women often report incontinence and urinary retention as the initial symptoms. Pre-syncope and syncope are often the most common presenting complaints, occurring more frequently in the morning, after meals, in hot weather and after a hot bath or shower. In contrast to neurocardiogenic syncope, patients with PAF do not experience nausea, diaphoresis, or pallor associated with syncope. Rather these patients either experience syncope as a gradual fading of consciousness or have amnesia to the events preceding syncope and (describing it as a "drop attack").[16] As the disorder progresses patients display even more significant orthostatic hypotension associated with recurrent syncope and near syncope, fatigue, weakness, neck pain, and blurred vision. Supine hypertension is not uncommon. Symptoms of more diffuse autonomic involvement include inability to sweat, temperature intolerance, early satiety, constipation, dry mouth and urinary retention. The disease usually progresses slowly over decades or more and, while potentially causing severe functioned impairment, it rarely leads to death.[17]

A very different situation is seen when primary autonomic failure is accompanied by additional defects in somatic nerve function, a condition first reported by Shy and Drager in 1960.[17] The term Multiple System Atrophy (MSA) is now used to describe this devastating disorder.[18] In contrast to PAF, patients with MSA will display severe orthostatic hypotension, but also demonstrate urinary and rectal incontinence, iris atrophy, external ocular palsy, rigidity, and tremor, loss of sweating and erectile dysfunction. Patients with MSA often first develop symptoms in the fifth to sixth decade of life, (although we have seen cases where symptoms begin in the mid forties). Men are reported to develop MSA twice as frequently as women. Similar to PAF, MSA patients will most often present to the physician complaining of syncope and near syncope. However, while the initial signs and symptoms may be similar to PAF, MSA patients develop progressive defects in somatic nerve (and later central nervous system) function.

MSA is currently divided into three major subgroups based on the type of somatic involvement.[19] The first subgroup displays symptoms of autonomic failure in addition to features that are suggestive of Parkinson's disease (also referred to as the striatomigral degeneration form "based on brain autopsy findings). Many of these patients may experience stiffness, clumsiness, as well as an alteration in handwriting early in the course of the illness. As opposed to patients with true Parkinson's disease the MSA patient tends to exhibit more rigidity than tremor (often associated with a loss of facial expression and akinesa of the limbs). Also MSA rigidity tends to lack the classic "cogwheel" or "lead pipe" features commonly observed in Parkinson's.[9]

The second form of MSA is distinguished by progressive cerebellar and or pyramidal features (also known as "olivopontocerebellar atrophy" based on autopsy findings). In these patients there is a significant disturbance in gait with concominent truncal ataxia that can be severe enough to prevent the patient from standing without support. Slurred speech is not uncommon, often associated with a progressive loss of dictation. Some patients may exhibit a mild intention tremor in the arms or legs. The third subgroup of MSA patients appear to have a mixed form of the disorder and display both parkinsonian and cerebellar symptoms in association with autonomic failure (referred to as "mixed" MSA). Some studies suggested that somewhere between 7% and 22% of patients thought to have Parkinson's disease during life were discovered to have pathological changes associated with MSA at autopsy.[18] As opposed to PAF, the natural history

of MSA is one of near relentless progression; with the majority of patients dying within 5 to 8 years of onset (rare cases have survived as long as 20 years). In the final stages of the illness aspiration and apnea are common and death is usually due to respiratory failure.[7,18,19]

Recently it has become increasingly evident that true Parkinson's disease itself may be associated with orthostatic hypotension.[20] Previously it was felt that OH in Parkinson's disease occurred principally due to the effects of inactivity or medications. However, investigators now realize that some patients with Parkinson's disease may develop progressive autonomic failure late in the course of their illness.[21] Kaufman has suggested that a similar neurodegenerative process may underline MSA, PAF and Parkinson's disease, based on the fact that in all three disorders pathologic specimens demonstrate cellular accumulation of alpha-synuclein (or related proteins) may cause degeneration of the catecholamine-containing neurons.[22] This raised the intriguing possibility that the chronic primary autonomic failure syndromes are three different clinical manifestations of the same disease process.

