Understanding syncope in the framework of transient loss of consciousness

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CHAPTER I

General introduction

General introduction and scope of this thesis

Syncope, commonly but imprecisely also known as 'fainting' or 'blackout', is the most frequent form of transient loss of consciousness (TLOC). It differs from all other forms of TLOC in that it is associated with cerebral hypoperfusion.[3] Apart from unconsciousness, syncope shares the following features with other forms of TLOC: a transient, self-limited nature, a short duration (seconds-minutes) and spontaneous complete recovery.[3,4]

The lifetime prevalence of syncope is high: around 30-40% of the population experiences vasovagal syncope, the most common cause of syncope, at least once in their lifetime with a peak incidence during adolescence. No less than 5% of the population have at least five episodes during their lives.[3,18]

In syncope, loss of consciousness is frequently preceded by a variety of prodromal features, such as blurred vison (caused by hypoperfusion of the retina) or lightheadedness.[5] These prodromal symptoms may help patients to recognize an upcoming attack and to prevent losing consciousness by sitting down, or, better, lying down. Other counter manoeuvres include squatting, leg crossing or body tensing.[6,36] Syncope is often accompanied by abnormal movements such as myoclonic jerks (51-90%)[37,45,47]or oral movements (50-79%)[37,45] A seminal video study on the semiology of syncope was performed by performing the 'fainting lark'.[37] This manoeuvre, which is frequently carried out at schoolyards or parties, consists of a combination of hyperventilation, orthostasis, and a Valsalva manoeuvre, and causes an abrupt-onset syncope. In all subjects the eyes remained open during loss of consciousness. 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. Other movements included a flaccid or a stiff posture.[37] Semiology studies in tilt-induced syncope[37,38,45,47] found similar percentages for eye opening (92-100%)[45] and also reported several other ictal events. Urinary incontinence is reported frequently (but in less than 25%), as well in abrupt-onset syncope, for instance in cardiac arrest, as in vasovagal syncope.[38,39,40] Fecal incontinence can be seen but is extremely rare.[39]

Tongue biting may occur but is rare and is associated more often with biting the tip of the tongue and not a lateral tongue bite.[38] The latter type of tongue biting is seen in focal or generalized tonic clonic seizures.

Vocalisations are frequently observed (40-60%) but may also occur after the event, like yawning (40-60%).[37,45] The pathophysiology of this last phenomenon is not completely clear.

As unconsciousness causes amnesia, the clinician often depends on an eyewitness account to extract features during the event. However, those accounts should be interpreted with caution, especially if only one event was observed, as many signs are frequently overlooked or inaccurately recalled.[40]

Syncope is a symptom, and in itself not a disease nor a diagnosis. In all cases it is therefore important to find an underlying cause.

Pathophysiology of reflex syncope

Reflex syncope is the most frequent form of syncope in all ages; it is probably unique to humankind, especially in the form of fainting by emotional triggers.[54]

The pathophysiology of syncope is poorly understood as most processes in the central and peripheral nervous system are difficult to measure. Current concepts regarding the pathophysiology are derived from information we can measure directly, like blood pressure, total peripheral resistance, cardiac output and neurohumoral changes.[51]

Figure 1 shows the presumed pathophysiology of reflex syncope.[3] The afferent pathway transfers signals from circulatory (like baroreceptors in the carotid sinus and aortic arch) and visceral stretch receptors to the brain. This pathway can be triggered in various ways, for instance by pain and gastrointestinal symptoms but also by standing. Emotional triggers, fear and pain in particular, can also facilitate activation or trigger it directly, sometimes without any physical stimulus at all. It is unclear how such an external trigger in the form of pure information can elicit the vasovagal reflex.

The main efferent components of the reflex are bradycardia, through the vagal nerve, and vasodilation of vessels in the splanchnic region and lower limbs through a release of sympathetic vasoconstriction. The lowering of heart rate, and perhaps also of contractility, is called 'cardioinhibition'. A decrease of vasoconstriction is called 'vasodepression'; while some reserve this concept to arteriolar vasodilation, in recent years several papers regarded venous vasodilation as an expression of vasodepression as well, giving it an arterial as well as a venous component.[48, 49,50] In most cases it is the combination of vasodepression and cardioinhibition that ultimately results in reflex syncope. According to the most important component in a specific case, the pathophysiology of reflex syncope is classified as vasodepressor, cardioinhibitory or a mixed type.

