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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.

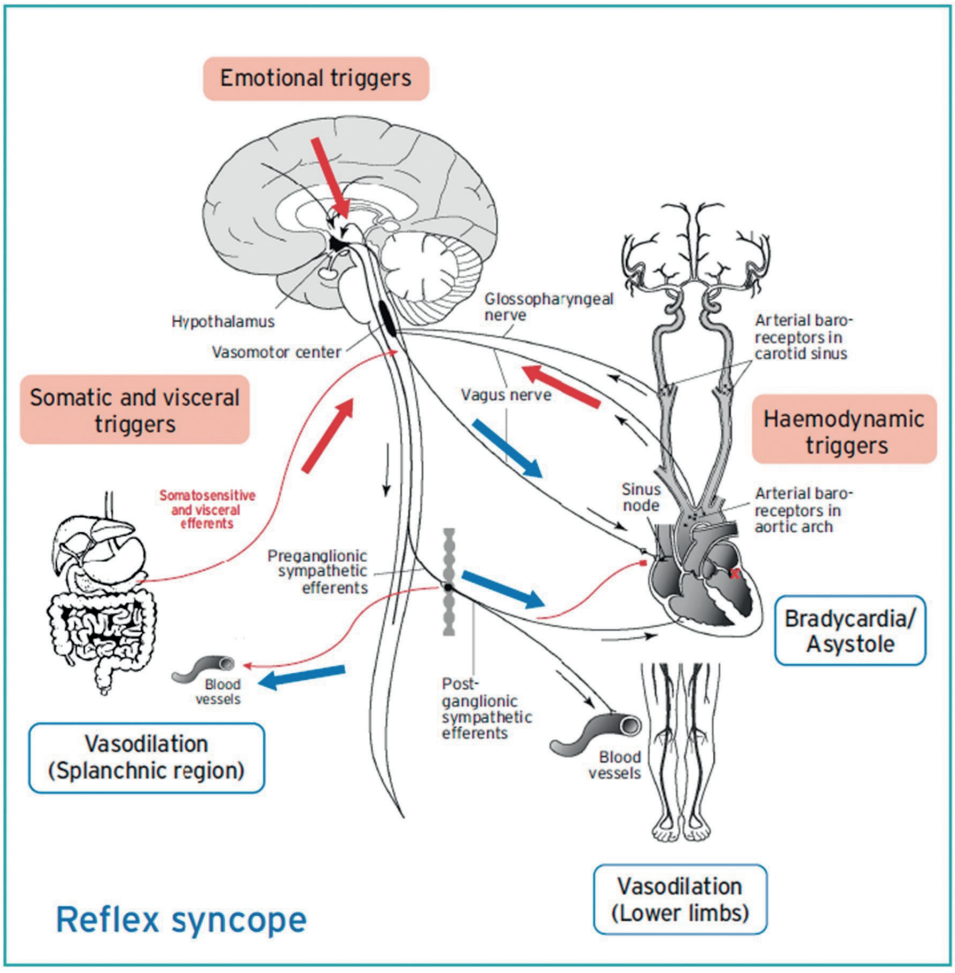


**Figure 1. The mechanism of reflex syncope: anatomical view.**
Afferent pathways (shown in red) transfer information from the circulatory and visceral receptors to the brain. Arterial baroreceptors are in the aortic arch and the carotid sinus; these are stretch receptors that are activated when distended 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.

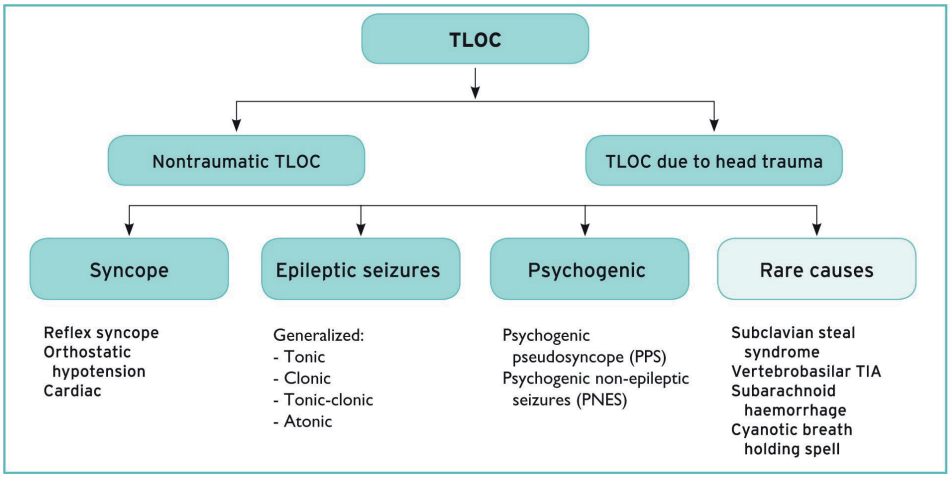


**Figure 2. Syncope in the context of transient loss of consciousness.**
Non-traumatic transient loss of consciousness classified into one of four groupings: syncope, epileptic seizures, psychogenic transient loss of consciousness, and a miscellaneous group of rare causes. This order represents their 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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# CHAPTER II

# Classifying syncope

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## Abstract

An unambiguous definition of syncope is important for care, research and teaching purposes. Unfortunately, many published definitions described 'syncope' as a broad category of transient loss of consciousness (TLOC) but still appeared to use a much narrower concept, creating confusion. The ESC-classification from 2001 and subsequently distinguished between 'transient loss of consciousness', i.e. disorders sharing unconsciousness of short duration with a rapid and spontaneous recovery and syncope, the form of TLOC that is due to cerebral hypoperfusion. Adding the cerebral hypoperfusion element sets syncope apart from other forms of TLOC, mostly epileptic seizures and psychogenic attacks. We provide short descriptions of different forms of syncope and other forms of TLOC.

## 1. Why classify syncope?

Syncope is common; the causes vary from relatively harmless to deadly conditions; syncope may be mistaken for other disorders such as epilepsy; finally, it is associated with high costs.[6,11,17]

In view of all these factors, it is reasonable to expect that an unambiguous definition of syncope would have been formulated decades ago. However, a 2004 study showed that syncope and episodes of transient loss of consciousness (TLOC) were defined in top medical journals using variable definitions and a very inconsistent terminology. [19] As stated above, the diagnosis of syncope is often managed inefficiently. This may in part be due definitions of 'syncope' that do not succeed in delineating it clearly from conditions with a similar presentation, so nonsyncopal conditions such as epileptic seizures and concussion may be included in a broad 'syncope' concept, in turn leading to the use of inappropriate diagnostic tests.[10]



Until 2001 the classification of TLOC and syncope was problematic because of the lack of a widely accepted and comprehensive classification and terminology aimed at aiding diagnosis. The decision by the ESC to distinguish between a wider concept of TLOC, bundling conditions that all cause a short-lived loss of consciousness, and a narrower one of syncope[4,5,13,19] was agreed on by many other professional societies, but not all. The American College of Cardiology and the American Heart Association used the term 'syncope' for the broad concept that would be labelled TLOC in ESC terms[16], but this approach was criticized subsequently.[2] At the time of writing of this chapter most papers on syncope adhere to the ESC definition, but some still define 'syncope' as a broad concept, and others introduce forms of 'syncope' that do not feature in the ESC classification; continuing themes are the use of 'neurological syncope' and 'psychiatric syncope', terms that are usually not defined or specified in the papers using them.

The lack of a precise definition carries a risk of diagnostic confusion which may in turn may make it difficult to provide structured high quality care for patients with syncope, something necessary not just because of high costs but also because syncope can signify potentially lethal diseases, e.g. structural heart disease and arrhythmia. To establish the cause or causes of syncope serves two principal purposes.[10] First of all, an etiologic diagnosis permits estimation of prognosis and risk of recurrence. Secondly, identifying the etiological cause is the only way to provide a treatment recommendation with confidence.

The problems described above provided the impetus to create comprehensive guidelines for optimizing care of syncope patients by the European Society of Cardiology (ESC)[13] discussed in further detail in the following chapters.

## 2. Distinguishing TLOC and syncope

Many textbooks and papers defined 'syncope' using phrases such as 'transient loss of consciousness (LOC) with loss of postural control leading to falling', to which 'sudden' or 'self-limited' were sometimes added. Scrutinising the result of studies using this type of definition commonly shows that the authors aimed to include arrhythmia, reflex syncope or syncope due to orthostatic hypotension, i.e. causes resulting in transient short-lived cerebral hypoperfusion, which are indeed comprised in this definition. The authors of such papers evidently did not wish to include other conditions even though these fell under this heading equally well. The reasons why such a definition is not sufficiently restrictive are, firstly, that by not specifying the duration of 'transient' the duration of LOC might conform to that of a vasovagal episode, i.e. about 25 seconds, but will also encompass events lasting up to hours such as hypoglycemia, or even a coma lasting weeks. Secondly, there is no restriction as to the cause of LOC at all, so concussions, intoxications, epileptic seizures and other causes would all have to be inappropriately labelled 'syncope'.

The ESC solution to narrow this overly wide definition problem was to set a group of causes of LOC apart that are often mistaken for one another. This group is labelled 'transient loss of consciousness (TLOC) and was defined as a transient loss of consciousness of short duration (minutes or less), rapid recovery (minutes or less) and spontaneous recovery (thereby excluding disorders that require resuscitation) (Figure 1). In doing so LOC lasting minutes or longer was excluded, i.e. TLOC does not include intoxications, metabolic derangements and coma.

The 'loss of postural tone' in the commonly found definition may have been added as a help in describing or recognizing LOC, but it is doubtful whether it has the intended effect. It may be argued that loss of postural control is an integral part of LOC that does not need to be emphasized over other items that also help describe LOC. If a more detailed description of LOC is needed, adding 'loss of postural tone ' alone is not enough. In the TLOC context LOC is usually over when patients see a doctor, meaning the presence of LOC has to be established after the fact, by taking a history from patients and eyewitnesses. Useful descriptors of LOC that can be established after the fact are, firstly, a loss of normal motor control. This is established through the absence of normal movement, the presence of abnormal tone (stiffness or flaccidity), through abnormal movements or through the absence of any movement at all. Secondly, patients later have amnesia for the event. Thirdly, unconsciousness causes unresponsiveness, so there was an absence of normal responses to touch or being spoken to during the event.

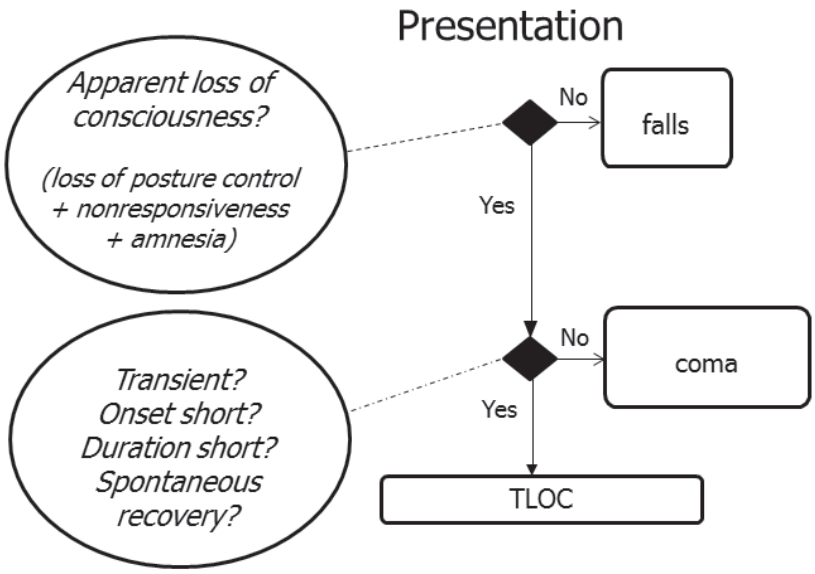


**Figure 1. Main features of TLOC and differential diagnosis.**

Deviation from any of the cardinal features of TLOC (apparent loss of consciousness, transient nature, short duration, spontaneous recovery) suggests a diagnosis other than TLOC. (TLOC= transient loss of consciousness)

The causes of TLOC are divided into traumatic and non-traumatic forms, and the non-traumatic form is further divided into major groups of which syncope is the most common one (Figure 2, Table 1). Syncope as defined by the ESC is that form of TLOC that is due to cerebral hypoperfusion. The use of a pathophysiological criterion –cerebral hypoperfusion- in defining a clinical entity may appear counterproductive, but is essential. The main reason is that a putative concise clinical definition would on the one hand have to encompass all expressions of syncope, while on the other hand also excluding epileptic seizures, psychogenic attacks, and some minor causes. Syncope is too variable clinically to be defined in such a way: items such as warning symptoms, pallor, nausea, opening of the eyes, incontinence, myoclonic jerks, stiffness and many others may all be present or absent in syncope. The only criterion shared by all forms of syncope and by no other form of TLOC is a pathophysiological one; no clinical criterion fits the bill.[21]

**Table 1. A classification of TLOC and Syncope.**
The following classification combines the 2009 ESC classification [13] with the classification of orthostatic hypotension published in 2011. [7]

**Syncope**

- Reflex syncope
    - Vasovagal syncope; triggered by fear, pain and standing for an extended period.
    - Situational syncope: triggered by coughing, sneezing, micturition, defecation
    - Carotid sinus syncope
    - Syncope due to mechanic or hydraulic factors; triggers include 'the mess trick' (self-induced syncope), playing wind instruments and straining.
- Syncope due to orthostatic hypotension
    - Initial orthostatic hypotension
    - Classical orthostatic hypotension
        - Primary autonomic failure (e.g. Pure autonomic failure, Parkinson's disease, Multiple system atrophy)
        - Secondary autonomic failure (e.g. diabetes mellitus, amyloidosis)
        - Drugs
        - Volume depletion
    - 'Delayed orthostatic hypotension'
- Cardiac/cardiopulmonary syncope
    - Arrhythmias as primary cause
        - Bradycardia (sinus node dysfunction)
        - tachycardia (supra- or ventricular)
    - Structural cardiac disease
        - Valvular disease, pulmonary embolus, cardiomyopathy

**Epilepsy**

- Generalized
- Tonic, clonic, tonic-clonic

**Psychogenic / functional**

- Psychogenic non-epileptic seizures (PNES):mimicking epileptic seizures
- Pseudosyncope: mimicking syncope

**Miscellaneous disorders and causes of confusion**

- Vertebrobasilar TIA's , 'subclavian steal syndrome'
- Cataplexy
- Metabolic disorders (hypoglycemia)
- 'Drop attacks'
- Partial complex seizures

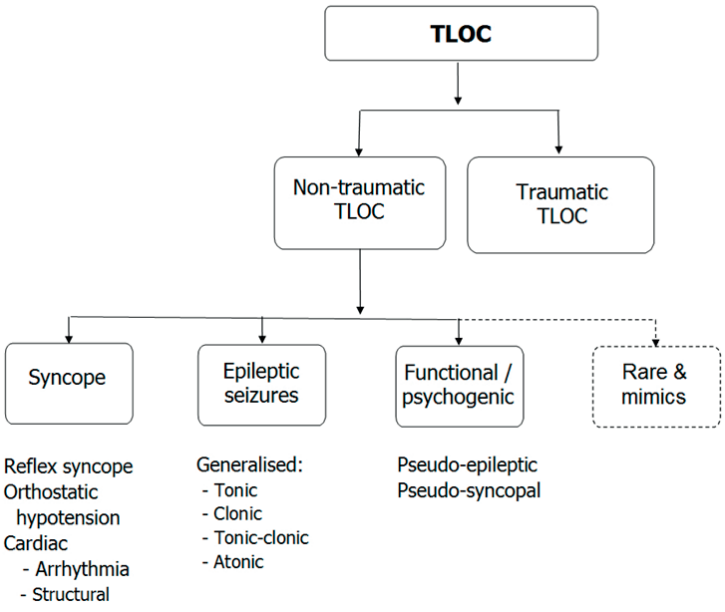


**Figure 2. Main forms of TLOC.**

Traumatic TLOC (concussion) can usually be recognized easily as the cause tends to be obvious. Nontraumatic TLOC is divided into four groups: syncope, TLOC, and a miscellaneous group encompassing rare disorders that cause TLOC and conditions that can be mistaken for TLOC; the disorders in the latter group do not share a common pathophysiology. (TLOC= transient loss of consciousness). [20]

Note that epilepsy is also defined on pathophysiological grounds for similar reasons: it is also a heterogeneous group of disorders with a remarkably variable clinical expression. An argument sometimes raised against the pathophysiological criterion of syncope is that it cannot be applied clinically in a direct manner. This is true in the sense that the definition is not the type of checklist definition containing major and minor clinical criteria. In fact, the ESC only defined TLOC clinically, not syncope. Those seeking a clinical aid to describe syncope can implement the ESC definition in a manner based on the following:

*Suspected syncope is operationally described as transient loss of consciousness of short duration, rapid onset and spontaneous recovery (i.e. minutes or less) with at least one of two elements:*

1. *clinical features specific for reflex syncope, syncope due to orthostatic hypotension or cardiac/cardiopulmonary syncope*
2. *the absence of clinical features specific for another form of transient loss of consciousness*

TLOC can be operationally defined using history taking to seek for amnesia, abnormal motor control and lack of normal responsiveness as outlined above. Note that such a description rests on recognition of forms of syncope or of other disorders on clinical grounds that are not specified in the description; as such, the implementation is incomplete, somewhat academic and has aspects of circular reasoning, but it does offer an aid for those seeking an implementation.

