Vasovagal Syncope: An Enigma

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Abstract

Syncope is a common clinical problem affecting 3.5% of the general population. About 40% of cases remain undiagnosed and 30% experience recurrent episodes. The article presents an update on the etiopathogenesis and theories of syncope.

The pathophysiology of syncope remains elusive. Lewis introduced the term “vasovagal” implying therein that both vasodilatation and bradycardia were involved in the response. Individuals susceptible are unable to maintain adaptive neurocardiovascular responses to upright posture for prolonged periods of time. A complex hemodynamic response develops, with marked hypotension, bradycardia and a loss of consciousness. The “empty ventricle theory”, first proposed by Sharpey-Schafer, widely accepted for several years, has been challenged and various other aspects of the vasovagal response have now been studied and implicated in contributing to the episode of unconsciousness. These include baroreflex dysfunction, neuroendocrine responses, role of respiration and cerebrovascular dysfunction.

An episode of syncope represents an episode of unconsciousness. Even a single episode of unconsciousness in the present day lifestyle is a source of distress to a patient, warranting a workup and diagnosis. The etiopathogenesis of the simple faint is complex and we may well be dealing with a constellation of responses and a more detailed classification than hitherto imagined.

INTRODUCTION

Syncope (Greek, Synkope, meaning cessation, pause) is a transient loss of consciousness and postural tone with spontaneous recovery and no neurological sequelae. Syncope is a common clinical problem that affects up to 3.5% of the general population, in 40% of cases the exact cause of syncope remains elusive and 30% of affected patients experience recurrent episodes.

Syncope is caused by a decrease in perfusion to the reticular activating system, the neuronal network in the brainstem which supports consciousness. It most often occurs while standing. In the vertical position blood pressure and blood flow to the brain are critically dependent on a normally functioning cardiovascular system and abnormalities in cardiac output or in autonomic reflexes controlling blood pressure can cause syncope. It may also be induced by hypocapnia, which causes cerebral vasoconstriction leading to a reduction in cerebral blood flow. In addition as the brain is enclosed in the nondistensible cranium, maneuvers that raise intracranial tension may suddenly reduce cerebral blood flow, leading to loss in consciousness.

A syncopal episode represents an episode of unconsciousness, which may be due to a benign condition with no prognostic implications, or on the other hand may be of a more sinister nature indicating life-threatening conditions like cardiac disease. Appropriate diagnosis of an episode of syncope often represents a significant diagnostic challenge, as syncope being a sporadic and infrequent event rarely lends the opportunity for the physician to examine a patient or obtain an ECG during an actual episode. The diagnosis arrived at is therefore usually a presumptive one. Recurrence of the syncope in such a patient adds to the confusion, as it is often unclear as to whether the recurrence was due to a failure to identify the cause of syncope or due to ineffective treatment of a correctly identified cause.

Further complicating appropriate diagnosis, some patients may present with presyncope, an often ill-defined transient episode of altered consciousness accompanied with features of autonomic abnormality. Increased sympathetic activity may present with features such as diaphoresis, palpitations, piloerection (goosebumps), pallor and vasoconstriction. The peculiar combination of diaphoresis and vasoconstriction may give the typical sensation of cold sweat. Vagal activation may lead to abdominal discomfort, nausea and vomiting.

Although there are conflicting views on this, even a single episode of unconsciousness in the present day complex lifestyle is a source of extreme distress to a patient and
ETIOLOGICAL FACTORS IN SYNCOPE

Syncope results from three basic haemodynamic abnormalities (Table 1).
1. A fall in systemic blood pressure, which usually occurs in the standing position (orthostatic hypotension) and is mainly due to ineffective control of peripheral vascular resistance;
2. An acute decrease in cardiac output;
3. An acute increase in cerebrovascular resistance.

<table>
<thead>
<tr>
<th>Table 1: Causes of syncope</th>
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<tr>
<td><strong>Orthostatic hypotension</strong></td>
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<td>Drugs: antihypertensives, dopamine agonists.</td>
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<td>Neurally mediated syncopal syndromes (vasovagal or vasodepressor syncope)</td>
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<td>-carotid sinus syncope</td>
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<td>-micturition or gastrointestinal syncope</td>
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<td>-glossopharyngeal or trigeminal syncope</td>
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<td>-ventricular, neurocardiogenic syncope</td>
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<td>-exercise syncope in aortic stenosis</td>
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<td>-cardiovascular deconditioning due to prolonged bed rest</td>
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<td>-exposure to microgravity</td>
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<td>Chronic autonomic failure syndromes</td>
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<td>Acute decrease in cardiac output</td>
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<td>Cardiac arrhythmias</td>
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<td>Obstruction to flow (aortic stenosis, pulmonary embolism)</td>
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<td>Myocardial infarction</td>
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<tr>
<td>Acute increase in cerebrovascular resistance</td>
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<tr>
<td>Cerebral vasoconstriction</td>
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<td>-hyperventilation</td>
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<td>-panic attack</td>
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<td>Increase in intracranial pressure</td>
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<td>-cough syncope</td>
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<td>-trumpet player syncope</td>
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<td>-craniocervical malformations</td>
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PATHOPHYSIOLOGY OF SYNCOPE

