Clinical Disorders of the Autonomic Nervous System Associated With Orthostatic Intolerance: An Overview of Classification, Clinical Evaluation and Management

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Introduction

For millennia, sudden episodes of loss of consciousness have both fascinated and perplexed physicians. Commonly referred to as fainting, the preferred medical term is syncope (which itself is derived from the Greek term “syncopetein” meaning “to cut short.”)\(^1\) Recurrent syncope may occur due to a wide range of quite varied disorders. Over the last decade, considerable attention has been focused on syncope that results from centrally mediated periods of hypotension, a phenomenon that has most commonly been referred to as vasovagal syncope.\(^2\) However, investigations into the nature of this disorder have demonstrated that it is but one aspect of a broad, heterogenous group of disturbances in the autonomic nervous system, each of which are manifested by hypotension, orthostatic intolerance and often syncope. Indeed, the rapid pace of new discoveries has caused us to re-evaluate the classification of autonomic disorders, and to devise a new clinical system of classification that more accurately reflects our current understanding of these conditions.\(^3\) The classification system that has evolved is both practical and clinically useful, (yet, like any system of organization, is somewhat arbitrary) that includes disorders that most investigators have realized to be uniquely autonomic in nature.\(^4\) Since it is the clinical cardiac electrophysiologist who is now often called upon to recognize and treat these disorders the following review is designed to acquaint the interested reader with clinical aspects of these conditions, their diagnosis and potential management options.

The Autonomic Nervous System

The autonomic nervous system is amazingly extensive and is involved in the function of virtually every organ system.\(^5\) Therefore, the clinical manifestations of autonomic dysfunction can be quite diverse in nature.\(^6\) Indeed, the autonomic nervous system may be involved in virtually all
diseases. Any structural pathologic process affecting the brain (whether infectious, inherited, neoplastic or degenerative in nature) may result in an autonomic syndrome. Since each of these disorders all result from some form of disturbance in normal autonomic function, it would seem appropriate to briefly (and simply) review some aspects of its structure and operation. This brief review is not designed to be comprehensive, rather, it tries to provide an accessible framework for the non-neurologist, and focuses principally on autonomic regulation of orthostatic tolerance.

The human nervous system can be thought of as having two basic components: The central nervous system, made up of the brain and the spinal cord; and the peripheral nervous system, which is comprised of groups of neurons that are termed ganglia and of peripheral nerves that lie outside the brain and spinal cord. Although anatomically separate, the two systems are functionally interconnected. The peripheral nervous system is further divided into somatic and autonomic divisions. The somatic division is principally concerned with sensory information about the environment outside the body as well as muscle and limb position. The autonomic division (usually called the autonomic nervous system or ANS) is the motor system for the viscera, the smooth muscles of the body (especially those of the vasculature), and the exocrine glands. It is composed of three distinct parts: The sympathetic, parasympathetic, and enteric nervous systems. The sympathetic nervous system helps control the reaction of the body to stress, while the parasympathetic system works to conserve the body’s resources and to restore equilibrium to the resting state. The enteric system controls the function of the gut. The organ systems governed by the ANS are, for the most part, independent of volitional control (although they sometimes can be affected by volitional or emotional inputs) and include the cardiorespiratory organs, the gastrointestinal and genitourinary tracts. The autonomic system is vital to the maintenance of internal homeostasis and achieves this by mechanisms that regulate
blood pressure, fluid and electrolyte balance, and body temperature. The ANS is directly involved in tonic, reflex, and adaptive control of autonomic function, and integrates autonomic with hormonal, immunomodulatory, and pain controlling responses to internal and external environmental challenges.\textsuperscript{7}

Although representative of one of the defining aspects in the evolution of homosapiens, the adoption of upright posture presented a novel challenge to a blood pressure control system that is felt by some investigators to have developed to meet the needs of animals that were, for the most part, in a dorsal position.\textsuperscript{9} Indeed, the very organ felt to define our humanity, the brain, seems to have been placed in a somewhat precarious position in regards to both vascular perfusion and oxygenation.\textsuperscript{10}

