**Neurally-mediated Syncope: An Overview and Approach**

JS Shah*, AK Gupta+, YY Lokhandwala**

This is the commonest form of neurocardiogenic syncope encountered in the emergency room. It is typically a disease of the young. Though generally considered benign, it may cause significant impairment of quality of life in some patients.

**Pathophysiology of vasovagal syncope**

The Bezold-Jarisch reflex has been incriminated for the vasodepressor and cardioinhibitory response seen in vasovagal syncope. By animal studies it has been shown that venous pooling leading to decrease in the end-diastolic volume and increase in ventricular inotropy. This leads to stimulation of the stretch receptors in the inferoposterior wall of the ventricular and increased afferent signals via the vagus. This leads to a reflex increase in the parasympathetic output and decrease in the sympathetic outflow leading to vasodepression and cardioinhibition. Thus resulting in hypotension and bradycardia leading to decreased cerebral perfusion and syncope.

Observations in transplant patient have led to the understanding that mechanisms other than Bezold-Jarisch reflex may also be responsible for vasovagal syncope. Emotional stress has led to the hypothesis that serotonin, adenosine, opioids and other CNS modulators may play a role in vasovagal syncope. It has been hypothesized that even in the same patient there may be different triggering mechanisms for the induction of vasovagal syncope. It has been suggested that cholinergic vasodilator nerves, which are active in the skeletal muscles, mediate the sympathetic changes. Role of nitric oxide has been hypothesized in the vasodilatory response, though this has been recently challenged.

**Symptomatology of vasovagal syncope**

Clinical history has a major role in the diagnosis of vasovagal syncope. Postural, situational and exercise-induced symptoms may be suggestive of vasovagal syncope. Emotional stress, stressful condition, and pain may trigger vasovagal syncope especially among the young. Other associated premonitory symptoms such as pallor, weakness, yawning, lightheadedness, nausea, diaphoresis, hyperventilation, blurred vision, decreased hearing etc. which carry the evidence of decreased systemic and cerebral perfusion may be present. The patients may soon learn that sitting down or lying down aborts syncope. The syncope event usually resolves in a matter of seconds to minutes. After the syncope, the patients may experience weakness but neurological and cognitive deficits are absent.

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Received: 10.6.2002; Revised: 18.6.2003; Accepted: 20.6.2003
Futility of various tests in diagnosis of neurocardiogenic syncope

In a review of the utility of EEG in a patient with syncope, Brenner concluded that EEG findings suggest cerebral hypoperfusion only and do not differentiate between vasovagal attack, cardiac arrhythmia and hypotension as the underlying cause of the same. CT scan and MRI are also largely useless as routine tests for syncope, the diagnostic yield being less than 1%. They are recommended only when there are symptoms or signs of brain disease.

The role of echocardiography among patient suspected to have a cardiac anatomy related cause of syncope is well established. On the other hand, unsuspected findings on echocardiography are reported in only 5-10% patients. The yield being similar to that of ECG. Hence, this expensive test is of no utility in unsuspected patients and hence cannot be recommended on routine basis, especially in those with neurocardiogenic syncope.

Exercise testing has definite utility in exertional syncope but not in neurally-mediated syncope. Post-exertional syncope is neurally-mediated but is appropriately diagnosed on tilt table test thus obviating the need for exercise stress test.