## 3. The major groups of TLOC

The causes of TLOC are divided in non-traumatic or traumatic forms. Concussion causes loss of consciousness, but most often the presence of a trauma is quite clear, limiting the risk for confusion with other forms of TLOC. Non-traumatic TLOC is divided in syncope, epileptic seizures, psychogenic TLOC and a rest group containing mimics and rare causes.

### 3.1. Syncope

As said, syncope is TLOC due to cerebral hypoperfusion, which can be caused by a low peripheral resistance or low cardiac output, both of which can in turn be due to various mechanisms (Figure 3). Syncope consists of three major groups: reflex syncope, syncope due to orthostatic hypotension, and syncope with a cardiac/cardiopulmonary cause.

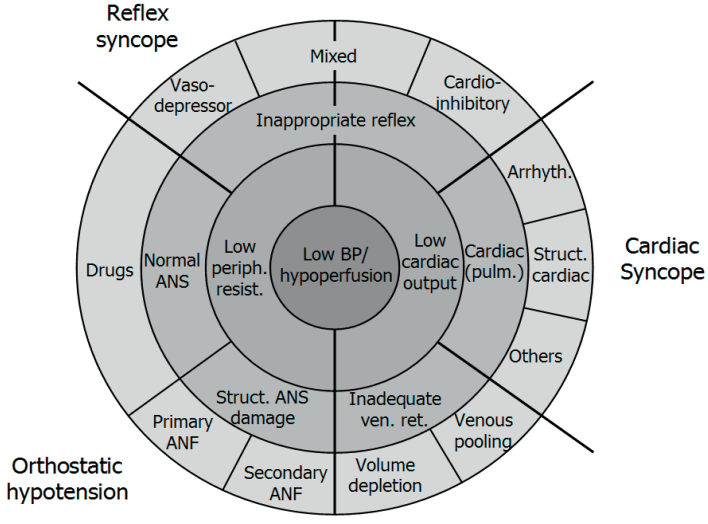


**Figure 3. Pathophysiological mechanisms in syncope.**

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 and low cardiac output.[13]

### *3.1.1. Reflex syncope*

Reflex syncope, also called 'neurally mediated syncope' consists of a heterogeneous group of conditions in which there is a sudden change in autonomic nerve system activity leading to a fall in blood pressure, heart rate and cerebral perfusion.[7]

The presence of a trigger is a key diagnostic element in reflex syncope. The three groups of reflex syncope, vasovagal, situational and carotid sinus syncope, are distinguished by the nature of their triggers. Anatomically the trigger can be situated centrally (pain, emotion, blood phobia) or peripherally (prolonged standing, carotid sinus afferent activity). The precise afferent pathways of reflex syncope are largely unknown. Reflex syncope is typically preceded by prodromal symptoms and signs (pallor, nausea, diaphoresis, abdominal discomfort) that may occur up to 60 seconds or more prior to the loss of consciousness.



During reflex syncope efferent sympathetic vasoconstrictor activity decreases, leading to loss of vasoconstrictor tone. Parasympathetic (vagal) activity increases, leading to slowing of the heart rate.[7,23] Blood pressure typically decreases rapidly at an increasing rate just before syncope (Figure 4). The decrease in arterial pressure is thought to result from splanchnic blood pooling, thoracic hypovolemia and increased ventilation. Altogether, this process may decrease cerebral autoregulation and finally override the baroreflex. Recovery is immediately after restoration of venous return.[9]

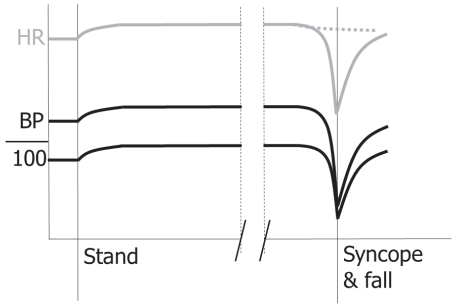


**Figure 4. Circulatory patterns in vasovagal syncope.**
Schematized blood pressure and heart rate patterns for vasovagal syncope evoked by standing. In both vasodepressor and cardioinhibitory vasovagal syncope, a fall in blood pressure signifies the onset of the reflex proper.[20]

### *3.1.2. Syncope due to orthostatic hypotension*

In contrast to reflex syncope, in which the autonomic nervous system may be said to cause harm by a wrong action that occasionally shuts down the circulation, in classical orthostatic hypotension the efferent sympathetic activity is impaired but attempts to do its job. In effect it fails to provide sufficient vasoconstriction. Changes in blood pressure

and heart rate differ from those in reflex syncope (Figure 5): whereas blood pressure and heart rate decrease with increasing speed in reflex syncope, the decreases in orthostatic hypotension start quickly after which the rate of change decreases. In other words, orthostatic hypotension is due to a failing normal reflex, while reflex syncope concerns an abnormal action. Many drugs can cause orthostatic hypotension, among them antihypertensive medication. The most important pathophysiological mechanism of classic OH consists of an impaired increase in systemic vascular resistance which results in pooling of venous blood or severe volume depletion. It is defined as a decrease in systolic BP >=20 mmHg or in diastolic BP >=10 mmHg within three minutes of standing up or being tilted head up.[7]

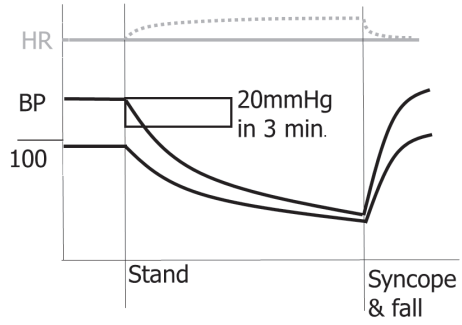


**Figure 5. Circulatory patterns in syncope due to orthostatic hypotension.**
Schematized blood pressure and heart rate patterns. Blood pressure drops immediately after standing up.[20]

There are two forms that differ from classical OH: in initial orthostatic hypotension (OH) there tends to be a mismatch between cardiac output and peripheral vascular resistance when people stand up quickly. An important difference with classical OH is that the mismatch is corrected by the autonomic nervous system in seconds, so blood pressure will increase quickly even while people remain standing. In classical OH blood pressure will usually only increase again when other actions are taken, such as exercise or sitting down.

Delayed orthostatic hypotension occurs after 3 minutes of standing up and is probably caused by a progressive fall in venous return. It is more common in the elderly and it is related to age-related impairment of compensatory reflexes and stiffer hearts sensitive to a decrease in preload.[13] Orthostatic intolerance refers to the symptoms and signs which occur in the upright position due to an imbalance in circulatory control. Syncope is only one of them, others are light-headedness, dizziness, weakness, sweating and palpitations.[7]

***3.1.3. Cardiac syncope***

Cardiac syncope can be divided into two separate groups, which have a sudden dramatic decrease of cardiac output in common.

*3.1.3.1 Arrhythmia:* Bradyarrhythmias causes syncope more often than tachyarrhythmias. In bradyarrhythmia, syncope occurs when the ventricular rate is low for some time; usually this occurs when the rate is less than 30 bpm for 15-30 seconds. LOC sets in earlier when heart rate is lower, which is most dramatically the case when heart beat completely ceases: LOC then sets in after about eight seconds of asystole. The most important causes of arrhythmia include sinus node dysfunction and ventricular tachycardia, but several drugs can also cause brady- or tachyarrhythmias.[13,21] In recent years attention has been focused on various genetic channelopathies, which are rare but may cause sudden death through tachyarrhythmia.[1,22]



*3.1.3.2 Structural heart disease:* Structural heart diseases will cause syncope when the demands of the body outweigh the impaired ability of the heart to increase its output. This explains why syncope in structural heart disease more often occurs during exercise.[21] The basis for the faint is inadequate blood flow due to mechanical obstruction, but a reflex mechanism plays a role in the sudden onset of syncope in such cases.[13]

## 3.2. Epileptic seizures

Generalized epileptic seizures cause TLOC and are sometimes difficult to distinguish from syncope. Abnormal neuronal activity of major parts of both hemispheres generally results in loss of consciousness.[19] Epileptic seizures usually last about one 1 minute, longer than syncope.[20]

Note that the TLOC classification (Figure 2) contains only generalized forms of epileptic seizures. Exclusively partial seizures are purposely not included in TLOC, because they typically do not usually cause a loss of tone. During such seizures patients stay upright, which effectively means that such attacks can hardly be mistaken for syncope. Hence, seizures without loss of postural tone were excluded from TLOC.

Some diagnostic pointers favoring epileptic seizures are one-sided movements, a tongue bite on the lateral side of the tongue and prolonged confusion after the event.[8] In contrast to syncope, in epileptic seizures movements of extremities may rarely occur before a fall, while in syncope they occur after the patient has fallen.[4]

## 3.3. Psychogenic pseudosyncope

Psychogenic pseudosyncope is occasionally referred to as 'psychogenic syncope', which in the ESC classification is a misnomer because it implies a true loss of consciousness

as well as cerebral hypoperfusion. In patients with psychogenic pseudosyncope there is a normal, reactive electroencephalogram; blood pressure and heart rate are usually relatively high during the event.[18] Pseudosyncope is closely related to psychogenic non-epileptic seizures (PNES; sometimes called pseudoseizures). Their main difference is a lack of gross movements in pseudosyncope, which are the main feature in PNES. Another related condition is 'psychogenic pseudocoma', which is the exact same condition as pseudosyncope but simply lasts longer. Describing the psychological nature of such events in terms that are not considered pejorative can be difficult. A term probably used more frequently than 'psychogenic' is 'functional'. A possible benefit of this term is that its tone is neutral, without any negative judgement by the doctor, real or attributed by the patient. It does however not stress psychological factors, usually at the root of the problem. Regardless of the chosen terms, it is crucially important that the cause of the attack is explained clearly to patients and relatives without insulting them.

Hints to distinguish true syncope from psychogenic pseudosyncope are that psychogenic pseudosyncope often occurs several times a day, which is extremely rare in syncope.[18,15] Other clues are the long duration and the fact that the eyes are almost always closed, in contrast to syncope and epileptic seizures.

## 3.4. Mimics and rare causes

This category contains disorders that may be mistaken for TLOC or which can under unusual circumstances cause LOC of a duration short enough to be categorised as TLOC.

### *3.4.1. Cerebrovascular disorders*

There are no reliable reports of attacks of TLOC in the subclavian steal syndrome without focal neurological symptoms or signs.[19] A TIA concerning one carotid artery will not cause TLOC. A TIA of the vertebrobasilar system can cause LOC, but here too focal neurological signs are the norm. Although TIAs are still often mentioned as mimics or causes of TLOC or even syncope, in daily practice syncope and TIAs hardly ever need to be confused with one another. Carotid artery TIAs do not belong in the differential diagnosis of TLOC. In fact, a TIA may be stated succinctly to represent a focal deficit without LOC, while syncope concerns the opposite: LOC without focal deficit.

### *3.4.2. Hypoglycemia*

Along with some other metabolic disorders hypoglycemia may cause unconsciousness but with a much longer duration than syncope, which means hypoglycemia should not feature in the usual differential diagnosis of syncope).[19]

***3.4.3. Cataplexy***

Although patients with cataplexy have a triggered loss of muscle tone, causing a fall, and may not be able to respond at all, their consciousness is completely intact. This cannot be established during the attack as patients then cannot respond. However, after the attack is over patients can recount what happened around them during the attack, so no amnesia was present. The triggers differ from those causing syncope; laughter in particular is a common trigger in cataplexy.[14] Note that cataplexy is very rare and almost always associated with excessive daytime sleepiness as it is part of narcolepsy; in clinical practice the differentiation with syncope should not cause problems.



## 4. Does the classification work?

A useful classification helps to structure thinking about TLOC causes and how to differentiate between them. The ESC-classification (2001, 2004 and 2009)[4,5,13] is frequently used and the basic distinction between TLOC and syncope is used increasingly by cardiologists, neurologists and internists. As said earlier, some less focused definitions remain. This may not matter much in cases where the diagnosis is straightforward and mostly based on intuition, the way most experts approach a diagnosis. However, in complex cases the intuitive process may fail, and then syncope experts fall back on logical reasoning, comparing the items in a structured hierarchical list, using clinical clues and pathophysiological reasoning. Less experienced doctors will have to apply logical clinical reasoning in more cases, and have an accordingly larger need for aids to help structure their differential diagnosis. The type of classification that bundles disorders that do not really resemble one another mush, such as arrhythmia, concussions, TIAs and hypoglycemia is therefore most likely to confuse those who need help the most. The schemes presented in this paper were formulated in the hope that they help structure differential diagnostic thinking on all levels.

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# CHAPTER III

# Temporal relationship of asystole to onset of transient loss of consciousness in tilt-induced reflex syncope

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## Abstract

**Background**

The presence of asystole in VVS may prompt physicians to consider pacemaker therapy for syncope prevention, but the benefit of pacing is limited in VVS.

**Objectives**

To **i**nvestigate the relation between the onset of asystole and of transient loss of consciousness (TLOC) in tilt-induced reflex syncope and estimate how often asystole was the principal cause of TLOC.

**Methods**

We evaluated electrocardiographic (ECG), electroencephalographic (EEG), blood pressure (BP) and clinical findings during tilt table tests. Inclusion required TLOC (video), EEG slowing, accelerating BP decrease and an RR-interval ≥3 seconds. We excluded cases with nitroglycerin provocation. Asystole after onset of TLOC (group A) or within 3 seconds before TLOC (Group B) was unlikely to cause TLOC, but an earlier start of asystole (Group C) could be the cause of TLOC

**Results**

In one third of 35 cases (Groups A,n=9; B,n=3) asystole was unlikely to be the primary cause of TLOC. The median of the mean arterial pressure at the onset of asystole was higher when asystole occurred early (45.5 mmHg, group C) than when it occurred late (32.0 mmHg, groups A and B), suggesting that vasodepression was not prominent at the start of asystole in early asystole, suggesting that early asystole was the prime mechanism of syncope.

**Conclusions**

In one third of cases of tilt-induced asystolic reflex syncope, asystole occurred too late to have been the primary cause of TLOC. Relying on ECG data only is likely to overestimate the importance of asystole.


**Keywords:** asystole, reflex syncope, tilt table testing, TLOC

## Introduction

Syncope is the form of transient loss of consciousness (TLOC) that is caused by brief and self-terminating diminution of global cerebral hypoperfusion.[1] 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. Vasovagal syncope is by far the most common cause of reflex syncope. In many instances, susceptibility to vasovagal syncope may be unmasked by head-up tilt-table testing.[2]

Reflex syncope encompasses both vasodepressor and cardioinhibitory mechanisms. While either mechanism can cause syncope, in most cases both tend to occur together in reflex syncope (i.e. the 'mixed' pattern). The basis by which the vasodepressor response contributes to syncope remains controversial, but has been considered to be primarily due to venous pooling in the lower parts of the body, resulting in decreased cardiac venous return and a reduced cardiac output.[3,4] The cardioinhibitory mechanism is effected primarily through an increase in vagal tone.[5,6] Its most extreme expression is abrupt prolonged asystole (usually defined as a cardiac pause ≥3 seconds), which on its own causes blood pressure to fall precipitously. If asystole is sustained for a sufficiently long period of time, the resulting cerebral hypoperfusion causes unconsciousness about 6-8 seconds (s.) after the last heartbeat. [7,8]



The presence of asystole in VVS may prompt physicians to consider pacemaker therapy to prevent syncope recurrence. However, it is increasingly recognised [2] that the benefit of pacing is limited in VVS patients. In fact, recent observations from the ISSUE-3 and SUP-2[9,10] suggest that amongst patients with documented spontaneous asystole during VVS, pacing efficacy was primarily of value in those individuals without evident vasodepressor susceptibility (i.e., the latter observation implies that the VVS origin was truly due to cardioinhibition). Unfortunately, when vasodepression and cardioinhibition act at the same time, it is not usually feasible to quantify how much each contributes to cerebral hypoperfusion. However, during head-up tilt-induced syncope with continuous EEG monitoring, it is possible to determine both when asystole starts and when onset of TLOC occurs; thus, if asystole starts after the onset of TLOC, it cannot have been the principal cause of TLOC. Similarly, if asystole starts within 3 s. of TLOC, the bradycardia is unlikely to be the cause of syncope. On the other hand, if asystole begins >3 s. before TLOC there is a reasonable likelihood that the bradycardia did contribute to TLOC.

