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Pathophysiological Basis of Syncope and Neurological Conditions that Mimic Syncope

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ABSTRACT

The definition of syncope has clinical and pathophysiological parts. The clinical part is that syncope is a form of transient loss of consciousness (TLOC), while the pathophysiological element is that syncope differs from other forms of TLOC by virtue of the basis of true syncope – specifically cerebral hypoperfusion. As such, the signs and symptoms of syncope rely on three steps, starting with the cause of syncope and including the response of the systemic circulation and neurological effects. The causes of syncope all result in low blood pressure through low peripheral resistance and/or low cardiac output. The next step is the cerebral circulation, which is a large-volume and low-resistance system, characterized by relatively high diastolic flow. The cerebral circulation is usually protected against swings in arterial pressure by cerebral autoregulation, but in abrupt syncope, autoregulation acts too slowly to have much effect. In syncope, diastolic flow velocity is more impaired than systolic flow velocity, probably because closing vascular forces then opposes flow. The third step concerns neurological signs and symptoms; the cerebral cortex first responds by disruption of normal activity, followed by a complete cessation of activity when hypoperfusion deepens. The latter is likely when there is asystole or marked bradycardia. The neurological signs and symptoms suggest different principles: a loss of normal cortical activity, abnormal cortical activity and activity due to disinhibition of brainstem activity.

The importance of pathophysiology in understanding syncope is emphasized by its inclusion in the definition as the one item that sets syncope apart from all other forms of transient loss of consciousness (TLOC). In essence, syncope is TLOC due to transient global cerebral hypoperfusion, characterized by rapid onset, short duration and spontaneous complete recovery[1] (Fig 1).

Except for cerebral hypoperfusion, the clinical features associated with syncope are shared by all three major TLOC groups: syncope, epileptic seizures and psychogenic TLOC. Consequently, while it may seem counterproductive to use a pathophysiological criterion to define a clinical entity, it is essential to do so in this case for at least two reasons. The first is that there is no practical way to define clinical criteria that encompass all expressions of syncope and also exclude epileptic seizures and psychogenic TLOC. For example, the following items can be present or absent in syncope: pallor, nausea, opening of the eyes, incontinence and myoclonic jerks. The second is that without a criterion specific to syncope it becomes impossible to distinguish it from other

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Abbreviations and Acronyms

CBF = cerebral blood flow

EEG = electroencephalogram

ESC = European Society of Cardiology

MAP = mean arterial pressure

PNES = psychogenic non-epileptic seizures

PPS = psychogenic pseudosyncope

SFS = slow-flat-slow

TCD = trans-cranial Doppler ultrasound

TLOC = transient loss of consciousness

TSLB = time since last beat

forms of TLOC and thereby develop appropriate treatment options.[2]

Pathophysiological knowledge helps clinicians understand the nature of signs and symptoms in syncope, which in turn helps them infer the cause of a particular spell. For instance, syncope beginning while supine suggests that gravity does not play a role. Inasmuch as a prime task of blood pressure regulation is countering the effects of gravity in the upright position, supine syncope is not likely to be due to a primary failure of blood pressure regulation. Instead, a low cardiac output, for instance as a result of arrhythmia, is much more likely to be the basis for supine syncope, as it causes the circulation to come to a halt regardless of body position.

This paper focuses on the pathophysiology of the systemic and cerebral circulation and the neurological consequences of cerebral hypoperfusion in syncope, and briefly touches upon the pathophysiology of epileptic seizures and psychogenic TLOC.

Key factors in cerebral perfusion

The human brain is an expensive organ; even at rest it requires 15 to 20% of cardiac output, although at 1400 grams it constitutes only about 2% of an adult's mass.[3] In children of around two years of age, no less than 50% of cardiac output subserves the brain.[4] It is also a 'spoiled' organ with an extremely small metabolic reserve capacity. In fact, loss of consciousness starts only about eight seconds after the heart stops.[5] The arterial system still pumps some blood through the body after the heart has stopped, so this short period does not reflect the pure metabolic reserve of the brain. Early experiments abolished that arterial pump effect by occluding all neck arteries instantly with a cuff around the neck. Unconsciousness then started six to seven seconds after cuff inflation.[6] This latter finding vividly illustrates how little reserve capacity the brain has, and also suggests that the arterial pump does not appreciably prevent loss of consciousness after cardiac standstill. In the end, apart from cardiac output, cerebral perfusion depends on the baroreflex system to maintain systemic blood pressure, and cerebral autoregulation maintains cerebral blood flow in the face of changes in arterial pressure.

The baroreflex system

The baroreflex sensors are located in the carotid sinus and in the aorta; those in the carotid sinus are located where the