The vasodepressor response may be triggered by a myriad of stimuli, including orthostatic stress, emotional stress, relative or absolute blood loss, severe pain or a sudden rise in intracranial pressure as occurs with cough or micturition. Elucidating the mechanisms responsible for the control of arterial blood pressure has intrigued physiologists and physicians for more than a century. In the 17th century Hunter inadvertently reported the first description of vasodepressor syncope when he wrote: “I bled a lady but she fainted and while she continued in the fit the color of the blood that came from the vein was a fine scarlet. The circulation was very languid”. It is suggested that in this Hunter noticed the effects of vasodilatation during syncope. In the late 19th century Hill suggested that emotional syncope results from the withdrawal of vasomotor neural traffic. In 1932, Lewis first introduced the term “vasovagal” implying therein that both vasodilatation and bradycardia were involved in the response. He demonstrated that the bradycardia was vagally mediated by blocking the response with atropine. He further demonstrated in this work that hypotension persisted despite blocking the vagal response. It is accepted universally now that neurocardiogenic syncope represents an abnormal autonomic response with components of both bradycardia and hypotension. The most common and most easily simulated trigger for syncope is the erect position and the physiology of the neuroendocrine reflexes in “standing” are basic to the understanding the circumstances in which syncope results.

NEUROENDOCRINE RESPONSES TO ERECT POSTURE

Neural mechanisms responsible for the control of blood pressure with change in posture are modulated by arterial and cardiopulmonary baroreceptors that regulate arterial pressure and vascular tone. Aortic and carotid sinus baroreceptor discharge is directly related to stretching caused by arterial pressure. These receptors send afferent impulses to the brainstem that inhibit efferent sympathetic cardiac and peripheral circulation activity and increase cardiac vagal activity. Nerve impulses from the baroreceptors are carried to the nucleus tractus solitarius via the myelinated and unmyelinated fibres of the vagus and glossopharyngeal nerves. Axons from the tractus solitarius in turn project to the caudal ventral lateral medulla, which further send inhibitory fibres to the sympathethoexcitatory neurons in the rostral ventral lateral medulla. In addition there are fibres from the tractus solitarius to the nucleus ambiguous that mediate parasympathetic outflow to the heart. Abrupt fall in arterial blood pressure results in an increase in the efferent sympathetic nerve traffic and vagal withdrawal. In contrast, when the arterial pressure rises, these receptors increase their firing rate, resulting in sympathetic withdrawal and bradycardia mediated by increased cardiac vagal activity. This tightly regulated reflex serves as a buffer for sudden changes in blood pressure. Under normal circumstances, this reflex invariably ensures adequate cerebral perfusion with changes in posture.

Volume control in orthostatic stress is also of vital importance and is regulated by a complex neuroendocrine regulation of water and salt balance. In the vertical position, cardiac output falls because gravitational forces shift about one-third of the blood volume to the lower part of the body thus reducing venous return to the heart. Blood pressure at the level of the carotid sinus also decreases because the hydrostatic pressure in the vessels above the heart falls. The dual stimuli of the low thoracic volume and low arterial pressure initiate the rapid autonomic reflex that increases the
sympathetic outflow. Increased sympathetic renal nerve activity induces tubular sodium reabsorption directly and indirectly by stimulating the secretion of renin from the juxtaglomerular apparatus. Renin and converting enzyme convert circulating angiotensinogen into angiotensin II, which is a vasoconstrictor and induces the secretion of aldosterone from the adrenal cortex. Aldosterone retains sodium and increases the extracellular fluid volume. Furthermore, unloading of the atrial baroreceptors in the standing position releases antidiuretic hormone (ADH) from the posterior pituitary. ADH in turn acts on the vascular smooth muscle causing vasoconstriction and on the kidney retaining water and further expanding the extracellular fluid volume.