Tilt table test

This is carried out using a specially designed tilting table with a footboard. Initially the patient rests in the supine position for a period of about 15-30 minutes so as to stabilize the cardiovascular system. Then the patient is tilted in the vertical angle ranging from 60-90 degrees for a variable time period (15-45 minutes) and the hemodynamic changes are recorded. If the test fails to reproduce the syncopal attack, pharmacological agents are used and the test is repeated. These agents either augment or mediate the Bezold-Jarisch reflex and hence induce vasovagal syncope in a percentage of patients. Though isoproterenol is most commonly used, adenosine, nitroglycerin and edrophonium also produce comparable results. The protocols for the head up tilt table test vary from centre to centre and hence the sensitivity reported in the literature varies widely from 30-85%. Following the HUT guidelines set by the ACC the sensitivity of the test is around 65%. The specificity of HUT test has generally been reported to be between 80-90%. The use of pharmacological agents induces vasovagal syncope in 75% of the young patients with negative HUT test. The addition of pharmacological agents decreases the specificity to 80%. When performed according to the ACC guidelines, it yields 100% specificity for the test. It is also known that the changes in the hemodynamic response as well as induction of syncope during a HUT test vary depending on the physiologic susceptibility of the patient at the time of the test. Hence the reproducibility of the HUT is about 81% though it varies from 50-95% depending on the patient selection. Indications for HUT test include: recurrent syncopal episodes, single syncopal episode associated bodily injury, single syncopal episode in high-risk occupation. The test is contraindicated in those with critical coronary or cerebrovascular stenosis as well as in those with critical mitral stenosis and left ventricular outflow obstruction. Pregnant patients generally should not undergo HUT. Adverse effects during HUT include hypertensive crisis, chest pain, coronary vasospasm, tachyarrhythmias and rarely transient asystolic episodes (> 5 sec), which resolved spontaneously.

Vasovagal International Study Classification for Tilt-Induced Vasovagal Syncope

Type 1; Mixed: Heart rate increases with HUT and later decreases but remains about 40 beats/min (bpm) or is less than 40 bpm for less than 10 seconds and without asystole. The blood pressure may increase initially but decreases later on before the heart rate decreases.

Type 2A; Cardioinhibitory: Heart rate increases with HUT, then decreases to less than 40 bpm for more than 10 seconds or has asystole for > 3 sec. Blood pressure may increase initially but decreases before the heart rate decreases.

Type 2B; Cardioinhibitory: Heart rate increases initially; then decreases to less than 40 bpm for > 10 seconds or has asystole for > 3 sec. Blood pressure decreases to a hypotensive level only at or after the time at which heart decreases.

Type 3; Pure vasodepressor: Heart rate increases initially and decreases less than 10% from the peak value at the time of syncope. Blood pressure decreases to account for syncope.

Natural history of vasovagal syncope

It is known that among those with positive HUT test, the symptoms come in clusters. Each episode increases the probability of recurrence. Among those with recurrent episodes in a relatively short period of time, the chances of recurrence are high. But overall, only 28% of the patients with positive HUT test had recurrent episodes in 3-year follow up. Interestingly, the number of syncopal episodes in this study decreased from 0.3 per month before the clinical evaluation to 0.03 per month after the evaluation. This probably reflects the importance of patient reassurance, guiding the patient through the postural manipulation and avoidance of precipitating situations.

Treatment of vasovagal syncope

The natural history of the disease and lack of complete understanding of the trigger mechanisms have led to management approaches of this disease, which can largely be described as empirical. Patients with infrequent episodes especially those having prodromal symptoms need not be subjected to aggressive management. Meticulous attention to hydration and appropriate salt intake may keep the syncope at bay. Anticholinergics, beta blockers, disopyramide, adenosine receptor blocker, alpha agonists, selective serotonin reuptake inhibitors, mineralocorticoids, compression hose, and permanent pacemakers have been tried empirical and have been studied in the treatment of vasovagal syncope.
The Table 1 summarizes the available literature as to the effectiveness of these agents. Table 2 provides guidelines for treatment of vasovagal syncope.

**Table 1**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study</th>
<th>Sample</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midodrine</td>
<td>PCRT</td>
<td>16</td>
<td>Improved QOL, free duration</td>
</tr>
<tr>
<td>Etilefrine</td>
<td>MCRCT</td>
<td>126</td>
<td>No change in time/incidence of recurrence</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>PCRT</td>
<td>68</td>
<td>Decrease in recurrence</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>PCRT</td>
<td>21</td>
<td>No change in incidence of recurrence</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>OS</td>
<td>118</td>
<td>Only 10% had recurrent symptoms*</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>PCRT</td>
<td>54</td>
<td>Large benefit; premature termination of study*</td>
</tr>
</tbody>
</table>