Acute Autonomic Faliure

While relatively uncommon, acute autonomic neuropathy is often quite dramatic in its clinical presentation. Also referred to as acute panautonomic polyneuropathy (and acute pandysautomia), onset is usually sudden and characterized by widespread severe failure of both the sympathetic and parasympathetic systems, with little or no somatic nerve involvement.[23] The majority of cases we have seen have been in relatively young people who were previously quite healthy. Many patients report an antecedent febrile illness followed by the acute onset of symptoms. Orthostatic hypotension in these patients is often so profound that they are unable to sit up in bed without losing consciousness. Near total loss of sweating occurs as does severe bladder and bowel dysfunction. The later results in abdominal pain, bloating, nausea and constipation may occur (that may alternate with diarrhea). Many patients display a fixed heart rate of 45 to 55 beats per minute as well as profound chronotropic incompetence. Some patients will have extremely dilated pupils that respond poorly to light.[7] Several recent studies have suggested that in many of these patients the illness is autoimmune in nature. Verino et al. have isolated high levels of autoantibodies to ganglionic acetylcholine receptors that appear to correlate with the severity and progression of the illness.[24] There are, most likely, other antibodies that await discovery. The prognosis of these patients is quite variable. While some make remarkable recoveries others are left chronically debilitated. It is now thought that these antibodies may play an important role in the pathogenisis of other autonomic disorders.[25]

Secondary Autonomic Syndromes

These encompass are a wide variety of different disorders that can significantly affect autonomic function (Table 1).[14] The term secondary autonomic failure (or dysfunction) is used when there is a clear association with another illness. For example, systemic illnesses that affect multiple organ systems, (amyloidosis, diabetes mellitus and renal failure) may disrupt autonomic function such as that OH occurs. In some cases autonomic failure may be the presenting sign of a much larger disease process (such as malignancy, multiple sclerosis, and Alzheimer's disease). In rare cases OH may develop to single enzyme deficiencies (such as beta-hydroxylase deficiency and nerve growth factor deficiency).[26] It should also be kept in mind that virtually any systemic illness may have some degree of effect on autonomic tone and function, and that this can impact on any diseases presentation and management. In addition a wide variety of drugs can interfere will normal vascular function resulting in orthostatic hypotension. Symptoms such as prolonged bed rest or muscle wasting conditions may disrupt the muscular-skeletal pump to such an extent that the ability to tolerate normal orthostatic stress is compromised, as can dehydration anemia and blood loss. A more complete discussion on secondary causes of autonomic dysfunction is available elsewhere.[7,26]

Clinical Aspects

The principal aspect shared by each of the aforementioned conditions is an impairment of normal cardiovascular regulation to such an extent that orthostatic (or postural) hypotension occurs. Traditionally orthostatic hypotension has been defined as a fall of >20 mmHg systolic blood pressure or a >10 mmHg in fall in diastolic BP within 2–3 minutes after standing (2, 21). However it should be kept in mind that this definition is somewhat arbitrary, and a less dramatic fall in

Table 1. Autonomic disorders associated with orthostatic intolerance.

Primary autonomic disorders
Acute pandysautonomia
Pure autonomic failure
Multiple system atrophy
Parkinsonism
Pyramidal/cerebellar
Mixed
Reflex Syncope
Neurocardiogenic syncope
Carotid sinus hypersensitivity
Secondary autonomic failure
Central origin
Cerebral cancer
Multiple sclerosis
Age-related
Syringobulbia
Peripheral forms
Afferent
Guillain-Barre syndrome
Tabes dorsalis
Holmes-Adie syndrome
Efferent
diabetes mellitus
nerve growth factor deficiency
dopamine B-hydoxylase deficiency
Afferent/efferent
Familial dysautonomia
Spinal origin
Transverse myelitis
Syringomyelia
Spinal tumors
Other causes
Renal failure
Paraneoplastic syndromes
Autoimmune/collagen vascular disease
Human immunodeficiency virus infection
Amyloidosis

blood pressure, if associated with symptoms, may be of equal importance. Some patients will demonstrate a more gradual, yet progressive fall in blood pressure over a much longer time frame (around 10 to 15 minutes) that will be associated with symptoms (sometimes referred to as "delayed orthostatic hypotension"). The development of symptoms is dependant not only on the absolute fall in blood pressure, but also in the rate at which falls and on the ability of a particular patient's cerebral vasculature to autoregulate so as to lesson the effects of a decline in systemic pressure. It should also be kept in mind that OH is frequently but one aspect of a much broader disturbance in autonomic regulation. Patients may also display supine hypertension as well as dramatic swings in blood pressure, or may experience excessive responses to a number of pharmacologic or physiologic challenges.