The ANS is a principal component in both the short and long-term responses to positional change.\textsuperscript{11} In the normal subject roughly 25 to 30\% of the circulating blood is in the thorax.\textsuperscript{12} Upon assuming upright posture there is a gravity-mediated downward displacement of between 300 ml to 800 ml of blood to the abdomen and dependent extremities.\textsuperscript{13} This constitutes a volume drop of 26-30\% with up to 50\% of this fall occurring within the first few seconds of standing.\textsuperscript{14} Almost 25\% of the body’s total blood volume may be involved in this process. This rapid redistribution in central blood volume causes a decline in venous return to the heart. The heart cannot pump what it does not receive, therefore stroke volume declines about 40\% due to this decrease in cardiac filling pressure.\textsuperscript{15} The reference point for determination of these changes is known as the venous hydrostatic indifference point (or HIP) and represents the point of the vascular system where pressure is independent of “posture.”\textsuperscript{12} In humans the venous HIP is approximately at the diaphragmatic level while the arterial HIP lies close to the level of the left ventricle. The venous HIP is dynamic in nature and is significantly affected by venous compliance
and can be altered by factors such as muscular activity. While standing, contractions of the leg muscles along with the venous valve system serve to push blood back to the heart and thereby move the venous HIP toward the right atrium. Respiration may also serve to increase venous return. With deep inspiration there is a decline in thoracic pressure that facilitates inward flow of blood. Concomitantly, with respiration there is an increase in intra-abdominal pressure which lowers retrograde flow due to compression of both the iliac and femoral veins.

In addition to the changes mentioned above, upright posture also produces a substantial increase in the transmural capillary pressure in the dependent areas of the body, producing an increase in fluid filtration into the tissue spaces. This transcapillary shift reaches equilibration after about 30 minutes of upright posture, over which time this process can result in a net fall in plasma volume of up to 10%.

In order to successfully attain upright posture several cardiovascular regulating systems are initiated to help preserve a consistent level of arterial pressure (and thus cerebral perfusion) against the force of gravity. Orthostatic stabilization is normally achieved in roughly one minute or less. Over the years it has become apparent that the exact circulatory responses brought on by standing (an active process) are somewhat different than those brought on by head-up tilt (a passive process). Studies by Wieling and Lieshout have suggested that the orthostatic response consists of three phases. These consist of the initial response (during the first 30 seconds, the early “steady state” alteration (at 1-2 minutes) and lastly the prolonged orthostasis period (at least five minutes upright).

Immediately following head upright tilt, cardiac stroke volume stays relatively normal despite the fall in venous return (felt to be due to the blood in the pulmonary circulation). Thereafter a slow decline in both arterial pressure and cardiac filling occurs. This activates two
separate groups of pressure receptors consisting of high pressure areas in the carotid sinus and aortic arch areas, and low pressure receptors in the heart and lungs.\textsuperscript{20} Within the heart, these unmyelinated vagal afferents are linked by unmyelinated vagal afferents in both atria and ventricles. These mechanoreceptors produce a tonic inhibitory effect on the cardiovascular areas of the medulla (in particular on the nucleus tractus solitarii or NTS).\textsuperscript{21} Baroreceptive NTS neurons directly activate cardiovagal neurons of the nucleus ambiguous and the dorsal vagal nucleus, and inhibit sympathoexcitatory neurons of the rostral ventrolateral medulla.\textsuperscript{22} The decline in venous return and filling pressure that occurs with upright posture reduces the stretch on these receptors, decreasing their firing rates, resulting in a change in medullary input with a resulting increase in sympathetic outflow.\textsuperscript{11} This causes a constriction of the systemic resistance vessels but also in the splanchnic capacitance vessels. In addition there is a local axon reflex (the venoarteriolar axon reflex) which can also constrict flow to skin, muscle and adipose tissue, which may contribute up to 50\% of the rise in limb resistance seen during upright posture.\textsuperscript{19}

Head-upright tilt also activates the high pressure receptors located in the carotid sinus. The carotid sinus itself is a group of baroreceptors and nerve endings located in the enlarged area of the internal carotid artery after its origin from the common carotid artery.\textsuperscript{23} The mechanoreceptors themselves are situated in the adventitia of the adventitia of the arterial wall. The afferent impulses generated by localized stretch on the arterial wall are then transmitted through the sensory fibers of the carotid sinus nerve that travels with the glossopharyngeal nerve. These afferent pathways also terminate in the nucleus tractus solitarii of the medulla, in close proximity to the dorsal and ambiguous nuclei.\textsuperscript{22} The initial increase in heart rate that occurs during tilt is thought to be modulated by a fall in carotid arterial pressure. The slow increase in
diastolic pressure that is seen with upright tilt is felt to be more closely related to an increase in peripheral vascular resistance.\textsuperscript{24}