* - Study had no control group; # - Study had small sample size and no control group; PCRT - Placebo controlled randomized trial; OS - Observational study; MCRCT - Multicentric randomized controlled trial; QOL - Quality of life

**Table 2 : Guidelines for treatment of vasovagal syncope**

<table>
<thead>
<tr>
<th>Infrequent episodes with prodrome</th>
<th>Adequate hydration and salt intake</th>
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<tbody>
<tr>
<td>Bezold Jarisch reflex as primary causes</td>
<td>Beta-blockers</td>
</tr>
<tr>
<td>Predominant vasodepressor response</td>
<td>Midodrine, fludrocortisone, compression hose</td>
</tr>
<tr>
<td>Resting bradycardia</td>
<td>Anticholinergic agents</td>
</tr>
<tr>
<td>Failure to above therapy pacemaker and rate smoothing features</td>
<td>Permanent dual chamber</td>
</tr>
</tbody>
</table>

**Tilt training**

In a study by Ector et al showed that tilt training has a positive effect on the symptomatology of neurocardiogenic syncope. Patients who are tilt-trained also had a negative tilt table test on follow-up. It has been suggested that reconditioning of baroreceptor or mechanoreceptor response may be underlying mechanism for this effect.22 The tilt training should be ideally started in the hospital setting and preferably in the presence of a relative. The patient should be advised to stand against a wall (with united ankles 15 cm from the wall) twice a day for a planned duration. The tilt training should be performed in a comfortable and safe environment to avoid the risk of physical trauma under the supervision of a family member. Initially, the patient should start with a short duration of five minutes and gradually by 10 minutes per day to a maximum of 40 minutes of training. The patients should continue this training for about 3-6 months.

**Primary Autonomic Failure Syndromes**

In contrast to the intermittent periods of hypotension seen in reflex syncope (in which patients are fairly asymptomatic between episodes), a second group of patients develop orthostatic intolerance resulting from a failure of the autonomic nervous system to function under normal circumstances. Assuming upright posture, the patient with autonomic failure is not able to make or maintain the gravity-mediated decline in venous return. This failure to adapt may be caused by a disturbance in the afferent or efferent (or both) limbs of the baroreflex or from diminished end-organ responsiveness to vasoconstrictive signals. When this failure is severe, classic orthostatic hypotension results. Many patients with autonomic nervous system failure develop a somewhat slower progressive decline in blood pressure (once referred to as delayed orthostatic hypotension). The longer these patients are upright, the more blood pools in the mesentery and lower extremities, and failure to compensate produces a progressive decline in blood pressure, leading ultimately to cerebral hypoperfusion and loss of consciousness. When this pattern is observed during tilt-table testing, it is referred to as a dysautonomic response.

**Orthostatic Hypotension**

Orthostatic hypotension is defined as a fall in blood pressure of over 20 mm Hg systolic, (or 10 mm Hg diastolic), on standing or during head-up tilt to at least 60 degrees,23 Orthostatic hypotension refers to the condition associated with abnormality of the autonomic nervous system. This could be related to a defect in the central control of the autonomic system, in which case other neurological deficiencies may be associated. The prevalence of this disease ranges from 6-30% in the older population. Low BMI, hypertension, Parkinson’s disease, CVA, CAD are associated with this disorder. Before making this diagnosis, it should be confirmed that the patient is not on antihypertensives, antidepressants or antipsychotics, which may lead to orthostatic hypotension.

**Causes of dysautonomia**

The condition is diagnosed in the clinic by measurement of the blood pressure once with the patient in the lying down position and then repeating it two minutes after the patient stands up. Lack of postural fall does not rule out the diagnosis and in the presence of other symptoms suggestive of postural hypotension/dysautonomia, further investigations should be carried out. Other associated symptoms for postural hypotension may include visual disturbance, cognitive dysfunction, paresthesias and muscle weakness associated with postural changes.24 The symptoms may or may not be present with every instance of postural changes. Certain conditions predispose patients to postural drop in the blood pressure such as: sudden changes in the posture, after prolonged recumbency, warm weather conditions, food and alcohol consumption, prolonged or intense exercise, increasing intrathoracic pressure by coughing, defeation and micturition. In patients with mild or moderate autonomic failure, it may be necessary to verify these events.24

**Signs**

Measuring blood pressure while lying and after two
minutes of standing often confirms a postural fall. Patients should be further evaluated with various autonomic function tests.