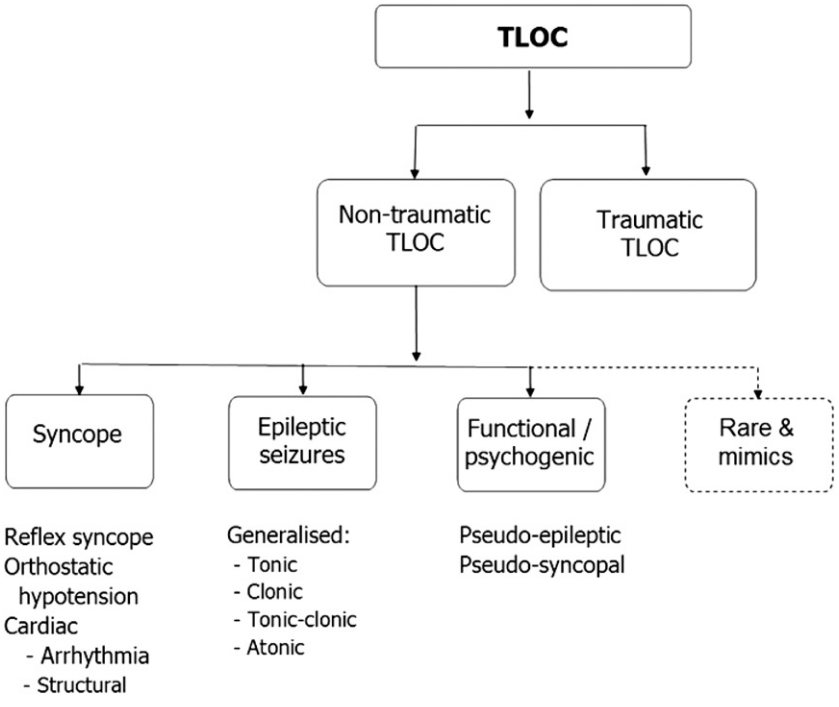

Fig 1 – Forms of transient loss of consciousness (TLOC). Traumatic TLOC concerns concussions that usually do not pose diagnostic confusion. The three major groups that do cause confusion are syncope, epileptic seizures and psychogenic TLOC. The 'rare and mimics' group is not discussed in this paper. For further discussion, see Refs. [1] and.[24]

common carotid artery splits into the internal and external carotid arteries. As the arterial system has no valves, hydrostatic factors affect actual blood pressure depending on the height of the artery in question. In the upright position, a distance of 30 cm between the aorta and the brain at eye level means that arterial pressure at eye level is 22 mmHg less than at the level of the heart and upper arm where blood pressure is conventionally measured. In the supine position the upper arm, heart and brain are at the same height. If blood pressure at the heart stays the same, lying down will therefore increase arterial pressure at brain level by about 22 mmHg. This simple effect partly explains the beneficial effects of lying down when blood pressure is low; another effect is that the change in posture often allows blood pressure at heart level to increase.

The baroreflex arc involves afferent fibers running from the carotid sinus baroreceptors through the glossopharyngeal nerve, and from the aortic arch through the vagal nerve, to the nucleus tractus solitarii in the medulla oblongata, where integration with other incoming inputs takes place. The efferent signals course through sympathetic nerves running to peripheral blood vessels and to the heart, and parasympathetic (vagal) nerve branches to the heart. The fibers to the heart control heart rate and contractility, while the fibers to peripheral vessels control peripheral vascular resistance. An increase in blood pressure at the carotid sinus causes increased vagal and decreased sympathetic nerve activity, resulting in a lower heart rate, lower cardiac contractility and lower peripheral resistance. Together these changes counteract the increase in blood pressure that set the reflex in motion. Vagally mediated changes can affect heart rate almost instantaneously, whereas sympathetic effects take 2–3 seconds to start.[7,8]

Basics of cerebral flow

Conventionally, cerebral perfusion pressure is defined as the difference between mean arterial and intracranial pressures,[9,10] but this simplification ignores several factors that can play a role in syncope (Fig 2). A more detailed view holds that cerebral blood flow (CBF) firstly depends on a pressure difference between arterial pressure and venous pressures; without that, there is no flow. The second consideration is whether blood vessels are closed by forces opposing the pressure in their lumen that keeps them open: the closing forces are vessel wall tension and tissue pressure.[3,10] All elements in this equation can affect the result. Tissue pressure, which for the brain means intracranial pressure, is normally very low. The exception occurs when the volume of the content of the skull increases, through brain swelling or bleeding. As the rigid skull prohibits any significant changes of the volume of its contents, intracranial pressure will increase quickly. This increase of pressure diminishes cerebral blood flow. When pressure rises sufficiently high that it exceeds the arterial pressure, cerebral blood flow stops entirely. This latter termination of flow is the major mechanism in brain death. A temporary increase in intracanial pressure probably also explains the temporary self-limiting loss of consciousness that can occur in subarachnoid hemorrhage (luckily, other features in its presentation make diagnostic confusion with syncope very unlikely).

The venous flow of blood out of the brain is surprisingly complicated. In the supine position blood exits the brain through the jugular veins, but not in the vertical position. The difference is due to the fact that when in an upright position, pressure in the right atrium is about 0 mmHg resulting in a negative pressure in veins above it, that are accordingly closed by atmospheric pressure.[3] In the standing position, blood exits the skull through veins in the vertebral canal, suggesting that circumstances must be different there.[11,12]

When central venous pressure increases, blood flow out of the brain can decrease. This can contribute to syncope under special circumstances: when people play wind instruments, intrathoracic pressure can increase to such a degree that cerebral venous outflow is impaired.[3] Increased pressure in the cerebrospinal fluid compartment may also play a role,

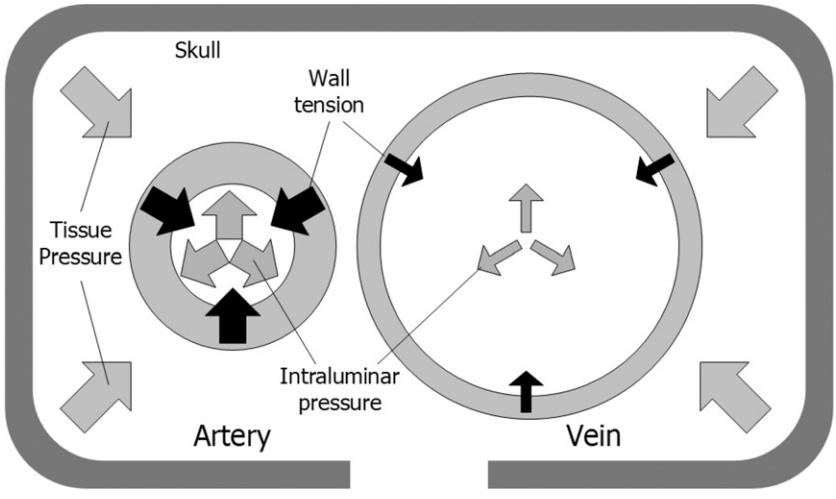

Fig 2 – Scheme of factors influencing cerebral blood flow. The intraluminar pressures keep blood vessels open. Wall tension and tissue pressure, here intracranial pressure, have a closing effect on the vessels. When intraluminar pressure drops below a certain value, the closing pressures gain the upper hand and vessels close: the 'critical closing pressure' (Ref. [10]).

translating as an increase of tissue pressure. A similar mechanism might play an ancillary role in cough syncope,[13,14] a condition that may otherwise be considered a true reflex syncope.[15]

Compared to other organs CBF can be characterized as a high-volume low-resistance system.[16] This set of features can be demonstrated easily by comparing flow in the internal and external carotid arteries: there is little flow in the external carotid artery during diastole, but there is a sizable diastolic flow in the internal carotid artery. Differences between systolic and diastolic flow in the internal carotid artery reveal much about local circumstances. During diastole arterial pressure is lower than during systole, so forces opposing flow, venous pressure, wall tension and intracranial pressure, will affect flow relatively more during diastole than during systole. There are several disorders in which diastolic flow is preferentially impaired.

