

REVIEW ARTICLE

Symptoms and signs of syncope: a review of the link between physiology and clinical clues

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Detailed history taking is of paramount importance to establish a reliable diagnosis in patients with transient loss of consciousness. In this article the clinical symptoms and signs of the successive phases of a syncopal episode are reviewed. A failure of the systemic circulation to perfuse the brain sufficiently results in a stereotyped progression of neurological symptoms and signs culminating in loss of consciousness; when transient, this is syncope. Prior to loss of consciousness the affected individual tends to exhibit unclear thinking, followed by fixation of the eyes in the midline and a 'frozen' appearance. Narrowing of the field of vision with loss of colour vision ('greying' out) and finally a complete loss of vision (hence 'blacking' out) occurs. Hearing loss may occur following loss of vision. This process may take as little as ~7 s in cases of sudden complete circulatory arrest (e.g. abrupt asystole), but in other circumstances it may take longer depending on the rate and depth of cerebral hypoperfusion. Complete loss of consciousness occurs with the 'turning up' of the eyeballs. Profound cerebral hypoperfusion may be accompanied by myoclonic jerks.

Keywords: blood pressure; cerebral blood flow; syncope; reflex; vasovagal

Abbreviations: TLOC = transient loss of consciousness; EEG = electroencephalogram

Introduction

Detailed history taking is essential to establish a diagnosis in patients with transient loss of consciousness (TLOC); in particular to distinguish syncope from epilepsy (Hoefnagels *et al.*, 1991; Sheldon *et al.*, 2002; Thijs *et al.*, 2008b). In this context, TLOC is the term used to describe a short-lived transient loss of consciousness with spontaneous recovery; and syncope is defined as a

transient loss of consciousness due to cerebral hypoperfusion (Brignole *et al.*, 2004; Thijs *et al.*, 2004). Syncope is the subject of this review.

Comprehensive medical history taking helps to distinguish the various forms of syncope. Obtaining diagnostic clues requires assessing as many events as possible in detail to search for patterns and common features (Colman *et al.*, 2004). The circumstances immediately prior to the attack often suggest a specific

aetiology in syncope, much more so than in epilepsy. Obtaining a sequential record of details, beginning with the setting of the events, any provocations or triggers, the clinical symptoms and signs of the prodromal phase, progressing through the period of actual unconsciousness (necessitating eyewitness descriptions), up to and including the recovery phase are all crucial elements of the interview (Weiss, 1935; Sharpey-Schafer, 1956; Gastaut, 1974; Stephenson, 1990; Thijs *et al.*, 2008b).

This review outlines the symptoms and signs that may occur in these successive phases of a syncopal episode. Our aim is to review the link between physiology and clinical clues.

Before doing so, the main forms of spontaneous syncope relevant for this review will be discussed briefly with a focus on pathophysiology. Next, the various laboratory approaches used to evoke syncope will be discussed, as these are the source of knowledge regarding haemodynamic measurements, precise recordings and the exact timing of events. The succession of events during syncope will then be reviewed using data obtained in the laboratory as well as through history taking.

Types of spontaneous syncope

Cardiac syncope

There are two causes of cardiac syncope: arrhythmia and structural cardiac disease, of which aortic stenosis is a classical example. In both cases a decrease in cardiac output is responsible for syncope. Most clinical observations regarding cardiac syncope deal with tachy- or brady-arrhythmia (Scherf and Bornemann, 1970; Aminoff *et al.*, 1988; Calkins *et al.*, 1995). Abrupt syncope caused by asystole with intermittent atrioventricular block has in the past been commonly termed a Stokes-Adams attack. Other arrhythmias that can cause a sudden decrease in cardiac output such as sino-atrial block and malignant ventricular tachycardia produce similar attacks. During cardiac standstill blood will continue to flow as long as there is a gradient of pressure from the aorta through the greater and lesser circulation to the left atrium and ventricle. As asystole continues, the pressure

throughout the still intact vascular bed approaches a uniform static pressure of $\sim 10\text{--}20$ mm Hg (Fig. 1) (Dowling *et al.*, 1952; Barlow and Howarth, 1953).

Reflex syncope

Reflex syncope (synonym: neutrally mediated syncope; Brignole *et al.*, 2004) refers to a group of conditions in which cardiovascular effector mechanisms that are normally useful in controlling the circulation become overactive, resulting in vasodilatation and/or bradycardia. The outcome is a fall of arterial blood pressure and cerebral perfusion (Hainsworth, 2004). A prerequisite for reflex syncope is therefore that the autonomic nervous system is functionally intact. Classical examples are 'vasovagal' syncope, triggered by pain or emotions, as well as through orthostatic stress (Fig. 2) (van Lieshout *et al.*, 1991); spontaneous carotid sinus syncope is another classical example of reflex syncope (Weiss and Baker, 1933; Kenny and Traynor, 1991). Apart from these reflex effects, additional physical factors play a role in the occurrence of reflex syncope (Sharpey-Schafer, 1956; Wayne, 1961; Johnson *et al.*, 1984). Examples of contributory factors include patient-related circumstances such as straining (e.g. defaecation syncope, trumpet blower's syncope), but also external environmental physical factors such as heat exposure.

Syncope due to orthostatic hypotension: autonomic failure

In terms of cardiovascular system control, autonomic failure may be defined as the inability of the autonomic nervous system to adapt to the demands of stress (e.g. upright posture, exercise, extremes of temperature etc.). The most common of these is an inadequacy of response to upright posture. Defective vasoconstriction and excessive pooling of venous blood then result in orthostatic hypotension (Smit *et al.*, 1999). Medications are a frequent cause of inadequate autonomic control, but structural autonomic damage in the context of neurodegenerative diseases (primary autonomic failure) and systemic diseases such as diabetes

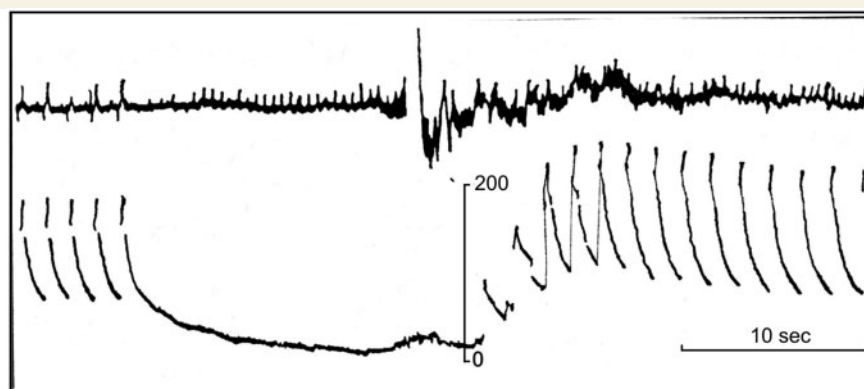


Figure 1 Effects of blood pressure during a Stokes-Adams attack. Above: Lead II of the electrocardiogram. Convulsive movements produced interference with the record after 16 s asystole. Below: Continuous brachial artery pressure record. Note overshoot of blood pressure during the recovery. Time (top) in seconds. Calibration in mm Hg. Taken with permission from Barlow and Howarth, 1953.