The initial circulatory adjustments that occur with standing are somewhat different than those seen during tilt.\textsuperscript{15} Standing is a much more active process that is accompanied by contraction of muscles in the legs and abdomen, causing compression of both the capacitance and resistance vessels with an elevation in peripheral vascular resistance.\textsuperscript{12} This increase is sufficient to produce a slight short-lived increase in right atrial pressure as well as cardiac output, which in turn results in activation of the low pressure receptors of the heart.\textsuperscript{14} The resultant augmentation in neural traffic to the brain produces a sudden decrease in peripheral vascular resistance that can fall by as much as 40%. This can allow for a fall in mean arterial pressure of up to 20 mmHg that may last for up to 6 to 8 seconds.\textsuperscript{25} This fall in pressure is then addressed by the same mechanisms as during tilt.\textsuperscript{18}

The early steady state adjustments to upright posture consist of an increase in heart rate of roughly 10 to 15 beats per minute, an increase in diastolic pressure of around 10 mmHg and little or no change in the systolic blood pressure.\textsuperscript{25} At this point, as compared to the supine position, the blood volume of the thoracic area is reduced by approximately 30%, the total cardiac output is decreased by 30%, and the average heart rate is between 10 to 15 beats per minute higher.\textsuperscript{27}

Continued upright posture also brings into play neurohumoral responses, the exact degree of which vary with the volume status of the patient. The more significant the degree of volume depletion, the greater the amount of activation of the renin-angiotensin-aldosterone system, as well as vasopressin.\textsuperscript{28} However, the most significant factor that helps the body compensate for continued orthostatic stress appears to be the arterial baroreceptor influence (in particular those of the carotid sinus) on peripheral vascular resistance.\textsuperscript{25} The inability of any one of these factors to
perform adequately (or in a coordinated fashion) may result in a failure of the system to compensate to initial or prolonged postural challenge. This would lead to a state of hypotension which, if sufficiently profound, could lead to cerebral hypoperfusion and loss of consciousness.

Disorders of Orthostatic Control

A number of different disorders of orthostatic control have been identified which, although sharing certain characteristics, are in many ways unique. It should be remembered that when we observe nature, we see what we want to see according to what we believe we know about it at the time. At one point, supraventricular tachycardia was felt to be a single entity, only later was it found to be composed of multiple subtypes. In order to make some sense of the apparent chaos of nature, we try to classify it into a coherent system that conforms to our observations and expectations. Thus, any system of classification is in some ways arbitrary and open to debate. The following system conforms to that developed by the American Autonomic Society and the American Academy of Neurology in 1996. A basic somewhat simplified outline of the system is provided in Figure I. Many investigators like to divide these disorders into primary and secondary forms. The primary forms tend to be idiopathic and are divided into acute and chronic forms. The secondary types are usually seen in association with a particular disease or are known to arise secondary to a known biochemical or structural abnormality. What follows is a brief description of each subtype with references for the reader who wants a more in-depth discussion.

Reflex Syncopes

Physicians tend to be most familiar with this form of syncope and as such, our discussion of it will be limited. First described by both Gower and Sir Thomas Lewis as vasovagal syncope, it is better known today as either neurocardiogenic or neurally-mediated syncope. Although diverse in presentation, it most frequently occurs in younger people and is characterized by a distinct prodrome (often consisting of lightheadedness, diaphoresis and nausea) of variable duration followed by an abrupt loss of consciousness. Recovery is rapid and is usually not accompanied by a postictal state. These episodes are felt to represent a “hypersensitive” autonomic system that over-responds to various stimuli. Most commonly this is prolonged
orthostatic stress, which is felt to increase venous pooling to the point where venous return to the right ventricle falls so precipitously that an increase in ventricular inotropy causes activation of mechanoreceptors that would normally fire only during stretch. This sudden surge in neural traffic to the brain stem is thought by some to mimic the conditions seen in hypertension, thus provoking an apparently “paradoxical” sympathetic withdrawal with resultant hypotension, bradycardia, and syncope. It is important to remember, however, that other stimuli such as strong emotion or epileptic discharge can provoke identical responses, thus suggesting that these individuals have an inherent increase in sensitivity to such stimuli. During head upright tilt table testing, these individuals have a sudden profound fall in blood pressure, that is closely followed by a fall in heart rate (sometimes to the point of asystole).