The objective of this study, using head-up tilt testing with continuous video-EEG recording, was to describe the temporal relation between the onset asystole and of TLOC during tilt-induced syncope. A second goal was to use the observed temporal relation to estimate how often asystole could be the prime cause of TLOC in tilt-induced syncope.

# Methods

## Patients

This report is based on all tilt-table tests performed between 2006 and 2015 for evaluation of TLOC at two tertiary syncope referral centres: the Department of Neurology of the Leiden University Medical Centre (LUMC), and the syncope clinic of 'Stichting Epilepsie Instellingen Nederland' (SEIN). These institutions share expertise, use the same indications and protocols for tilt-table testing, the same brand of tilt table, and have collaborated on studies assessing the semiology and pathophysiology of tilt-induced syncope and psychogenic pseudosyncope.[11-15]

Suspected susceptibility to vasovagal syncope is the most common indication for tilt-table tests in both centres. Part of the present patient group has been described before.[14] In that study, tilt-induced reflex syncope was defined using the following triad: video records compatible with loss of consciousness, EEG changes showing a slow or slow-flat-slow pattern, and blood pressure (BP) showing the pattern of tilt-induced reflex syncope, i.e. an increasing rate of decline with or without bradycardia. We now incorporated one additional inclusion criterion: the ECG showed asystole, defined as an RR-interval of ≥ 3 s.; we also added one exclusion criterion: tilt tests in which syncope developed after administration of sublingual nitroglycerin were excluded on the assumption that nitroglycerin administration might influence the relative contribution of vasodepression and cardioinhibition.

## Clinical tilt protocol and data extraction

We used EEG machines to store data sampled at 200 Hz. Recordings comprised continuous video, EEG, BP (derived from finger plethysmography) and a one- or two-lead ECG. In the LUMC the video camera is attached to the tilt table and is aimed at the head and shoulders, while at SEIN a ceiling-mounted camera covers the entire tilt table.

Tilt table tests were performed using a modified 'Italian protocol'.[16] The usual test protocol consisted of 10 min. of supine rest followed by 20 min. of head-up tilt to 70 degrees, after which, if syncope did not occur, sublingual nitroglycerin was used and patients were observed for another 20 minutes. However, as noted earlier, the present study included only tests in which TLOC occurred in the drug-free first 20 min. after head-up tilt. Reasons to tilt patients back before the expiration of the allotted protocol time included the presence of syncope (i.e. the circulatory pattern of reflex syncope with clinical TLOC); presyncope (similar circulatory changes without clinical TLOC); slowing of the EEG, asystole, or a combination of these factors. Tilting back to the supine position required 12 s. at both centres.

Non-invasive beat-to-beat BP was recorded continuously with either a Finometer (Finapres Medical Systems, Amsterdam, the Netherlands) or a Nexfin (BMEye, The Hague, the Netherlands) device. We measured BP from the middle phalanx with the hand held at heart level in a sling to ensure immobility and reduce the need for height correction.

We assessed the time of onset of clinical TLOC and its duration using video records as described previously. [14] In brief, the onset of TLOC was defined as the first event indicating a loss of motor control (e.g. head dropping, eye opening, jaw dropping). We used EEG slowing as an additional quality indicator; besides proving brain hypoperfusion, abnormal EEG findings reduced the possibility of misidentification of voluntary behaviour as a sign of syncope. All video records were reviewed by two of three examiners (DPS, RDT, JGvD), well acquainted with the semiology of syncope.



We searched for asystole (i.e., cardiac pause ≥3 s.) in a period beginning approximately 30 s. before and continuing during loss of consciousness. The ECG in syncope may show more than one RR-interval longer than three s.; we only analysed the first such episode. No attempts were made to quantify bradycardia preceding or following periods of asystole.

To illustrate BP changes in relation to the start of asystole, we noted mean arterial pressure (MAP) at the heartbeat defining the onset of asystole. In some cases BP could no longer be measured at that point in time, resulting in missing values. MAP was calculated as the mean of the continuous BP signal over two s. in LUMC cases, and as one third of the sum of systolic BP and double the diastolic BP in SEIN cases.

### Analysis of the temporal relation between asystole and TLOC

We set the start of TLOC as 'time zero' and expressed the start of asystole in integer s. relative to time zero. We divided patients into three groups based on the temporal relation of asystole to TLOC:

- Group A: asystole started after the onset of TLOC. In these cases asystole could with certainty not have been the principal cause of TLOC.
- Group B: asystole started at most three s. before the onset of TLOC. We postulate that asystole in this group was very unlikely to have been the principal cause of TLOC, based on prior observations indicating that pure asystole causes loss of consciousness seven to ten s. after the last heartbeat.[7,8] In these studies, the shortest estimate of the interval between the last beat and the onset of TLOC was four s. in standing subjects. Hence, we used a three s. threshold to increase confidence that asystole was not the cause of TLOC in this group.
- Group C: asystole started more than 3 s. before TLOC. In this group asystole may have been the major contributor causing TLOC.

### Statistical analysis

The study was descriptive in nature. To analyse the MAP at the onset of asystole between groups, we combined groups A and B to represent those with 'late asystole', unlikely to cause TLOC, and compared their MAP with that of group C, representing 'early asystole', in which asystole may have caused TLOC. To do so we estimated the standardized mean difference between groups by dividing the difference of the group MAP averages by their pooled standard deviation, and calculated the 95% confidence interval.

## Results

### Patient group

A total of 1551 tilt-table tests with video-EEG were performed at the LUMC from 2006 to June 2015, and 412 tilt-table tests from 2009 to 2015 at SEIN. After excluding patients without syncope, with syncope without asystole, syncope due to other mechanisms (e.g. carotid sinus syndrome, orthostatic hypotension, use of nitroglycerin), multiple causes of apparent but not true TLOC (such as additional psychogenic pseudosyncope) or those with incomplete video data, 35 cases remained. The median age of patients was 35 years (range 12-84); 21 were female, 14 male (Table 1).

**Table 1. Characteristics of the groups according to onset of asystole related to TLOC.**

| | **Group A** Asystole starting after TLOC | **Group B** Asystole starting at most 3 seconds before TLOC | **Group C** Asystole starting more than 3 seconds before TLOC | **Total** |
|---|---|---|---|---|
| Subjects | 9 | 3 | 23 | 35 |
| Mean age (range) | 46 (18-84) | 34 (27-40) | 32 (12-60) | 35 (12-84) |
| Gender (M:F) | 2:7 | 1:2 | 11:12 | 14:21 |
| Mean duration asystole (s., mean ± SD) | 8.9 ± 8.5 | 8.3 ± 4.9 | 14.6 ± 14.0 | 12.6 ± 12.4 |
| Mean duration TLOC (s., mean ± SD) | 27.8 ± 8.9 | 32.7 ± 10.4 | 33.0 ± 15.1 | 31.7 ± 13.3 |
| Mean difference asystole -onset TLOC (s., mean ± SD) | 4.4 ± 3.97 | -2.3 ± 0.58 | -7.5 ± 2.66 | -4.1 ± 5.9 |

The groups were formed based on assumptions regarding the role of asystole in causing syncope: group A concerns those in whom asystole started after TLOC started, so asystole was certainly not the cause of syncope. In group B asystole started at most three seconds before the onset of TLOC, making a major role of asystole unlikely. In group C asystole started at least three seconds before syncope and may have played a major role.

## Timing of asystole

Figure 1 and Table 1 show the relative timing of asystole and TLOC onset. In nine patients asystole started after onset of TLOC (Group A). MAP at the onset of asystole was missing in four cases, and for the remaining five cases median MAP was 32 mmHg (range 24-35).

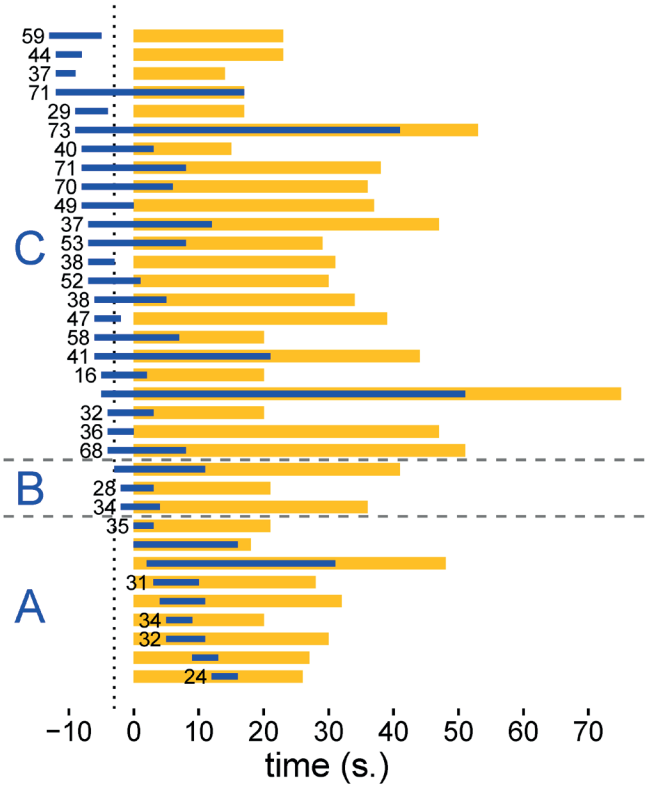


**Figure 1. Relative time of asystole and transient loss of consciousness**

Each line of horizontal bars concerns one subject. Orange bars denote the duration of clinically observed TLOC and blue bars denote the start and duration of asystole. Data are aligned to the start of TLOC, defined as occurring at zero seconds. The dotted line shows a period of 3 seconds before onset of TLOC. The numbers at the beginning of the asystole bars denote mean arterial pressure of the heart beat just before asystole; when MAP is not stated, it was too low to be measured at that point in time.

In three patients asystole coincided or preceded TLOC by at most three s. (Group B). The median MAP at the onset of asystole for two cases with measurable BP was 31 mmHg (range 28-34).

Group C comprised 23 patients in whom asystole preceded TLOC by at least three s.; the median MAP at the onset of asystole of 22 cases was 45.5 mmHg (range 16-73).

Figure 2 summarizes the number of subjects with asystole, related to the beginning of TLOC. Groups A and B together comprised 12 of 35 cases (34%): in these subjects asystole was considered unlikely to have primarily caused syncope. In the remaining 23 cases (66%) asystole may have played a major role.

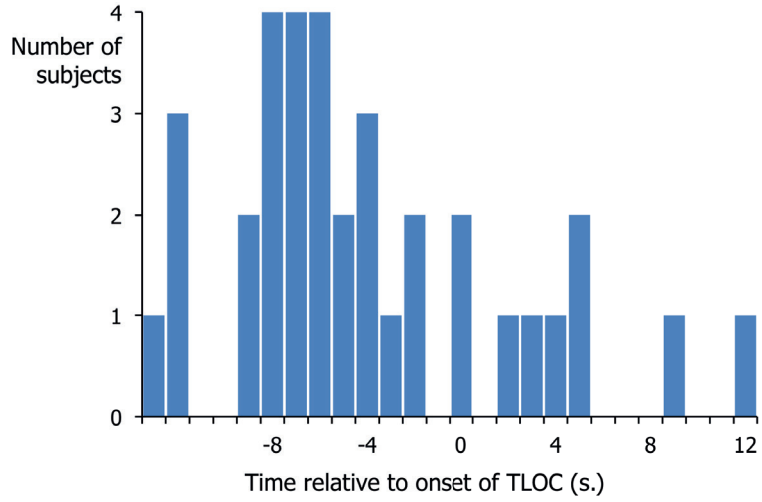


**Figure 2. Histogram of the start of asystole in relation TLOC**

On the horizontal axis the start of asystole is shown relative to the start of TLOC. The vertical axis shows the number of subjects. TLOC: transient loss of consciousness

The median MAP of groups A and B together (n=7) was 32 mmHg (range 24-35 mmHg), and that of group C was 45.5 mmHg (range 16-73). The standardized mean difference was -1.22 (95% confidence interval -2.12 to -0.31).

## Discussion

The main finding in this study was that in one third of cases (34%) asystole as defined above started after the onset of TLOC, or within such a short time (≤3 s) before TLOC, that in either case it was very unlikely that the bradyarrhythmia would have been the prime cause of TLOC. On the other hand, in 23 of 35 cases (66%) asystole preceded TLOC by a sufficiently long time to allow asystole to have played a key role in triggering unconsciousness.

Our analysis was based solely on the time of onset of asystole relative to that of TLOC. At no point did we assume that vasodepression was absent. In fact, blood pressure at the onset of TLOC is likely to represent the combined effects of vasodepression and

cardioinhibition. As noted earlier, there is no practicable way to disentangle the combined effects of vasodepression and cardioinhibition on blood pressure and hence on cerebral hypoperfusion. We chose to estimate vasodepression at the onset of asystole by measuring MAP at that point in time. Median MAP was higher when asystole occurred early, i.e. > 3 s. before TLOC (group C, 45.5 mmHg) than when it started later (group A+B, 32 mmHg). The fact that MAP was higher for early than for late asystole suggests that vasodepression was less pronounced in early asystole, and that early asystole was reasonably likely to be the prime cause of TLOC.

## Clinical implications

Figure 3 provides a schematic view illustrating how the magnitude as well as the timing of the vasodepressive and cardioinhibitory mechanisms may determine when syncope occurs. A key implication of these effects is that relying on heart rate data alone may overestimate the importance of asystole as the cause of TLOC. For instance, diagnostic studies based on ECG data only would show asystole in three of the four patterns of Figure 3 (patterns 2, 3 and 4), suggesting that pacemaker therapy might be efficacious in all three, whereas it may only be expected to do so in the absence of important vasodilation: pattern 2.[9] Note that we do not state that all those with early asystole (Group C) conform to pattern 2; they may also conform to pattern 3.



Clinical experience illustrates that pacing does not always work in asystolic reflex syncope.[2,17,18] Our findings provide a possible explanation for the lack of pacemaker efficacy in certain cases, specifically those in which asystole occurs after onset of TLOC or very soon before TLOC. Another important issue determining pacemaker response in asystolic reflex syncope concerns a possible additive vasodilatory component. Recent thinking concerning tilt-table testing stresses that a positive tilt test suggests an underlying clinically important vasodepressive tendency and consequently a low probability that pacing therapy will be effective.[19] In Figure 3 that vasodepression tendency would result in an abnormal tilt test in patterns 1, 3 and 4. These considerations were inspired by the ISSUE III sub-study, in which pacing was performed in patients in whom an implantable loop recorder had previously shown asystole.[9] In that study, pacing usually did not prevent syncope if a previous tilt table test had been positive, suggesting a vasodepressor contribution to the syncope. The SUP-2 study also showed more benefit from pacing in those with a negative tilt table test. In that study the group with asystole during TTT (n=38) had a recurrence rate of 23% after 3 years. It is tempting to think that this group corresponds to our groups A and B (together 34%) in the present study, i.e. those with late asystole.[10] Potentially, some patients with VVS in whom asystole commences well before TLOC may benefit from pacing. If this concept proves valid, next steps would include measuring the onset of asystole in relation to that of TLOC, determining whether the

relative timing of asystole onset is reproducible, and finally whether pacing for early onset asystole reduces syncope risk.

In principle the same reasoning also applies to bradycardia, but we chose to limit our study to asystole as it reflects cardioinhibition in its most severe form.

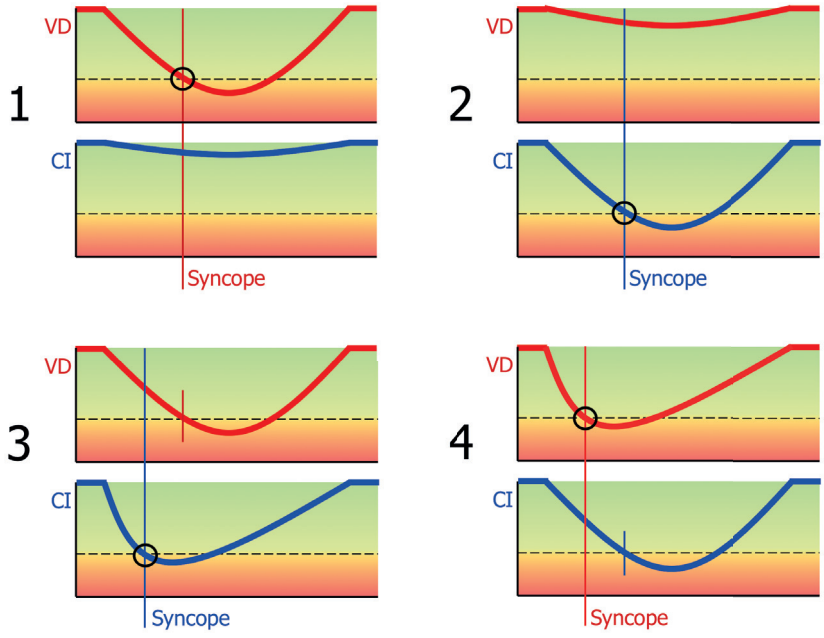


**Figure 3. Schematic representation of possible relationships between strength and timing of vasodepressive and cardioinhibitory mechanisms in reflex syncope**

Each of the four patterns 1-4 shows the time course of cerebral perfusion (bold lines) as affected by vasodepressor (VD) and cardioinhibitory (CI) mechanisms, as if these act independently. The orange zone in each panel denotes significant hypoperfusion: as soon as perfusion drops into this zone, syncope is thought to occur. This simplification is limited to situations when at least one mechanism is strong enough to cause syncope on its own.