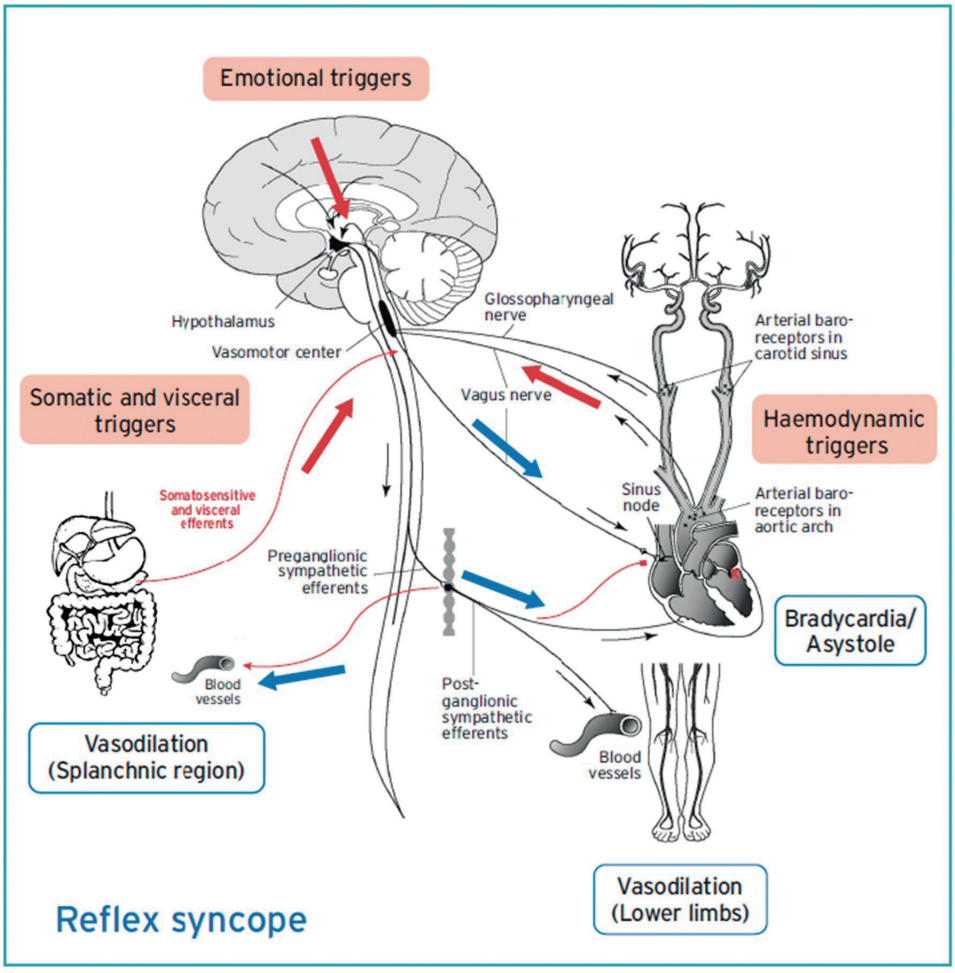

Figure 1. The mechanism of reflex syncope: anatomical view.
Afferent pathways (shown in red) transfer information from the circulatory and visceral receptors to the brain. Arterial baroreceptors are in the aortic arch and the carotid sinus; these are stretch receptors that are activated when distended by an increase in arterial pressure. Afferent nerve fibres from the carotid sinus and the aortic arch join the glossopharyngeal nerves (IX) and vagus nerves (X), respectively, toward the vasomotor centres in the brainstem. Higher brain functions (emotional triggers) can also activate the reflex. The efferent pathways (shown in blue) consist of the vagus nerve to the heart and sympathetic fibres to the heart and blood vessels. The effector paths may evoke bradycardia/asystole in most but not all patients, while dilation of vasoconstrictor vessels and capacitance vessels is seen in all patients. [3]

History of syncope

This section will elicit the history of syncope, with attention to the evolution of patho-anatomical theories and clinical description. Furthermore, we will spread some light on the technological inventions which helped diagnosing syncope.