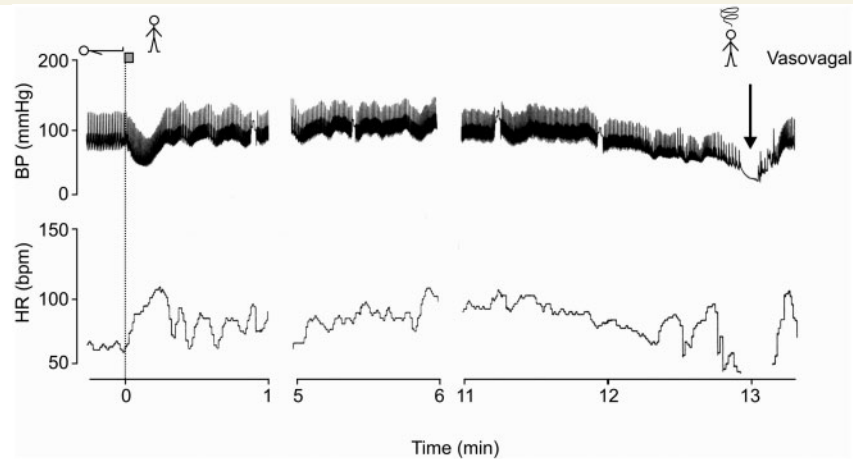


Figure 2 Vasovagal syncope in a healthy 22-year-old male subject. Note normal initial heart rate and blood pressure response and marked increase in heart rate after 6 min standing. After 11–12 min standing, blood pressure and heart rate decrease to very low values ending in a faint; the period when heart rate drops to values below 50 beats/min represents a period of asystole of 7 s. On lying down, heart rate and blood pressure recover quickly, but blood pressure does not overshoot. Blood pressure was measured with a Finapres device. Taken with permission from van Lieshout *et al.*, 1991.

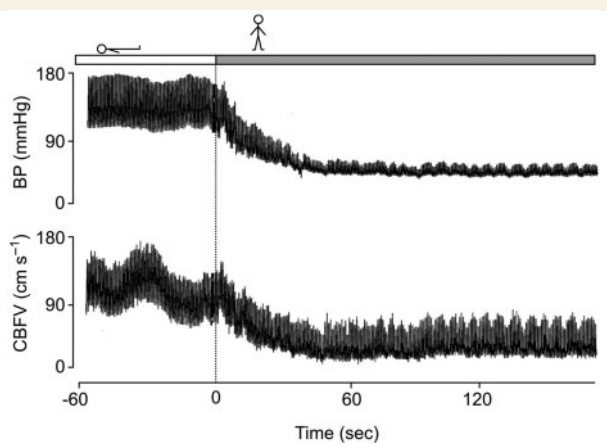


Figure 3 Blood Pressure and cerebral blood flow velocity in autonomic failure. Changes in finger blood pressure and cerebral blood flow in the medial cerebral artery in a 54-year-old patient with pure autonomic failure. Despite the very low blood pressure the patient experienced no symptoms (M.P. Harms and W. Wieling, unpublished results).

mellitus (secondary autonomic failure), are also important considerations. In these settings, apart from upright posture alone, failure of autonomic response to exercise (particularly standing still after cessation of exercise, so-called post-exercise hypotension) and inadequate response after a heavy meal (post-prandial hypotension) may trigger syncope in patients with autonomic failure.

In orthostatic hypotension, blood pressure classically drops relatively quickly directly upon standing, followed by a slower decrease (Fig. 3). Blood pressure in orthostatic hypotension approaches a stable level after a variable time, ranging from ~30 s in some patients to many minutes in others. Note that the final stable level need not be low enough to cause any symptoms.

Laboratory assessment of syncope

The various approaches to induce syncope can be divided in those with an abrupt and those with a more gradual onset (Table 1).

Fainting lark

The 'fainting lark' classically consists of squatting with the knees fully bent while over-breathing by taking ~20 deep breaths relatively rapidly. The subject then stands up suddenly and performs a forced expiration against a closed glottis (Fig. 4). As such the 'fainting lark' involves a combination of many factors: hyperventilation causes peripheral vasodilatation and cerebral vasoconstriction, a sudden shift of blood towards lower parts of the body occurs on standing up from squatting and straining is an impediment to venous return (Howard *et al.*, 1951; Lempert *et al.*, 1994a; Wieling and van Lieshout, 2002). Together these ensure a sudden and severe drop in systemic blood pressure and cerebral perfusion.

The fainting lark has been used by children, high school students and military recruits as entertainment for their friends or to obtain some other gain, such as avoiding imminent examinations (Howard *et al.*, 1951, Johnson *et al.*, 1984). The manoeuvre can evoke unconsciousness of short duration in almost anyone. Lempert and colleagues (1994a, 1996) used it to document the sequence of events during abrupt-onset syncope. Fifty-nine students aged 20–39 years volunteered, and complete syncope was induced in 42. Klein *et al.* (1964) asked young adult men to combine hyperventilation with vigorous straining, and found that syncope occurred at a mean blood pressure of ~50 mmHg at heart level. Note that blood pressure at heart level does not equal arterial cerebral pressure in the upright

Table 1 The various approaches used to induce syncope and study symptoms and signs of syncope

Abrupt-onset syncope
– Fainting lark
– Neck cuff (now considered unethical)
– Anoxia
– Electrophysiological examinations with induction of VT/VF
– Eyeball pressure, carotid sinus massage
Gradual onset syncope
– Tilt table or lower body negative pressure induced vasovagal syncope
– Posture induced orthostatic hypotension in patients with pure autonomic failure
– Centrifuge