Pattern 1 shows a strong VD effect and a negligible CI effect on cerebral perfusion: the VD mechanism decreases perfusion by itself to such a degree that syncope ensues. Pattern 2 shows the opposite situation in which VD will not cause syncope on its own, but CI will. Patterns 3 and 4 show 'mixed forms'. Patterns 3 shows 'early CI': here, VD and CI would each cause syncope if they were the only active mechanism, but CI acts earlier and is the prime cause of the beginning of syncope. Pattern 4 shows 'late CI', in which the beginning of syncope is due to VD.

## Limitations

The results reported here must be interpreted in the light of several important limitations. First, the number of patients was fairly low, due to the combined demands of syncope and asystole without the use of nitroglycerin. Second, the study focused on findings obtained during tilt-induced syncope. Heart rate may well behave differently between tilt table tests and spontaneous events, so we do not know whether our findings apply to real life. Third, this study is unable to inform on the reproducibility of the findings.

Fourth, the impact of our observations on therapeutic interventions, particularly pacemaker therapy, is unclear. Specifically, the ISSUE-III sub-study alluded to above suggests that pacing to prevent asystole and TLOC is less useful in those patients with an evident vasodepressor susceptibility based on prior tilt table testing.[9] In this regard, we stress that our study only comprised patients with positive tilt-table tests; we did not examine how these patients would have responded to pacing. Consequently, we cannot state whether pacing is more useful in patients in whom asystole occurs early with regard to TLOC versus late onset asystole. However, it should be realised that the ISSUE-III investigators did not attempt to ascertain whether asystole occurred before during or after TLOC onset. Consequently, a useful next step would be to combine ILR recordings with comprehensive video-EEG analysis and TLOC onset assessment as was used here.



Finally, our approach to assess the timing of asystole relative to onset of TLOC was robust, but not perfect. We used a three second asystole threshold since previous studies show that TLOC is unlikely to occur with loss of cerebral blood flow of that duration or less. Consequently, asystole occurring three s. or less before TLOC could reasonably be argued to be non-contributory. However, it is recognized that in some patients, consciousness may be unaffected for 8 to 10 s.[8] Because of this variation in the syncope threshold, the proportion of cases without a primary cardioinhibitory mechanism may thus be higher.

## Conclusion

In one third of cases with tilt-induced reflex syncope with asystole, asystole occurred too late to have been the primary cause of loss of consciousness. These results may help to explain the apparent ineffectiveness of pacemaker therapy in many cases of cardioinhibitory reflex syncope, and suggest that efforts to prevent syncope by pacing intervention should focus on the timing of asystole in relation to that of TLOC.

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# CHAPTER IV

# Unexplained loss of consciousness: the diagnosis is never based on one symptom

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## Abstract

Patients with transient loss of consciousness are often seen by a variety of specialists. Even if typical signs occur, it can be difficult to diagnose specific causes. We discuss two patients with complex presentations. The first patient was diagnosed with sleep syncope, a relatively unknown type of reflex syncope. The prodromal symptoms of discomfort and the subsequent loss of consciousness occurred while the patient was in bed or got up to go to the toilet due to abdominal symptoms. The onset in supine position was misleading, since this is a well-known alarm symptom for a possible cardiac cause. The second patient had vasovagal syncope followed by a psychogenic pseudosyncope. This resulted in frequent loss of consciousness of long duration with typical and atypical triggers and uncommon syncopal signs, including eye closure. These conflicting symptoms can be a pitfall and clinical expertise is required to identify the type of syncope.

## Dames en Heren,

Huisartsen, neurologen, cardiologen, geriaters, internisten en eerstehulpposten krijgen veelvuldig patiënten met een wegraking te zien. Belangrijk voor een juiste differentiële diagnose is het gedetailleerd uitvragen van de anamnese en de heteroanamnese. De medicus kan in bijzondere gevallen op een dwaalspoor worden gebracht, zelfs als er kenmerkende klinische verschijnselen zijn en een richtlijn voor patiënten met syncope is gevolgd. Wij presenteren 2 patiënten bij wie kenmerkende verschijnselen een valkuil vormden.

Bij 3% van de patiënten die naar de SEH komen is er sprake van een wegraking.[1] Om te bepalen of er sprake was van syncope is een gedetailleerde anamnese essentieel, zo stelt de syncope-richtlijn van de European Society of Cardiology (ESC).[2] Denk hierbij aan het uitvragen van aspecten als frequentie, uitlokking, prodromale verschijnselen, positie, duur, bijkomende verschijnselen en het beloop tijdens herstel. Toch kan het ook met de richtlijn van de ESC in de hand moeilijk zijn om syncope te onderscheiden van andere aandoeningen.[2] Dit kan leiden tot onzekerheid bij de patiënt, verkeerde diagnosen en overdiagnostiek.



**Patiënt A**, een 45-jarige vrouw, bezoekt de polikliniek Neurologie wegens recidiverende wegrakingen. Haar voorgeschiedenis is blanco, behoudens subklinische hypothyreoïdie; ze gebruikt geen medicatie. Er komt geen epilepsie of plotse dood in de familie voor. Als kind viel ze makkelijk flauw, bijvoorbeeld bij bloedprikken, maar hiervoor is ze nooit onderzocht. Nu heeft zij al ruim 10 jaar lang wegrakingen 's nachts, ongeveer 2 per jaar.

De aanvallen verlopen altijd op dezelfde manier: patiënte wordt wakker zonder aanwijsbare reden, begint na 20 s heftig te transpireren en voelt zich onwel, met misselijkheid, buikpijn en aandrang tot ontlasting. Patiënte probeert door spieren aan te spannen en de benen hoger te houden een wegraking te voorkomen, maar dat is zelden succesvol. Op grond van ervaring rolt zij zich meestal uit bed, omdat zij in bed geen incontinentie voor urine wil krijgen. Tijdens het rollen of op de grond liggend verliest ze dan haar bewustzijn. Haar echtgenoot meldt dat er wel eens een verkramping te zien is, maar nooit waren er schokken van enige omvang, een tongbeet of uitvalsverschijnselen nadien.

De aanvallen duren ongeveer een minuut. Nadien voelt zij zich trillerig en labiel, maar weet ze zich meteen goed te herinneren wat er is gebeurd. Na zichzelf te hebben gewassen vanwege de incontinentie, slaapt zij vlot weer in en de volgende dag na ontwaken heeft zij vrijwel altijd eenmalig diarree.

Bij lichamelijk en neurologisch onderzoek worden geen afwijkingen gevonden. Een ecg toont geen bijzonderheden. Bij een kantelproef ('tilt table test') , waarbij patiënte met het hoofd omhoog wordt gebracht tot bijna verticale positie, tonen bloeddruk en hartslag, continu non-invasief gemeten aan de vinger, eerst geen afwijkingen. Tien min na het kantelendalen de bloeddruk en hartfrequentie echter plotseling snel. De laagste bloeddruk is 48/32 mmHg en er ontstaat een asystolie gedurende 9 s tijdens terugkantelen. Patiënte geeft kort van tevoren aan dat ze niet lekker wordt. Ze voelt zich licht in het hoofd, heeft darmklachten en het wordt zwart voor de ogen. Ze wordt bleek, raakt buiten bewustzijn, verkrampt en is incontinent voor urine. Het EEG toont een vertraging en wordt vlak gedurende circa 18 s. Na afloop herkennen zowel patiënte als haar echtgenoot de verschijnselen als gelijk aan die bij de nachtelijke wegrakingen. Hierop wordt de diagnose slaapsyncope gesteld.

Het onderzoek werd gevolgd door een korte oefensessie waarin bloeddrukverhogende manoeuvres geoefend worden, zoals het kruisen van de benen met aangespannen spieren.

**Patiënt B**, een 16-jarige scholiere met een blanco voorgeschiedenis, werd verwezen naar de polikliniek Neurologie in verband met recidiverende wegrakingen. Zij gebruikt geen medicatie en er komt geen epilepsie of plotse dood in de familie voor. Zij is eenmalig op de SEH geweest en door de kinderarts gezien, voorafgaand aan het bezoek aan de neuroloog. De aanvallen begonnen op 9-jarige leeftijd. Op de basisschool maakte zij 3 aanvallen door. Sinds haar 12e nemen de aanvallen toe en op het moment dat de ze de polikliniek bezoekt treden ze maandelijks op.

De eerste aanval ooit kreeg ze tijdens de gymles na het maken van een koprol. Toen ze daarna opstond werd ze licht in het hoofd en verloor ze kortdurend het bewustzijn. Later traden aanvallen ook op in het bijzijn van ouders bij een vaccinatie en bij het 'schieten' van gaatjes voor oorbellen. Ze wordt dan bleek en valt slap neer. De ouders hebben nooit schokken opgemerkt. Er was 1 maal sprake van urine-incontinentie, nooit van een tongbeet.

Patiënte ligt bij een aanval lang slap op de grond met de ogen dicht. De geschatte duur van de bewusteloosheid is 6 min. Na de wegraking is ze meteen helder; wel is zij moe en heeft zij hoofdpijn. Een enkele maal is het gelukt een wegraking te voorkomen door bij duizeligheid direct te gaan zitten. De recente aanvallen treden onder wisselende omstandigheden op: tijdens sporttraining, liggend op bed of zittend achter de computer. Vergeleken met vroeger voelt ze de aanvallen nu niet altijd aankomen en duren ze langer.

Bij lichamelijk en neurologisch onderzoek worden geen afwijkingen gevonden. Het ECG is niet afwijkend. Bij een kantelproef wordt een aanval opgewekt: na 10 min passief omhoog gekanteld staan treden klachten van duizeligheid op die gepaard gaan met een daling van de bloeddruk van 98/59 naar 70/44 mmHg; de hartslag stijgt van 100 naar 110 slagen/min. Enkele seconden later verslapt zij opeens en vallen haar hoofd en romp opzij en reageert zij niet op aanspreken. Haar ogen zijn gesloten. Bij terugkantelen is er vlot herstel van de bloeddruk, maar aanspreken lokt geen reactie uit, aanschudden evenmin. Op het eeg is tijdens deze episode geen afwijking te zien. Na 3 min opent patiënte weer de ogen. Na afloop geeft zij aan dat zij zich niets van de hele situatie kan herinneren. Hierop worden de gecombineerde diagnosen vasovagale syncope en psychogene pseudosyncope gesteld. De kantelproef wordt direct benut om bloeddrukverhogende manoeuvres te onderwijzen.

Patiënte wordt naar een psycholoog verwezen voor gerichte behandeling, waarbij met name exploratie plaatsvindt naar mogelijke onderliggende problematiek.

## Beschouwing



Wegrakingen worden onderverdeeld in 3 hoofdtypen, waaronder syncope (tabel 1). Syncope is een plotseling, vanzelf overgaand verlies van bewustzijn door globale cerebrale hypoperfusie.

**Tabel 1. Indeling van niet-traumatische wegrakingen.***

| syncope | insult | psychogeen |
|---|---|---|
| reflexsyncope | gegeneraliseerd | pseudo-epilepsie (PNES) |
| orthostatische hypotensie | tonisch | pseudosyncope (PPS) |
| cardiaal | clonisch | |
| ritmestoornis | tonisch-clonisch | |
| structureel | atoon | |

* Kortdurend bewustzijnsverlies met spontaan herstel

Ook syncope kan weer onderverdeeld worden in 3 subtypen: reflexsyncope, orthostatische hypotensie en cardiale syncope (tabel 2). Binnen de syncopegroep zijn de prodromale verschijnselen transpireren, bleekheid en misselijkheid kenmerkend voor reflexsyncope. Het optreden van syncope in liggende houding geldt vaak als een krachtige aanwijzing voor een mogelijke cardiale oorzaak.[2] De achterliggende reden is dat het in liggende houding in de regel een complete circulatiestilstand vergt om bewusteloosheid te doen ontstaan. In staande houding volstaat een lage bloeddruk zonder circulatiestilstand om bewusteloosheid te veroorzaken.

**Tabel 2. Vormen van syncope.**

| reflexsyncope | orthostatische hypotensie | cardiale syncope |
|---|---|---|
| vasovagaal<br>emotie (angst, pijn, bloedfobie)<br>orthostatische stress<br>atypische vormen, waaronder slaapsyncope | initiële orthostatische hypotensie (direct na het opstaan) | ritmestoornis<br>bradycardie<br>sinusknoopdisfunctie<br>geleidingsziekten<br>tachycardie<br>supraventriculair<br>ventriculair (idiopathisch, kanalopathie et cetera) |
| situationeel<br>hoesten<br>niezen<br>lachen<br>defecatie<br>slikken<br>mictie<br>overige | klassieke orthostatische hypotensie (binnen 3 min na opstaan)<br>primair autonoom falen (bijvoorbeeld multipele systeematrofie, ziekte van Parkinson, 'Lewy Body' -dementie)<br>secundair autonoom falen (bijvoorbeeld bij diabetes mellitus of amyloïdose)<br>geneesmiddelen, (bijvoorbeeld diuretica) | structurele aandoeningen<br>acute cardiale ischemie, hypertrofische cardiomyopathie etc. |
| sinus-caroticussyncope | late orthostatische hypotensie (later dan 3 min. na opstaan) | |

* Syncope: plotseling, vanzelf overgaand verlies van bewustzijn door globale cerebrale hypoperfusie.

Er is een uitzondering op de regel dat bewusteloosheid bij een liggende patiënt pas optreedt bij een circulatiestilstand: slaapsyncope. Dit is een relatief kort geleden herkend subtype van reflexsyncope.[3]

## Slaapsyncope

Bij patiënt A wezen de aanvallen zeer sterk op syncope, niet op insulten of psychogene wegrakingen. Het moment van optreden, 's nachts tijdens de slaap, verschilt wel sterk van een klassieke vasovagale syncope. Toch berust het wegraken bij slaapsyncope op hetzelfde mechanisme, met bradycardie en een bloeddrukdaling.

De meeste patiënten met slaapsyncope ontwaken wegens prodromale verschijnselen en buikklachten waarna zij het bewustzijn verliezen, ofwel liggend in bed, ofwel na het opstaan, wat ze vaak doen om naar de wc te gaan. De abdominale verschijnselen bij slaapsyncope kunnen lijken op de kenmerkende 'epigastric rising sensation' bij temporale epilepsie. Maar ook bij een klassieke reflexsyncope kan al een opstijgend gevoel in de buik optreden, en bij slaapsyncope lijken de aandrang tot defecatie en mictie tot de autonome uitingen van de reflex zelf te behoren.[3]

In vergelijking met klassieke vasovagale syncope gaan aanvallen van slaapsyncope vaker gepaard met ernstige cardio-inhibitie en asystolie en treden ze vaker op bij patiënten in horizontale positie. Hoewel syncope bij een liggende patiënt geldt als cardiaal risicoteken, is dit niet altijd juist; bij syncope geeft de combinatie van verschijnselen de doorslag, niet een enkel symptoom. Waarschijnlijk is slaapsyncope niet zeldzaam; bij personen met

klassieke vasovagale syncope treedt soms ook een slaapsyncope op. Waarschijnlijk wordt deze aandoening onvoldoende herkend.