1. Increased intracranial pressure in which the following may occur:
   - Initial changes as measured with transcranial Doppler (TCD) consist of a decrease in diastolic velocity.
   - When intracranial pressure increases more, diastolic flow ceases completely, leaving so-called 'systolic spikes'.
   - Finally, flow ceases altogether or a 'reverberating pattern' is seen in which a minuscule systolic flow into the brain is matched by an equal diastolic flow back into the artery again.
2. The second circumstance is cerebral vasoconstriction; here wall tension increases, again hampering diastolic flow more easily than systolic flow.
3. The third example is syncope. When arterial pressure is extremely low, even normal venous and tissue pressure will impair diastolic flow (Fig 3).[17,18]

In short, a relative decrease in diastolic cerebral flow can be caused by changes in various elements in the equation determining cerebral flow.

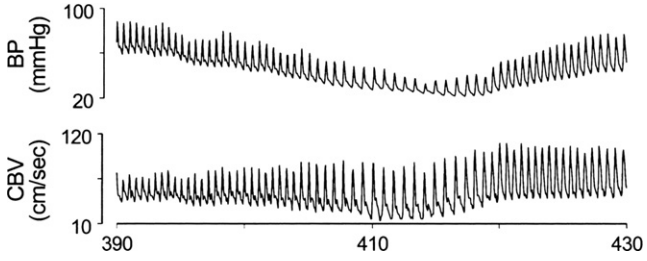

Fig 3 – Cerebral flow velocity in syncope. From Ref.[18]. The upper curve shows continuous blood pressure (BP), while the lower one shows Transcranial Doppler data (cerebral flow velocity, CBV). The blood pressure shows a characteristic pattern, in which systolic pressure falls relatively more than diastolic pressure, so their difference decreases as well. Flow velocity follows a markedly different pattern: systolic flow velocity does not change much in the period when blood pressure is low, while diastolic velocity decreases markedly. Their difference therefore increases.

Cerebral autoregulation

Mean arterial pressure (MAP) is a major determinant of CBF. CBF normally remains stable over a wide MAP range of about 60–160 mmHg, a process labeled 'cerebral autoregulation'. If MAP falls below the lower limit of autoregulation at 60 mmHg, CBF will decrease quickly, following MAP.

Cerebral autoregulation depends on interplay among endothelial, myogenic, metabolic and neurogenic pathways.[3,9,16] The endothelium produces factors with vasoconstrictor and vasodilator properties, among them nitric oxide. The myogenic part of the response depends on an intrinsic ability of smooth muscle cells to exert vasoconstriction in response to an increase in cerebral blood pressure.[16] There are various metabolic factors, of which CO_2 is a very potent one. Hypercapnia induces cerebral vasodilatation and hypocapnia causes cerebral vasoconstriction. Hyperventilation causes cerebral vasoconstriction and in doing so decreases CBF. Neurogenic effects on cerebral autoregulation are mediated through the autonomic nervous system. Sympathetic nerves exert vasoconstriction, and their effect is thought to help protect the brain against high arterial pressure, in effect shifting the autoregulation curve towards higher limits.[16] Parasympathetic effects appear less important, although they have a potential vasodilator effect through release of endothelial factors.[16] Cerebral autoregulation is considered to have a static and dynamic components; the latter concerns changes on a time scale of two to ten seconds[9]; the timescale of most causes of syncope.

Syncope

Pathophysiology of the systemic and cerebral circulation

The pathophysiology of the various forms of syncope is discussed below. First, it pays to organize all forms according to their pathophysiology (Fig 4). In almost all cases a low

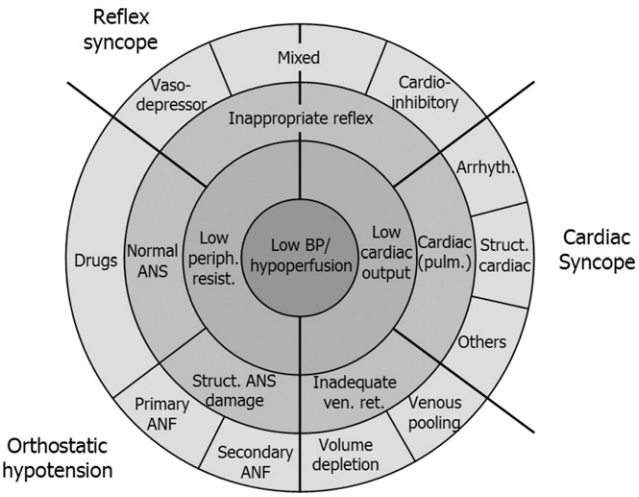

Fig 4 – Pathophysiological mechanisms in syncope. After Ref.[1]. The three clinical main groups of syncope, reflex syncope, syncope due to orthostatic hypotension and cardiac syncope, all cause syncope through a low peripheral resistance or a low cardiac output.

arterial blood pressure is the ultimate mechanism. Low pressure is in turn due to either a low volume of blood entering the arterial system (low cardiac output) or a low peripheral resistance. As Fig 4 shows, the scheme can be detailed further resulting in the three main groups of syncope: reflex syncope, syncope due to orthostatic hypotension and cardiac syncope.

