Editorial

Syncope in the Older Patient

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Syncope, defined as the transient loss of consciousness and postural tone with spontaneous recovery, is a common clinical problem. Each year in the United States syncope accounts for approximately 3% of all emergency room visits and around 6% of all hospital admissions, (80% of which are over 65 years of age)[1,2]. Both a sign and a symptom, syncope can result from a wide variety of different causes, some of which ultimately culminate in death. Given this fact it is not surprising that syncope frequently provokes a deep sense of anxiety among patients, their families and their physicians[3]. Even if the cause of a patient's recurrent syncope in benign, the consequences of the resultant fall may not be.[4] Injuries from syncope occur in 17 to 35% of patients, and bone fractures occur in 5-7% of patients (often in the elderly) and traffic accidents in 1-5% of syncope patients[5-8]. Recurrent unpredictable episodes of syncope have been found to create a level of functional impairment similar to levels seen with chronic debilitating diseases such as rheumatoid arthritis[3].

Until relatively recently, patients with recurrent unexplained syncope were subjected to a series of tedious, expensive and all too often, unrewarding tests administered in an attempt to uncover a potential etiology[7,8]. This often included ambulatory electrocardiography, glucose tolerance testing, electroencephalography and exercise tolerance testing, as well as computed axial tomography and/or magnetic resonance imaging of the brain. Cardiac electrophysiology testing and cardiac catheterization were often performed as well. However, despite this extensive series of examinations (that cost close to $16,000 per patient) a cause for recurrent syncope was elucidated in less than 40% of patients[2]. This represents a cost of approximately $800 million per year spent on syncope evaluations in the United States alone[1,9].

The epidemiology of syncope in the general elderly population has not been well studied. Part of this problem lies in the poor availability of eye witness accounts of syncopal events and in an overlap with the diagnosis of falls[10]. In one study of the institutionalized elderly, the incidence of syncope was 6% annually with a recurrence rate of 30%. The morbidity associated with syncope is often greater in the geriatric population where falls may be complicated by fractures, subdural hematomas and other serious injuries[11,12]. In one study of elderly patients with syncope due to carotid sinus hypersensitivity, over half had sustained a serious injury during syncope, either a fracture or a injury of sufficient severity to require hospital admission[12]. Therefore a single syncopal episode could potentially convert a functional independent older person into a patient that requires permanent nursing home placement at great cost to the individual, their family and society at large[13].

The elderly seem particularly prone to syncope due to age-related changes in

the cardiovascular system with respect to control of the circulation, the concurrence of multiple illnesses and the use of numerous medications[14].

The full spectrum of potential etiologies of syncope is quite wide and far beyond the scope of this paper, and the interested reader is directed to several excellent works on the subject[1]. The remainder of the editorial will focus on potential causes of syncope related to various states of insufficiency in autonomic nervous system function.

The autonomic nervous system

Since these nervous disorders all result from a disturbance in normal autonomic function, it would seem appropriate to briefly review some aspects of its structure and operation[1].

The human nervous system has 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.

Although representative of one of the defining aspects of the evolution of homosapiens, the adoption of upright posture presented a novel challenge to a blood pressure control system that developed to meet the requirements of an animal in the dorsal position. Indeed, the organ that defines our humanity, the brain, was placed in a somewhat precarious position with regards to vascular perfusion and oxygenation. It is the ANS that governs both the short and medium term blood pressure responses to positional change. Normally, around 25% of the circulating blood volume is in the thorax. Immediately following the assumption of upright posture, gravity produces a downward displacement of roughly 500 cc of blood to the abdomen and lower extremities. Approximately 50% of this amount is redistributed within seconds after standing and almost one quarter of total blood volume may be involved in the process. The process causes a decrease in venous return to the heart and cardiac filling pressures and stroke volume may fall by 40%. The reference point for determination of these changes is known as the venous hydrostatic indifference point (or HIP) and represents the part of the vascular system where pressure is independent of posture. In humans, the venous HIP is around the level of the diaphragm while the arterial HIP is at the left ventricle. The venous HIP is somewhat dynamic in that it can be altered by changes in venous compliance brought on by muscular activity. Following standing, the normal subject achieves orthostatic stabilization in one minute or less. It should be noted 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). In the moments following assumption of upright posture, a slow decline in arterial pressure and cardiac filling occurs. This causes activation of the high pressure receptors of the carotid sinus and aortic arch, as well as the low pressure receptors of the heart and lungs. The mechanoreceptors that are within the heart are linked by unmyelinated vagal afferents in both the atria and ventricles. These fibers have been found to cause continuous inhibitory actions on the cardiovascular areas of the medulla (the nucleus tractus solitarii). The fall in venous return that results from upright posture produces less stretch on these receptors, then discharge rates decrease, and the change in input to the brain stem causes an increase in sympathetic outflow resulting in systemic vasoconstriction. At the same time, the fall in arterial pressure while upright actuates the high pressure receptor in the carotid sinus which stimulates an increase in heart rate. These early