Sutton has made the insightful observation that the responses seen during neurocardiogenic syncope and carotid sinus hypersensitivity are quite similar and may be different aspects of the same disorder. Indeed, in such a predisposed individual, rapid mechanoreceptor activation from any site (blood, bladder, cough) could elicit similar responses. More detailed descriptions of these disorders can be found elsewhere. What seems to distinguish these disorders from the remainder of those discussed herein, is that in between episodes these patients are quite normal and report few, if any, other symptoms. Indeed, their autonomic systems appear to function normally despite their “hypersensitive” nature, as opposed to other conditions where the autonomic system seems to “fail”.

Primary Disorders of Autonomic Failure

Chronic Disorders

The physician is more likely to encounter the chronic forms of autonomic failure than their acute counterparts. The first report of chronic autonomic failure was the groundbreaking report by Bradbury and Eggleston in 1925, where they labeled the condition “idiopathic orthostatic hypotension” due to an apparent lack of other neurologic features. However, since then, it has become quite apparent that in these patients there exists a generalized state of autonomic dysfunction as manifested by orthostatic hypotension and syncope, as well as disturbances in bowel, bladder, thermoregulatory, sudomotor, and sexual function. The American Autonomic Society has named this disorder Pure Autonomic Failure (or PAF). While the cause of PAF
remains unknown, several investigators have postulated that there is a degeneration of the peripheral post ganglionic autonomic neurons.\textsuperscript{39,40} While the condition is more commonly seen in older adults, it can occur in almost any age group (including children).\textsuperscript{41}

Another type of autonomic failure was reported in 1960 in a landmark paper by Shy and Drager.\textsuperscript{42} In contrast to Pure Autonomic Failure, this more severe condition is manifested by severe orthostatic hypotension, progressive urinary and rectal incontinence, loss of sweating, iris atrophy, external ocular palsy, impotence, rigidity, and tremors.\textsuperscript{39} Both muscle fasciculations and distal muscle wasting may be seen late in the disorder. In order to better identify this complex multi-system disorder, the American Autonomic Society has named this disease Multiple System Atrophy (MSA) and has divided it into three major subtypes.\textsuperscript{43} The first group of patients demonstrate tremor that is surprisingly similar to Parkinson’s disease (some authors prefer to refer to this group as having striatonigral degeneration).\textsuperscript{44,45} A second group of these patients display mainly cerebellar and/or pyramidal symptoms (some investigators have termed this the olivopontocerebellar atrophy/degeneration form).\textsuperscript{46} A third group displays aspects of both these types.\textsuperscript{43} As was alluded to previously, MSA can appear surprisingly similar to Parkinson’s disease.\textsuperscript{39} An autopsy study recently found that somewhere between 7 and 22\% of people thought to have Parkinson’s disease actually had neuropathologic findings diagnostic for MSA.\textsuperscript{44,47} While the vast majority of MSA patients do not present until somewhere between the 5th and 7th decade of life, there are some unfortunate individuals who begin to have symptoms in their late thirties.\textsuperscript{41}

Recently, a considerable amount of attention has been focused on a milder form of chronic autonomic failure that is referred to as the Postural Orthostatic Tachycardia Syndrome (or POTS).\textsuperscript{48} The hallmark of the syndrome is a persistent tachycardia while upright (that sometimes reaches rates of 160 beats/minute or more), that is associated with severe fatigue, near syncope, exercise intolerance, and lightheadedness or dizziness.\textsuperscript{49} Many will also complain of always being cold, while at the same time unable to tolerate extreme heat. During head upright tilt, these patients will display a sudden increase in heart rate of greater than 30 beats/minute within the first five minutes, or achieve a maximum heart rate of 120 beats/minute associated with only mildly reduced blood pressures.\textsuperscript{50}
The mechanism underlying this condition appears to be a failure of the peripheral vasculature to appropriately vasoconstrict under orthostatic stress, which is then compensated for by an excessive increase in heart rate. Several authors have felt that POTS represents the earliest sign of autonomic dysfunction, and some of these patients (approximately 10%) have later progressed onto having pure autonomic failure. It is important to recognize this disorder, as we have seen several patients with POTS who had been misdiagnosed as having an inappropriate sinus tachycardia and who had undergone radio frequency modification of the sinus atrial node (at other centers). After the apparently successful elimination of their “sinus tachycardia”, they were left with profound orthostatic hypotension. These patients may also be misdiagnosed as suffering from Chronic Fatigue Syndrome. Several recent reports have suggested that there may be a great deal of overlap between these two disorders. Some investigators have felt that there are at least two different subgroups of POTS, a Pure Orthostatic Intolerance group as well as a beta-hypersensitivity group. However, these subgroups are still in the process of being defined.