Reflex syncope

'Reflex syncope' is synonymous with 'neurally mediated syncope'.[1] There are various forms, classified through their triggers: vasovagal syncope is triggered by standing with a downward venous pooling of blood, emotions and/or pain; situational syncope is triggered by a large variety of triggers such as coughing, swallowing, micturition and defecation. The course of events will be discussed in the reverse order as they appear: the effector pathway is discussed first, followed by the less well-known afferent pathway.

Efferent pathways. This part of the reflex is relatively well known because relevant variables can be measured directly. Blood pressure drops in all syncope cases and heart rate in many. The latter is caused by increased vagal commands to the sinus node, known as the 'cardioinhibitory' effector part of the reflex. Cardioinhibition can cause an immediate asystole, lasting up to 40 seconds or longer in rare cases. Note that an abrupt asystole will cause an immediate and profound drop in blood pressure, even if vascular tone remains intact. As long as there is a pressure difference between the aorta and the right atrium, blood will flow from the first to the second. Arterial pressure drops very quickly at first, decreasing in speed as the pressure difference decreases.[5] After only three seconds blood pressure is already about halved, reaching 60 mmHg. The circulation may come to a standstill in about 10–15 seconds at a mean filling pressure of 10–20 mmHg.[5] Even without any decrease in heart rate, blood pressure can decrease enough to cause syncope.[19]

Blood pressure is the product of heart rate and total peripheral resistance. So , even without a heart rate decrease the cause must be sought in peripheral resistance. In reflex syncope the decreased peripheral resistance is conventionally attributed to a 'vasodepressor' part of the effector reflex part, in the form of a decrease of sympathetically-mediated arteriolar vasoconstriction. A release of vasoconstriction decreases peripheral resistance and also allows pooling of blood in the venous system, together resulting in a low arterial pressure. The two mechanisms are not exclusive, so there are 'mixed' variants as well as purer 'vasodepressor' and 'cardioinhibitory' ones.

In recent years the 'vasodepressor' explanation has been challenged: in the last 30 seconds or so before syncope a decrease in cardiac output emerged as a major cause of decreasing blood pressure.[20–23] In many cases the decrease in cardiac output coincided with a decrease in vascular resistance, but in one third of cases in a recent study on presyncope low heart rate and low cardiac output occurred without a decrease in vascular resistance[23]; a complete loss of vasoconstrictor activity in sympathetic nerves does occur in syncope, but only during or just before syncope itself.[23] Such studies suggest that the conventional 'vasodepressor' concept is too simple and needs to be replaced by a scheme allowing more interindividual variability in mechanisms as well as room for fairly complex changes in mechanisms before and during syncope.

A curious but characteristic feature of reflex syncope is that heart rate and blood pressure decrease ever more quickly until they either cannot decrease further or syncope stops. This pattern is fundamentally different from that in orthostatic hypotension and can be used to tell the two apart.[24] Yet, its nature has received little attention. The pattern suggests that autonomic control becomes more and more counterproductive during this phase, almost as if the sign of feedback control has been reversed. An inappropriate baroreceptor effect with an effect on heart rate in the opposite direction of what would be expected has in fact been documented during syncope.[25]

Reflex syncope can presumably stop in various ways. When sitting, lying down or during physical counter maneuvers to avert syncope, central hypovolemia is abolished, so the afferent pathway is probably interrupted. Cardioinhibitory reflex syncope must be self-limiting: asystole depends on active inhibition of the heart; ischemia will in the end silence the vagal nucleus, allowing the heart to resume its intrinsic rhythm.

Afferent pathways. The afferent paths are much less clear. In some cases the pathways are obvious: eyeball pressure excites ocular afferents and results in profound vagal cardioinhibition. Massage of the carotid sinus produces mixed cardioinhibitory and vasodepressive effects. In both these cases the response can be regarded as in principle functional: an increased pressure is followed by a response that decreases that pressure, so 'correcting' it, albeit excessively. For micturition syncope, cough syncope or other forms of situational syncope the anatomical structures involved can be named, but the causes and mechanisms are complex and probably differ substantially between the various forms. Two trigger mechanisms will be discussed briefly; these were chosen because they cause syncope very often: standing and emotions.

In 'orthostatic vasovagal syncope', the concept of 'central hypovolemia' attempts to link prolonged standing and activation of the reflex. In this view a gradual change in circulatory control results in changes in volume or pressure in the thorax or abdomen that are apparently not counteracted. In this early phase 'autonomic activation' occurs (nausea, pallor, sweating), whose function is unclear; are they side effects of gradually more abnormal autonomic control? This early phase changes over 10–20 seconds into the phase described above in which blood pressure and/or heart rate suddenly collapse at an increasing rate.

How emotions cause vasovagal syncope is not well understood. Emotions can trigger syncope without any physical stimulus, evidenced by mentioning venipuncture or showing a needle to susceptible patients.[26] Purely emotional faints can occur in people lying down, suggesting that 'central hypovolemia' does not need to play a role in emotional syncope. There may be additional influences besides emotions themselves: patients with blood phobia tend to hyperventilate,[27] and in patients prone to reflex syncope the responses of blood vessels to hyperventilation are stronger than in controls, contributing to syncope.[28]

The origin and purpose of the vasovagal reflex are unclear. It appears to be a purely human peculiarity.[29] Its putative evolutionary purpose has been debated,[30,31] but it is hard to find advantages in a mechanism that shuts down the circulation and thereby the brain.[31] Its very frequent occurrence and genetic propensity[32–34] suggest it is not selected against either, complicating the riddle.