Syncope comes from the Greek word 'συγκοπτειν', which means to 'cut short'/'cut off'. The first descriptions of syncope date from ancient Greece. Hippocrates (c. 460- 377 B.C.) described the following:

'οἱ ἐκλυόμενοι πολλάκις καὶ ἰσχυρῶς, ἄνευ φανερῆς ροφάσιος, ἐξαπίνης τελευτῶσιν.' ('*Persons who have had frequent and severe attacks of swooning, without any manifest cause, die suddenly')*[1]

Aretaeus of Cappadocia, living in the second century in what nowadays is known as Turkey wrote the following in his book ' De causis et signis acutorum morborum'[31]:

"*It is, indeed, the name of a very acute malady; for what is there greater or more acute than the power of Syncope and what other name more appropriate for the designation of this matter? What other organ more important than the heart for life or for death? Neither is it to be doubted that syncope is a disease of the heart, or that it is an injury of the vital powers thereof—such is the rapidity and such the mode of the destruction."*[31]

Hippocrates and Aretaeus explicitly referred to what we know recognize as cardiac syncope, probably of an arrhythmic nature, in which there is no obvious trigger. Claudius Galen (c. 129-200), a famous Greek physician and follower of the Hippocratic school, believed that:

"Syncope is a sudden prostration of the vital powers, without suspension of the respiration and it is usually a sign or complication of fever."[2]

According to Galen, the solution for this problem was phlebotomy (bloodletting).[33] We may well wonder how often that particularly therapy in fact elicited a recurrence of vasovagal syncope in his patients. Galen's view of pathophysiology was centred on the four humours (blood, bile, black bile and phlegm) and he saw syncope as 'the dissolution and deterioration of vital powers.[34,46] However, he was the first to describe the vagal nerve and his route from the brain to the heart.[2] He believed that syncope was a sign that the heart was weakened by an abnormal irritation. This concept is in fact quite similar to the current idea of cardioinhibition, in which overly strong inhibitory impulses slow down heart rate, up to and including a complete cessation of all beats for up to one minute.[34] These ideas held authority for hundreds of years, as in medieval times medicine was still largely practiced on the basis of teachings of the ancient Greeks.[42]

In literature there are many examples of syncope in medieval times and later. A brilliant paper from the BMJ Christmas Edition shows all descriptions of syncope or near-syncope in Shakespearean plays.[11,35] In Hamlet, for instance, the main character is frightened by his father's ghost and speaks:

"Hold, hold, my heart, and you, my sinews, grow not instand old, but bear me stiffly up"[10]

suggesting palpitations of the heart and buckling knees. These symptoms suggest a near-syncopal attack or rapid drop in cardiac output. In several other plays syncopal events are described, often in situations of deep grief or fear.

William Harvey (1578-1657) was the first to challenge the ideas of Galen and came with the revolutionary idea of the heart as a pump:

"The movement of the blood occurs constantly in a circular manner and is the result of the beating of the heart"[42]

He also introduced the idea that a slow heart rate created a reduction in blood flow, resulting in syncope.[8] In Exercitatio anatomica de motu cordis et sanguinis in animalibus, he wrote:

"Yet if fear or any other cause, or something do intervene through passion of the mind, so that the heart do beat more faintly, the blood will by no means pass through but drop after drop."

Herman Boerhaave (1668-1738), at the time a world famous physician from Leiden, viewed the body in terms of mechanical structures, as a plumbing network of pipes and vessels. Boerhaave, a great admirer of Isaac Newton, stated the following on syncope in his oration *De usu ratiocinii mechanici in medicina*:[42]

"Now let us consider the case of an over-sensitive person (homo mollis) who is upset by the sight of blood gushing from a wound, and faints away. We see, then, a dead man: but in what sense dead? In this body all solid and liquid parts which suffice for life and health are present – the only thing which is lacking is the motion which causes the humours to circulate. And when eventually the nerves of this patient are roused to activity, by whatever means you will, so that the matter which sets the heart in motion resumes its course, then at once happy life returns, the sad spectrum of death is banished. Not only does death return; at the same time warmth, a blushing colour, mobility, the faculty of though, every vital, natural, human activity is resumed. What ferment, effervescence, what aggressive salt, oil or spirit is created or destroyed in such a situation? Nothing is added or taken away, except motion; yet life itself was lost and has been restored." [52]

In 1907, William Gowers (1845-1915) introduced the term 'vasovagal'.[19] For Gowers, vasovagal was a purely descriptive term for episodes of a variety of gastric, respiratory, and cardiac symptoms, which he ascribed to vagal activity together with complaints of pallor and coldness, which he attributed to vasomotor activity. In 1932, Lewis rejected this

idea and described this reaction as being characterized by a combination of bradycardia, hypotension, and syncope.[20]

A major turning point in physiological syncope research came with the invention of the sphygmomanometer (1896, Riva-Rocci) and electrocardiograph (Einthoven, 1901).[42]

Until then, syncope was commonly attributed to a slow pulse rate causing a decrease in cardiac output. With these inventions it became possible to measure blood pressure and heart rate simultaneously and thereby relating clinical observations to physiological findings.