As was mentioned earlier, the syncopal episodes that occur from OH will sometimes be described by older patients as "drop attacks" that occur with little or no prodrome. The loss of consciousness is often reported by observers as occurring over 30–60 seconds, usually while standing or walking (and sometimes while seated). A frequent symptom that may precede loss of consciousness is an aching or painful sensation in the neck that radiates to the occipital area of the skull and to the shoulders (a "coat hanger" headache). The mechanisms are unclear but thought to reflect ischemia in continuously contracting skeletal muscles. Blurred vision is also a common complaint, as is tunnel vision and scotomata. Symptoms frequently occur after several minutes of standing or walking, at which time the patient may stumble fall or sink to their knees as they lose consciousness. Symptoms usually resolve within three to five minutes after becoming supine (although in some patients symptoms may last much longer). Symptoms are more frequent in the morning after walking from sleep and are exacerbated by any condition that favors peripheral venous pooling of blood (heat, exercise, alcohol and fatigue). Large meals may also result in redistribution of blood to the mesenteric vasculature resulting in a significant decline in blood pressure (postprandial hypotension). A common complaint is of nocturnal polyuria. This is thought to occur when pooled peripheral blood is redistributed to the central areas while supine (a mechanism similar to that seen in paroxysmal nocturnal dyspnea). These patients may lose as much as 1 liter of urine in a single evening, exacerbating the tendency toward morning hypotension. As the disease progresses some patients will develop a neurogenic bladder, and many experience severe constipation.

Patient's suffering from MSA can display a significant amount of progressive muscle wasting, although rarely to the extent seen in the motor neuron

disorders such as amyotrophic lateral sclerosis.[18] Dementia is not usually associated with either PAF or MSA, as opposed to Parkinson's disease were intellectual impairment is not uncommon. Patient's suffering from either MSA or PAF may develop a significant degree of chronotropic incompetence resulting in a relatively static heart rate of 50–70 beats/minute. Patients with MSA often develop either obstructive or central sleep apnea, manifested by loud snoring or involuntary inspiring gasps during sleep. Table 2 highlights some of clinical features that may help distinguish PAF from MSA and acute autonomic neuropathy.

Evaluation

As in all disorders that first and most critical step is a detailed history and physical examination. Laboratory testing is then ordered based upon the findings of the history and physical examination and information from all these sources is used to arrive at a diagnosis and outline a reasonable complete management plan.

The first step is to determine whether or not an autonomic disorder is present and then to determine the scope of the involvement. Here the physicians should try to uncover particular patterns that indicate one disorder as opposed to another. At the same time one should attempt to determine if the autonomic disturbance present may be secondary to another disorder. Patients with syncope in the setting of severe structural heart disease may require evaluation for significant arrhythmias. In some older patients dehydration may contribute to OH, and can be identified by examination of the skin turgor, the mucus membranes and serum and urine analysis. More detailed descriptions of specific clinical patterns of specific autonomic disorders and their evaluations can be found elsewhere.[2,10,14]

As the autonomic centers of the brain are not accessible to direct measurement, evaluation of autonomic function is accomplished by determining the responses of the system to a variety of physiologic or pharmacologic challenges. The simplest of these is to determine the blood pressure and heart rate in the supine, sitting, and standing positions as well as at 3 and 5 minutes after standing. The blood pressure should be measured with the arm extended horizontally (to reduce the hydrostatic effects that can be produced when the arm is in a dependant position). As the responses seen during standing and passive tilt may differ, we perform tilt table testing in patients in whom we feel further evaluation in warranted. Detailed descriptions of tilt table testing are available elsewhere.[27,28] Other tests of autonomic system function may be useful in select patients as a way of measuring the degree of systemic autonomic nervous system involvement. Sudomotor function can be determined by quantitive thermoregulatory sweat testing or by measurement of skin conductance, skin

Table 2. Distinguishing features among pure autonomic failure, autonomic neuropathy, and multiple system atrophy (adapted from Low [4]).