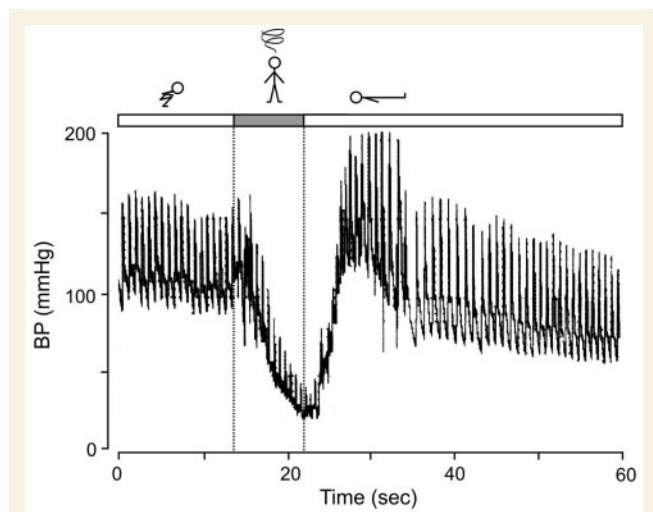


Figure 4 Effect of the fainting lark on finger arterial pressure. See text for details about the procedure. Tracing obtained in a 54-year-old subject (WW). Note instantaneous, deep fall in arterial pressure on arising. At the nadir of blood pressure the subject experienced seeing black and then did fall on the floor. On lying down, blood pressure recovers almost immediately and did overshoot. The time between standing up from the squatting position until onset of the faint amounts to 7 s. The duration of the loss of consciousness was short. Finger arterial pressure was measured at heart level with a Finapres device (N. van Dijk and W. Wieling, unpublished results).

position: the brain is then 25–30 cm above the heart, corresponding to a hydrostatic pressure of 15–20 mm Hg (Henry *et al.*, 1951; van Dijk, 2003; Hainsworth, 2004). Subtracting the pressure needed to overcome this height from pressure at heart level means that cerebral arterial pressure is then ~30 mm Hg.

Neck cuff

Rossen *et al.* (1943) evoked syncope with a specially designed pressure cuff around the neck that could be inflated to 600 mm Hg within one heartbeat thereby stopping the cerebral

circulation immediately. Note that this study was performed prior to the Belmont Report and would now be considered ethically unacceptable. One hundred and twenty-six male inmates and schizophrenic patients, ranging in age from 17 to 31 years underwent the procedure.

Anoxia

Instantaneous anoxia induced by very rapid decompression in a pressure chamber has been used as another approach to induce abrupt onset loss of consciousness (Luft and Noell, 1956). Although anoxia does not strictly fall under the modern definition of syncope, i.e. loss of consciousness due to cerebral hypoperfusion (Brignole *et al.*, 2004), anoxia does cause a loss of neuronal function as does anoxic ischaemia induced by cerebral hypoperfusion. It has been suggested that syncope does not solely rely on a lack of oxygen, but also of nutrients such as glucose (Gastaut, 1974). Induction of anoxia offers the possibility to study the hypoxic effects selectively.

Cardiac syncope

Ventricular arrhythmias may be induced in the course of electrophysiological examinations. These circumstances also allowed measurements of blood pressure at the onset of unconsciousness: the examinations were performed with the patients in supine position. Mean blood pressure at heart (and brain) level was reported to be ~20 mm Hg (Aminoff *et al.*, 1988).

Reflex syncope

There are various ways to trigger abrupt-onset reflex syncope in a laboratory setting. Examples include carotid sinus massage, specifically in elderly subjects (Weiss and Baker, 1933; Engel *et al.*, 1944; Kenny and Traynor 1991) and eyeball pressure, specifically in young ones (Gastaut and Fischer-Williams, 1957; Stephenson, 1990).

The best-known provocation technique to induce vasovagal syncope is tilt-table testing. If the vasovagal reflex is of the 'cardioinhibitory' type, it may involve a sudden asystole and an abrupt-onset reflex syncope. When bradycardia is less pronounced, vasovagal syncope usually takes longer to develop during tilt-table testing; this occurs especially often in the elderly (Verheyden *et al.*, 2007).

The preferred tilt-table method in patient evaluations entails relatively long duration (20–45 min) passive head-up tilt on a table with a footboard, often followed by pharmacological provocation using nitroglycerine or isoproterenol if the passive tilt is non-diagnostic (Benditt *et al.*, 1996; Brignole *et al.*, 2004). Additional procedures to induce vasovagal syncope have been used for research purposes; these include prolonged head-up tilt while subjects are suspended in a parachute harness so the legs are unsupported (Stevens, 1966), bleeding and venous occlusion tourniquets (Barcroft *et al.*, 1944; Barcroft and Edholm, 1945), lower body negative pressure (Murray *et al.*, 1968) and the combination of lower body negative pressure and head-up tilt (Newbury *et al.*, 1970; El-Bedawi and Hainsworth, 1994).

These experiments confirm that cerebral blood pressure has to decrease quite profoundly before consciousness is lost: systolic blood pressure values of 50–60 mmHg or even less at heart level were observed at the moment of the faint (Karp *et al.*, 1961; Newbury *et al.*, 1970; Chen *et al.*, 1989; Giese *et al.*, 2004), suggesting systolic values of 30–45 mmHg at brain level.

Syncope due to orthostatic hypotension

Observations in patients with serious primary autonomic failure have contributed considerably to the understanding of those forms of syncope that exhibit a gradual onset. In these patients with long-standing orthostatic hypotension, prodromal symptoms typically occur only when systolic blood pressure has dropped to ~60 mmHg (Ellis and Haynes, 1936; Jeffers *et al.*, 1941; Hickler *et al.*, 1959; Thomas and Bannister 1980). Henry *et al.* (1951), using data from the literature, calculated that mean blood pressure at eye level had to decrease to 30–40 mmHg for visual symptoms to occur; as in other investigations, unconsciousness appeared at about 20 mmHg, also at eye level.

Centrifuge

A 'human centrifuge' can induce such a rapid and high acceleration that cardiovascular reflexes cannot cope, neither in time nor in magnitude (Lambert and Wood, 1946). Military pilots have been subjected to rapid-onset acceleration of 4–6 G for up to 20 s. 'Blackout', i.e. a loss of vision with preserved consciousness, occurred at a mean pressure at eye level of 20–30 mmHg; true syncope occurred at 20 mmHg (Beckman *et al.*, 1954; Whinnery and Whinnery, 1990). Whether syncope occurs abruptly or gradually in a centrifuge depends on the rate and magnitude of acceleration; with a slow increase, reflex compensation has the time to operate, and when this fails, a gradual onset syncope is obtained.

In conclusion, a mean blood pressure at eye level as low as 20 mmHg at the moment of true syncope seems a remarkably constant finding under a wide variety of conditions.

Symptoms and signs in the course of syncopal attacks

Prodromal phenomena

There are two main groups of prodromal symptoms. The first are consequences of retinal and cerebral hypoperfusion, and the second concerns 'autonomic activation' due to sympathetic and parasympathetic activity (see below). Note that patients can only report prodromal symptoms if the fall in arterial pressure was slow enough for them to perceive symptoms and 'store' the sensations for later recall (compare Figs 2–4). The following summarizes sensations reported by individuals subjected to certain of the syncope-induction investigations noted earlier.