Autoregulation and reflex syncope. If reflex syncope occurs very quickly, as in abrupt cardioinhibition, it is not likely that cerebral autoregulation can act to prevent or even postpone loss of consciousness. Firstly, autoregulation is stated to take 2–10 seconds to act and loss of consciousness starts about eight seconds. Secondly, by that time blood pressure may well be lower than the operational range of autoregulation. Dynamic autoregulation may however be expected to open cerebral vessels in response to the falling blood pressure when blood pressure decreases less abruptly. A typical trans-cranial Doppler (TCD) finding in this phase, when blood pressure decreases but consciousness is not yet lost, is that systolic flow velocity stays intact but diastolic flow velocity decreases. Vasoconstriction, which can indeed explain this pattern was an early explanation. However, vasoconstriction would be the opposite of what cerebral autoregulation would be expected to do.[35] Later studies suggested another explanation: estimates of cerebral vascular resistance based on the ratio of blood pressure and flow velocity suggested that resistance was in fact low, i.e. autoregulation was doing its best to keep CBF going[18] (Fig. 3). Similar conclusions were drawn by others.[36,37] As explained above, a preferential decrease of diastolic versus systolic flow can be caused by various influences, of which vasoconstriction is one. In syncope, blood pressure probably becomes so low that some vessels may collapse in diastole.[37] This explanation is in line with the expected action of cerebral autoregulation, but is not accepted by all.[16]

Orthostatic hypotension

The upright position has a marked effect on the circulation and cerebral blood flow even in healthy subjects.[3,38–40] Normally, 500 to 1000 ml of blood shifts from the upper to the lower body on standing. This is followed by a loss of plasma volume into tissues, a transfer that approaches stability in a period of 20–30 minutes.[3,39]

Orthostatic hypotension is defined as a drop in systolic blood pressure of ≥20 mmHg or of diastolic blood pressure of ≥10 mmHg within three minutes of standing.[41] When the supine systemic tension is over 160 mmHg, a systolic fall of 30 mmHg is required. Note that this definition concerns the so-called 'classic' orthostatic hypotension, distinguished from two other forms. The first is initial orthostatic hypotension, in which a usually normal autonomic nervous system lags in adapting the circulation after subjects stand up.[41] This corrects itself within 30 seconds in the standing position, unless syncope intervenes. The other form is 'delayed orthostatic hypotension', often found in the elderly in whom blood pressure may take longer than three minutes to decrease.[41]

'Classic' orthostatic hypotension occurs through various mechanisms, classified in various ways.[42,43] Drugs are by far the most common cause, mostly causing vasodilatation, hypovolemia or sympathetic inhibition. Secondary causes are disorders that are accompanied by a low cardiac output, such as hypovolemia, excessive venous pooling or impaired vasoconstriction by autonomic nerve damage secondary to other diseases. The smallest group of causes concerns 'primary autonomic failure' in which the disease in question damages the sympathetic autonomic nervous system, either in the periphery (pure autonomic failure, auto-immune autonomic neuropathy) or in the central nervous system (multiple system atrophy, Parkinson's disease with orthostatic hypotension, Lewy body dementia).[38,43] The mechanisms in primary autonomic failure have been studied in most detail. The resulting 'neurogenic orthostatic hypotension' occurs as a result of a failure of the peripheral sympathetic vasoconstrictor mechanism to close arterioles in the standing position. Peripheral resistance does not increase as it should and may even fall, so blood will pool in veins in the splanchnic, pelvic and leg areas.[3,19,38,39,44,45]

In neurogenic orthostatic hypotension, blood pressure usually drops quickly at first, leveling out until a new stable state ensues. As such the decrease is reminiscent of a leak in a tire or a balloon, in which air leaks out quickly at first until its escape lowers the pressure differential, slowing the leakage.

Note that a decrease of >20 mmHg need not lead to syncope or even complaints, provided blood pressure in the standing position remains high enough to ensure cerebral perfusion. In some cases blood pressure does decrease quickly enough to cause syncope within about 20 seconds of assuming the vertical position. Even with severe autonomic damage the actual blood pressure fall depends on the circumstances, with hypovolemia an important modifier: a relative hypovolemia explains why orthostatic hypotension is often worst in the morning.

Note that the three minute period in the definition is accepted for routine clinical purposes,[1,38] but does not include all cases with a failing control while standing. It yields abnormal results in at least 50% of patients with autonomic disturbances,[46,47] so normal findings in three minutes do not exclude a clinically relevant blood pressure drop.

Autoregulation and orthostatic hypotension. When orthostatic hypotension is due to causes that do not impair cerebral autoregulation, cerebral autoregulation should limit the consequences of a falling blood pressure, provided the fall occurs slowly enough to be counteracted. In autonomic failure the situation is more complicated, as cerebral autoregulation depends in part on the sympathetic system. As a result it is conceivable that autoregulation is impaired in autonomic failure; then again, the non-autonomic parts of autoregulation such as myogenic actions could possibly compensate for the failure of the autonomic contribution.

Clinical experience suggests that patients with neurogenic orthostatic hypotension remain fully conscious at extremely low blood pressure values, suggesting excellent autoregulation.[48] Several authors investigated autoregulation through the relationship between paired blood pressure and flow velocity measurements: if autoregulation works there should be no relationship, because flow velocity should remain stable in spite of changing arterial pressure. If velocity does vary with MAP, the

relationship would signify defective autoregulation. Most studies suggested normal autoregulation,[48–52] whereas others pointed to defective autoregulation.[53,54]

Cardiac syncope

There are two major groups of causes of cardiac syncope: arrhythmia and structural cardiac diseases. In both, the major determinant of syncope is a sudden impairment of cardiac output. Arrhythmias commonly occur with antecedent heart disease. Among arrhythmias, a bradyarrhythmia causes syncope more often than a tachyarrhythmia. In bradyarrhythmia, syncope occurs when there either is sustained low ventricular rate, usually less than <30 beats per minute for 15–30 seconds, or when heart beats cease altogether (asystole), which probably needs to last for about eight seconds to cause loss of consciousness. The classic example of the latter is a Stokes–Adams attack due to intermittent atrioventricular heart block. In cases of abrupt severe bradycardia, premonitory symptoms are either absent or last for such a short time that patients may not be able to act on them.