Factor	PAF	Autonomic neuropathy	MSA
Onset	slow	acute	slow
Primary symptom	Orthostatic hypotension	Diverse symptoms	Orthostatic hypotension
Gastrointestinal Problems	Rare (except constipation)	Common	Uncommon
CNS disturbance	Absent	Absent	Present
Somatic neuropathy	Absent	Mild	Occurring in 15%–25%
Pain	Absent	Common	Absent
Progression	Slowly Progressive	Usually not progressive	Progressive
Principal lesion site	Principally postganglionic	Postganglionic Some somatic	Mainly preganglionic and central
Supine plasma Norepinephrine	Low	Low	Normal
Prognosis	Fair to good	Fair to good	Poor

Abbreviations: CNS, central nervous system; MSA, multiple system atrophy; PAF, pure autonomic failure.

resistance or sympathetic skin potentials employing methods such as quantitative sudomotor axon testing (QSART) ... Serum catecholamine levels of epinephrine, noreinepherine and dopamine should be obtained in both standing and supine positions as they can be used to help determine the type of autonomic failure. In patients who have defects in the post ganglionic sympathetic vasomotor fibers, the supine norepinephine levels will be low, in contrast to MSA were the level is usually normal. In both conditions the usual increase in plasma norepinephrine levels seen during tilt or standing may be either blunted or absent, reflecting a disturbance in sympathetic outflow. Heart rate variability (HRV) determinations as well as barereceptor gain evaluation can also useful assessments of the cardiovascular autonomic system. More detailed descriptions of autonomic testing can be found elsewhere.[7,14,19]

Therapy

The initial step in the treatment of orthostatic hypotension is to try and identify and correct any potentially reversible causes. Dehydration, drug effects, anemia, and adrenal insufficiency are all potentially correctable causes. Any drug that could be contributing to the problem should be discontinued if possible (Table 3). Any potential underlying cause of OH should be identified (malignancy, amylodsis etc) (4). When no reversible cause is apparent therapies aimed at reducing symptoms are started. Education of the patient and family as to the nature of the disorder is critical. Potential aggravating factors such as extreme heat, prolonged standing and dehydration should be avoided. Patients should be instructed to change positions slowly allowing the system time to adjust, and to pay attention to subtle symptoms that indicate a decline in blood pressure. As large meals may worsen symptoms, patients should be encouraged to eat smaller meals spaced out through the day. In general alcohol should be avoided, as its vasodilator and diuretic effects may worsen symptoms.[7]

Both patients and their physicians need to remain aware of the fact that these disorders tend to be chronic in nature and that treatment is palliative rather then curative, requiring adjustment and attention over time. Both patients and their families benefit from psychologic counseling to help them deal with the hardship and distress caused by chronic illness.

Table 3. Pharmacologic agents that may cause or worsen orthostatic intolerance.

Angiotensin-converting enzyme inhibitors
Alpha-Receptor blockers
Calcium-channel blockers
Beta-blockers
Phenothiazines
Tricyclic antidepressants
Bromocriptine
Ethanol
Opiates
Diuretics
Hydralazine
Ganglionic-blocking agents
Nitrates
Sildenafil citrate
Vardenafil HCl
MAO inhibitors

MAO, monoamine oxidase.

Sleeping with the head of the bed elevated is reported to be helpful as it appears to lesson the sudden pooling of blood the patient experiences upon arising after sleep as well as reducing the degree of supine hypertension and nocturnal diuresis. Elevating the bed by 10–15 cm (4–6 inches) appears the most practical, and can be easily accomplished by placing a brick under each back bedpost. If a hospital bed is used we use an angle of 30–45 degree.

Custom fitted elastic support hose are useful in causing a type of counter gradient effect in the lower extremities that reduces the degree of venous pooling (25). They are most effective when waist high and should provide at least 30mmHg ankle counter pressure. While effective they can be difficult to put on and uncomfortable in hot weather.