Fainting lark

In Lempert's *et al.* study (1994a), the time between standing up from the squatting position until onset of the faint was only 5–10 s. Some subjects reported a short sensation of feeling warm and light-headed (T. Lempert, personal communication). Prodromal symptoms and signs were also minimal in prior studies using hyperventilation and straining to induce abrupt-onset syncope; these consisted primarily of light-headedness, darkened vision and pallor. Occasionally there was a stare with a fixed gaze at the onset of syncope (Duvoisin, 1961, 1962). Other features included intense mydriasis as well as drooling, particularly in older patients (Duvoisin, 1961; Gastaut, 1974). Amnesia spanning a few seconds before syncope was also reported (Duvoisin, 1962).

Neck cuff

In the study using a cuff around the neck (Rossen *et al.*, 1943) prodromal events followed a characteristic sequence: 5–6 s (range 4–10 s) after the cerebral circulation was arrested the eyes became fixed and gaze was directed straight ahead. Subjects, still conscious, were no longer able to move ('freeze'). This was followed by blurring of vision, loss of peripheral vision (grey-out) and loss of consciousness.

Anoxia

Results similar to those recorded using the neck cuff were reported following instantaneous anoxia induced by very rapid decompression in a pressure chamber (Luft and Noell, 1956). The sequence of events was a loss of peripheral vision, darkening of the visual fields, a brief period of staring, fixed eyes and inability to move, followed by drooping of the head and loss of consciousness. A short period (2–3 s) of amnesia prior to the loss of consciousness was reported. Automatic unusual behaviour, such as acting as if drunk or absentminded, was also observed.

Cardiac syncope

Symptoms and signs in abrupt-onset syncope due to cardiac standstill tend to be concordant with those observed under laboratory conditions. This means that the suddenness of onset and lack of warning signs forms a clinical clue towards the diagnosis. Stokes-Adams attacks are indeed known for their sudden onset. The clinical presentation depends on the duration of the cardiac standstill. When the duration of circulatory arrest is shorter than the cerebral ischaemic anoxia reserve time, i.e. less than ~7 s (see section on syncope induced by centrifuge), the event may go wholly unnoticed. A somewhat longer interruption may cause transient darkness of vision, light-headedness and fixation of gaze as described above. After a standstill of the circulation a striking pallor appears after 5–10 s. Loss of consciousness after cardiac standstill occurs more rapidly when the individual is standing (after 4–8 s) than when lying down (after 12–15 s) (Pomerantz and O'Rourke, 1969; Scherf and Bornemann, 1970).

Not every sudden syncope should be ascribed to a cardiac cause, however, as the circulation can also stop equally rapidly in some other conditions, such as cardio-inhibitory reflex syncope; examples of this are the spontaneous carotid sinus syndrome (Weiss and Baker, 1933; Kenny and Traynor, 1991) and syncope due to eyeball pressure (Wieling and Khurana, 2006).

The clinical features of syncope in ventricular tachycardia differ from those in a typical Stokes-Adams attack: loss of consciousness usually occurs later after the onset of ventricular tachy-arrhythmias (20–120 s) than after asystole (Aminoff *et al.*, 1988). The explanation is probably that cardiac output, while greatly reduced (depending on the tachycardia rate and status of left ventricular performance as well as vascular reactivity), is not necessarily completely arrested. Blood pressure therefore typically falls less rapidly, resulting in a more gradual loss of consciousness allowing time for prodromal symptoms to be noted.

Vasovagal syncope

Prodromal symptoms and signs, both those due to autonomic activation and to retinal and cerebral hypoperfusion, are usually present in younger individuals experiencing spontaneous vasovagal syncope during daily life or induced vasovagal syncope under laboratory conditions. A complete lack of any warning symptoms is reported by some patients (particularly older ones) during apparent spontaneous vasovagal episodes, but is rare during tilt-table testing. The discrepancy may be in part be accounted for by a failure of patients to recognize subtle prodromal symptoms as such, an effect perhaps exacerbated when attention is directed at other activities (Kenny and Traynor, 1991; Sutton, 1999). Male subjects are reported to be less symptomatic than females (Romme *et al.*, 2008). Prodromal symptoms are often not reported by elderly subjects; putative reasons for this are a greater susceptibility to retrograde amnesia, less autonomic activation (see below) or diminished sensitivity to the sometimes subtle symptoms (Kenny and Traynor, 1991; Benke *et al.*, 1997; Parry *et al.*, 2005). Blood pressure tends to fall at a lower rate in older subjects during a vasovagal faint than in the younger (Verheyden *et al.*, 2007); this might be expected to enhance recall of prodromal events, but that does not appear to be the case.

On average prodromal symptoms start 30–60 s prior to an actual vasovagal faint, but this duration is notoriously variable (Weiss, 1935; Weissler *et al.*, 1959; Karp *et al.*, 1961; Wayne, 1961; Stevens, 1966; Newman and Graves, 2001; Alboni *et al.*, 2002; del Rosso, 2005). Subjects first begin to feel uncomfortable in an ill-defined way, or experience a feeling of warmth, epigastric discomfort and vague nausea, abdominal cramps and a desire to sit down or to leave the room. Some patients report a strong urge to defaecate. If subjects act on these warning signs by sitting or lying down, syncope may be prevented. However, if these warnings are ignored, light-headedness, described as a sense of 'emptiness in the head' or a 'swimming' sensation, dizziness, 'cold sweat', fatigue, blurred and fading vision, palpitations, sounds 'coming from a distance' and buzzing in the ears may occur (Lewis, 1932; Weiss, 1935; Weiss *et al.*, 1937; Edholm, 1952; Weissler *et al.*, 1959; Karp *et al.*, 1961; Calkins *et al.*, 1995; Graham and Kenny, 2001; Newman and Graves, 2001).

Hyperventilation frequently precedes tilt-induced syncope (Lipsitz *et al.*, 1998; Carey *et al.*, 2001; Martinon-Torres *et al.*, 2001). Current thought is that hyperventilation by itself is not a sufficient physiological stressor to induce syncope in healthy subjects (Thijs *et al.*, 2008a), but it may well play a role in patients with frequent vasovagal syncope, since cerebral vasoconstriction

and systemic vasodilatation is exaggerated in these patients (Norcliffe-Kaufmann *et al.*, 2008).

Facial pallor is often the first sign of an impending vasovagal faint. It is followed by yawning, sighing and tachypnoea, sweating, restlessness, salivation, pupillary dilatation and accentuated peristaltic sounds (Lewis, 1932; Weiss and Baker, 1935; Weissler *et al.*, 1959; Murray *et al.*, 1968; Sutton, 1999). The ghostly white pallor results from reduced skin blood flow (Benditt *et al.*, 1995) due to sympathetically and vasopressin-induced vasoconstriction in addition to low blood pressure (Edholm, 1952). The pale colour is that of subcutaneous connective tissue, composed principally of collagen fibres of a whitish hue (Guyton, 1986). Deoxygenated haemoglobin is responsible for the additional greenish hue observed in some patients (Blount, 1971). Pupillary dilatation occurs just before losing consciousness, probably due to a combination of central inhibition of parasympathetic outflow, peripheral sympathetic drive and high levels of circulating adrenaline.