Atrial natriuretic factor (ANF) a circulating vasoactive peptide also contributes to the maintenance of orthostatic blood pressure. ANF is secreted from the atrial myocytes when the right atrial pressure increases. The factor produces natriuresis, relaxation of vascular smooth muscle tone, and inhibition of renin and aldosterone secretions. In the upright posture the ANF secretions decrease inducing vasoconstriction and an expansion of the extracellular fluid volume. Two other factors, endothelin and nitric oxide, may also contribute to the maintenance of orthostatic blood pressure but their mechanism of secretion and roles are as yet not clearly defined.9

The exact pathophysiology of syncope still remains elusive. Individuals susceptible to vasovagal syncope are unable to maintain the adaptive neurocardiovascular response to upright posture for prolonged periods of time. In all cases there develops a complex hemodynamic response with marked hypotension, variable bradycardia and a loss of consciousness. The initiating events for syncope are still mired in controversy. One study suggests that an abnormality in the peripheral veins may result in exaggerated orthostatic pooling. Two other factors, endothelin and nitric oxide, may also contribute to the maintenance of orthostatic blood pressure but their mechanism of secretion and roles are as yet not clearly defined.9

The vigorous contractions of the hypovolemic ventricle are the result of increased myocardial contractility in a setting of ventricular hypovolemia large pressure gradients are evoked by the contractions of the ventricular muscle on an empty chamber. The vigorous contractions of the hypovolemic ventricle are thought to stimulate mechanosensitive C unmyelinated afferents from the left ventricle. This in turn is thought to trigger an inhibitory response similar to the Bezold Zarich reflex resulting in hypotension and bradycardia.3,14,15

Various experimental inputs over the last decade have challenged the validity of this theory. A significant one has been that in humans it has been seen that syncope can be evoked in patients with heart transplants and with totally denervated hearts.16 It may in turn be proposed that receptors in other regions of the cardiovascular system may be excited by hypovolemia, but evidence of such increased afferent traffic under these circumstances is as yet not available.

In recent studies it has also been seen that there are no significant decreases in cardiac chamber size or volume as measured by echocardiography during tilt, at the time of presyncope or syncope.17

**Baroreflex Dysfunction Theory**

This theory results from the reports of several workers in the field who have found one or the other type of baroreceptor dysfunction resulting in the inability to sense or compensate for changes in gravitational forces in subjects of syncope. Sympathetic withdrawal in may result from a paradoxical activation of baroreceptors and some studies have shown the resetting of baroreceptors leading to inhibition of sympathetics, in severe hemorrhage and at very low pressures. This theory is further supported by the observation that the inhibition of muscle sympathetic nerve activity declines with continued electrical stimulation of the carotid sinus nerve in humans, suggesting a resetting of baroreceptors.18

**Neuro-endocrine Response Theory**

A recent study by Goldstein and his colleagues gives strong experimental evidence that, during an episode of syncope in a susceptible patient, dissociation between the sympathetic noradrenergic and adrenomedullary responses seems to develop. There is an inappropriate increase in epinephrine secretion, and a decrease in norepinephrine. Under these circumstances, epinephrine may produce unopposed peripheral vasodilatation, resulting in severe hypotension.15

Another group has suggested the probable role of serotonin in syncope. They found that selective serotonin reuptake inhibitors were effective in the treatment of
neurocardiogenic syncope and postulated that serotonin surges may precede syncope in humans and the inhibitors reduce the sensitivity of receptors and thus prevent syncope. This theory has little experimental proof and the potential involvement of serotonin is found to be highly speculative. 19

Other diverse neurohumoral agents implicated in the pathophysiology of syncope include renin, vasopressin b endorphin, endothelin and nitric oxide. Experimental proof to validate their role is still limited and restricted by methodological limitations as it is very difficult to quantitatively estimate these agents at the point of a syncope event. 20

**Role of respiration**

Hyperventilation and yawning often accompany an episode of syncope. Although increase in ventilation may help to dephase the onset of syncope in some cases, it also serves to enhance oscillations of blood pressure. 21 In addition yawning and altered breathing patterns may result in inhibition of sympathetic nerve activity and the accompanying hypocapnia enhances the vasodepressor response. 22

**Cerebrovascular Dysfunction**

Hypotension and bradycardia of the syncope syndrome are essentially manifestations of autonomic dysfunction, but loss of consciousness occurring during syncope would be due to cerebral hypoperfusion. More than 35 years ago some authors indicated that patients of syncope exhibited an abnormal cerebrovascular response. 23 This view is supported by a recent study that investigated the dynamic cerebral autoregulatory responses in the face of rapid changes in systemic arterial pressure found that cerebral vascular autoregulation is impaired in cases of recurrent vasovagal syncope. 24 Indeed abnormalities in cerebrovascular homeostasis may play a central role in the pathogenesis of neurally mediated syncope.

**Conclusion**

The exact mechanisms in the development of syncope remain unresolved. In patients of recurrent syncope, alterations in cerebrovascular homeostasis, baroreflex activity or neurohumoral secretions or reactivity, may each play roles to a greater or lesser extent. Delineating these responses, would help in appropriate pharmacological and lifestyle interventions for patient's syncope. With further research in the field, as is with the blind man and the elephant, we may well be dealing with a constellation of responses and the simple faint may find itself a more complex classification than hitherto imagined.

**References**