Physical maneuvers can be used to activate the skeletal muscle pump and briefly elevate pressures. These include crossing the legs and pushing them against each other, arm flexing and rocking up on the toes. In each case the elevation in blood pressure is transient and is intended to maintain blood pressure long enough to allow the patient to get to a safe place and then to sit or lie down.[29]

A major focus of therapy is reconditioning using a combination of both aerobic and resistance training, working toward a goal of performing at

least 20–30 minutes of aerobic training three times per week. Water activities are particularly helpful, but often require the supervision of a physical therapist. A fluid intake of around 2 liters per day is encouraged. While patients who are purely orthostatic may benefit from an increased salt intake (3–5 grams per day) we do not recommend this in patients with supine hypertension.

A number of pharmacologic agents have been used to treat orthostatic hypotension (Table 4). One of the most commonly used medications is fludrocortisone, a mineral corticoid that acts on the distal tubule to promote reabsorbtion of sodium and fluid.[7,15] It has also been reported to increase the quantity and sensitivity of peripheral alpha receptors, promoting an increase in vascular resistance. The usual dose employed 0.1 mg orally once or twice daily, (do not exceed 0.4 mg daily as adrenal suppression may occur). The agent DDAVP can also provide volume expansion (0.1–0.2 mg orally at bedtime) and decrease the degree of nocturnal polyuria.

A second approach to therapy is to use agents that result in sympathetic stimulation to increase peripheral vascular resistance.[7,26] These tend to act by stimulation of alpha adrenergic receptor sites to augment arteriolar and venous constriction. Principal among these is the agent midodrine (the only agent approved by the US Food and Drug Administration to treat OH).[30] Midodrine is a prodrug that is metabolized to the active form, desglymidodrine, which stimulates alpha-1 adrenoreceptors to cause constriction of arterial resistance and venous capacitance vessels. It is rapidly absorbed with a peak concentration obtained within 20–40 minutes, with a half –life of 30 minutes. Dosages are between 2.5–10 mg orally 3–4 times daily. Side effects include nausea, piloerection ("goosebumps") tingling of the scalp, and supine hypertension. Patients should not lie supine for at least 4 hours after a dose of midodrine, and the drug is usually not given after 6 pm. In cases where midodrine is poorly tolerated methylphenidate can be an effective alternative, in particular since it comes in several once a day preparations. Modonifil can also be a useful agent, as it can not only provide vasoconstriction it may also relieve some of the intense fatigue these patients mat experience. Yohimbine can also be effective, as it is both central and peripheral alpha-2-adrenoreceptor antagonist that increases blood pressure by stimulating sympathetic outflow centrally and increasing norepinephrine release from postganglionic sympathetic neurons.

Interestingly the drug clonidine, an alpha-2-adrenoreceptor agonist, can actually be used as a treatment of OH that occurs due to postganglionic receptor lesions. Postjunctional alpha- receptors are common throughout the vasculature and can become hypersensitive in autonomic failure. Even though the drugs central activity produces a reduction of sympathetic outflow in normal subjects (causing a reduction in blood pressure), in patients with autonomic failure who have little remaining sympathetic activity (in particular PAF and spinal cord lesions) the peripheral effects of the drug will predominate causing an increase in heart rate and blood pressure. Clonidine is particularly useful in treating the patient with both OH and supine hypertension.

Beta blocker therapy has been reported to be helpful by fostering unopposed alpha receptor stimulation. In our experience these have not proven useful, except in blunting the degree of supine hypertension. Beta blockers processing intrinsic sympathetic activity have been reported to be more useful than those without. The serotonin reuptake inhibitors may be useful in managing select patients with OH. Fluoxetine and venlafaxine have been reported to be the most effective. Buproprion may also be useful in some patients.

A very promising new therapy is pyridostigmine, an acetylcholinesterace inhibitor that increases nerve transmission at the level of the ganglia of both the sympathetic and parasympathetic nerves. Several double blind placebo controlled trials have shown it to be remarkably effective in controlling OH. Indeed it seems to do so without exacerbating supine hypertension. The usual starting dose is 30 mg orally twice daily, and can be slowly titrated to a dose of 90 mg orally three times daily. Side effects include nausea and diarrhea.[31,32] A long acting (time span) formulation is available that allows for once a day dosing. The drug is usually not given in the evenings before lying down as the effects on the autonomic ganglia are clinically present only with orthostatic change in body position.

