The pathophysiology of common causes of syncope

W Arthur, G C Kaye

Syncope is a transient loss of consciousness secondary to inadequate cerebral perfusion with oxygenated blood. It is a common medical problem, accounting for around 5% of acute medical admissions and 3% of emergency department visits. Syncope secondary to cardiac causes carries the worst prognosis, with a one year mortality rate of 20–30%. An understanding of the events preceding syncope is essential if the correct diagnostic strategy is to be implemented.

General pathophysiological concepts

A state of consciousness is maintained by adequate cerebral blood flow. Cerebral vascular autoregulation ensures that the cerebral blood flow is kept within a narrow range, independent of the underlying systemic blood pressure. In a young healthy adult the systolic blood pressure may fall to 70 mm Hg without significant cerebral ischaemia. Elderly people and those with chronic hypertension are susceptible to relatively small falls in systemic blood pressure, leading to an increased incidence of syncope in this population.

The term “vasovagal” as applied to syncope has been used since the early 1900s and has become synonymous with the common “faint”. Early studies found that vasovagal syncope was the most common cause of fainting, being found in 58% of patients who had experienced this symptom. As our understanding of human neuroautonomic regulation has evolved it has become apparent that the vasovagal episode, although the most common, is one of a number of neurally mediated syncope syndromes.

Neurally mediated syncopal syndromes

Neurally mediated syncope can be classified into several distinct syndromes (box 1). These are all associated with acute vasodilatation of the arterial and venous beds and relative or absolute bradycardia. All of the neurally mediated syncopal syndromes involve an inappropriate reflex with afferent, central, and efferent pathways. During tilt table testing, the triggers for vasovagal syncope are thought to arise from the heart. As a result, the term “neurocardiogenic syncope” has been used to define one of the commonest responses found during tilt testing (fig 1).
NEUROCARDIOGENIC SYNCOPE

In order to maintain adequate cerebral blood flow in the upright position, man has evolved a series of autonomic reflexes. On standing, 300 to 800 ml of blood shift from the thorax to the lower extremities. This lowers the venous return and hence the cardiac output. Normally this leads to reduced stimulation of baroreceptors in the carotid sinus and aortic arch and mechanoreceptors (vagal C fibres) in the wall of the left ventricle. These receptors inhibit the brain stem neurones responsible for sympathetic stimulation; they also promote the neurones in charge of parasympathetic drive. The end result is increased sympathetic tone and maintenance of the blood pressure. Conversely a rise in blood pressure or intravascular volume increases baroreceptor and mechanoreceptor output, which leads to sympathetic withdrawal and parasympathetic stimulation.

It is thought that the mechanoreceptors in the left ventricle are not only innervated by stretch but also by vigorous and forceful systolic contraction. In patients with neurocardiogenic syncope, overzealous left ventricular contraction occurs in response to reduced venous return. Hence the afferent signals from the left ventricle override the baroreceptor responses, leading to an inappropriate decrease in sympathetic tone and an increase in parasympathetic (vagal) tone. Paradoxically the clinical picture is one of sudden hypotension reflecting diminished sympathetic vasoconstrictor tone accompanied by vagally induced inappropriate bradycardia.

The other forms of neurally mediated syncope share with neurocardiogenic syncope a triggering event stimulating adrenergic tone, followed by a clinical prodrome of vagal overactivation and then sympathetic withdrawal. In the case of the emotionally induced vasovagal faint, higher cortical sites are the predominant triggers of the afferent limb of the reflex arc, which result in increased sympathetic nervous system stimulation. This is then followed by the presyncopal or aura phase characterised by diaphoresis, epigastric discomfort, dizziness/vertigo, and nausea. These prodromal symptoms are induced by the increased parasympathetic tone. They may last anywhere from less than one second to several minutes. These events proceed to syncope unless the subject lies supine or removes the triggering stimulus. The lack of warning signs does not exclude the possibility of neurocardiogenic syncope; a “malignant” form has been described in which there is a rapid deterioration in the haemodynamic state.

The haemodynamic responses evoked in neurally mediated syncope may be predominantly vasodepressor, cardioinhibitory, or mixed. The mixed response is most common, although the vasodepressor component of the mixed response appears to be the dominant factor in up to 85% of affected patients. In the malignant type of neurocardiogenic syncope the cardioinhibitory component is pronounced.

CAROTID SINUS HYPERSENSITIVITY AND CAROTID SINUS SYNOCOPE

Pressure exerted on the internal carotid artery just above the bifurcation of the common carotid artery leads to slowing of the sinus rate and impaired atrioventricular node conductivity. This is a normal response resulting from stimulation of the carotid sinus. In carotid sinus hypersensitivity this reflex is exaggerated and is described in three forms: cardioinhibitory, giving rise to asystole of three seconds or more; vasodepressor, leading to a fall in systolic blood pressure of 50 mm Hg or more; or the response may be mixed. Studies have shown that 5–25% of asymptomatic older men have carotid sinus hypersensitivity. At the same time only 5–20% of patients showing carotid sinus hypersensitivity actually have syncope of carotid sinus origin. Diagnosis of carotid sinus syncope requires that spontaneous symptoms of presyncope or syncope be reproduced by carotid sinus massage.