As blood pressure continues to fall, symptoms and signs of cerebral and retinal dysfunction come to the fore: subjects have difficulty concentrating, become unaware of their surroundings and fall down as they lose consciousness (provided they were standing). Hearing loss may occur following loss of vision. A brief period of staring and an inability to move voluntarily may occur prior to syncope. This is very similar to what was reported in the case of neck cuff inflation, where the ability to act was lost before loss of consciousness. The prodromal phase is often associated with sinus tachycardia. Younger patients often complain of palpitations in this period (Romme *et al.*, 2008). The subsequent heart rate decrease is variable, but when slowing does occur it usually occurs after the onset of hypotension. It becomes most marked just prior to the actual faint (Karp *et al.*, 1961; Sander-Jensen *et al.*, 1986; Chen *et al.*, 1989; de Jong *et al.*, 1997). In tilt-table studies, asystole of over 3 s occurred in 5%–20% of patients (Brignole *et al.*, 1992; Dhala *et al.*, 1995; Deal *et al.*, 1997; Alboni *et al.*, 2002). Pauses from 40 to 70 s have, however, also been documented (Maloney *et al.*, 1988; Pentousis *et al.*, 1997; van Dijk *et al.*, 2001; Barón-Esquivivias *et al.*, 2002). The patients involved are often young.

Syncope due to orthostatic hypotension

Typically, the premonitory phase of autonomic activation observed in vasovagal fainters is absent in patients with syncope due to orthostatic hypotension, especially in primary autonomic failure. Symptoms of hypoperfusion of the retina and brain in patients with orthostatic hypotension are similar but not identical to those in patients with gradual onset reflex syncope (Ellis and Haynes, 1936; Jeffers *et al.*, 1941; Low *et al.*, 1995; Mathias *et al.*, 1999). The differences can be explained by the fact that blood pressure can remain at a very low fixed level for prolonged periods in these patients. For example, visual symptoms not only include blurring, colour changes and seeing black spots as seen in reflex syncope; but also scotomas and visual hallucinations, suggesting occipital ischaemia (Ross Russell and Page, 1983; Mathias *et al.*, 1999). Furthermore, symptoms of ischaemia of other parts of the body may be present in patients with autonomic failure: the best-known is a neck ache radiating to the occipital

region of the skull and to the shoulders ('coat hanger pain') (Robertson *et al.*, 1994; Bleasdale-Barr and Mathias, 1999). This occurs during prolonged standing or walking, and often precedes loss of consciousness. It resolves on lying down. The postulated mechanism of this unique symptom is ischaemia in continuously contracting postural muscles. Posture-related pain in the lower back, the buttocks and the chest has also been reported in autonomic failure, but the underlying mechanism of these complaints is less clear. Exercise-related pre-cordial pain may occur in the absence of coronary artery disease suggesting that these complaints should be attributed to systemic hypotension (Asahina *et al.*, 2006). Symptoms typically develop in minutes or after longer periods of standing or walking and resolve on lying down (Schirger *et al.*, 1961; Robertson *et al.*, 1994; Bleasdale-Barr and Mathias, 1999; Mathias *et al.*, 1999). Patients with autonomic failure learn to use such symptoms as a warning sign that they must lie down or sit down to restore an adequate perfusion pressure. If the patient remains upright a gradual fading of consciousness over about half a minute occurs and the patient falls slowly to his/her knees. A very quick onset of syncope may, however, also occur. Some patients have no warning symptoms at all. Hypotensive transient ischaemic attacks (TIA) may also occur, especially in the presence of occlusive carotid artery disease: so-called orthostatic TIA's (Mathias *et al.*, 1999).

Centrifuge

Visual disturbances preceding loss of consciousness are of great interest in military aviation, since they act as a warning of impending loss of consciousness (Lambert, 1945; Lambert and Wood 1946; Wood *et al.*, 1946; Whinnery and Shender, 1993; Yilmaz *et al.*, 1999). These begin with dimming or greying of the peripheral field of vision, i.e. loss of colour vision ('greying out'), followed by peripheral light loss, and then complete blindness ('blacking out'). The origin of these sensations lies in hypoperfusion of the retina when brain perfusion is still adequate. This may seem surprising, as the ophthalmic artery stems from cerebral arteries. The explanation lies in the presence of the intraocular pressure, which at ~18 mmHg (Lambert and Wood, 1946; Whinnery and Shender, 1993) adds an impediment to eye perfusion that is not present in brain perfusion. Proof of the retinal origin of the visual symptoms resides in the fact that a suction force of 30–40 mmHg applied to the eyeball with a special mask prevents blacking out during exposure to centrifugal force. Reversely, applying a positive pressure at 1 G acceleration lowers the threshold at which visual symptoms occur (Lambert, 1945).

'Human centrifuge' studies confirm that an abrupt stop of cerebral circulation leads to loss of cerebral function in young adults after about 7 s. This period, the cerebral ischaemic anoxia reserve time, is shorter in the young and longer in the elderly (Stephenson, 1990).

Ictal events: loss of consciousness

Fainting lark

In Lempert's *et al.* study (1994a), unconsciousness and confusion together lasted on average 12 s (range 5–22 s). The end of

this period was defined by the resumption of verbal responses. This duration was probably longer than that of true unconsciousness, as it involved not just unconsciousness but also the period immediately afterwards in which subjects failed to reply to oral requests. In this period, some subjects remained sitting upright staring ahead; others made automatic movements such as ruffling their hair. Automatism, observed in 80%, included lip-licking, chewing, fumbling and reaching for the head. Growling or moaning vocalizations were noticed in 40% of the subjects (Lempert *et al.*, 1994a). Duration of loss of consciousness and time to recovery elicited by neck cuff inflation, eyeball pressure, acute anoxia and abrupt-onset G forces were also short, usually lasting no more than ~20 s.

Cardiac syncope

Observations during induced ventricular arrhythmia indicate that the duration of the loss of consciousness and time to recovery is closely correlated with the duration of the disturbance. Aminoff *et al.* (1988) studied 14 patients with implantable cardioverter defibrillators (ICDs) placed after previous cardiac arrest or life-threatening cardiac arrhythmia. The correlation coefficient between the duration of loss of consciousness and the duration of induced ventricular tachycardia and fibrillation was 0.99 (Fig. 5).