In several OH patients where other forms of therapy have been ineffective or poorly tolerated erythropoietin has been valuable.[33] Erythropoietin (EPO) is a polypeptide produced in the kidney that stimulates red blood cell production.[34] It also appears to have a vasoconstrictive effect due to its effects in nitric oxide production.[35] A series of studies have shown that it can be remarkably

Table 4. Treatment Options for Orthostatic Hypotension.

Therapy	Method or dose	Common problems
Head up tilt of bed	45 head-up tilt of bed (often will need footboard)	Hypotension, sliding off bed, leg cramps
Elastic support hose	Require at least 30–40 mmHg ankle, counter pressure, work best waist high	Uncomfortable, hot, difficult to get on
Diet	Fluid intake of 2–2.5 L/day	Supine hypertension.
	NA intake of 150–250 mEq/day	Peripheral edema
Exercise	Aerobic exercise (mild) may. Aid venous return Water exercise particularly helpful	May lower blood pressure if done too vigorously
Fludrocortisone	Begin at 0.1–0.2 mg/day may work up to doses Not exceeding 0.4 mg/day	Hypokalemia, hypomagnesemia, peripheral edema, weight gain, congestive heart failure
Methylphenidate	5–10 mg p.o. t.i.d. given with meals, give last Dose before 6 pm	Agitation, tremor, insomnia, supine hypertension
Midodrine	2.5–10 mg every 2–4 h.	Nausea, supine hypertension
	May use up to 40 mg/day	
Clonidine	0.1–0.3 mg p.o. b.i.d. or patches placed 1/week	Dry mouth, bradycardia, hypotension
Yohimbine	8 mg p.o. b.i.d-t.i.d.	Diarrhea, anxiety, nervousness
Ephedrine Sulfate	12.5–25 mg p.o. t.i.d	Tachycardia, tremor, supine hypertension
Fluoxetine	10–20 mg p.o. q.d. (requires 4–6 weeks of therapy)	Nausea, anorexia, diarrhea
Venlafaxine	75 mg XR form p.o q.d. or b.i.d.	Nausea, anorexia, hypertension
Erythropoietin	10,000 IU once weekly	Requires injections, burning of site, increase, Hematocrit, CVA
Pindolol	2.5–5.0 mg p.o b.i.d.-t.i.d.	Hypotension, congestive heart failure, Bradycardia
Desmopressin (DDAVP)	An analog of vasopression used as a nasal spray Or pill at 0.2 mg p.o. q.h.s	Hyponatremia
Octreotide	25 micrograms 2 b.i.d. may titrate to 100–200 ug t.i.d.	Nausea, abdominal pain, muscle cramps, Hypertension
Pyridostigmine	60 mg p.o. b.i.d.	Nausea, abdominal cramping, diarrhea, diaphoresis

effective in the treatment of hypotension.[26] Prior to starting EPO one should obtain a complete blood count (CBC) as well as a serum iron, total iron binding capacity and ferritin level should be obtained. The usual starting dose is 10,000 units subcutaneously once weekly. It often takes 4–6 weeks to see the full effect of a particular dose. Even though the increase in red cell count caused by EPO is independent of its vasoconstrictive effect, the two tend to rise in parallel. The best hemodynamic effects of EPO tend to occur when the hematocrit (HCT) is in the low to mid – 40 range. Following indication of the EPO therapy a CBC should be checked on a monthly basis to ensure that the HCT does not exceed 50. If the HCT does exceed 50 while on EPO therapy we usually ask the patient to skip doses until the HCT falls below 50, and then resume EPO at a reduced dose (a sequence similar

to that employed while adjusting the dose of warfarin to maintain a target international normalized ratio [INR]. The most frequent complaint during EPO therapy is pain at the injection site. This can be diminished somewhat by allowing the EPO (which is stored refrigerated) to warm up before injection. An easy way to do this is to roll the vial between the hands until it becomes warm. Additional measures to minimize injection site pain are to apply topical lidocaine, in cream or patch form, 15–30 minutes prior to use of the site, or to place an ice cube over the site 3–5 minutes before use. A number of patients will require oral iron supplementation to get an adequate red cell response. If no hemodynamic effect is seen from starting EPO after 4–6 weeks we increase the weekly dose to 20,000 units, (it is rare to have to go beyond this dose). An occasional patient will develop a "serum sickness" reaction to EPO characterized by fever, nausea, chills, and malaise, which resolves quickly when the agent is stopped.