## Psychogene pseudosyncope

Bij patiënt B was sprake van een veranderend patroon van de aanvallen. Het debuut van de aanvallen, met onder meer pijn als uitlokkende factor, de prodromen en de ictale verschijnselen passen in feite alleen bij vasovagale syncope.[2] Later duurden de aanvallen langer, wat meestal geassocieerd wordt met een gegeneraliseerd insult. Consistent gesloten ogen tijdens bewusteloosheid passen echter noch bij syncope noch bij epilepsie, maar goed bij een psychogene oorzaak.[4,5]

Deze patiënte bleek 2 aandoeningen tegelijk te hebben: bij de kantelproef werd de vasovagale aanval gevolgd door een psychogene wegraking, ofwel een psychogene pseudosyncope. Dit is een psychiatrische aandoening met uiterlijke kenmerken van bewusteloosheid – de patiënt is bewegingsloos en niet responsief – maar zonder afwijkingen van de bloeddruk, hartslag of het EEG tijdens de episoden. De gesloten ogen en de lange duur van de aanval vormen krachtige argumenten voor de diagnose.[6]
Vrijwel hetzelfde klinische beeld kan gezien worden bij patiënten met vasovagale syncope en direct aansluitende slaap, maar dit is zeldzaam en komt vrijwel uitsluitend voor bij kinderen onder de 8 jaar.[7] Deze mogelijkheid was bij onze patiënte uitgesloten, aangezien het EEG tijdens de uitgelokte aanval niet paste bij slaap maar bij waak. Het optreden van een aanval tijdens de kantelproef staat een zekere diagnose toe, vooral als men gelijktijdig de bloeddruk registreert, een ECG en een EEG maakt en de aanval op video vastlegt. De dubbelpresentatie van een vasovagale plus psychogene variant van syncope is tot op heden zelden beschreven in de literatuur.[6] Onze ervaring is dat deze combinatie regelmatig gezien wordt op tertiaire syncopepoliklinieken. Onderzoeken naar het beloop ontbreken vooralsnog.



## Etiologie en indeling van syncope

Bij syncope zijn de aanwezigheid en de aard van een uitlokkende factor essentieel voor de diagnose. Bij reflexsyncope worden enkele typen onderscheiden (zie tabel 2): (a) vasovagale syncope bij langdurig staan of bij emotionele stress (angst, pijn); (b) situationele syncope bij specifieke prikkels (hoesten, niezen, lachen, defecatie, slikken, mictie); (c) de sinus-caroticussyncope.[2] Hiernaast kan syncope door staan ook optreden via orthostatische hypotensie.

De 3 vormen van orthostatische hypotensie worden ingedeeld naar het tijdstip van optreden: direct na het opstaan (initiële orthostatische hypotensie), binnen 3 min na het opstaan (klassieke orthostatische hypotensie) of bij lang staan (late orthostatische hypotensie, > 3 min na opstaan).[8] De snelste bloeddrukveranderingen kunnen alleen

worden vastgesteld met continue bloeddrukmetingen, bijvoorbeeld via non-invasieve vingerplethysmografie. De klassieke vorm kan een uiting zijn van schade van het autonome zenuwstelsel –waarbij men onderscheid maakt tussen primair autonoom falen (puur autonoom falen, multipele systeematrofie, ziekte van Parkinson, 'Lewy body'-dementie) en secundair autonoom falen (bijvoorbeeld diabetes of amyloïdose) –, door medicatie worden uitgelokt of optreden bij volumedepletie.[2] Orthostatische hypotensie duidt op een afwijkende bloeddrukregeling, maar is geenszins een bewijs van autonoom falen; het kan asymptomatisch voorkomen bij ouderen.[8]

### Provocatie met kantelproef

Om de oorzaak van wegrakingen te achterhalen is provocatie nuttig, bijvoorbeeld door de patiënt actief te laten opstaan of met een kantelproef ('tilt table test').[2] De essentie van de kantelproef is dat men probeert een aanval op te wekken. De patiënt ligt eerst 10 min plat op de kanteltafel terwijl de bloeddruk en het ECG continu wordt gemeten; in sommige instituten, waaronder het LUMC, wordt hierbij tevens een video-EEG verricht. Daarna wordt, terwijl alle metingen doorgaan, de tafel zo gekanteld dat de patiënt met het hoofd omhoog in een hoek van circa 70° komt te staan, dus vrijwel rechtop.
De beenspieren worden bij het kantelen niet aangespannen, zodat de spierpomp inactief blijft; normaliter draagt die ertoe bij dat in staande houding bloed vanuit de benen terug wordt gepompt naar het hart. Deze houding wordt 20 min volgehouden waarna, als er geen wegraking heeft plaatsgevonden, de patiënt een vaatverwijdend middel krijgt toegediend en nogmaals 20 min wordt gewacht. Als vaatverwijder gebruikt men meestal nitroglycerine 0,4 mg, onder de tong. Het onderzoek wordt gestaakt als een wegraking plaatsvindt, wanneer klachtenherkenning optreedt of de tijd verstreken is.[2]

**Dames en Heren**, een incomplete anamnese van een patiënt met syncope kan verwarrend werken, zoals de 2 ziektegeschiedenissen illustreren, vooral als elk symptoom afzonderlijk beoordeeld wordt; de diagnose berust namelijk vrijwel nooit op één symptoom.[5,9,10] Het symptoomcomplex kan al vrij snel enkele conflicterende symptomen bevatten en dan het is de kunst voor de clinicus om signaal van ruis te onderscheiden. De diverse elementen in het verhaal van de patiënt staan niet op zichzelf, maar moeten als geheel worden bekeken. Dit is bij uitstek een vaardigheid waarin de expert zich van een beginnend arts onderscheidt.

Waar een niet-expert nog geen referentiekader heeft om de verschillende argumenten af te wegen, kan een expert elk argument stuk voor stuk van een gewicht voorzien. Bij diagnostische twijfel is verwijzing naar een tertiaire syncopepolikliniek dan ook zeker op zijn plaats. Overleg met een expert, bijvoorbeeld via het bestaande syncopenetwerk, kan in een vroeg stadium na afronding van de initiële analyse plaatsvinden. Dit kan tijd besparen en overmatige diagnostiek of zelfs een onnodige behandeling voorkómen.

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# CHAPTER V

# Five cases of complete atrioventricular block induced by bending forward: unusual but not unique

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## Abstract

**Aims**

We describe five patients with syncope caused by a complete AV-block (AVB) while they were bending forward, not rising after bending, and aim to describe the occurrence and the association between bending forward and AVB.

**Methods and results**

In two patients, bending forward was the exclusive trigger for syncope, while in the remaining three other postural changes (sitting down, standing up, exertion) could also provoke syncope. Complete AVB as the cause of syncope was documented using ECG monitoring in two cases and an implantable loop recorder in the other three. Ectopic beats without preceding sinus slowing occurred before syncope in four cases. Two cases had a left bundle branch block. All patients responded favourably to cardiac pacing.

**Conclusion**

This is the first case series on complete AVB provoked by bending forward. Syncope during bending forward should suggest a search for an AVB. Arguments in favour of a vagal mechanism were syncope triggered by bending forward and that other triggers could also evoke syncope. However, the absence of sinus slowing before syncope in some cases and the fact that bending forward did not seem to provoke reflex syncope without AVB, cast doubts on a reflex mechanism. There were also arguments favouring conduction disorder: i.e. ectopic beats before syncope and pre-existing conduction disturbances in two cases. The cases are reminiscent of paroxysmal AVB. Discrimination between paroxysmal AVB and vagal AVB is important because a pacemaker is warranted in arrhythmic complete AVB, while the benefit is limited or absent in reflex AVB.


**Keywords:** paroxysmal AVB, reflex syncope, bending forward, intrinsic AVB

## Introduction

The diagnosis of syncope rests on history taking, and, when that does not yield a highly probable diagnosis, on documenting attacks with ECG or blood pressure measurements.[1]

The encounter with one patient with a complete atrioventricular block (AVB) during bending forward led us to search for other cases, which revealed four. In all five cases, history taking revealed that syncope could be triggered by bending forward, although it was not the only syncope trigger in some cases. The ECG showed a complete AVB during syncope in all five cases.

We describe the five cases and discuss them in the context of AVB in reflex syncope and as an expression of diseases of the conduction system.

### Case 1

A 73-year-old former physician had a history of vasovagal syncope since childhood. He was referred because of episodes of transient loss of consciousness (TLOC) that felt different from his earlier vasovagal syncope. He had had attacks once a month for two years. They started with a tingling sensation in the head that he had learned to recognise as a certain warning of impending TLOC. To avoid injury, he tried to take off his glasses and lie down, but often did not have enough time to do so. He had fallen repeatedly and had sustained injuries. He had broken his glasses on several occasions. Even when he lay down in time to prevent a fall, he still always lost consciousness a few seconds after lying down. His wife, a former nurse, observed that the signs of his spells depended on their duration: during short attacks, his eyes remained closed, he did not become cyanotic and did not snore. During longer attacks, lasting about a minute, his eyes opened, he became cyanotic, made snoring sounds and could become incontinent. Afterwards he was usually disorientated for a few seconds and always felt tired afterwards. The attacks were always triggered: they could occur after sitting down heavily on a chair, straining on the toilet or exerting force on a bicycle pedal, but they were particularly often provoked during bending forward. He therefore tried to prevent this and no longer tied his own shoelaces.

Visits to a neurologist resulted in a normal brain MRI and EEG; two cardiologists had reporting a normal echocardiogram and exercise ECG; no-one had tried to provoke an attack.

A tilt table test with video-EEG monitoring with nitroglycerin provocation and carotid sinus massage was performed, which showed no abnormalities. Afterwards he was asked to stand and bend forward, during which he felt an attack come on. He lay down on a mat and immediately lost consciousness. The ECG showed a third degree AVB with asystole of

28 seconds, preceded by several ventricular escape beats. He snored during the attack, and the EEG flattened during syncope (Figure 1). His wife, present at the recording, recognised this as a typical long attack. He was referred to the cardiology department where he received a pacemaker (Boston Scientific, type: Ingenio MR DR J176, mode DDD with AV search 50-130 beats/min), after which a 12-month follow-up showed an absence of attacks. Follow-up revealed less than 1% pacing.

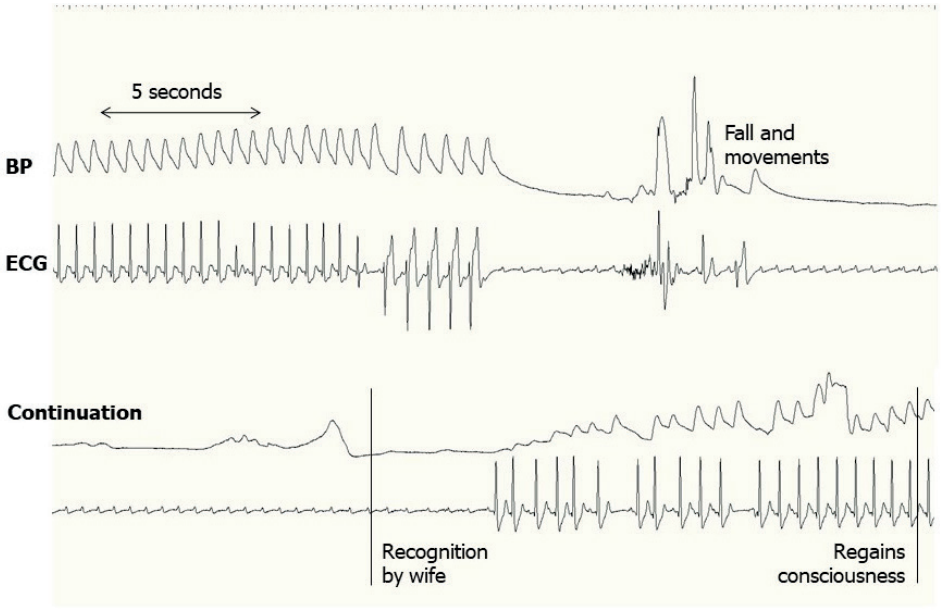


**Figure 1. Blood pressure and ECG recording of case 1.**

Blood pressure was taken from a finger plethysmograph. Note that the attack starts with several ventricular escape beats, followed by a complete AVB. One or two heart beats appear when he lost consciousness, followed by a longer period of complete AVB. The ECG was recorded using EEG equipment with filter setting different to those of ECG machines, meaning ECG waveforms may be distorted. BP; blood pressure, ECG; electrocardiography, EEG; electroencephalography.

## Case 2

A 55-year-old woman with a history of vasovagal syncope in childhood was referred because of about eight TLOC incidents in 18 months, with an increasing frequency. The attacks started with ringing of the ears directly followed by blurred vision. She had no time to sit or lie down as she always lost consciousness within seconds after first noticing the ringing. Bystanders reported pallor of the face and kicking of the legs during attacks. When she regained consciousness, she at first felt like she was waking up and then felt tired, which she recognised as similar to her earlier vasovagal episodes. The attacks were

triggered by bending forwards; examples were picking groceries from a low supermarket shelf, trying on new shoes and bending over to pick up the turds of her dog. After recognising bending forward as a trigger, she tried to avoid doing so, which appeared to help.

Earlier neurological (MRI and EEG) and cardiological examinations had shown no abnormalities, including a normal tilt table test. A Valsalva manoeuvre resulted in a blood pressure decrease to 80/40 mmHg with nausea, but she did not recognize this as similar to the recent spells. A 24-hour ECG and echocardiogram were normal, but no episode had occurred during the recording period. A repeat tilt table test including carotid sinus massage showed no abnormalities. Bending forward did not result in an attack or ECG changes.

After implantation of an Implantable Loop Recorder (ILR) (Reveal Linq, Medtronic) she suffered a typical spell, accompanied by asystole of eight seconds accompanied by an AVB without preceding sinus slowing (Figure 2). A pacemaker (Medtronic, type; Advisa DR MRI A3DR01, Mode: DDD with a lower rate of 50 beats per minute (BPM) and upper 130 BPM ) was implanted, and during 9-month follow-up she had no more attacks. The pacemaker reported right atrial (RA) pacing of 0,5% and right ventricle (RV) pacing 0%.

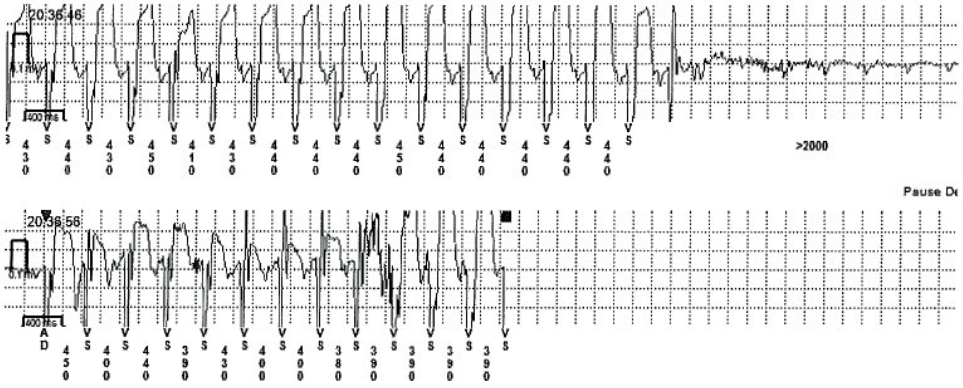


**Figure 2. ILR data in case 2.**

The ECG shows an asystole for eight seconds without preceding sinus slowing. ILR; implantable loop recorder.

## Case 3

A 70-year-old woman with a history of diabetes mellitus type II, had had six TLOC episodes over 10 years. She had been admitted twice because of resulting concussions. The attacks had happened while bending forward. She felt nauseous, followed almost instantaneously

by loss of consciousness and a fall. Eyewitnesses reported that she appeared stiff during unconsciousness. The attacks had taught her not to pick up objects from the floor.

ECG, echocardiogram, a 24-hour ECG recording and a coronary angiogram had showed no abnormalities. A tilt table test including carotid sinus massage, bending forward and a Valsalva manoeuvre showed no abnormalities. After implantation of an ILR (Reveal Linq, Medtronic), several periods of asystole and complete AVB were observed. She subsequently received a pacemaker (Medtronic, type: Advisa DR, MRI/A3DR01, Mode: DDD with AV delay 180ms ), resulting in a cessation of attacks (pacing RA 1.6% and RV 1.1% at follow-up).

## Case 4

This case has been published previously.[2] In short, a 64-year-old woman with a history of type 2 diabetes mellitus presented with more than 40 TLOC incidents over seven months. The attacks were triggered by changes in posture, including standing up, bending forwards and sitting down. Her husband described that she became pale, lost consciousness for 30-60 seconds and kicked her legs during the attacks. The ECG had showed a left bundle branch block. A tilt table test showed no abnormalities. She was asked to mimic the last spontaneous attack that had occurred while she picked up fallen oranges from the floor. While doing so, she grunted and slumped forwards to the floor. The ECG showed slowing of a sinus rhythm followed by a complete AVB with asystole of about 10 s. (Figure 3). After implantation of a pacemaker, she suffered no further attacks.

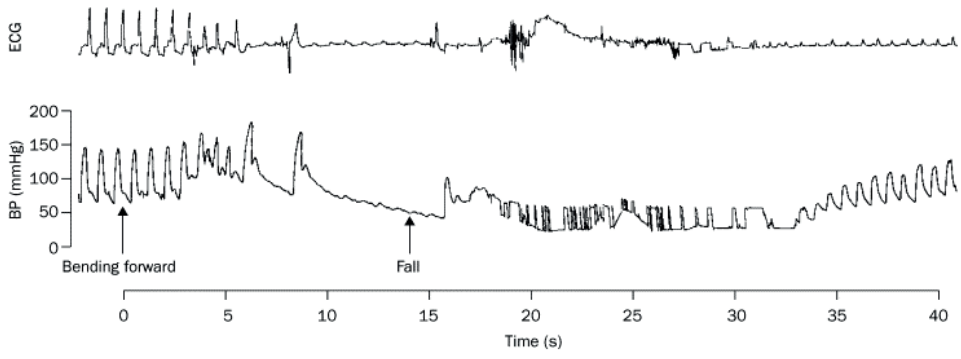


**Figure 3. ECG and BP in case 4.**

The ECG first showed slowing of a sinus rhythm, followed by a complete AVB with asystole of about 10 s. As in case 1, the ECG was recorded using EEG equipment.