steady state adaptations to upright posture therefore result in a 10 to 15 beat per minute increase in heart rate, a diastolic pressure increase on 10mm/Hg, and little or no change in systolic blood pressure. Once these adjustments are complete, as compared to the supine state, during upright stance the thoracic blood volume is 30% less as is the total cardiac output, and the mean heart rate is 10-15 beats/minute higher. Furthermore, detailed descriptions of this process are available to the interested reader.

As a person continues to stand there is activation of neurohumoral responses, the amount of which is dependent on the subject's volume status. As a rule, the lower the volume, the higher the degree of the renin-angiotensin-aldosterone system involvement. The inability of any of these processes to function adequately (or in a coordinated manner) can potentially result in a failure in the normal responses to sudden shifts in posture (or their maintenance) with resultant hypotension that may be sufficiently great as to result in cerebral hypoperfusion, hypoxia, and loss of consciousness.

Age-related changes in autonomic control

The sympathetic nervous system undergoes a series of changes as a person ages. Plasma norepinephrine levels have been noted to increase, possibly due to an increased spillover from sympathetic nerve terminals as well as a decreased rate of clearance[15-17]. There is a reduction of ß-adrenergic mediated cardioacceleratory response to sympathetic activation that is observed even though circulating norepinephrine levels are increased[18,19]. There is also a reduction in beta-adrenergic vasodilatory and alpha-adrenergic vasoconstrictive responses[20]. This may occur due to a reduced number of adrenergic receptors that occur due to down regulation in the face of high serum norepinephrine levels[21]. This reduction in beta-adrenergic vasodilatory response may account in part for the increased peripheral vascular resistance observed in the elderly[22-24].

While the mechanisms involved remain elusive, aging is also associated with a reduction in parasympathetic tone. This data comes from observations of heart rate variability in older subjects that demonstrate a reduced parasympathetic response to the Valsalva maneuver, respiration and cough[25-31]. Older syncope patients have been reported to demonstrate a lower degree of heart rate variability in response to deep breathing as compared to matched controls.

As was alluded to previously reflex alterations in heart rate that occur in response to sudden changes in blood pressure are controlled by the baroreflex. The baroreflex appears to lose its sensitivity with age as demonstrated by a reduced augmentation in heart rate in the face of hypotension, (perhaps related to the aforementioned reduction in beta-adrenergic responsiveness)[32]. While the majority of older subjects compensates for this with a greater degree of vasoconstriction this mechanism may be attenuated by hypovolemia or by vasodilatory drugs. Thus, older patients treated with vasodilators or diuretics may show an enhanced susceptibility to syncope.

The previously mentioned alterations in sympathetic and parasympathetic tone seen with aging result in disturbed heart rate control in the elderly. In addition there is a reduction in the number of cardiac pacemaker cells in the sinus node associated with aging, as well as a generalized increase in collagenous and elastic tissue in the entire cardiac conduction system. It has been reported that by the age of 75 years there are less than 10% of the sinoatrial cells that were present during young adulthood[33]. This reduction in baroreflex control of heart rate makes vasoconstriction even more important in the compensatory responses to orthostatic stress[34]. However, the elderly exhibit alterations in atrial natriuretic peptide, renin aldosterone levels that favour an increased rate of water and salt excretion by the kidneys. In addition the normal thirst-sensing mechanisms diminish with age and thus favour states of relative dehydration[14]. Therefore the elderly are particularly sensitive to the effects of low fluid intake, diuretics and vasodilatory agents of all forms.