Vasovagal syncope

The duration of unconsciousness during laboratory-induced vasovagal faints or in prospective studies in blood donors also lasted no more than 10–20 s (Karp *et al.*, 1961; Lin *et al.*, 1982; Newman and Graves, 2001). However, much longer periods of unconsciousness (up to 5 min) have been reported (Cotton and Lewis, 1918; Lewis, 1932; Weiss and Baker, 1935; Wayne, 1961; Robinson and Johnson, 1988). Eyewitnesses often report long periods of unconsciousness, but without actual measurements the reliability of such estimates of syncope duration is debatable. The impairment of consciousness may not be profound, making the determination of its duration somewhat arbitrary (Karp *et al.*, 1961). It is likely that body position plays a role: cerebral perfusion may remain insufficient for longer in those who remain upright during syncope, either by being kept upright by bystanders or by slumping in a chair.

Ictal events: eye movements/closure

In Lempert's investigation the eyes remained open in all cases. The most consistent ocular motor sign accompanying syncope was an upward turning of the eyes in the course of syncope, which could be preceded by a few seconds of downbeat nystagmus (Lempert, 1996). Similar eye movements were described for other procedures that provoke abrupt-onset syncope (Rossen *et al.*, 1943; Luft and Noell, 1953; Gastaut, 1974; Stephenson, 1990). However, nystagmus is not always present in reflex syncope: in 100 ocular compression experiments upward deviation was observed in 19% and downbeat nystagmus in 33% (Stephenson, 1990). The rapidity of the pressure fall is likely to be responsible (Weiss, 1935; Gastaut and Fischer-Williams, 1957; Stephenson, 1990).

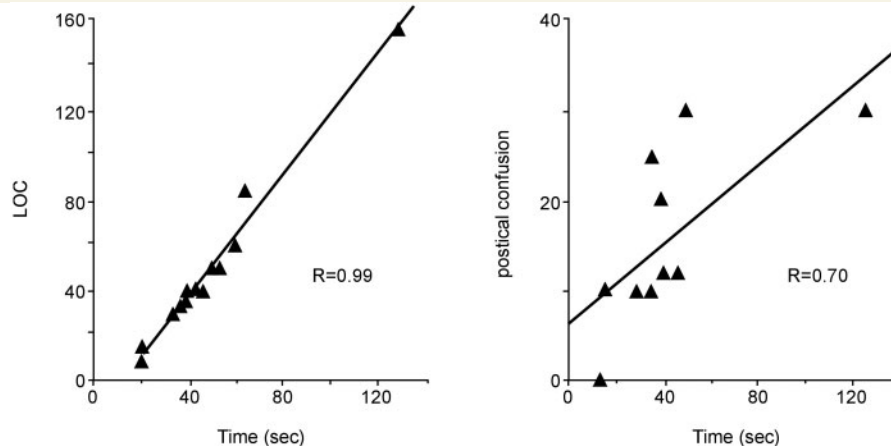


Figure 5 Determinant of duration of unconsciousness and confusion. Left panel shows the relation between duration of loss of consciousness (LOC) and that of induced arrhythmia. There is a close correlation between these two measurements ($r=0.99$). Right panel shows the relation between duration of induced ventricular tachycardia and fibrillation (VT/VF) and duration of postictal confusion. Duration of postictal confusion ranged from 0 to 30 s and was related to the duration of the arrhythmia ($r=0.70$). Taken with permission from Aminoff *et al.* (1988).

Ictal events: incontinence urine/faeces

Urinary incontinence has been reported during abrupt-onset syncope (Duvoisin, 1962; Gastaut, 1974; Stephenson, 1990). In circulatory cardiac standstill for >20 s, sphincters release tone (Formijne 1937; Pomerantz and O'Rourke, 1969; Scherf and Bornemann, 1970). Loss of urine during a vasovagal episode is reported to occur in <25% of cases (Lin *et al.*, 1982; Stephenson, 1990; Hoefnagels *et al.*, 1991; Newman and Graves, 2001; Romme *et al.*, 2008). Faecal incontinence is very rare (Wayne, 1961; Stephenson, 1990; Newman and Graves, 2001; Romme *et al.*, 2008).

Ictal events: posture and movements

Whereas most subjects are flaccid during syncope, stiff opisthotonus during syncope has also been described (Cotton and Lewis, 1918; Gastaut and Fischer-Williams, 1957; Stephenson, 1990). Stephenson, studying children with induced syncope, found that stiffening was a 'probably universally' accompaniment when syncope lasted long enough to produce a flat EEG (Stephenson, 1990). Consistent turning of the head to one side is also reported as a specific sign for epilepsy (Sheldon *et al.*, 2002), but is not impossible in syncope, as it was observed in experimental syncope induced by ocular compression (Gastaut and Fischer-Williams, 1957).

Myoclonic jerks were observed in almost all of the 42 syncopal episodes of abrupt syncope induced by the fainting lark (Lempert *et al.*, 1994a). These jerky movements always occurred after the individual had fallen down (an important feature distinguishing them from epileptic seizures) and lasted 1–16 s. Myoclonic jerks appear to be less common in spontaneous vasovagal syncope than in syncope induced using ocular compression or the fainting lark. It is possible that low-amplitude jerks are frequently missed in accounts after the fact, but are missed less often under controlled circumstances: in agreement with this view myoclonic jerks were

reported in only 12% of blood donors who had fainted in a retrospective study (Lin *et al.*, 1982), but in 42–46% in the same setting in a prospective study (Newman and Graves, 2001). The origin of myoclonic jerks has not been proven; a release phenomenon of brainstem neurons no longer suppressed by higher centres has been postulated (Gastaut, 1974).

Tongue biting seems to be extremely rare in syncope (Stephenson, 1990; Hoefnagels *et al.*, 1991; Newman and Graves, 2001; Sheldon *et al.*, 2002), therefore its presence suggests epilepsy instead. In generalized seizures, tongue biting involved the side of the tongue in all eight cases with a tongue bite out of 34 seizures, while the one tongue bite in 45 syncope cases concerned the tip of the tongue (Benbadis *et al.*, 1995). Only once has a lateral tongue bite been described in syncope, in a subject with forceful multifocal myoclonus that involved the muscles of mastication (Lempert *et al.*, 1994a).

Ictal events: breathing

During abrupt-onset syncope in Adams-Stokes attacks or induced by the fainting lark, neck cuff or eyeball pressure, breathing usually continues, indicating that respiratory centres in the brain stem are more resistant to ischaemia than the cerebral cortex. Respiration during vasovagal syncope is variable: it may be shallow and slow or deep, and sighing or snoring may occur (Weiss, 1935; Newman and Graves, 2001). The brainstem is not completely impervious to ischaemia, so breathing will eventually stop. This has indeed been described for an asystole duration of 35–40 s. Patients then become cyanotic with maximally dilated pupils (Formijne, 1937; Scherf and Bornemann, 1970; Sutton, 1996).