HUT plays a central role in the diagnosis of postural hypotension. Drugs that can interfere with the results of the test by causing hypotension (for e.g., levodopa, nitroglycerin) should be omitted before the test. In patients with postural hypotension, with the patient in the head up tilt at 60 degrees or more, the systolic blood pressure drops by more than 20mm Hg and/or the diastolic pressure falls to more than 10mm Hg. Valsalva maneuver, changes in the pressure and heart rates with respiratory cycles test the function of the sympathetic vasoconstrictor and cardiac parasympathetic function. Various studies have successfully demonstrated the utility of HUT in diagnosing dysautonomia. The sensitivity has ranged from 73% to 100%, with increased tilt for prolonged duration increasing the sensitivity.

Aim of treatment includes prevention of symptoms, fall and affording good quality of life. Both non-pharmacological and pharmacological modality of treatment could be used for the management of this disease. Postural management forms a key aspect to the management of this disease. Training the patient to avoid sudden postural changes especially in the morning, maneuvers that increase intrathoracic pressure, warm baths, exposure to warm weather, avoidance of vigorous exercise, avoidance of alcohol, etc. are the non-pharmacological methods of avoiding postural hypotension. The morning hypotension while getting up from the prolonged recumbency could be avoided by head up tilt during sleep at night. Postprandial hypotension could be significantly decreased in intensity by small frequent meals. Exercises such as swimming and rowing, which avoid vertical posture should be advocated. Support elastic bands may be useful but are poor tolerated. Increase in the blood volume by increased hydration and increased salt intake, should be tried.

Pharmacological treatments have been used for the management of this disease with some success. The first line therapy is fludrocortisone, used at night so as to reduce salt and water loss. Central cause of dysautonomia patient will benefit from ephedrine; a drug, which simulates norepinephrine, from which is deficient in these patients. In patients with peripheral causes of dysautonomia, sympathomimetic drug such as midodrine should be tried. Drugs such as octreotide have found utility in postprandial hypotension and should be used if this is the predominant symptom. Fluoxetine, indomethacin, flurbiprofen and various ergot derivatives have been used in this disorder but little evidence exists for their utility. In case of secondary dysautonomia, the treatment has to tailor to the primary cause of the disease. Diabetics need good glycemic control for the management of dysautonomia. In amyloidosis, fludrocortisone finds limited utility. In high spinal cord lesion, head up tilt at night and ephedrine would be useful. Patients with dopamine beta-hydroxylase deficiency, the ideal therapy is the prodrug L-threodihydroxyphenylserine, which converts to noradrenaline. Recently pacemaker devices have been investigated as the treatment modality in this condition. Both atrial and ventricular pacing have been shown to be effective in decreasing the disabling symptoms in this disease.

Prognosis: Patients with diastolic orthostatic hypotension one minute after the standing up and systolic orthostatic hypotension measured three minutes after standing up have increased long term vascular mortality.

Orthostatic hypotension related to diabetes: Autonomic disturbance following diabetes leads to orthostatic hypotension. The diagnosis is clinched by associated symptoms of dysautonomia in a diabetic patient. It starts of as an observation in the physicians office of decrease in blood pressure on standing up but progresses to mild giddiness or muzzy headedness. It may be associated with gray mistiness in vision and is associated with pain in the “coat hanger” distribution. The symptoms may follow administration of insulin and may be confused with hypoglycemic episodes. The management of glucose control helps in preventing the progress of the disease. Diabetics with orthostatic hypotension fare worst than their counterparts without this complication. The management of these patients is similar to that of patients with orthostatic hypotension without diabetes.