Disorders of orthostatic control

A variety of disorders of orthostatic control may affect the elderly. While they share certain characteristics each disorder is nonetheless unique. The classification of these disorders is still in a state of evolution and will undoubtedly change over time. The system used here is based on the one developed by the American Autonomic Society. It is useful to think of these disorders as being primary or secondary in nature. The primary forms occur in the absence of other diseases and are usually subgrouped into acute and chronic forms. The secondary types are usually seen to occur due to a particular disease state or biochemical disturbance.

Reflex syncope

The reflex syncopes are those characterized by sudden abrupt falls in blood pressure and often in heart rate as well[1]. These include neurocardiogenic (vasovagal), carotid sinus hypersensitive, micturition, cough and defecation syncope. There is usually a distinct prodrome followed by an abrupt loss of consciousness. There is usually a quick recovery and prolonged postictal states are rare. Each of these states is characterized by "hypersensitive" response to various stimuli. In the case of neurocardiogenic syncope this occurs in response to prolonged orthostatic stress, which increases venous pooling to a degree such that venous return to the right ventricle falls to such a degree that a dramatic increase in ventricular inotropy occurs which causes activation of mechanoreceptors that would normally fire only during stretch. This sudden increase in neural traffic to the brain stem is felt to mimic the conditions normally seen with hypertension, thereby activating an apparently "paradoxic" decrease in sympathetic output that leads to hypotension, bradycardia and loss of consciousness[35]. It should be kept in mind that activation of other mechanoreceptor beds (such as in the bladder, rectum or carotid sinus) or stimuli such as profound emotion or an epileptic discharge may cause identical responses[36]. This would suggest that these patients have an inherent predisposition to these stimuli[37]. During headup tilt table testing these patients demonstrate a sudden dramatic fall in blood pressure that is often followed by a fall in heart rate (occasionally producing prolonged periods of asystole)[1]. What appears to distinguish these illnesses from the other forms of autonomic insufficiency is that between the episodes of decompensation these individuals seem to be quite healthy and exhibit few if any other symptoms, with relatively normal day to day autonomic function in spite of hypersensitive predisposition. This is as opposed to situations where the autonomic system seems to fail.

Primary autonomic insufficiency syndromes

Acute autonomic neuropathy

While the acute autonomic neuropathies that result in hypotension and syncope are less common than their chronic counterparts, their presentations can be quite dramatic. The onset or these disorders is quite sudden and is manifested by diffused severe failure of both the parasympathetic and sympathetic nervous systems while somatic nerve functions are relatively unaffected. Onset can be at any age and often, prior to presentation these individuals were quite healthy. Many patients report having suffered an acute viral illness (presumably viral) prior to the onset of symptoms, suggesting to some investigators that there may be an autoimmune component.

The function of the sympathetic nervous system is so profoundly disrupted that there can be severe orthostatic hypotension that is so pronounced that the patient can not sit up without experiencing syncope or near syncope. Many patients will lose the ability to sweat and will experience disruptions in both bowel and bladder function. Complaints of nausea, bloating, abdominal pain and vomiting are common. Pupils may be dilated and poorly responsive to light. Chronotropic incompetence is common and contributes to the patients' orthostatic intolerance. The long-term outcome of these patients varies considerably, with some making complete recoveries and others having permanent impairments. We recently have observed that high dose immunoglobins appear to shorten the course of the illness

Chronic disorders

Chronic autonomic failure was first reported in 1925 by Bradbury and Eggleston who described what they referred to as "idiopathic orthostatic hypotension" because of a presumed lack of other neurological deficits[39]. Since that time however it has been realized that these patients suffer from a chronic state of autonomic failure characterized by alterations in thermoregulatory, bowel, bladder sexual and sudomotor function. The American Autonomic Society has now termed this disorder Pure Autonomic Failure (or PAF)[40]. While the etiology of PAF remains obscure some researchers have suggested that a progressive degeneration of peripheral post ganglionic autonomic neurons may be to blame.