Despite the fact that the cardioinhibitory response is dominant, a vasodepressor component of the syndrome can be elicited by carotid sinus massage in the majority of patients with carotid sinus syncope. The vasodepressor reflex in these patients peaks at the end of carotid sinus massage and may last for up to two minutes. This is in contrast to the cardioinhibitory response, in which the maximum asystolic pause normally occurs within a few beats of the application of carotid sinus massage.

Orthostatic syncope and dysautonomic disturbances of blood pressure control

Orthostatic syncope results from the venous pooling of blood that occurs upon changing from a supine to an upright position. There is no vagal hyperactivity associated with this venous pooling and this distinguishes orthostatic syncope from neurocardiogenic syncope. Orthostatic syncope may be the consequence of transient or chronic volume depletion or abnormal vasomotor compensatory mechanisms. Owing to a relative lack of intravascular volume, the patient’s blood pressure does not become sufficiently increased regardless of the increase in heart rate. Actual or relative central vascular volume depletion may occur because of gastrointestinal bleeding, dehydration, excessive diuresis, or the use of vasodilating drugs.

Following change in posture to the upright position, baroreceptors provoke an increase in medullary sympathetic outflow. This leads to vasoconstriction of the systemic resistance vessels and the splanchnic capacitance vessels. Compensation for continued orthostatic stress depends principally on the arterial baroreceptors. Disorders of abnormal autonomic vasomotor control leading to orthostatic hypotension may be primary or more commonly secondary. Primary pure autonomic failure and multiple system atrophy are both characterised by autonomic dysfunction, where the patient is unable to produce the appropriate vasomotor response following baroreceptor stimulation. Secondary autonomic disturbances leading to
Cardiac arrhythmias, paraneoplastic syndromes, myocardial infarction, and pro-thrombotic states are among the most common causes of syncope. Arrhythmias due to poor left ventricular function, whatever the mechanism, are a major cause of syncope and sudden death. Other causes of syncope include exertional hypokinesis, neurocardiogenic syncope, drug-induced syncope, and systemic disorders such as hypothyroidism, pheochromocytoma, and diabetes mellitus.

ARRHYTHMIC SYCONE

Rhythm disturbances are among the most frequent causes of syncope. Atrial tachyarrhythmias may cause syncope by disturbing cardiac output and hence blood pressure maintenance because of fixed mechanical obstruction. Cardiac conduction system disease may represent acute or long standing cardiovascular causes of syncope are relatively rare, such as left atrial myxoma, severe mitral stenosis, or prosthetic valve dysfunction.

Box 2: Possible causes of syncope in aortic stenosis

- Inadequate increase in cardiac output and hence blood pressure maintenance because of fixed mechanical obstruction
- Arrhythmias
- Raised left ventricular systolic pressure giving rise to mechanoreceptor stimulation and hence neurally mediated syncope
- Concurrent degenerative disease of the atrioventricular node and His bundle leading to bradyarrhythmias
- Atrial tachyarrhythmias may substantially reduce ejection fraction in those with severe diastolic dysfunction
Common causes of syncope

Summary points
- The commonest form of syncope, the “vasovagal” faint, is associated with a good prognosis.
- Elderly people are susceptible to acute changes in cerebral blood flow, predisposing them to syncope.
- Syncope in the presence of structural heart disease and a low left ventricular ejection fraction is associated with a high mortality rate.

Neurological and psychiatric diseases
In the absence of accompanying focal neurological symptoms and signs, syncope from cerebrovascular disease is rare. Transient ischemic attacks caused by vertebrobasilar insufficiency may cause syncope. Those affected tend to be elderly men with ischemic heart disease. Concurrent neurological symptoms include mainly vertigo, ataxia, or sensory disturbances. Transcranial Doppler ultrasonography has been used during head up tilt testing to demonstrate cerebral vasoinconstriction associated with syncope that precedes, or even occurs in the absence of, systemic hypotension. This phenomenon has been termed cerebral syncope.

Distinguishing seizures from syncope can be difficult, especially if a patient experiences “convulsive syncope.” Convulsive movements, similar to tonic-clonic seizure activity, can occasionally result from cerebral hypoxia secondary to cerebral hypoperfusion. While neurally mediated syncope may mimic seizure-like activity, it should also be acknowledged that seizure foci in certain cerebral sites (particularly the temporal lobe) may be the source of apparent neurally mediated syncopal events. Localised seizure activity may initiate the reflex arc previously described, leading to hypotension and bradycardia.

The prevalence of psychiatric illness in patients with syncope of unknown origin is around 24%. Hyperventilation, particularly in panic disorder, leads to hypocapnia, causing a transient increase in cerebrovascular resistance coupled with simultaneous peripheral vasodilatation. Vasovagal syncope can be caused by acute stress or fear and is therefore implicated in anxiety, panic, and major depressive disorders. Certain individuals continue to have recurrent unexplained syncope despite thorough investigation. Some patients may actually experience syncope during tilt testing, with no measurable change in blood pressure, heart rate, EEG pattern, or transcranial blood flow. This finding has been termed “psychogenic syncope” and is believed to be a somatoform disorder.