## Case 5

A 74-year-old woman presented with TLOC of recent onset. About once every two weeks she experienced episodes of light-headedness, blurred vision and TLOC during standing up, bending forwards or sitting down. Her spouse reported that her eyes widened and turned upwards, and that she then fell over, stiff as a log. There was no time for her to sit or lie down to prevent TLOC. The events caused her great distress and she no longer dared to walk alone or to drive.

Previous cardiological work-up revealed a left bundle branch block. A 24-hour ECG, echocardiogram and exercise testing revealed no new findings. A tilt table test with nitroglycerin provocation and carotid sinus massage did not provoke an attack. Arrhythmic syncope was considered because of the presence of an LBBB[1] and her inability to prevent TLOC by sitting down, so an external loop recorder was ordered. This approach failed to capture the next attack that happened when she bent forward to pick up a piece of soap while showering, because she had detached the electrodes before showering. An ILR was implanted, which did capture a typical event while lying in bed. This was accompanied by asystole and a complete AVB (fig 4) with an asystole of eleven seconds without preceding sinus slowing. A pacemaker (Medtronic, type: Advisa DR MRI A3DR01, Mode: DDD with lower rate 60 and upper rate 130 BPM) was implanted and the patient had no further attacks. Follow-up showed RA 2.7% and RV 9.2% pacing.

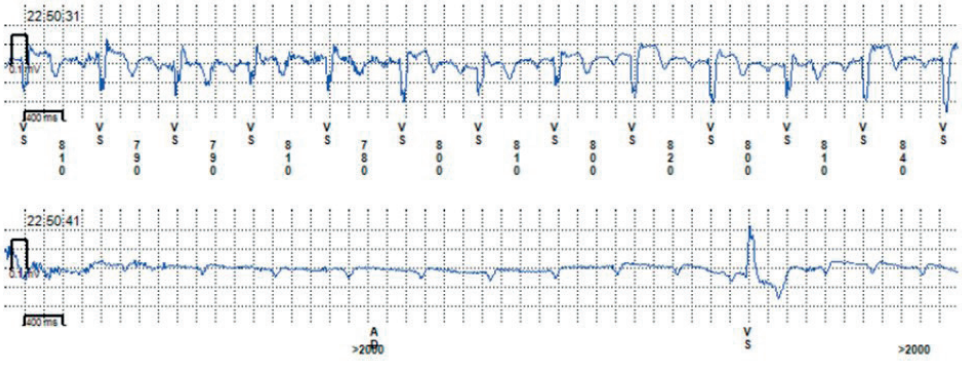


**Figure 4. ILR data in case 5.**

The ECG shows a complete AVB with asystole for eleven seconds, without preceding sinus slowing.

## Discussion

This appears to be the first description of syncope due to complete AVB triggered by bending forward. The diagnosis rested on provoking an attack in two cases and on an ILR in three. Recognising the association between bending forward and an AVB may prompt attempts to provoke syncope and may suggest pacemaker implantation.

### Reflex AVB or intrinsic conduction disorder?

A complete AVB may occur as an acquired high-degree or complete heart block, a vagally mediated AV block, a congenital heart block and as 'paroxysmal AVB'.[3] The presence of a trigger for syncope usually suggests reflex syncope.[1] However, syncope can also be triggered by external circumstances in some cardiac arrhythmias.

### AVB as an expression of reflex syncope

AVB as part of a reflex mechanism was recently described.[4] Such a 'reflex AVB' is in the majority of cases preceded by slowing of the sinus rhythm.[4,5,6] This bradycardia suggests that the block is due to parasympathetic influences on the SA- as well as the AV-node.

A preceding bradycardia is however absent in 20% of reflex AVB, as shown by the ISSUE 2 &3 studies.[4] An alternate explanation is syncope associated with low adenosine levels.[4]

Reflex AVB has most often been described in syncope with a clear external trigger, such as swallowing[7], coughing[8] or emotional distress. However, a trigger can also occur in arrhythmias, such as in 'paroxysmal AVB' (see below), the long QT syndrome (cold water, loud noise)[9] or the Brugada syndrome (large meal). In the Brugada syndrome, the ST segment change to a type 1 and the occurrence of ventricular fibrillation are related to high vagal tone. This suggests that autonomic influences may trigger arrhythmia.[10]

Reflex AVB occurred in approximately 5% of tilt-evoked vasovagal syncope.[11,12] Patients with reflex AVB often had a long history of syncope, including syncope in childhood.[13]

### Complete AVB as an expression of a conduction disorder

The term 'paroxysmal AVB' has been used to indicate any sudden AVB; reflex AVB has in fact been classified as paroxysmal AVB.[4] However, Lee et al. (2009)[3] defined paroxysmal AVB as a sudden, pause-dependent phase 4 AVB, occurring in a diseased conduction system. Paroxysmal AVB in this sense is typically precipitated by slowing of a heart rate, which may be confused with a vagal mechanism. The following characteristics were stated to help differentiate it from reflex AVB. First, paroxysmal AVB was initiated by atrial, His-bundle or ventricular premature extrasystole. Second, tachycardia could suppress AV conduction

and initiate paroxysmal AVB. Third, paroxysmal AVB in the setting of baseline complete AV nodal block has been reported. Fourth, sinus acceleration has been observed during ventricular asystole without affecting the block.[3]

## Finding a balance

Distinguishing between AVB due to a conduction disorder or to a reflex is important, as a pacemaker is warranted in arrhythmic AVB, while studies showed no benefit from a pacemaker in reflex AVB.[14,15]

The sinus slowing in cases 1 and 4 can be interpreted as a reflex mechanism. Arguments favouring a paroxysmal AVB were ectopic beats before AVB in three cases (cases 1, 4, 5), pre-existing conduction disturbances (i.e. LBBB) in two cases (case 4 and 5), and excellent pacing results in all cases, in line with a study on paroxysmal AVB.[16]

A slight modification of heart rate in a bundle branch block may trigger a tachy-dependent or brady-dependent intrinsic AV block.[3] Ventricular beats occurred at the beginning of syncope in cases 4 and 5, with a LBBB. Ectopic atrial or ventricular beats can cause paroxysmal blocks.[3] AVB was triggered in 19 of 30 cases by atrial or premature ventricular beats or His extrasystole; the trigger in the remaining 11 cases included a Valsalva manoeuvre, reminiscent of bending forward.[3] Bending forward may also cause an increase in ventricular preload, with a resulting sudden dilatation of the right heart. The opposite haemodynamic change seems to trigger vasovagal syncope, namely falling venous return. The right atrial baroreceptors are 'stretch' type receptors and could be affected similarly by decrease or increase in right heart volume.

Some of our cases could represent the low adenosine type, given the lack of prodromes; this type also responds well to pacing.[4]

## Diagnostic hints

Our study underlines the importance of history taking and documenting circulatory events in syncope. Attempts to provoke syncope with unusual triggers can easily be added to a tilt table test, as recently advocated.[17] If this is unsuccessful, ECG monitoring may be indicated.

Syncope due to bending forward should be distinguished from syncope due to straightening up after bending, as occurs in initial orthostatic hypotension[18,19] and in classical orthostatic hypotension.

A consistent case feature was a very short warning period before syncope. In a sudden cardiac standstill, the time between the last beat and the onset of loss of consciousness

is only 7-10 seconds.[20] Patients may only become aware of something amiss after 4-5 seconds of asystole, leaving them only a few seconds to act. Case one stressed that lying down did not prevented syncope; a failure of lying down to prevent syncope suggests that syncope is due to circulatory standstill rather than to low blood pressure with normal heart rhythm.

## Conclusion

AVB should be considered in those presenting with syncope provoked by bending forward.

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# CHAPTER VI

# Tilt table testing in neurology and clinical neurophysiology

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*Clin Neurophysiol. 2016 Feb; 127(2):1022-1030*

## Abstract

Reflex syncope is responsible for 1–6% of hospital admissions and the economic burden of syncope is huge. A considerable part of these high costs is still spent on tests that are not indicated. Till now few neurologists have taken an interest in syncope and tilt table testing (TTT). However, reflex syncope and epilepsy are often in each other's differential diagnosis and require a similar emphasis on history taking and deductive reasoning. A TTT can be helpful for diagnosis and treatment. 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. Various indications and methods of the TTT are discussed in this paper.

**Keywords:** syncope, reflex syncope, orthostatic hypotension, tilt table test, head-up tilt

# 1. Background

Syncope and its mimics pose many diagnostic difficulties,caused in part because terms may be used loosely and becausenot everyone uses a standardised and understandable scheme for classification and terminology. We advocate using the scheme from the most authoritative syncope guideline, the one from the European Society of Cardiology (ESC).[36] In that scheme, transient loss of consciousness (TLOC) is defined as unconsciousness of short duration and spontaneous recovery.[36,47,68] The main TLOC forms are syncope, epileptic seizures and episodes of psychogenic apparent unconsciousness (Fig. 1). Syncope is defined as TLOC due to cerebral hypoperfusion.[36] There are three major groups of causes of syncope: reflex syncope, syncope due to orthostatic hypotension and cardiac syncope (ESC 2009). Reflex syncope, also known as neurally mediated syncope, affects about one third of all people.[18] It is divided into vasovagal syncope, mainly evoked by emotions, pain and standing, situational syncope and carotid sinus syncope. Reflex syncope is worldwide responsible for 1–6% of hospital admissions and a frequent reason for referral to internists, cardiologists and neurologists.[6] The economic burden of syncope is huge: annual admission costs for syncope were estimated to be about US$ 2.4 billion dollar in the USA, comparable to those of asthma and HIV.[60] A considerable part of these high costs may be spent on admissions and tests that are not necessary according to the ESC guidelines on syncope.[9,25,34,36] The underlying reason for this inefficient management strategy is probably that syncope forms a 'blind spot' in medicine. Reflex syncope is not claimed by any speciality and hence not taught in detail. The resulting limited training and expertise with reflex syncope prompts specialists, faced with such patients, to order diagnostic tests for disorders they are familiar with. Neurologists will try to prove or exclude epilepsy and order MRIs and EEGs, while cardiologists aim to exclude structural heart disease or arrhythmia. More knowledge of reflex syncope would suggest a different diagnostic strategy, i. e., appropriate history taking and tests including tilt table testing.



Until recently few neurologists took an active interest in syncope, which is surprising as syncope and epilepsy often feature in one another's differential diagnosis. A clinical interest in syncope may prove beneficial to neurologists, if only to prevent misdiagnosis. Likewise, neurophysiological departments may benefit from adding the TTT to their diagnostic repertoire. The aim of this paper is to review the usefulness of the tilt table test in diagnosing TLOC and associated disorders of orthostatic intolerance, i.e., postural orthostatic tachycardia syndrome.[14]

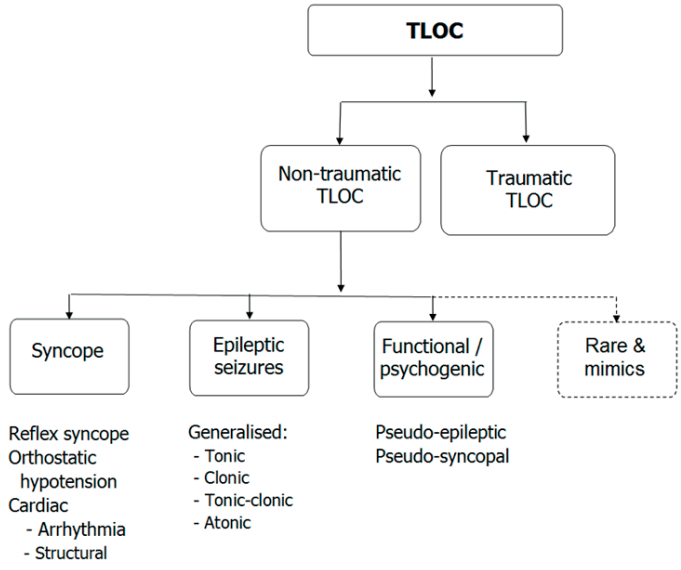


**Figure 1. Main forms of TLOC.**
Traumatic TLOC (concussion) can usually be recognized easily as the cause tends to be obvious. Nontraumatic TLOC is divided into four groups: syncope, epileptic seizures and a miscellaneous group encompassing rare disorders that cause TLOC and conditions that can be mistaken for TLOC; the disorders in the latter group do not share a common pathophysiology. (TLOC= transient loss of consciousness).[68]

## 2. Pathophysiological rationale for tilt table testing

Tilt table tests were initially used to study physiological compensatory responses to orthostatic stress. In the middle of the 20th century air force investigators recognized the ability of tilt-table tests to induce syncope in a population of pilots.[51] Tilt table testing was first used as a clinical test by Kenny et al.[24] who observed a high rate of tilt-induced syncope in patients with previously unexplained syncope. The rationale for the tilt table test can be best understood through the physiology of standing. When one stands up from the supine position, gravity will cause blood to be transferred from the thoracic cavity to the lower limbs.[57,70] Normally, 500–1000 ml of blood shifts from the upper to the lower body. Approximately 80% of the blood pooled in the lower limb is contained in the thighs.[33] Excessive pooling is prevented by neurovascular and neurohumoral mechanisms, aided by the mechanical forces of the 'muscle pump' in the legs. Standing up immediately increases heart rate, resulting from central mechanisms related to the initiation of the postural change together with deactivation of the baroreceptors. These so-called 'stretch receptors' are found in the walls of the carotid sinus and the aorta. These baroreceptors sense the drop in blood pressure caused by a downwards shift of blood and

decreased venous return. The deactivation of the baroreceptors has several reflex effects: vagal outflow to the sinus node decreases which increases heart rate, and sympathetic vasoconstriction is augmented which increases blood pressure. Furthermore, it induces neurohumoral changes including a release of vasopressin.[21,] The orthostatic heart rate response is characterised by a primary peak within 3 s, increasing further to a second peak around 12 s. This increase is more gradual and mainly due to further reflex inhibition of cardiac vagal tone together with an augmented sympathetic outflow to the sinus node. Once the increase of vasomotor tone has successfully counteracted the drop in arterial blood pressure, baroreflex mediated mechanisms will result in a subsequent relative heart rate decrease, resulting in a steady state of blood pressure and heart rate about 30 s after standing up; heart rate increases by 15–30%. The net increase of BP upon standing is explained by the height difference between the baroreceptors and the heart.[74] Reflex syncope can be triggered by gradual pooling of blood in the thighs, buttocks, pelvis and the splanchnic circulation. The pooled blood is situated in the distensible venous capacitance system, probably mainly in the splanchnic vascular bed.[59]The result of this pooling is a decrease in venous return.[14,49,71] It is not completely known how excessive pooling triggers the vasovagal reflex. 'Central hypovolemia', i.e., reduced filling of the heart and the thoracic great vessels probably plays an important role in triggering the reflex. For an overview of the various causes of syncope and their symptoms see ESC 2009.[36,68,75] TTT provokes pooling and may hereby induce reflex syncope. Interestingly, TTT not only provokes syncope in those in whom fainting is induced by standing, but also in those with emotional triggers for syncope.

## 3. Tilt test methods

### 3.1. Common features and variants

Several methods for tilt table testing have been developed, with or without pharmacological challenges. The test should be performed in a quiet room. Blood pressure can change dramatically in seconds in syncope and should be measured at a high temporal resolution. Conventional sphygmomanometric measurements at best allow measurements every minute, inadequate for syncope assessment. Several commercial devices offer finger photoplethysmography, which relies on a cuff around a finger. The pressure in the cuff is constantly adapted to the pressure in the finger, resulting in a fully continuous measurement of blood pressure, i. e., beat-to-beat, as well as heart rate.[23] Another advantage is that additional software may allow additional circulatory parameters to be calculated, such as cardiac output and total peripheral resistance, which allow a detailed circulatory analysis. At least one ECG lead is required to detect bradycardia or asystole. The angle of the table should be between 60 and 80 degrees (Fig. 2).[13] The reason for such angles instead of a fully vertical position is that they hardly diminish the gravity effect,

while allowing subjects to relax. An additional effect of tilting to 60–80_ may be that it prevents leg muscle action, which abolishes the leg muscle pump.[5] The subject should be protected against falling by using safety straps. The duration of the test varies, but the available evidence suggests that 30–45 min is optimal. Patients should be tilted back when pronounced hypotension or bradycardia and presyncope ensues[52], although some prefer to provoke complete syncope. The ESC-guideline recommends a duration of 40 min.[36] Additional pharmacological challenges will be discussed later.