A second type of autonomic failure syndrome was reported by Shy and Drager in 1960[41]. As opposed to PAF, they described a condition that was much more severe, characterized by profound orthostatic hypotension, loss of sweating, rectal and urinary incontinence, impotence, external ocular palsy, rigidity and tremor. Distal muscle wasting and fasciculations may be seen late in the disorder. The American Autonomic Society has termed this condition Multiple System Atrophy and has sub-divided it into three sub-types[40,41]. The first sub-group displays a

tremor that can be remarkably similar to that seen in Parkinson's Disease (some refer to this group as having striatonigral degeneration). The second group seem to have principally cerebellar and/or pyramidal symptoms (also known as the olivopontocerebellar degeneration group). The third type appears to be a mixture of these two. As was mentioned previously, MSA may appear quite similar to Parkinson's disease. An autopsy study performed in the United Kingdom found that between 7 and 22% of patients felt to be suffering from Parkinson's Disease during life were found to have neuropathologic evidence for MSA instead. The majority of cases begin between ages 50 and 70 years and follow a progressive downhill course. Death usually occurs between seven and nine years after onset of symptoms, usually from respiratory failure.

A milder form of chronic autonomic insufficiency has recently been identified referred to as the Postural Orthostatic Tachycardia Syndrome (POTS)[43]. The defining feature here is a marked tachycardia that occurs while the patient is upright that can reach rates of over 160 beats per minute. Patients with POTS often complain of lightheadedness, severe fatigue, exercise intolerance, dizziness and near syncope. During head upright tilt table testing patients with POTS will have a sudden increase in heart rate of more than 30 beats/minute in the first five minutes upright, or will achieve a rate of greater than 120 beats per minute associated with only modest reductions in blood pressure.

The most common pathophysiological mechanism that causes POTS is a failure of the peripheral vasculature to adequately vasoconstrict during orthostatic stress. A second form of POTS has been identified that appears to result from an excessive production of norepinephrine due to a genetic defect in a norepinephrine transporter protein.

Secondary autonomic syndromes

A surprisingly large number of diseases may result in disturbances in normal autonomic function. Physicians should remain alert to the fact that a patient's autonomic symptoms may be but one aspect of a greater disorder. In the elderly several different conditions may co-exist at the same time that may display additive detrimental effects an autonomic function. Conditions such as diabetes mellitus, amyloidosis and the autoimmune disorders may all compromise autonomic function, as can renal failure, cancer and the Acquired Immune Deficiency Syndrome. Recently a link between senile dementia and orthostatic hypotension has also been demonstrated[44].

One of the most important things to look for is whether a medication may be causing or worsening autonomic insufficiency. The most common agents in this regard are vasodilators such as prazosin, guanethidine, hydralazine and the angiotensin converting enzyme inhibitors. Beta blockers may sometimes cause problems, and alcohol is well known for causing or exacerbating autonomic dysfunction.

Clinical manifestations

The cardinal feature of all of these disorders is orthostatic hypotension. This was once defined as being a greater than 20mmHg fall in BP over 2-3 minute period after standing, although it has been found that a somewhat lesser drop in blood pressure that produces symptoms may be equally important. A significant group of patients will demonstrate a gradual continuous fall in blood pressure over a longer time frame that will result in symptoms. The rate at which blood pressure falls may be as important as the absolute degree of fall. In most patients suffering from dysautonomic forms of syncope, fall in blood pressure and hence the loss of consciousness tends to be gradual. However an interesting finding has been that many elderly patients do not perceive this fall in blood pressure and will experience sudden loss of consciousness that they will describe as a "drop attack". Those patients who do experience prodromes will describe a number of symptoms such as lightheadedness and dizziness, blurred vision and disorientation. Syncope tends to be more common in the morning. Any condition or agent that favors peripheral vascular pooling, (heat, alcohol, fatigue) will tend to facilitate episodes. Some patients will display a syndrome of supine hypertension associated with upright hypotension which can prove quite challenging to treat. It may sometimes be difficult to distinguish the various disorders from one another.

Patient evaluation

The single most important part of the evaluation is a detailed history and physical examination. Particular attention should be paid to the description of the syncopal event itself, the setting and frequency of events. Laboratory testing should then be obtained in a directed manner to either confirm or deny one's suspicions.