Other Chronic Autonomic Insufficiency

Pure autonomic failure (PAF) is a general state of autonomic failure present with disruptions in bladder, sudomotor, gastrointestinal, and sexual function that occur together with orthostatic hypotension. Although the exact cause of PAF remains enigmatic, some researchers have postulated that there is a degeneration of the peripheral postganglionic autonomic neurons. Although the condition is observed most frequently in older adults, it can affect patients of all ages, including children.

Shy and Dragger described a second form of chronic autonomic failure in 1960. In comparison with PAF, this condition is a much more severe and devastating disorder. Not only is profound orthostatic hypotension present, but also there is progressive rectal and urinary incontinence, loss of sweating, external ocular palsy, iris atrophy, rigidity, tremors, and impotence. Distal muscle wasting and muscle fasciculations may occur late in the disease. To identify this complex degenerative disorder more accurately, the American Autonomic Society has named this entity multiple system atrophy (MSA). Investigations have led to the division of MSA into three major clinical subtypes. The first group consists of patients who display parkinsonian features (also called the striatonigral degeneration form). The second subgroup consists of patients with cerebellar or pyramidal features (referred to as the cerebellar or olivopontocerebellar atrophy/degenerative form). A third subgroup displays a combination of features from both forms. It sometimes is difficult to distinguish the parkinsonian form of MSA from classical idiopathic Parkinson’s disease.

Although the average age of onset of MSA is in 50s to 70s, there are rare patients in whom the disease may appear in the late 30s.
**Postural Orthostatic Tachycardia Syndrome (POTS)**

Also known as orthostatic intolerance, it is commonly a disorder of young women. It is defined as long standing reproducible symptoms of inadequate cerebral perfusion in assumption of upright posture with insignificant change in the blood pressure but significantly elevated heart rate (> 30 bpm) in absence of medications, dehydration, prolonged bed rest, neuropathy or substantial weight loss. It has predominant female preponderance (5:1) and generally considered a disease of the young (14-40 years). This disorder is associated with other diseases such as mitral valve prolapse, inappropriate sinus tachycardia, chronic fatigue syndrome, pseudopheochromocytoma, etc. It is generally thought to be due to abnormal withdrawal of the cardiac vagal input.

**Etiology**: This disease generally follows viral gastroenteritis or viral illness with flu-like or mononucleosis-like symptoms. This has led to the autoimmune hypothesis for this disease. Primary hypovolemia or exaggerated venous pooling seems to be one of the possible etiologies of this disease. Impaired renin-angiotensins system or renal denervation as the cause of this primary hypovolemia has been proposed. Circulating vasodilators such as bradykinin, histamine and ANF have been proposed to be causative factors for POTS but there is a lack of substantial evidence supporting the same.

Estrogen-mediated change in the blood volume may explain the predominance of these symptoms in premenopausal women. A defect in the norepinephrine transporter molecule resulting in decreased synaptic clearance of norepinephrine is a candidate hypothesis as the etiology for this condition.

**Symptoms**: These patients generally complain of lightheadedness, dizziness, palpitation, exercise intolerance, headache, near-syncope, nausea, etc.

**Use of HUT in patients in POTS**: Studies have shown 100% sensitivity of HUT for the diagnosis of POTS.

**Treatment**: Since there is a consistent finding of tachycardia associated with symptoms, beta-blockers have been successfully used in a large proportion of patients of POTS. Alpha-1 adrenergic receptors such as clonidine and ANF have also been used. Midodrine has been helpful in a small proportion of patients. Alpha-1 adrenergic receptors such as clonidine and ANF have also been used. Midodrine has been helpful in a small proportion of patients. Fludrocortisone can be used to improve the venous blood pumping by the muscles can also be tried. Resistance training to improve the venous blood pumping by the muscles can also be tried.

**REFERENCES**


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**Announcement**

Dr. SR Naik Memorial Workshop on Scientific Communication will be held at the Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGI), Lucknow on August 30-31, 2003.

The workshop is aimed at postgraduate medical students, young faculty members in medical institutions and scientists in biomedical research institutions and will focus on various aspects of biomedical writing, publishing papers in journals, presentations (poster and oral) at scientific conferences.

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