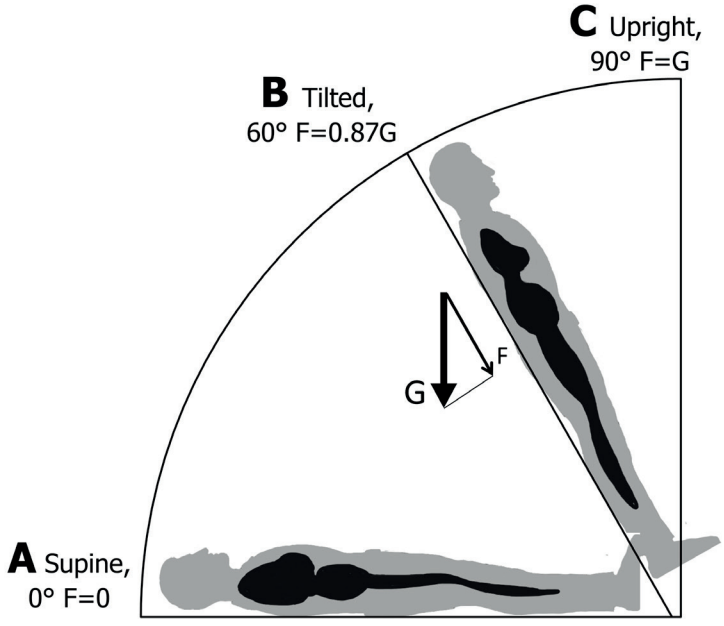


**Figure 2. Scheme of Tilt Table Test**

In situation A, a person is shown in the supine position, i.e. a tilt angle of 0 degrees. The black shape represents the blood volume, with relatively much blood in the thorax. The gravity force G always acts vertically down. It has a component F pulling blood in the direction of the feet, equalling the sine of the tilt angle. A tilt angle of 60 degrees (B) results in F=0.87G. The pull of blood towards the feet results in a change in the distribution of blood, as shown. The force F would be maximal at a tilt angle of 90 degrees (C), but a potential fall in this position is more threatening than in a tilted position. Angles of 60 degrees (F=0.87 G) or 70 degrees (F=0.94G) are less threatening while providing adequate forces displacing blood towards the feet.

## 3.2. Extensions

The use of a video-EEG recording during tilt table testing is recommended because it helps to differentiate syncope from epileptic seizures or psychogenic pseudosyncope.[29] EEG machines allow all signals to be recorded simultaneously, offering the added advantage that all records can be studied after the test, allowing a detailed analysis of semiology.[69]

The addition of EEG to TTT allows a further check on proceedings in that the onset of slowing of the EEG should always result in tilting the patient back, or in reverse that tilting back is not yet obligatory if the EEG is still normal. Furthermore, the EEG, slow or with flattening, provides additional information about the degree of cerebral perfusion.[69] The diagnostic yield of the TTT can be further enhanced with the use of carotid sinus massage (CSM), particularly in those with history of unexplained syncope or falls and a negative history for cardiovascular diseases.[4] In some centres lower body negative pressure is used as an additional method to trigger reflex syncope.[30] A key element of the test is to ask the patient for recognition of complaints. Eyewitnesses may help confirm whether the provoked event resembled the spontaneous episodes, which helps to reduce false positive results. Transcranial doppler (TCD) monitoring during TTT also helps to assess alterations in cerebral blood flow. This is of particular interest to investigate the pathophysiology of syncope, but has so far not been shown to be of diagnostic value.

## 4. Indications

The European Society of Cardiology[36] recommends the use of tilt testing when the initial examination of syncope, consisting of history taking, ECG and supine plus standing blood pressure measurements, has not yielded a diagnosis. The aim of the TTT is to provoke a typical event, to obtain a clinicalpathophysiological correlate and thus prove the cause of TLOC. Apart from syncope, TTT has been advocated in the elderly with unexplained falls.[22] Fig. 3 shows a pragmatic approach, beginning with the initial analysis of history taking, ECG and orthostatic blood pressure measurements (ESC 2009). If this results in obvious reflex syncope, a TTT is not necessary; the same holds if orthostatic hypotension explains the clinical problem fully. Hence, TTT is useful when syncope is likely but its cause is unclear. TTT is also useful to diagnose psychogenic pseudo syncope and POTS. In the next section we will discuss these disorders along with the specific patterns they exhibit during tilt table testing (Table 1).

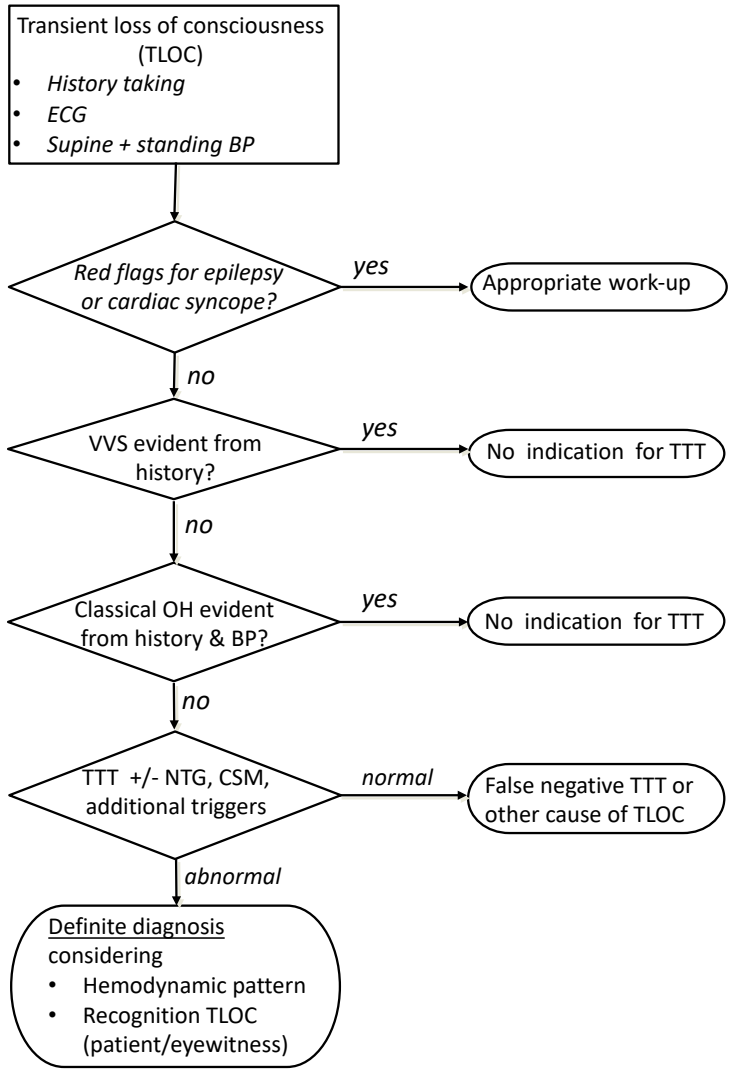


**Figure 3. Diagnostic flowchart for patients with transient loss of consciousness (TLOC).**
First check for red flags for epilepsy and cardiac syncope (see ESC guidelines,2009: table 11 and 13). If VVS or classical OH is evident from history a TTT is not necessary. In other cases a TTT should be performed. The execution of the TTT depends on the clinical suspicion from history taking. In case of an abnormal TTT the hemodynamic pattern together with the recognition by the patient or the eyewitness of the spontaneous attack facilitates a definite diagnosis. TTT patterns are discussed separately in section 5 for each diagnosis.
VVS: vasovagal syncope, TTT: tilt table test, OH: orthostatic hypotension, BP: blood pressure, NTG: nitroglycerin, CSM: carotid sinus massage.

**Table 1. Indications and methods for tilt table testing.**

| | TTT (passive) | NTG (after 20 min. passive phase) | Additional provocation | Active standing | CSM |
|---|---|---|---|---|---|
| **Reflex syncope** | | | | | |
| VVS | + | + | | - | - |
| CSS | + | + | | - | + |
| Situational | + | + | Triggers | - | - |
| **OH** | | | | | |
| Classical | + | - | | + | - |
| Initial | (+) | - | | ++ | - |
| POTS | + | + | | | |
| PPS | + | + | | + | - |
| **Cardiac syncope** | | | **No TTT** | | |

TTT; tilt table testing, NTG; nitroglycerine, CSM; carotid sinus massage, VVS; vasovagal syncope, CSS; carotid sinus syndrome, OH; orthostatic hypotension, POTS; postural tachycardia syndrome; PPS; psychogenic pseudosyncope.

## 5. Tilt table test patterns according to their underlying disorder

### Reflex syncope

Reflex syncope, also called 'neurally mediated syncope', is characterised by a sudden decrease in blood pressure and/or slowing of heart rate. This, in contrast with syncope due to neurogenic orthostatic hypotension (OH) where a progressive fall in BP with little or no decrease in HR are the main characteristics. In syncope due to non-neurogenic OH there is a progressive fall in OH with significant increase in HR.[15,70]

Reflex syncope consists of three subgroups: vasovagal, situational and carotid sinus syncope. The afferent pathways of reflex syncope are largely unknown. Reflex syncope is typically preceded by specific prodromal symptoms and signs (pallor, nausea, diaphoresis, abdominal discomfort, including an urge to void or defaecate and at times even causing explosive diarrhoea), that may occur up to 60 seconds or more prior to the loss of consciousness.[36,68,75] This 'autonomic activation' is not a direct effect of cerebral hypoperfusion, but is a marker of the underlying cause of the syncope.[75]

## 5.1. Vasovagal syncope

Vasovagal syncope is triggered most often by pain, fear or prolonged standing. It is characterised by autonomic activation before and sometimes after the event. These warning signs may be systematically absent in the elderly.[26] The factors triggering the vasovagal cascade can be divided into central emotional influences and peripheral circulatory ones, the latter in the form of pooling of blood. The contribution of reduced vasoconstriction in the minutes before a faint to the events culminating in syncope has been criticised recently.[42,72] Systemic vascular resistance decreases in only about one half of subjects before vasovagal syncope.[16] A decrease in cardiac output was however a consistent finding in all subjects prior to syncope. Regardless of how vasovagal syncope is triggered, the events during syncope are clear: blood pressure always decreases and heart rate may do so, but not always.

*5.1.2. Tilt table testing in vasovagal syncope*

Reflex syncope and in particular vasovagal syncope is the most common indication for a tilt table test. The test starts with a resting phase in which patients are kept supine for 10 minutes, followed by a 'passive phase', in which the table is tilted head up between 60 and 80 degrees for 20 minutes. When this does not provoke typical complaints, it is followed in many laboratories by administering a pharmacological agent.

Blood pressure and heart rate during tilt table testing in vasovagal syncope can show three different patterns: vasodepressive, mixed and cardioinhibitory.[8,62] The vasodepressive pattern consists of a fall in blood pressure falls while heart rate shows little or no decrease (Figs 4a and 4b). In this form heart rate should not fall more than 10% from its peak value and the fall in blood pressure precipitates syncope.[62] The cardioinhibitory pattern consists of pronounced bradycardia (ventricular rate ≤ 40) or asystole (> 3 sec) as the main cause of syncope.[64] The most common pattern is the 'mixed' one, in which the drop in blood pressure is followed by bradycardia.[36] The three different patterns can be distinguished with a TTT. Surprisingly, the TTT has a therapeutic effect in some cases: the recurrence rate of syncope is lower after a positive tilt table test (Sheldon et al. 1996). This is possibly due to a better recognition of warning symptoms, allowing patients to take adequate preventive measures. The occurrence of a recognised event during TTT helps convince patients of the certainty of the diagnosis. The TTT can be expanded by teaching patients physical counter-manoeuvres while offering them visual feedback of the circulatory effects using finger photoplethysmography.[73]

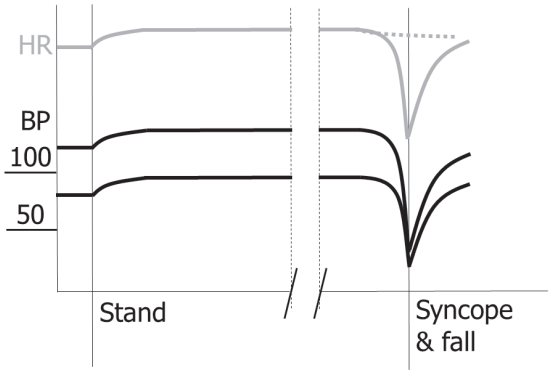


**Figure 4a. Circulatory patterns in vasovagal syncope.**
Schematic blood pressure and heart rate patterns for vasovagal syncope evoked by standing. In both vasodepressor and cardioinhibitory vasovagal syncope, a fall in blood pressure signifies the onset of the reflex. [68]

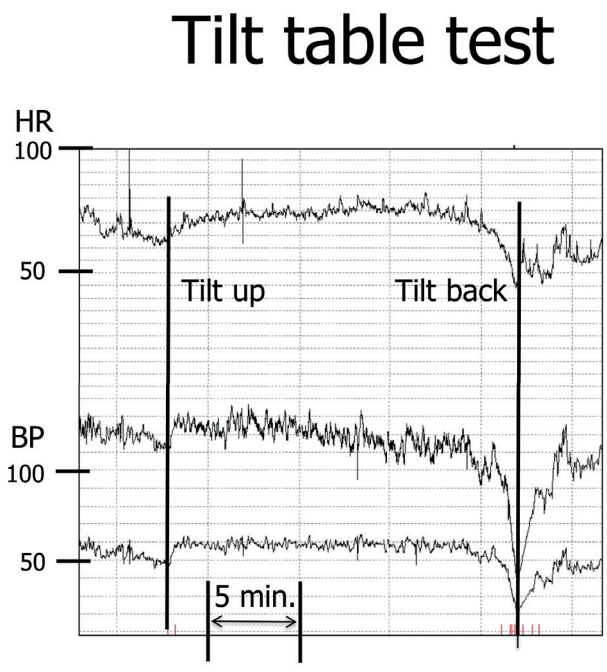


**Figure 4b. Circulatory patterns in TTT in a case of vasovagal syncope .**
HR; heart rate BP; blood pressure (top: systolic BP, bottom: diastolic BP)

### *5.1.3. Pharmacological agents*

Pharmacological provocation during head-up tilt testing helps to increase the diagnostic yield. Prior to the actual syncope in tilt-induced syncope, adrenomedullary activity is higher in individuals susceptible to fainting compared with controls[58], which prompted the idea of administering catecholamines to patients suspected of suffering from vasovagal syncope. The use of isoproterenol raised sensitivity from 50% to 80% at the cost of a fall in specificity in high dose regimens.[10, 38] Other centres used nitrates as a provocative agent.[7,46,67] Nitrates have a vasodilatory effect, with marked effects on the venous bed, which promotes the syncopal cascade through the peripheral route by increased venous pooling and a decrease in venous return. Nitrates they can be given sublingually, e.g. a spray of 400 micrograms of nitroglycerin, or intravenously; the latter approach has the advantage of a rapid onset of action and a relatively constant plasma concentration[1], but injection may provoke syncope by itself. The sublingual administration is easy and safe to administer. Sensitivity ranges from 51 to 81% and specificity from 85 to 94%(Parry & Kenny 1999).[39] Another drug used is clomipramine: it enhances serotonergic activity by inhibiting 5-hydroxytryptamine (5-HT) and has a central serotonergic response.[66] Some authors[17] showed that the use of clomipramine during TTT preferentially induced a cardioinhibitory response while nitroglycerin promoted a vasodepressor response.

## 5.2. Situational syncope:

Situational syncope is reflex syncope provoked by other triggers than those seen in vasovagal and carotid sinus syncope, such as miction, defecation, coughing, sneezing, laughing, stretching. They share the efferent pathway common to all forms of reflex syncope but differ in afferent pathways.[3]

### *5.2.1.Tilt table testing in situational syncope*

The test protocol in situational syncope is the same as in vasovagal syncope, as patients with situational syncope are often susceptible to an orthostatic challenge. Still, the positive rate in passive tilting in situational syncope has been stated to be lower than that for VVS (in one example 6% vs 27%).[32] It can be useful to provoke an event by having the patient reproduce his or her specific trigger, such as coughing or stretching.