In structural heart disease, a difference between the demands of the body and the actual cardiac output partly explains why syncope in cardiac disease tends to occur during physical exercise, an important clue towards a cardiac origin of syncope.[1] It is not likely that this is the only mechanism however, as otherwise a gradual inability to do physical work would seem more likely than an abrupt failure with syncope. In such cases and in arrhythmias an inappropriate systemic reflex response can contribute to syncope susceptibility.[2,24,55]

Autoregulation and cardiac syncope. There are few studies on how the cerebral circulation responds to arrhythmia. In a study on induced atrioventricular block, cerebrovascular resistance, estimated by the arterial pressure/cerebral flow velocity ratio, showed a short-lived increase in resistance attributed to passive behavior of the arteries before resistance dropped below baseline, 5–10 seconds after the onset of asystole.[56] Such results confirm that cerebral autoregulation is unlikely to prevent syncope when syncope is very abrupt, such as in cardiac standstill. Autoregulation is more likely to have beneficial effects when events happen more slowly, as in bradycardia; it also improves cerebral perfusion after syncope, when blood pressure is still low.

Signs and symptoms of cerebral hypoperfusion

Syncope causes cerebral ischemia, resulting in a bewildering variety of clinical signs but also in much more stereotypical findings on the electroencephalogram (EEG). The symptoms and signs of syncope generally fall into two groups[5,24]: the first group is related to the cause of syncope, such as palpitations in arrhythmic syncope, nausea in reflex syncope and neck pain in neurogenic orthostatic hypotension.[1] The second group concerns the consequences of cortical and retinal hypoperfusion, detailed in a previous review.[5]

The EEG

The electroencephalogram (EEG) provides an objective marker of brain dysfunction during syncope. The first EEG pattern of syncope to be described was the so-called 'slow-flat-slow' (SFS) pattern[57–59]: the first slow phase concerns a loss of normal activity such as the alpha rhythm that is supplanted by progressively slower waves (theta and delta bands) of increasing amplitude. These high-amplitude waves can disappear in less than two seconds, leaving a flat EEG. When cerebral circulation resumes, slow waves equally suddenly start again, and then decrease in amplitude and increase in frequency until the EEG is normal again (Fig 5). The second main EEG pattern consists of slow activity only, which increases to a maximum and then decreases.[58,5] The slow-flat-slow pattern points to more severe cerebral hypoperfusion: it was first described in asystolic syncope induced by eyeball pressure, and studies comparing both patterns in reflex syncope proved that cardioinhibition was strongly related to the presence of EEG flattening.[60,61] Fig 6 illustrates the differential behavior of heart rate changes in tilt-induced syncope between those in whom the EEG showed only slowing and those with flattening as well: heart rate indeed decreased much more strongly in those with flattening.

The EEG reflects events on cellular and network levels. The electrical potentials of the EEG start as inhibitory and excitatory postsynaptic potentials acting on cortical neurons, not the action potentials of those neurons themselves. The second level holds that EEG waves reflect summed activity of synchronous activity modulated by connected networks. Ischemia and anoxia cause synaptic activity to cease well before cell injury or death occur.[62] It is therefore reasonable to assume that the slow phases of the EEG in syncope reflect an increasing failure of networks due to decreasing synaptic activity. The flat EEG phase must reflect the complete stop of cortical function as a connected whole, either because there simply is no synaptic activity left or because there is too little of it to maintain network activity.

Carotid occlusion studies showed that EEG flattening occurs when hemispheric flow falls below 0.16-0.17 ml per gram per minute.[63] Once the EEG is flat it cannot indicate any further worsening of hypoperfusion. The cortex is particularly vulnerable to anoxia, but this does not mean that other brain areas remain functional. In fact, the corneal reflex disappears during syncope, proving local disruption of brainstem function. However, some brainstem areas do remain functional: respiration is known in neurology to be one of the last functions to cease, and thus appears resistant to a variety of noxious influences. Accordingly, respiration usually continues during syncope. The dorsal vagal nucleus also appears rather resistant to ischemia: the presence of asystole in cardioinhibitory reflex syncope proves it remains active for a long time after the cortex has stopped working.

Signs in syncope

The pathophysiology of neurological symptoms during syncope is largely unknown. Early studies on asystolic syncope induced by eyeball pressure resulted in opisthotonus and myoclonic jerks, interpreted as due to 'liberation of subcortical structures'.[57] This widely quoted disinhibition theory was never proven, and reflection on the nature of syncopal signs suggests that 'disinhibition' is not the only explanation of syncopal symptoms.

In fact, many symptoms reflect the absence of normal cortical function, with loss of consciousness as the prime