The EEG in syncope

The electroencephalogram (EEG) in syncope can show two patterns. The best known one, described by Gastaut, is the 'slow-flat-slow' pattern; this starts with slowing of the EEG,

i.e. normal phenomena such as the alpha rhythm disappear and make way for slow activity waves of increasing amplitude (Gastaut, 1974). This slow phase may last for up to ~ 10 s; thereafter the slow activity disappears abruptly, leaving a 'flat' EEG. The duration depends on the duration of insufficient flow. The resumption of cerebral blood flow gives rise to the same phenomena in reversed order, so a 'slow-flat-slow' pattern appears (Fig. 6). The second pattern consists of slow activity only; this may be regarded as the first 'slow' phase of the 'slow-flat-slow' pattern, and occurs when blood flow does not decrease long enough or deep enough to cause a flat phase.

The slow-flat-slow pattern has most often been described for syncope involving asystole (Gastaut, 1974; Stephenson, 1990; Breningstall, 1996), but can occur without asystole, such as during tilt tests using isoproterenol (Sheldon *et al.*, 1998), during arrhythmias and in orthostatic hypotension (Brenner, 1997). The same pattern was seen in instantaneous anoxia (Luft and Noell, 1955). The 'slow' pattern has also been described for various causes: it occurs in asystole of limited duration, and in vasodepressor syncope (Karp *et al.*, 1961).

While a flat EEG is invariably associated with loss of consciousness and postural control, the relation between the level of consciousness and the degree of slowing in the first phase is much less clear. Sheldon *et al.* (1998) studied the EEG during

syncope as well as during presyncope. Presyncope was associated with EEG abnormalities in 13 of 14 cases; the abnormalities involved theta activity ($n=8$), delta waves ($n=9$) or 'background suppression', i.e. a flat EEG ($n=1$). Similar findings were obtained in syncope: theta ($n=9$), delta ($n=11$) and background suppression ($n=6$). Note that EEG slowing is not always associated with loss of consciousness: there are observations of consciousness being preserved during the slow phase of the EEG (Karp *et al.*, 1961).

Motor phenomena occur at various phases. Flaccidity occurs during slowing of the EEG. Tonic spasms (e.g. stiffness with or without head aversion and opisthotonus) and/or myoclonic jerks may occur. Stephenson presumed that 'stiffening' (tonic spasm) was a 'probably universally' accompaniment of the flat phase of the EEG (1990). If so, the 'stiffening' does not have to be present from the onset of EEG flattening (Stephenson, 1990). Myoclonic jerks may occur both at the onset of syncope and during its occlusion (Stephenson, 1990).

Postictal events: consciousness

An almost universal feature of syncope is that patients recover quickly. The duration from the beginning of unconsciousness to once again being well-oriented and capable of performing

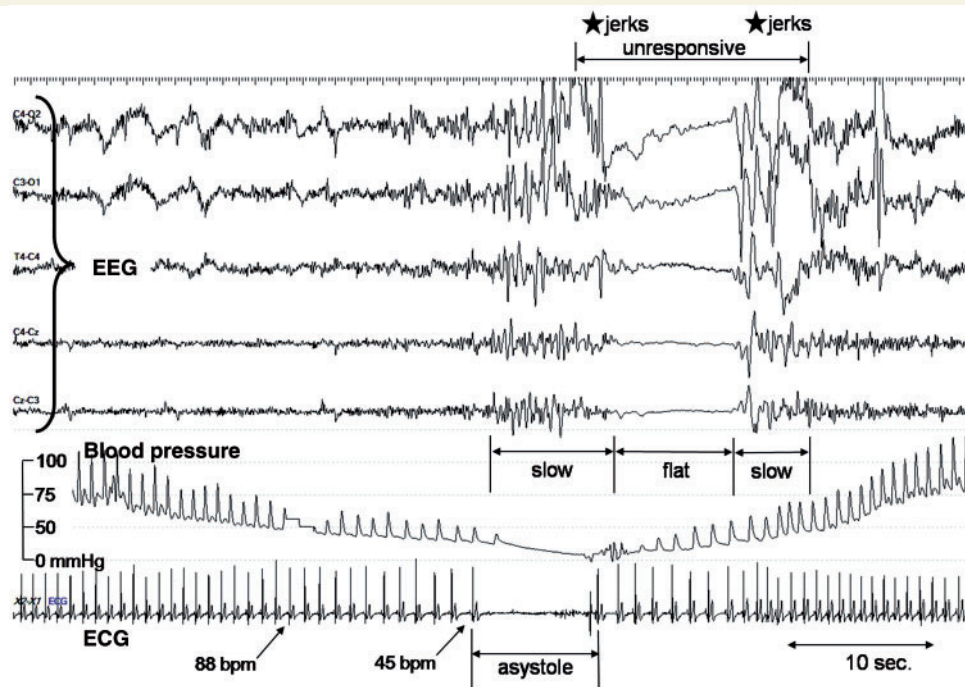


Figure 6 EEG in vasovagal syncope. A 1-min segment of a tilt-table test with a typical vasovagal syncope is shown of a 40-year-old man. No nitro-glycerine was used. Finger blood pressure was recorded continuously using a Finometer. A selection of EEG channels is shown. The patient was tilted back during asystole (not indicated). At the beginning of the segment he had already complained of nausea, sweating and light-headedness, and blood pressure had started to drop. EEG slowing starts when systolic blood pressure drops to ~ 50 mmHg; heart rate is then about 45 beats per minute. Asystole occurred, lasting about 8 s. The EEG flattens for a similar period, but with a delay. Transient loss of consciousness was observed, starting with sagging of the face and dropping of the head to one side. The eyes remained open and the patient was unresponsive for about 14 s. There were muscle jerks just before and just after the flat period of the EEG (J.G. van Dijk, unpublished results).

purposeful movements was only ~20–30s in abrupt-onset syncope (induced by the fainting lark, neck cuff, hypoxia, eyeball pressure and human centrifuge) (Rossen *et al.*, 1943; Lambert and Wood, 1946; Beckman *et al.*, 1954; Luft, 1956; Duvoisin, 1961, 1962; Gastaut, 1961; Klein *et al.*, 1964; Stephenson, 1990; Lempert *et al.*, 1994a). Recovery after a Stokes-Adams attack is also rapid, with a sudden return of the pulse. Instantaneous and full orientation of the patient is the rule after a cardiac standstill of <20s and the patient can be mobilized almost immediately (Scherf and Bornemann, 1970). However, in the recovery phase of a cardiac syncope fatigue, sweating and confusion are also reported to be common (Calkins *et al.*, 1995). The postictal confusion after longer periods of a circulatory arrest is closely correlated with the duration of the arrest (Fig. 5).

The rate of recovery from severe vasovagal attacks is usually slower than the rate of onset. Common post-syncope findings in a patients whose blood pressure remain low after a severe vasovagal syncopal episode include profound fatigue, a persistence of pallor, nausea, yawning, weakness, sweating and oliguria and a tendency towards recurrence of the reaction if the individual is returned to the upright posture (Weiss, 1935; van Lieshout *et al.*, 1991; Calkins *et al.*, 1995; Thijs *et al.*, in press).