Acute Autonomic Dysfunction

Even though these syndromes are rare, the acute autonomic neuropathies that produce hypotension and syncope are frequently dramatic in presentation. These disorders are sudden in onset, and demonstrate severe and widespread failure of both the sympathetic and parasympathetic systems while leaving the somatic fibers unaffected. Many of these patients tend to be young and, prior to the illness, were very healthy. The development of the illness is surprisingly rapid and patients can frequently relate the exact day symptoms first began. One interesting observation has been that a large number of these individuals report having had a febrile illness (presumed to be viral) prior to the onset of symptoms, giving rise to the notion that there may be an autoimmune component to the disorder.

Function of the sympathetic nervous system is often so severely disrupted that there is orthostatic hypotension of such a degree that the patient cannot even sit upright in bed without fainting. Patients often totally lose their ability to sweat, and suffer bowel and bladder dysfunctions. These patients frequently complain of bloating, nausea, vomiting, and abdominal pain. Constipation is frequent, and sometimes will alternate with diarrhea. One fascinating finding is that the heart rate will often be at a fixed rate of 40 to 50 beats per minute, associated
with complete chronotropic incompetence. The pupils are often dilated and poorly reactive to light. Patients may experience several syncopal episodes daily. The long-term prognosis of these patients is quite variable, with some enjoying complete recoveries while others suffer a chronic debilitating course. Patients are often left with significant residual defects.

Secondary Causes of Autonomic Dysfunction

A wide variety of disorders may cause varying degrees of autonomic disturbance. A partial list of some of these disorders is found in Table I. It is important for the physician to be able to recognize when autonomic dysfunction is but part of a greater disorder. In occasional patients, several conditions may coexist that produce synergistic detrimental effects on autonomic function. Over the last decade, a number of (relatively rare) enzymatic abnormalities have been identified which can result in autonomic disruption. Principal among these is isolated dopamine beta-hydroxylase (DBH) deficiency syndrome, a condition which is now easily treated by replacement therapy. Additional deficiency syndromes involving nerve growth factor, monamine oxidase, aromatic L-amino decarboxylase, and some sensory neuropeptides may all result in autonomic failure and hypotension. Diffuse systemic illnesses such as renal failure, cancer, diabetes mellitus, or the acquired immune deficiency syndrome (AIDS) may all cause hypotension and syncope. Studies have also demonstrated a link between orthostatic hypotension and Alzheimer’s disease.

Perhaps one of the most important things to remember are the vast number of pharmacologic agents that may either cause or worsen orthostatic hypotension (Table II). Chief among these are the peripherally acting vasodilatory agents such as the angiotensin converting enzyme (ACE) inhibitors; prazosin, hydralazine, guanethidine. Beta blocking agents may also worsen syncope in some patients. Lately we have observed an increased frequency of dysautonomic syncope in patients suffering from congestive heart failure. Heart failure is known to be accompanied by important disturbances in autonomic function. In this group, the combination of a low cardiac output, and volume depletion due to diuretics and vasodilator therapy serve to interfere with the body’s aforementioned mechanisms for adapting to upright posture and predispose them to periods of orthostatic intolerance. Centrally acting agents such as
the tricyclic antidepressants, reserpine methyldopa, and monamine oxidase (MAO) inhibitors may also exacerbate otherwise mild hypotension.