Studies performed by Barcroft and Sharpey-Schafer between 1940 and 1950, using volume-based plethysmography, demonstrated major forearm vasodilation during extreme hypotension and concluded that the main mechanism for hypotension was vasodilation.[21,22]

A final milestone came in the late 1970's when Pinaz and Wesseling developed the noninvasive beat-to-beat blood pressure monitor,[24] allowing continuous monitoring of blood pressure in physiological situations. This made it possible to identify rapid BP changes upon standing that cannot be captured with long-interval measurements and thus helped to differentiate syncope from other forms of loss of consciousness with certainty. Furthermore, in 1986, the tilt table test was introduced as a means of eliciting and diagnosing vasovagal syncope.[23]

Classification

Transient loss of consciousness (TLOC) is used to describe a group of several presentations which include syncope, epilepsy and psychogenic pseudosyncope (Fig 2). A reliable differentiation between those causes, or groups of causes, is essential because the cause and, more importantly, treatment differs significantly between causes. Till recently the definition of syncope varied substantially among medical journals.[4] This lack of a precise definition carried the risk of diagnostic confusion. In **chapter II** the logic behind the current classification of TLOC, used by the European Society of Cardiology (ESC) is explained. This classification goes back to 2001, and contains the three major groups of syncope, epileptic seizures and functional or psychogenic TLOC. In that chapter, we provide short descriptions of different forms of syncope and other forms of TLOC.

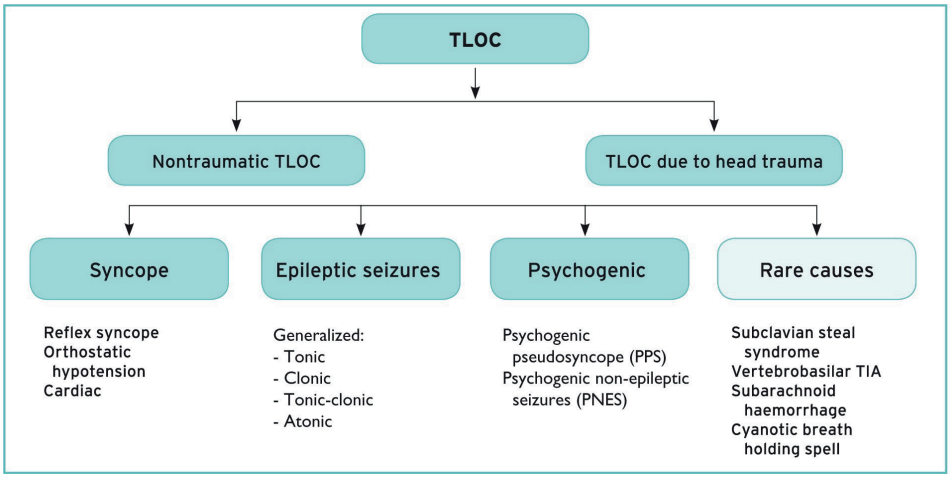

Figure 2. Syncope in the context of transient loss of consciousness.
Non-traumatic transient loss of consciousness classified into one of four groupings: syncope, epileptic seizures, psychogenic transient loss of consciousness, and a miscellaneous group of rare causes. This order represents their rate of occurrence. Combinations occur; e.g. non-traumatic transient loss of consciousness causes can cause falls with concussion, in which case transient loss of consciousness is both traumatic and non-traumatic. TIA = transient ischaemic attack; TLOC = transient loss of consciousness. [3]

Asystole

The term 'reflex syncope' refers to those forms of syncope in which neural reflex responses play a key role in causing transient hypotension and consequent diminution of cerebral blood flow. Reflex syncope may encompass both vasodepressor and cardioinhibitory mechanisms. Although either mechanism can cause syncope, in most cases both occur together. The cardioinhibitory mechanism is effected primarily through an increase in vagal tone[25,26]. Its most extreme expression is abrupt prolonged asystole, usually defined as a cardiac pause >3 seconds, which on its own is enough to cause blood pressure (BP) to fall precipitously.

The presence of asystole in vasovagal syncope (VVS) may prompt physicians to consider pacemaker therapy for syncope prevention. While this initially seemed straightforward, the limited success of pacing to prevent syncope suggested that asystole could not have been the prime mechanism in many cases of VVS, even in cases in which asystole was undeniably present. Why this was so was unclear; we wondered whether it would be possible for asystole to occur after patients had already fainted due to vasodepression. In **chapter III** we investigated the relationship between the onset of asystole and of transient loss of consciousness (TLOC) in tilt-induced reflex syncope. The approach allowed us to estimate how often asystole could not have been the principal cause of TLOC.