The somatostatin analog octreotide is sometimes useful in patients with refractory OH, due to its vasoconstricitve effects. It is given by subcutaneous injection usually starting at 50 micrograms two to three times daily and can be titrated up to 100 to 200 micrograms three times daily. The major side effects are nausea and muscle cramping. A long acting form of octreotide (that works for several weeks) has also been developed.

The synthetic catecholamine (L-DOPS) has been shown to increase upright blood pressure and decrease orthostatic hypotension. The drug is converted to norepinephrine that is released from sympathetic nerves. Currently approved in Japan, the drug is undergoing clinical trials in the U.S. It has been shown to be effective in patients with familial amyodotic polyneuropathy and severe orthostatic hypotension.[36]

Some patients with severe OH will fail to respond to any of the above therapies. In three patients Oldenburg et al. reported on using a controlled norepinephrine infusion pump (the same type of device used for ambulatory dobutamine infusions).[37] Ambulatory norepinephrine was infused intravenously in individually adjusted dosages via an indwelling infusion line and portable indwelling infusion pump. While we have only pursued this therapy in a limited number of patients it has proven remarkably effective and appears well tolerated (we have limited use of the therapy to patients without cardiac disease).

In the early stages of the acute autonomic neuropathies both intravenous immunoglobin therapy and plasmaphoresis have been reported to be effective.[7,38] It was thought that once the acute phase of the illness had passed these treatments were less effective, however recent evidence has challenged this concept. A recent report has suggested that immunosuppressive therapy may be effective in chronic autoimmune autonomic neuropathy.[39]

A particularly challenging situation occurs in the patient who suffers from both supine hypertension and orthostatic hypertension. In these individuals we tend to combine agents to minimize the swings in blood pressure. We have found that clonidine, combined alpha-beta blockers (such as labetalol or carvedilol) and the angiotension receptors blockers limit the swings upward in blood pressure with only modest effects on OH. We then often combine these with pyridostigmine as it prevents OH without exacerbating supine hypertension. It should be kept in mind that perfect control of blood pressure in these individuals is often difficult and realistic goals should be set. For example in severe supine hypertension we try to keep the supine BP less then 170/95 mmHg, while keeping the upright BP at whatever minimum level that prevents symptoms. In some patients blood pressures are so erratic that we construct a "sliding scale" of treatment such that when the BP is excessively high we give an additional dose of clonidine or additional midodrine when it is excessively low.

Of all the drugs discussed in this section it should be noted that only midodrine is approved by the United States Food and Drug Administration for the treatment of orthostatic hypotension. All the remaining agents are used "off label". It should also be remembered that the therapies discussed here are aimed at controlling orthostatic hypotension, and that they patient suffering from an automatic failure syndrome will have additional problems that these agents will not address. Both the patient and the treating physician should remember that some autonomic disorders may be progressive in nature, thus requiring periodic adjustments in treatment over time.

An important, yet often neglected consequence of these disorders is the tremendous social and emotional toll that these diseases take on both the patients and their families. The attitude of the treating physician can have a profound effect on

the patient with a chronic autonomic disorder. A positive (yet at the same time realistic) approach by a sympathetic and knowledgeable physician can have a tremendous impact on the patients sense of well being. Autonomic disorders may cause a wide range of personal and social problems that encompass occupational, educational, marital, psychosocial, financial and legal difficulties. Patients will often require the services of social workers, psychologists, rehabilitation specialists and lawyers to address these aspects of their illness. Hope and compassion are powerful medicines that should not be neglected.[40]

Summary

Orthostatic hypotension may occur either as a primary disturbance of the autonomic nervous system or as the consequence of another condition. Successful treatment involves identifying the subtype and pursuing a comprehensive treatment plan.

Dedication

This paper is dedicated to Barbara Straus MD, mother, wife, physician, soul mate, and source of all inspiration-BPG.

Disclosure

The authors report no conflicts of interest.

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