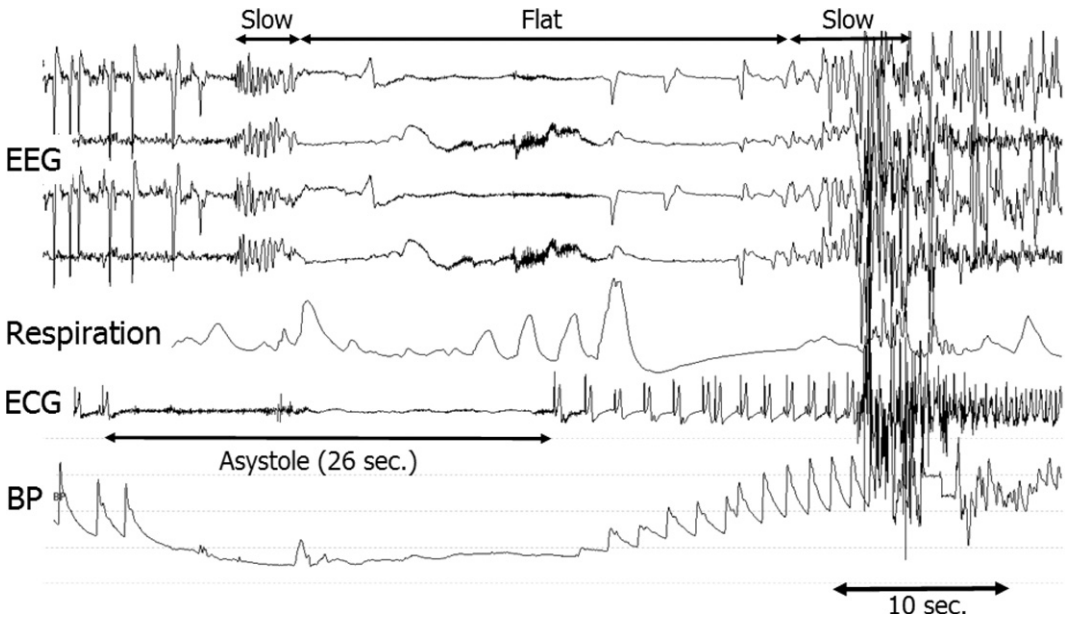

Fig 5 – EEG in syncope. The figure represents results from reflex syncope induced by a tilt table test. Blood pressure was already decreasing at the time shown in the left side of the figure. It decreases further and bottoms out after asystole, lasting about 26 seconds in this case. The EEG responds to asystole by slowing that starts about eight seconds after the last beat. The first slowing period lasts only a few seconds, a typical finding with long-lasting asystole. Note that respiration shows stertorous breathing during the period of the flat EEG, after which breathing appears to cease. After heart beats resume blood pressure builds up again. The second period of EEG slowing lasts longer than the first one. The EEG is contaminated by eye blinks in the beginning of the record, probable movement artifacts in the flat period, and abundant movement artifacts when the patient regained consciousness at the end of EEG slowing.

example. The ESC classification of TLOC was purposely defined to be useful clinically, so the definition of apparent loss of consciousness was restricted to data from history taking and eyewitness accounts.[1,24] The three key events[24] are:

1. A lack of normal motor control (falling, stiffness, myoclonic jerks),
2. Lack of responsivity during the attack
3. Later amnesia for the event.

A subtler and more complete view of consciousness acknowledges the presence of arousal and content aspects[64]: arousal describes the spectrum from awake through sleep and stupor to coma, and content describes awareness of ongoing external events or self-awareness. Recent developments are starting to unravel the underlying mechanisms of loss of consciousness. For instance, the 'default mode network' describes connected cortical areas that are mostly active while people are at rest, and quiet during goal-directed behavior; it may be crucial for self-awareness.[65] Likewise, the 'consciousness system' controls the level of consciousness.[66] It consists of major cortical areas as well as the upper brainstem, thalamus, hypothalamus and basal forebrain.[66] People who are fully conscious may be described as being 'awake, attentive and aware'.[66] Syncope usually abolishes all three aspects, but not at the same time. Older experimental studies showed that a loss of voluntary eye movements and the will to act are the very first expressions of brain dysfunction in syncope, before the loss of motor control.[6,67,68] A similar loss of the will to act can be seen when peoples with neurogenic orthostatic hypotension remain standing while their blood pressure drops very slowly. The fact that subjects later remember such events showed that awareness and memory storage still function, proving that different cortical areas in the default mode network and consciousness systems have different sensitivity to ischemia.

There is a variety of complex signs and symptoms in syncope that probably require cortical activity rather than a loss of it. Examples are an aura,[69] near death experiences and complex movements such as lip-licking, sitting upright or rubbing the head.[70,71] It is not credible that such activity can occur during EEG flattening, so these events are likely to occur only during slow phases, and presumably when limited hypoperfusion persists for some time. In Lempert's video head rubbing can be seen in subjects who remain sitting after induced syncope.[71]

Finally, disinhibition is likely to explain various other features of syncope, such as eye opening, incontinence and opisthotonus. The eyes in syncope are opened widely, which differs from the half-open position during neuromuscular blockade or death. This active open position is maintained throughout flattening of the EEG and must therefore be generated elsewhere than in the cortex.

Epileptic seizures

Epileptic seizures are caused by uncontrolled excessive repetitive neuronal cortical activity. As such, seizures differ fundamentally from syncope in which there is a cessation of

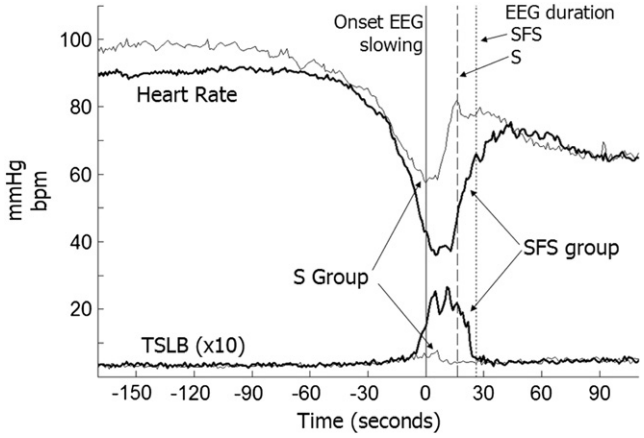

Fig 6 – Heart rate and EEG patterns. Data from 69 cases of tilt-induced syncope were divided in 31 cases in whom the EEG showed slowing (S) only and 38 cases in whom there was a slow-flat-slow (SFS) pattern. Individual heart rate data were arranged around the second at which the EEG started slowing (time zero). Heart rate was calculated from ECG RR-intervals and illustrated in two ways. The first is heart rate in beats per minute. The second was 'time since last beat' (TSLB): for each second the time was calculated since the last occurring heart beat. When heart rate is around 60 beats per minute TSLB will be between 0 and 1 second, and is then not informative, but in periods of asystole the value rises. Here, bold lines indicate heart rate and TSLB for the SFS group, while thin lines indicate the S group. In the SFS group, heart rate starts lower, drops earlier, deeper and rises later than in the S group. The mean duration of EEG slowing is shown, lasting longer in the SFS than in the S group.

cortical activity. While true, such simplicity disappears once signs and symptoms are scrutinized. For instance, in so-called primary generalized forms of epilepsy, such as 'absence seizures' and primary generalized tonic clonic seizures, one might aspect increased brain activity and hence increased blood flow over the entire cortex, but this is not the case.[66] Flow and electrical activity can be depressed in areas of the consciousness network, and this depression may cause loss of consciousness.[65,66] Rather surprisingly, loss of consciousness in epilepsy and syncope may therefore have depressed activity in the same networks in common.