Rare forms of syncope

In chapter IV we described two pitfalls in patients with unexplained TLOC. One is a relatively rare form of reflex syncope called 'sleep syncope', in which someone awakes due to abdominal discomfort or nausea, and then faints. It is often associated with a cardio-inhibitory reflex and most patients experience syncope while lying in bed or while walking to the toilet. Supine syncope is a well-known red flag for cardiac syncope, implying a severe arrhythmia that brought the circulation to a near or complete standstill. In the case of sleep syncope, there is however no cardiac cause but only an extreme vagal tone, with the same effect, i.e. a cessation of the circulation.

The second case concerned two forms of TLOC, vasovagal syncope and psychogenic pseudosyncope, in one patient. This is a relatively common situation, one that clinicians should pay attention to, as one of the two diagnoses can be easily missed.

Reflex syncope may occur due to a variety of triggers including fear, pain, standing, and more rare ones, for instance coughing. 'Situational syncope' is a form of reflex syncope and, as the name suggests, triggered by certain actions or situations. Triggers include micturition, defaecation, swallowing and vomiting; new triggers are still being added to the list.

In **chapter V** we described five cases of syncope during bending forward, not described as a trigger till now. All five patients experienced AV-block during bending and all responded favourably to pacemaker therapy. The key to the diagnosis was to find out wat triggered the attacks and to provoke an attack in the clinical setting, allowing proper diagnosis and treatment.

Tilt table testing (TTT)

Reflex syncope is responsible for 1-6% of hospital admissions; the economic burden of syncope is correspondingly huge.[27,28] A considerable part of these high costs is spent on tests with a very limited benefit, as they are aimed at disorders unlikely to have caused syncope in the first place.[30] A TTT can be helpful for diagnosis and treatment of syncope. The aim is to provoke a typical event and to obtain a pathophysiological correlate and thus prove the cause of syncope. The pathophysiological rationale behind the TTT is the fact that it uses gravity to provoke a downwards shift of blood that in turn triggers syncope. TTT provokes venous pooling[29] and may hereby induce reflex syncope. Interestingly, TTT not only provokes syncope in those in whom VVS is habitually induced by standing, but also in those with emotional VVS triggers, and even in those with specific types of reflex syncope usually labelled as 'situational syncope'. Various indications and methods of the TTT are discussed in **chapter VI**.

Psychogenic pseudosyncope (PPS)

Emotional faints and spells were already recorded in ancient Egyptian papyri. While some were probably vasovagal in nature, other may have been due to psychological mechanisms without any decrease of blood pressure. For centuries the concept of hysteria or 'wandering womb', aberrations in the position of the uterus within the abdomen, was an accepted theory and this remained largely unchanged until the 20th century.[9] One of the first to break with this theory was the famous neurologist Charcot (1825-1893). In la Salpêtrière, the famous hospital in Paris where he worked, many patients with hysteria where seen by Charcot. He regarded hysteria as a neurodegenerative disease with quasi-neurological symptoms, inherited from the mother, and he believed that there was an unidentified cortical substrate of the disease.[43]

In 1885 Freud (1856-1939) visited Charcot in Paris. As a result of this visit he became friends with Charcot and started to study ' hysteria'. In 1893 he wrote his famous article '*Quelques considérations pour une étude comparative des paralysies motrices organiques et hystériques',* in which h*e* pointed out a psychological explanation for the spells.[44]

Nowadays, such spells are known under a large variety of names. Here, we will avoid discussion of whether they should be called 'dissociative', 'functional' or 'psychogenic'; we will use the term 'psychogenic' as it has featured often in the literature. Psychogenic TLOC can be divided in psychogenic non-epileptic attacks (PNEA) and psychogenic pseudosyncope (PPS), with the first one resembling epilepsy, and the second one syncope. Patients with PPS typically lie immobile and unresponsive with closed eyes during attacks. Attacks last longer and are more frequent than in syncope.[12] The diagnosis rests on history taking from patients and eyewitnesses and preferentially also on documenting an event, with video or with a tilt table test.[13] Follow-up studies in PNEA have shown that not only attack frequency but also quality of life, use of health care facilities, and employment are important indicators.[14-17] As there were no studies on the prognosis of PPS, we carried out such a study. **In Chapter VII,** we studied the prognosis in a cohort of patients with PPS for the first time, taking these aspects into account.

In **Chapter VIII** overall results are discussed and summarized.

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