**Clinical Features**

The principal feature that all of these conditions share is that normal cardiovascular regulation is disturbed sufficiently such that postural hypotension can occur. While orthostatic hypotension was once defined as a greater than 20 mm/Hg fall in systolic blood pressure over a three minute period after standing upright, a smaller drop in blood pressure associated with symptoms can be just as important. A large percentage of these patients will display a slow steady fall in blood pressure over a longer time frame (around 10-15 minutes) that can be quite symptomatic. Whether the patient experiences symptoms is as much dependent on the rate of fall in pressure as it is upon the absolute degree of change. The loss of consciousness in the dysautonomic tends to be slow and gradual, usually when the patient is walking or standing. However, many older patients do not seem to perceive this decline in pressure and therefore report little or no prodrome prior to syncope and will describe these episodes as “drop attacks.” Those who do experience prodromes will describe a wide variety of symptoms such as dizziness, blurring of vision, “seeing stars”, and tunnel vision. A distinguishing feature between neurocardiogenic and dysautonomic syncope is that in the latter, bradycardia and diaphoresis are uncommon during an episode. Dysautonomic syncope tends to be more common in the early morning hours. Any factor that enhances peripheral venous pooling such as extreme heat, fatigue, or alcohol ingestion, will exacerbate hypotension. As time goes on, some patients may develop a relatively fixed heart rate (around 50-70 beats/minute) that shows little response to either postural change or exercise. In addition, some patients will develop a syndrome of supine hypertension that alternates with upright hypotension, presumably due to a failure to vasodilate when prone. Patient suffering from this combination of supine hypertension and upright hypotension can quite be difficult to treat. Sometimes distinguishing between these disorders can be difficult as there may be a considerable degree of overlap between them (a situation not dissimilar to that seen with the various forms of chronic obstructive lung disease). (Figure II)
Evaluation of Patients

The cornerstone of evaluation is a detailed history and physical examination. When do syncopal or near syncopal episodes occur and when did they begin? How often? Is there a pattern to the events or any known precipitating factors? What are episodes like to the patient and how do they appear to bystanders? What other organ systems are involved? Other than syncope, what symptom bothers the patient most? A careful and concise history and physical (which must include a concise neurologic examination) will have a far greater diagnostic yield than the mindless ordering of multiple tests. Laboratory examinations should be obtained in a careful and directed manner, based upon history and physical findings, to confirm one’s clinical impressions.

It is far beyond the scope of this paper to review every autonomic disorder and the various tests used in evaluation. The interested reader is directed to several excellent texts on the subject. One point that needs to be emphasized, is that any drugs the patient is taking that could produce hypotension should be identified. (Table II) This includes not only pharmaceuticals, but over-the-counter medications and herbal remedies as well (St. John’s wort for example appears to be an MAO inhibitor). Sadly, increasingly in the modern era, when a young person presents with symptoms of autonomic dysfunction the potential use of illicit drugs or alcohol should be considered. In women, symptoms may vary with the menstrual cycle or an otherwise mild tendency toward autonomic dysfunction may be exacerbated by the onset of menopause.

Since the autonomic areas of the brain are not accessible to direct measurement, one must measure the responses of various organ systems to various physiologic or pharmacologic challenges. In addition, recent advances have allowed for the determination of serum urine and cerebrospinal fluid levels of some autonomic neuromodulators and neurotransmitters. Foremost, however, is the determination of the blood pressure and heart rate response to positional change, with measurements taken while supine, sitting, and standing. The exact change in pressure considered to be significant is still under discussion, but is usually felt to be between 20-30 mm/Hg systolic and 10-15 mm/Hg diastolic. Remember that when standing, pressure determination should be performed with the arm extended horizontally (to avoid the possible hydrostatic effects of the fluid column of the arm). Since the body’s responses to active standing
differ from those of passive tilting, we also frequently perform tilt table testing on these patients, the details of which are given elsewhere. A number of other autonomic tests are also available, and are quite useful in selected patients, a detailed description of which can be found elsewhere.

Potential Treatments (Table III)

A complete discussion of the treatment options available is beyond the scope of this review; however, some basic principals will be very briefly outlined (more complete discussions can be found elsewhere). One of the physician’s most important tasks is to identify whether hypotensive syncope is primary or secondary in nature, and to determine if there are any potentially reversible causes (i.e., drugs, anemia, volume depletion).

It is equally important to educate the patient and their family as to the nature of the problem. Teaching the patient to avoid aggravating factors (such as extreme heat, dehydration, and alcohol consumption) as well as recognizing any prodromal symptoms and assuming a recumbent position at their onset, are extremely helpful measures. Increased fluid intake should be encouraged.

Nonpharmacologic therapies that are useful include sleeping with the head of the bed upright (around 6-12 inches), and elastic support hose (at least 30-40 mm/Hg ankle counter-pressure). Sleeping with the head of the bed upright is particularly helpful in patients who suffer from coexistent supine hypertension. Biofeedback has also proven useful in selected patients, especially these with neurocardiogenic syncope where definite psychologic triggers exist. Moderate exercise is often helpful in keeping up venous return by strengthening the skeletal muscle pump.

Pharmacotherapy should be used cautiously, and should be tailored to fit the needs of the patient based on the type of autonomic disorder being treated, as well as coexisting symptoms and conditions. It should also be remembered that virtually any drug used in treatment can occasionally worsen symptoms (a “prosyncopal” effect).