Postictal events: flushing

A noticeable scarlet flushing of the face occurs 2–4s after the circulation restarts in Stokes-Adams attacks. This also involves the arms and slightly later the legs ('inondation sanguine') (Hermann *et al.*, 1937; Formijne, 1938). The flush occurs during an overshoot in arterial pressure following the asystole (Barlow and Howarth, 1953) (Fig. 1) and has been attributed to filling empty skin vessels with well-oxygenated blood (Formijne, 1938). This post-syncope flush has been taken to indicate that syncope must have been due to a Stokes-Adams attack (Sharpey-Schafer, 1956; Sutton, 1996), but this is not true. A flush can also be observed in the recovery phase of a vasovagal event in patients with a very rapid recovery of blood pressure, so it denotes that syncope was rapid rather than cardiac (Fig. 7) (Engel *et al.*, 1944; Greenfield, 1951; Stephenson, 1990; Wieling *et al.*, 2006). Conversely, the persistence of pallor after the faint and the oliguria after a vasovagal episode have been attributed to the release of vasopressin (Brun *et al.*, 1945; Edholm, 1952; Sharpey-Schafer *et al.*, 1958).

Postictal events: apnoea

Prolonged apnoea during the period of re-circulation has been reported (Formijne, 1938). Patients then become deeply cyanotic because venous blood, having been deoxygenated during the standstill in the periphery, re-enters the circulation without being re-oxygenated in the lungs first (Formijne, 1938).

Postictal events: epileptic seizures

A few EEG-documented epileptic seizures have been reported to occur as a consequence of syncope, and almost all of the cases involved young children (Battaglia, 1989; Stephenson, 1990;

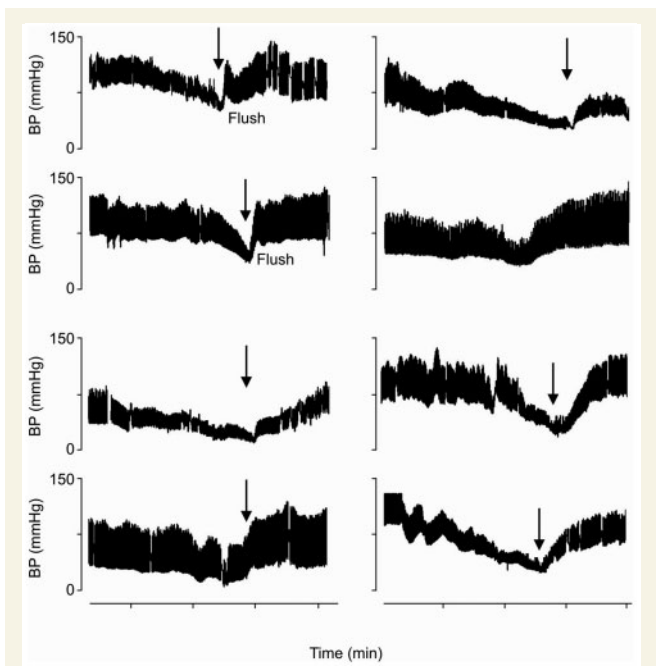


Figure 7 Blood pressure after vasovagal syncope. Recovery of blood pressure on tilting back in eight subjects with a tilt-induced vasovagal faint. Arrows indicate the moment of tilt back. A flush is observed in the two subjects with a rapid recovery and overshoot of blood pressure. Blood pressure was measured with a Finapres device. Taken with permission from Wieling *et al.* (2006).

Bergey *et al.*, 1997; Stephenson *et al.*, 2004; Horrocks *et al.*, 2005).

Postictal events: other effects

Retrograde amnesia for a period of 3–5s prior to the vasovagal faint is not unusual (Karp *et al.*, 1961), especially in older fainters. After-effects are usually brief following a vasovagal faint, but may last for hours, particularly in children. The duration/severity of an attack plays a major part in the subsequent recovery. Severe attacks may tire the subject so much that he or she wants to sleep. Some patients report feeling extremely fatigued for hours or even days following a spontaneous vasovagal faint (Weiss and Baker, 1935; Gastaut, 1974; Sutton, 1999). Severe emotional upset may occur after syncope (Weiss and Baker, 1935; Weissler *et al.*, 1959; Graham and Kenny, 2001).

A variety of mental symptoms may occur during and after syncope. Subjects may report to be dazed, excited, euphoric or frightened. There can be simple or complex visual and auditory hallucinations, including hearing rushing and roaring sounds, screaming and unintelligible human voices; out of body experiences may also occur that can be pleasant (Duvoisin, 1962; Forster and Whinnery, 1988; Stephenson, 1990; Lempert *et al.*, 1994a, Lempert, 1996; Blackmore, 1998). Unlike epileptic auras, syncopal hallucinations do not precede the attack, but rather occur as the individual is regaining consciousness (Lempert *et al.*, 1994b; Stephenson, 2002).

Table 2 Sequence of symptoms and signs in prodromal phase of syncope

<p>Abrupt syncope with acute standstill of perfusion of the brain and retina</p> <ul style="list-style-type: none"> • After approximately 6 s: darkened vision (black out), staring, 'freeze' • 7–13 s: fixation in the midline or upwards turning of the eyes, loss of muscle tone, loss of consciousness • After approximately 14 s muscle jerks <p>Gradual onset syncope with autonomic activation and symptoms of hypoperfusion</p> <p>Autonomic activation</p> <ul style="list-style-type: none"> • Sweating • Facial pallor • Nausea • Pupillary dilatation • Palpitations • Yawning^a • Hyperventilation <p>Symptoms of hypoperfusion</p> <ul style="list-style-type: none"> • Brain: light-headedness, unclear thinking • Retina: blurred vision, loss of peripheral and colour vision (grey out), darkened vision (black out) • Shoulders: coat hanger pain • Angina pectoris • Hypotensive TIA^b

a Precise mechanism unclear.

b Extremely rare, usually resulting from the combination of occlusive carotid artery disease and orthostatic hypotension.

Conclusion

Research into the symptoms and signs of syncope has yielded relatively consistent results. The different procedures used to make a richly oxygenated brain suddenly hypoxic induce a remarkably similar time sequence of deterioration of cerebral function with an orderly series of changes. The rapidity of onset of symptoms is related to the acuteness of the provocation, and the nature of the symptoms is a function primarily of the severity of autonomic activation. The duration of unconsciousness is determined by the length of the period of brain hypoxia. The clinical picture may vary from bobbing of the head of only momentary duration to a period of deep unconsciousness with myoclonic jerks and even opisthotonus. Familiarity by the attending physician with the symptoms and signs of patients with TLOC is crucial to establishing a correct clinical diagnosis.

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