It is beyond the scope of this paper to review all the various forms of autonomic testing available and the interested reader is directed to several excellent references on the subject[45-48]. Due to the fact that the autonomic areas of the brain are not easily accessible to direct measurement most autonomic tests measure the response of the system to a variety of physical or pharmacologic tests. It is also useful to measure serum and urine catecholamine levels. However the simplest and most important test remains an accurate determination of blood pressure and heart rate in the supine setting and upright positions. A fall of more than 20-30 mmHg systolic or 10-15 mmHg diastolic is usually considered significant. Details on other forms of autonomic testing can be found elsewhere[45-49].

Therapies

A comprehensive review of all the potential treatment options is beyond the scope of this editorial, with more extensive reviews available elsewhere[47]. One of the most critical points is to first establish a diagnosis and to determine if the dysautonomia is primary or secondary in nature. An equally important point is to educate the patient and their family as to the nature of the problem and to pursue behavior modification such that potential aggravating factors and situations can be avoided.

Non-pharmacological therapies include biofeedback, sleeping with the head of the bed elevated and elastic support hose[1].

Pharmacotherapy should be used carefully and cautiously and should be adapted to meet the needs of each patient. A number of different pharmacotherapies have been employed. In classic neurocardiogenic syncope beta adrenergic blocking agents have long been considered the mainstay of therapy[1]. They supposedly work via a combination of their negative inotropic actions that lessen the degree of mechanoreceptor activation and due to the increase in peripheral vascular resistance that accompanies unopposed beta receptor blockade. A very useful therapy in many patients is the mineral corticoid agent fludrocortisone[45]. The mechanism by which it raises blood pressure appears to be two fold in that it not only promotes fluid and sodium retention but it also seems to cause sensitization of peripheral vascular alpha receptors, thus promoting a vasoconstrictive state. When using fludrocortisone, serum magnesium and potassium levels should be followed.

As failure of the peripheral vasculature to constrict appropriately seems common to these disorders, drugs that promote vasoconstriction are frequently employed. At first drugs such as dextroamphetamine and methylphenidate were successfully employed, but problems with CNS stimulation, abuse and dependence have limited their utility[50]. An excellent alternative is the pure alpha - 1 stimulating agent midodrine hydrochloride[51,52]. It has little or no CNS or cardiac effects and provides significant constriction of the peripheral vasculature. A number of studies have demonstrated its utility in the treatment of autonomic disorders associated with orthostatic intolerance.

Clonidine, an alpha - 2 receptor agonist that is usually used to treat hypertension can actually be used to raise blood pressure in people whose hypotension is secondary to a severe post-ganglionic sympathetic lesion[53]. In individuals who suffer form severe autonomic failure it is felt that the post junctional vascular alpha - 2 receptors (that are densely packed throughout the venous beds) become hypersensitive. While in normal subjects clonidine causes a reduction in sympathetic output (and therefore blood pressure), in autonomic failure patients seem to have markedly reduced sympathetic output, this the peripheral effects of the drug become more manifest.

Interestingly, a number of patients with autonomic failure will be anemic. A landmark report by Hoeldtke and Streeten demonstrated that subcutaneous injections of erythropoietin while raising blood count will also produce dramatic increases in blood pressure[54]. This pressure effect seems to occur independent of the red cell effect, (but does appear to rise in parallel with blood counts)[55].

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[56]. 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[57].

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[58]. More detailed studies are ongoing.

It should be kept in mind, that in dysautonomic disorders (as opposed to the reflex syncopes), hypotensive syncope is but one aspect of a broader constellation of symptoms relating to a generalized state of 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.

Summary

Syncope in the elderly is a frequent, complex and potentially devastating problem. An increasingly important cause are disorders of autonomic nervous system function that allow for periods of sudden hypotension and bradycardia that may lead to loss of consciousness. A working knowledge of these disorders is important so as to provide adequate diagnosis and treatment. Ongoing research will help better define both the pathophysiology and clinical aspects of these disorders as well as uncovering enhanced diagnostic and treatment modalities.

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