In neurocardiogenic syncope, a number of reports have found that beta blocker therapy is effective, presumably because it’s negative inotropic effects lessen the degree of cardiac
mechanoreceptor activation associated with abrupt falls in venous return. The increase in peripheral vascular resistance that accompanies unopposed beta blockade may also contribute to its therapeutic effects. We have not found beta blockade as useful in other forms of reflex syncope and they may be detrimental in the dysautonomic syndromes. A useful agent in patients with dysautonomic syncope (and in younger patients with neurocardiogenic syncope) is the mineral corticoid agent, fludrocortisone. It results not only in fluid and sodium retention, but it also appears to raise pressure via an indirect vasoconstrictive effect resulting from sensitization of peripheral alpha receptors. Since the drug may cause hypokalemia and hypomagnesemia, serum potassium and magnesium levels need to be periodically monitored. Desmopressin has also been useful in selected patients.

Since failure to properly vasoconstrict the peripheral vessels is common to all of these disorders, vasoconstrictive substances can be employed. Initially, we employed the amphetamine-like agent, methylphenidate, with good results. However, the fact that it is a controlled substance with potent CNS stimulating activity tended to limit our use of the drug. An excellent alternative is the new alpha stimulating agent, midodrine. It has almost no CNS effects or cardiac stimulation, while providing identical degrees of peripheral alpha receptor stimulation. Several studies have demonstrated midodrine’s efficacy in both neurocardiogenic and dysautonomic disorders. Yohimbine and ephedrine has also been used.

It has been found that the alpha-2 receptor blocking agent, clonidine, can actually elevate blood pressure in dysautonomic patients where hypotension is secondary to a severe post ganglionic sympathetic lesion. It patients with severe autonomic failure, the post junctional vascular alpha-2 receptors (that are plentiful in the venous system) are actually hypersensitive. Although, in normal individuals, clonidine acts on the central nervous system to lessen sympathetic output and with it blood pressure; in autonomic failure, some patients exhibit little or no sympathetic output thus permitting its peripheral actions to become manifest. It must be used carefully as it may worsen hypotension.

Interestingly, a number of patients with autonomic failure will be anemic. A brilliant study by Hoeldtke and Streten demonstrated that subcutaneous injections of erythropoietin while raising blood count will also produce dramatic increases in blood pressure. This pressure effect seems to occur independent of the red cell effect.
A series of both animal and human studies have demonstrated that the neurotransmitter serotonin (5-hydroxytryptamine) plays an essential role in the central regulation of blood pressure and heart rate. It has been postulated that some patients with autonomic disorders may have disturbances in central serotonin production or regulation. In support of this concept has been the observation that the serotonin reuptake inhibitors can be effective in both the treatment of neurocardiogenic syncope and orthostatic hypotension.

The exact role of pacemaker therapy in the treatment of these disorders remains controversial, and is beyond the scope of this discussion; however, a number of investigators have found that in selected patients pacemaker therapy can be effective in reducing symptoms and may sometimes eliminate syncope altogether.

It should be kept in mind, that in dysautonomic disorders (as opposed to the reflex synapses), hypotensive syncope is but one aspect of a broader constellation of symptoms relating to autonomic failure. The physician should, therefore, not give the patient unrealistic expectations as to what symptoms can and cannot be eliminated. Both physician and patient should remain cognizant that these disorders can be progressive in nature, and that therapies may have to be altered over time.

Patients suffering from severe autonomic disorders (such as Multiple Systems Atrophy) may have a number of secondary problems that cover a broad spectrum of social and personal difficulties that may include marital, occupational, psychological, sexual, legal and frequently financial problems. Many physicians feel uncomfortable addressing these issues, yet it is often in these areas that the most can be done to help some patients. The physicians treating these patients should become familiar with the available community resources and be ready to enlist the assistance of social workers, psychologists, rehabilitation counselors, and even lawyers when necessary.