The precise origin of many signs in epilepsy is not known; examples are stiffening, myoclonic jerks and oral automatisms. The reasons for the lack of knowledge are that many brain areas are not amenable to testing during an attack that may cause injury; this limitation also holds for syncope.

Syncope and epileptic seizures may cause one another. The path from syncope to seizure involves ischemia, which regardless of its cause can trigger epileptic seizures. Hence, syncope can induce an epileptic seizure.[72,73] Most such seizures have been described in children with recurrent syncope. Parents, familiar with the attacks, may note the unexpected occurrence of prolonged clonic movements beginning during an otherwise typical attack. Several steps of increasing diagnostic confidence to recognize these attacks have been proposed.[73] They are probably rare: in one series 7–8% of syncopal attacks in children transformed into epileptic seizures.[73] Only one adult case seems to have been described, concerning a patient with known epilepsy[74]; this may represent a spurious occurrence.

An epileptic seizure can cause syncope through bradycardia or asystole, which probably only occurs in about 0.5% of seizures.[75] A relative tachycardia is expected instead, as it occurs in roughly 90% of all epileptic seizures; the resulting tachycardia is not fast enough to cause syncope. Sinus bradycardia or asystole occur in complex and simple partial seizures originating in the temporal lobes, not in generalized tonic–clonic seizures. Such events tend to occur well into the seizure, with a variable time after EEG-documented seizure onset. The duration of asystole varies from the definition threshold of asystole (3 or 4 seconds) up to 60 seconds.[75–78] Attacks may clinically be recognized when atonia and a fall suddenly occur during an otherwise typical complex partial seizure,[77] or when bilateral limb jerks and a collapse or head drop occur.[76] Full syncope terminates the epileptic seizure through a forced cessation of all cortical activity. How often such attacks occur is not known. Implantable loop recorders in a long-term study in 19 cases revealed bradycardic/asystolic events in 2% of seizures.[75] Studies on larger groups but with shorter observation resulted in lower estimates of ictal asystole.[77,78] Ictal asystole may play a role in sudden death in epilepsy, along with respiratory and intrinsic cardiac factors.[79]

Psychogenic apparent TLOC

'Psychogenic' TLOC (which is actually an 'apparent' but not real TLOC as there is no true loss of consciousness) does not sit easily in a section on pathophysiology, because understanding how the mind works is not easy to assess; one must rely on subjective accounts and on processes of which persons need not even be aware.

There are two types of psychogenic apparent TLOC: in the first the attacks resemble epileptic seizures because of the presence of motor abnormalities such as myoclonic jerks or a stiff posture. Such attacks are well-known by epileptologists, as they make up about 20% of cases in tertiary epilepsy clinics. This type goes under various names, of which 'psychogenic non-epileptic seizures' (PNES) is probably the best known one. In the second type the attacks resemble syncope or coma as they involving a sleep-like immobile state with closed eyes. This type may be labeled 'psychogenic pseudosyncope' (PPS) to stress what it resembles yet is not. Its prevalence is not well known: estimates were 6% of unexplained syncope[80] and 6% of possible syncope.[81] Some authors suspect a much higher prevalence.[82] In one of the authors' (JGvD) series of tilt tests, PPS was observed in 3.7% of 720 tests. Not all cases of psychogenic pseudosyncope will occur on a tilt table test. In the same series the estimated rate on clinical grounds was about double that of tilt-evoked psychogenic attacks.

There is probably no fundamental difference between the two psychogenic forms of apparent TLOC in psychological terms, although this has not been investigated in depth, as PPS has been studied much less often than PNES. In both there are often predisposing factors, such as sexual or non-sexual trauma,

bereavement, social/family factors or heath issues.[83] PNES occurs fairly often in those with epilepsy, and PPS during tilt testing followed real syncope or presyncope in one quarter of PPS cases in one of the authors' (JGvD) case series.

In psychiatry PPS and PNES fall under 'somatoform disorders' of the DSM-IV,[84] more specifically under 'conversion disorder'. The definition includes unexplained symptoms or deficits affecting voluntary motor or sensory function that suggest a neurological or other general-medical condition; psychological factors are judged to be associated with the symptoms or deficits.[85,86] In the authors' opinion this definition has little practical value. Instead, diagnosis is based on positive diagnostic clues, such as eye closure during attack (the eyes are almost always open during syncope and epileptic seizures), a high frequency, and attacks of long duration: ten attacks a day and a duration of half an hour are not exceptional. The attacks can often be provoked using a tilt table test with continuous blood pressure and heart rate; neurologists prefer to add an EEG and video recording. The EEG is extremely sensitive to cortical dysfunction, so a normal awake EEG with alpha activity during apparent complete loss of consciousness proves the absence of a somatic explanation nature, leaving no other explanation. Close inspection reveals that the attacks usually do not resemble syncope or coma that much; in fact, in one of the authors' series (JGvD), there were fewer myoclonic jerks in psychogenic pseudosyncope than in real syncope. Heart rate and blood pressure during such events are usually high rather than low, and the increase occurs before the clinical onset of the event, which probably indicates stress before the event.

If attacks cannot be provoked on a tilt-table, pathophysiological data may still be used to reach a diagnosis: attacks can be recorded using home video and/or blood pressure recordings. Inspection of the video will show events that are pathophysiologically incompatible with loss of consciousness, while a normal or high blood pressure during apparent loss of consciousness excludes syncope.

Conclusion

The pathophysiology of syncope, in all its forms and in its entire scope from cause to neurological signs, is based on the physiology of the heart, the systemic circulation, the autonomic nervous system, cerebral perfusion with its complex interplay of pressures and cerebral autoregulation, and finally of cortical and subcortical functions and their interplay. Pathophysiological knowledge is crucial for clinicians, as it allows them, through history taking, to distinguish between the many forms of syncope and TLOC.

Statement of Conflict of Interest

All authors declare that there are no conflicts of interest.

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