The physician’s attitude can have a powerful impact on the patient suffering from a severe autonomic disorder. A positive (but realistic) approach by a knowledgeable and sympathetic physician can greatly help the patient’s sense of well being, a fact which can have a beneficial effect on the course of the disease and the patient’s outcome. Hope is a powerful elixir that should be encouraged. The National Dysautonomic Research Foundation (http://www.ndrf.org) can serve as an information source and support group for these patients and their families.
Summary

The disorders of autonomic control associated with orthostatic intolerance are a diverse group of infirmities that can result in syncope and near syncope (as well as a host of other complaints). A basic understanding of these disorders is essential to both diagnosis and proper treatment. These infirmities are not new, what has changed is our ability to recognize them. It has been said that “the world undergoes change in the human consciousness. As this consciousness changes, so does the world.” Ongoing studies will continue to help better define the broad spectrum of these disorders, and to elaborate better diagnostic and treatment modalities.
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References


Table I: Autonomic Disorders Associated with Orthostatic Intolerance

I. Primary Autonomic Disorders
   A. Acute pandysautonomia
   B. Pure autonomic failure
   C. Multiple system atrophy
      1. Parkinsonian
      2. Pyramidal/Cerebellar
      3. Mixed
   D. Reflex syncopeces
      1. Neurocardiogenic syncope
      2. Carotid sinus hypersensitivity

II. Secondary autonomic failure
   A. Central origin
      1. Cerebral cancer
      2. Multiple sclerosis
      3. Age-related
      4. Syringobulbia
   B. Peripheral forms
      1. Afferent
         a. Guillian-Barré syndrome
         b. Tabes dorsalis
c. Holmes-Adie syndrome

2. Efferent
   a. Diabetes mellitus
   b. Nerve growth factor deficiency
   c. Dopamine beta-hydroxylase deficiency

3. Afferent/Efferent
   a. Familial dysautonomia

4. Spinal origin
   a. Transverse myelitis
   b. Syringomyelia
   c. Spinal tumors

5. Other causes
   a. Renal failure
   b. Paraneoplastic syndromes
   c. Autoimmune/collagen vascular disease
   d. Human immunodeficiency virus infection
   e. Amyloidosis
Table II: 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
MAO Inhibitors
<table>
<thead>
<tr>
<th>Therapy</th>
<th>Method or Dose</th>
<th>Common Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head up tilt of bed</td>
<td>45 head -up tilt of bed, (often will need footboard)</td>
<td>Hypotension, sliding off bed, leg cramps</td>
</tr>
<tr>
<td>Elastic Support Hose</td>
<td>Require at least 30-40 mmHg ankle counterpressure, work best if waist high</td>
<td>Uncomfortable, hot, difficult to get on</td>
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<tr>
<td>Diet</td>
<td>Fluid intake of 2-2.5 liters/day Na+ intake of 150-250 mEq/day</td>
<td>Supine hypertension, Peripheral edema</td>
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<tr>
<td>Exercise</td>
<td>Aerobic exercise (mild) may aid venous return. Water exercise particularly helpful</td>
<td>May lower blood pressure if done too vigorously.</td>
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<tr>
<td>Fludrocortisone</td>
<td>Begin at 0.1-0.2 mg/day may work up to doses not exceeding 1.0 mg/day</td>
<td>Hypokalemia, hypomagnesemia, peripheral edema, weight gain, congestive heart failure</td>
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<tr>
<td>Methylphenidate</td>
<td>5-10 mg po tid given with meals, give last dose before 6 pm</td>
<td>Agitation, tremor, insomnia, supine hypertension</td>
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<tr>
<td>Midodrine</td>
<td>2.5-10 mg every 2-4 hours. May use up to 40 mg/day</td>
<td>Nausea, supine hypertension</td>
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<tr>
<td>Clonidine</td>
<td>0.1-0.3 mg po bid or patches placed 1/week</td>
<td>Dry mouth, bradycardia hypotension</td>
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<tr>
<td>Yohimbine</td>
<td>8 mg po bid-tid</td>
<td>Diarrhea, anxiety nervousness</td>
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<tr>
<td>Ephedrine sulfate</td>
<td>12.5-25 mg po tid</td>
<td>Tachycardia, tremor, supine hypertension</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>10-20 mg po qd (requires 4-6 weeks of therapy)</td>
<td>Nausea, anorexia, diarrhea</td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>4,000 IU Sq twice a week</td>
<td>Requires injections, burning at site, increase hematocrit, CVA</td>
</tr>
<tr>
<td>Pindolol</td>
<td>2.5-5.0 mg po bid to tid</td>
<td>Hypotension, congestive heart failure, bradycardia</td>
</tr>
<tr>
<td>Desmopressin</td>
<td>An analog of vasopressin used as a nasal spray</td>
<td>Hyponatremia</td>
</tr>
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</table>