## 5.3. Carotid sinus syndrome (CSS)

Carotid sinus hypersensitivity (CSH) denotes an overly strong circulatory response to massage of the carotid sinus. Syncope related to CSH consists of two forms. Spontaneous CSS is a reflex syncope occurring mostly in the elderly, in which syncope is caused by external pressure on the neck, as can happen during shaving. Note that this spontaneous form is rare. The term CSS is also used for otherwise unexplained syncope in the elderly

who have CSH. The ESC guidelines[36] advocate to perform CSM in every patient with syncope over 40 years in whom no diagnosis was established after the initial evaluation.[4]

#### *5.3.2. Assessment of CSH*

The test is performed in supine and repeated after tilting upwards. The carotid arteries are sequentially massaged for 7 to 10 seconds.[4] CSH is present when one of two signs appear: asystole for more than 3 seconds, or a decrease in systolic blood pressure of more than 50 mm Hg (or an absolute systolic blood pressure lower than 80 mm Hg). The response to the test may be cardioinhibitory, vasodepressive or mixed. Some authors found these criteria overly sensitive [27] and proposed a more stringent cut-off in the form of an asystole (≥3s) or a fall in mean arterial pressure below 60 mm Hg lasting for ≥6 seconds. The incidence of transient neurological complications during CSM is low (0.1%). Because of the risk of neurological complications it should be avoided in patients with a transient ischaemic attack, stroke or myocardial infarction in the last three months[37,36], but these considerations are not evidence-based.

### 5.4. Syncope in the context of orthostatic intolerance.

The classification used in this paper (Fig. 1) is built around transient loss of consciousness (Fig. 1), but TTT can also be useful in disorders causing 'orthostatic intolerance' (OI), in which consciousness is not necessarily lost. OI refers to a range of symptoms evoked by the upright position due to an imbalance in circulatory control. Syncope is one; others are light-headedness, dizziness, weakness, sweating and palpitations.[15] Common causes of OI are reflex syncope, orthostatic hypotension and postural orthostatic tachycardia syndrome (POTS).[74] (Fig. 5) The classifications of TLOC and OI overlap partially because the various disorders differ in their tendency to cause OI or syncope. OI can develop very quickly, for instance in vasovagal syncope, but may also develop over many minutes, as can be seenin neurogenic OH. The duration of OI can likewise vary from seconds as in asystolic vasovagal syncope to many hours, such as in POTS.



#### *5.4.1. Classical and delayed orthostatic hypotension*

*5.4.1.1. Classical OH*

In classical orthostatic hypotension standing provokes hypotension through an impairment of sympathetic function resulting in insufficient vasoconstriction, in turn leading to venous pooling. Alternatively a similar response may result from hypovolemia, e.g. in people with a severe gastrointestinal bleeding. The pattern of changes in blood pressure and heart rate differ fundamentally from those in reflex syncope: whereas blood pressure and heart rate decrease with increasing speed in reflex syncope, the decreases in orthostatic hypotension start quickly after which the rate of change decreases. This may be likened to a leak in a balloon, in which the initial high pressure ensures a quick leak and the later lower pressure a slow one. Note that classical OH is due to failure of

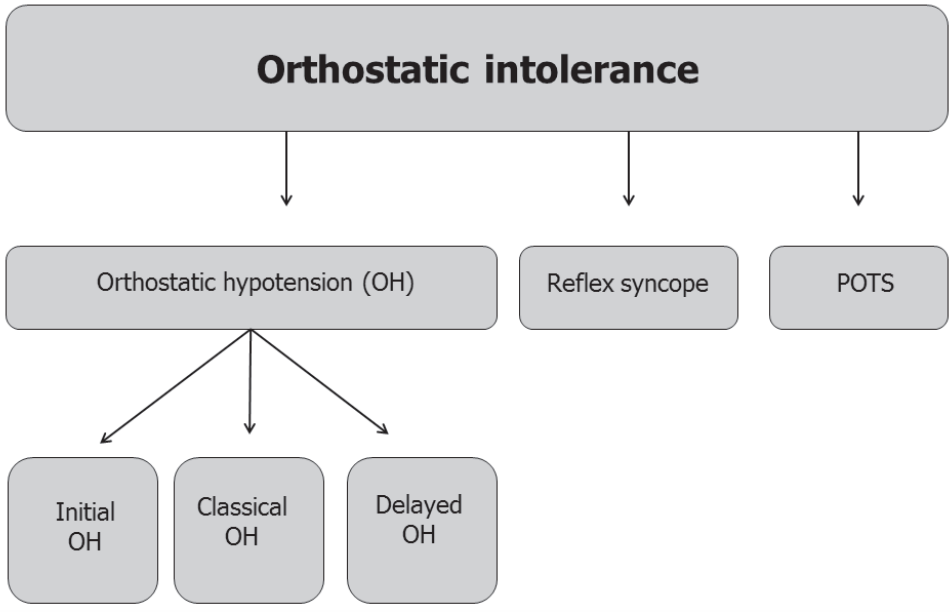


**Figure 5. Different forms of orthostatic intolerance.**
Note that orthostatic intolerance may be explained by reflex syncope, i.e. orthostatic vasovagal syncope. OH; orthostatic hypotension, POTS; postural tachycardia syndrome.

a normal reflex, while reflex syncope concerns an abnormal reflex action. Classical OH can be non-neurogenic and neurogenic. The first form is mostly due to drugs and is very common, especially in the elderly. Neurogenic OH occurs less often and is often a feature of synucleopathies ( Parkinson's disease, multisystem atrophy and pure autonomic failure) and some rare autoimmune disorders (e.g., acute autonomic ganglionopathy).[35]

Classical OH is operationally defined as a decrease in systolic blood pressure (BP) >=20 mmHg or in diastolic BP >=10 mmHg within three minutes of standing up or being tilted head up (Freeman et. al,2011). Note that such BP decreases need not be accompanied by complaints. The occurrence of syncope probably does not depend on the magnitude of the BP fall, but on the absolute BP level an 80 mmHg fall from 180 to 100 mmHg will not cause syncope, but a fall from 110 to 30 mmHg will.[75]

*5.4.1.2. Delayed OH*

Delayed orthostatic hypotension occurs later than 3 minutes after standing up. It is more common in the elderly and is probably caused by an increased peripheral pooling, increased fluid transudation or gradual failure of humoral and neural mechanisms.[19]

### *5.4.2. Tilt table testing in classical and delayed orthostatic hypotension*

As mentioned earlier, in syncope due to orthostatic hypotension blood pressure starts to drop immediately on standing up.[68] To compensate for this decrease heart rate will rise unless there is additional autonomic damage preventing this increase. The rate of the blood pressure falls and tends to stabilize at a low level, unless syncope occurs. (Figs 6a and 6b). As for vasovagal syncope , in case of an established event the physical counter manoeuvres can be taught in the same session with the use of finger photoplethysmography.

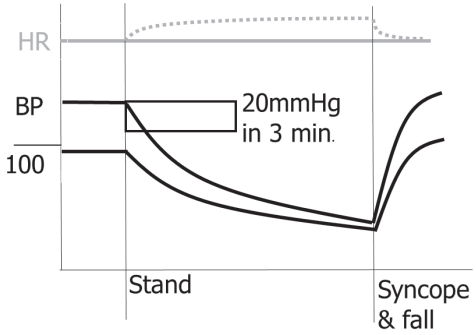


**Figure 6a. Circulatory patterns in syncope due to orthostatic hypotension, similar to figure 4a.** Note that blood pressure drops immediately after standing up and that the rate of drop decreases (van Dijk et al, 2009).

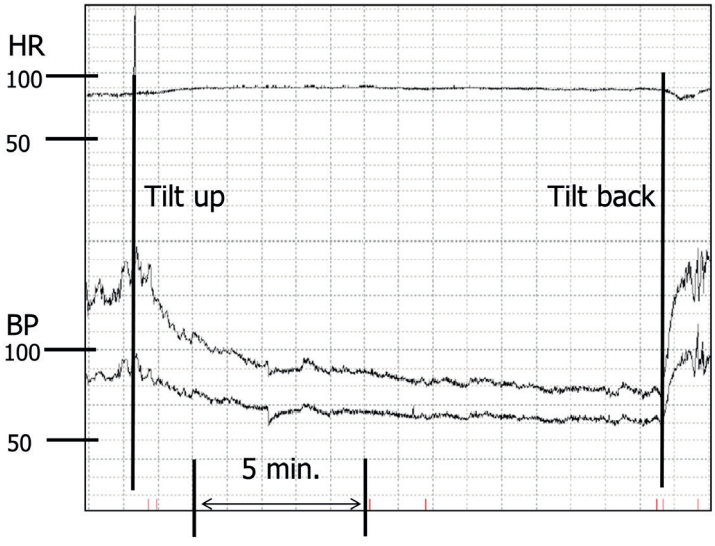


**Figure 6b. Circulatory patterns due to orthostatic hypotension in real life: similar to figure 4b.**

#### *5.4.3. Initial orthostatic hypotension (IOH)*

IOH results from a mismatch between cardiac output and peripheral vascular resistance when people stand up quickly. An important difference with classical OH is that the hypotension is transient even in the upright position, so blood pressure will normalise within seconds, while in classical OH blood pressure will usually only increase again when other actions are taken, such as exercise or sitting down. Groups at risk for IOH are, firstly, young, tall patients with an asthenic habitus[73] and secondly those of any age taking medication interfering with vasoconstrictor mechanisms.[74]

#### *5.4.4. Tilt table testing in IOH*

IOH only occurs during active standing, not during passive tilting. IOH therefore requires an active standing test.[11]

#### *5.4.5. Postural tachycardia syndrome (POTS)*

The main characteristic of POTS is a sustained heart rate increment within 10 minutes after standing of ≥30 beats/minute (in children ≥40 beats/minute).[15, 43] POTS is associated with OI, chronic fatigue and may be due to a limited autonomic neuropathy. POTS may be preceded by a recent viral illness. The syndrome is more common in young women. The orthostatic symptoms include blurred vision, palpitations, and weakness, especially of the legs. Only a minority of patients faint. In contrast to VVS or OH, the relation between the complaints and the circulatory alterations is not clear.

#### *5.4.6. Tilt table testing in POTS*

During TTT the heart rate increases on standing while the blood pressure remains unaltered or decreases a little. (Figure 7)

### 5.5. Psychogenic pseudosyncope (PPS)

This condition is psychologically probably very similar in nature to psychogenic non-epileptic seizures (PNES); the only difference between PPS and PNES may be a lack of gross movements in psychogenic pseudosyncope. This difference may still induce a different medical history though, as patients with PNES are likely to be seen by neurologists and may receive anti-epileptic drugs, while those with PPS are seen by those dealing with syncope.[65] PPS usually has a higher frequency than VVS, sometimes several times a day, and a longer duration of the episodes.[41] In contrast to syncope the eyes are almost always closed in PPS.[65]

#### *5.5.1. Tilt table testing in psychogenic pseudosyncope*

In patients with PPS the EEG is normal during the event, and blood pressure and heart rate are usually increased during the event.[65,39] A documented episode during a tilt table test with recognition by the patient or relatives makes the diagnosis certain, which is useful to help patients accept the diagnosis.[56]

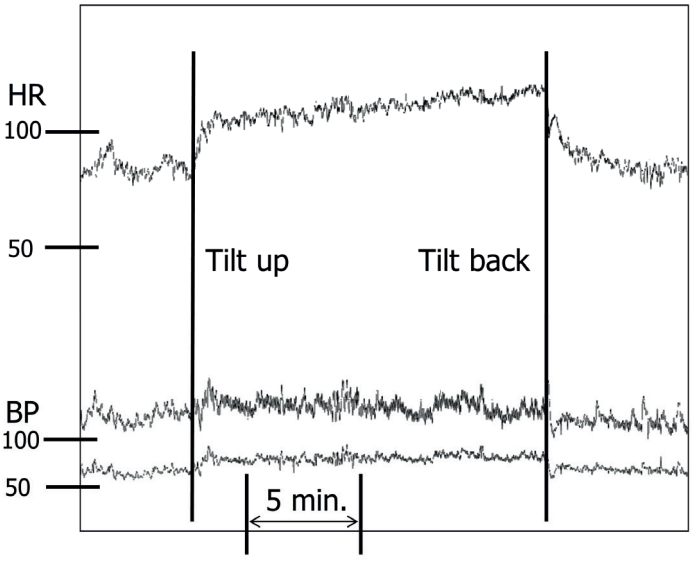


**Figure 7. Postural orthostatic tachycardia syndrome.**
Note the change in heart rate (HR) from 70 beats/minute to over 110 beats/minute.

## 6. Sensitivity, specificity and reproducibility

The specificity of tilt table testing is difficult to establish. While vasovagal syncope is essentially a lifelong condition with a lifetime prevalence of 20 to 40%.[6] with a tendency to begin before the age of 35 years[50] the first syncope can occur at any age. This raises two problems[51] firstly, how many 'control subjects' are in fact fainters who have not fainted yet, but will do so later? Secondly, if a tilt table test identifies people predisposed to fainting, then a population of young control subjects will result in more abnormaltilt tests than an older population. Moreover, pharmacological agents generally increase sensitivity while reducing specificity.[55,56] The reproducibility of the tilt table test has been debated: long-term reproducibility, varying from 1 day to 4 years, shows reproducible responses in 50% to 85% of subjects.[12,38,40,45] The degree of bradycardia and hypotension evoked during several tilt tests are only modestly reproducible, which suggests that a classification based on hemodynamic changes during a single tilt test has limited predictive value.[6] In fact, it should be understood that tilt table testing does not predict prognosis in syncope.[54]

In view of the above, tilt testing has been criticised both for its diagnostic yield and for problems concerning what it tests. An emerging view is that, in the context of reflex syncope, TTT does not so much test for the presence of a disease as for a susceptibility to reflex hypotension, which may be so widespread in the population that it may well

coincide with another condition causing syncope.[63] In the authors' view, understanding these aspects of TTT has several consequences. Firstly, tilt testing should never be merely summarised as normal or abnormal, but the result must be stated according to the circulatory pattern found. Secondly, an abnormal result is clinically most meaningful if there was recognition of the event as similar to spontaneous ones, by patients and preferably also by eyewitnesses. Thirdly, the test lends itself well to teaching patients how to perform counter manoeuvres. Patients often report more confidence in dealing with syncope after a tilt table test, which may partially explain why the syncope rate drops after a tilt table test.[53] This may be due to 'expectancy', which, while part of the placebo effect, is beneficial to patients.[48] Overall, tilt table testing should be seen as an important addition to history taking, and never as an isolated procedure.

## 7. Safety and potential side effects

As tilt testing is designed to provoke syncope, its safety has been a consideration since its introduction. Baron-Esquivias et al.[2] found that the long-term survival of patients with asystole did not differ from those without it, which included the elderly. Gieroba et al.[20] performed tilt table testing in 1096 subjects between 60 and 74 years of age and 873 people aged 75 or older and found only one case of atrial fibrillation during tilt table testing, and no neurological complications. One case was described in which a patient with ischaemic heart disease developed ventricular fibrillation with isoproterenol provocation in.[31] Hence, a tilt table test is safe and complications are very rare. Still, some cautionary notes are in order: firstly, the low blood pressure during syncope might harm those with ischaemic disorders of the heart or brain, so risks and benefits should be weighed in such patients. Secondly, an association between white matter lesions and frequent syncope, defined as five or more syncopal spells during life, has been described.[28] This association does not mean that frequent syncope causes brain damage, but should nevertheless prompt caution in evoking syncope. The authors feel that the advantages of a clear diagnosis, with possibly fewer future syncopal spells as a result, outweigh the possible risk of adding to white matter lesions by one syncopal spell during TTT.

## 8. Conclusions

In summary, a tilt table test helps establish whether episodes of transient loss of consciousness are due to syncope and, if so, yields ictal patterns of blood pressure and heart rate that define the type of syncope. Tilt testing provokes an event in a considerable number of patients, which shortens the delay to a certain diagnosis. Neurologists and clinical neurophysiologists have a potentially important role to play in this regard, but as

yet few of them take an active interest in syncope. This is unfortunate as the main strategy in reflex syncope is extensive history taking, so in this way neurologists are well-suited to deal with reflex syncope. We feel that even neurologists who wish to restrict their attention to epilepsy must be thoroughly familiar with reflex syncope, if only to prevent misdiagnosis. It is well known that a misdiagnosis of epilepsy may bring significant clinical, socioeconomic and psychological burden to the patient.[44]

The basic skills needed to diagnose syncope are the same as for epilepsy: patients are usually seen well after the event occurred, making history taking and deductive reasoning especially important. These qualities form the neurologist's basic skills, often allowing a diagnosis without additional testing. When tests are necessary, the paths of epilepsy and syncope diverge, as they require different approaches. A tilt table test measures physiological functions of the nervous system, and may be regarded as analogous to the EEG. While tilt table testing can become an important clinical neurophysiological tool for TLOC diagnosis, it should be seen as an important addition to history taking and never as an isolated procedure.

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# CHAPTER VII

# Long-term follow-up of psychogenic pseudosyncope

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## Abstract

**Objective**

To determine the outcome of patients with psychogenic pseudosyncope (PPS) after communication of the diagnosis.

**Methods**

A retrospective cohort study of patients with PPS referred in 2007 to 2015 to a tertiary referral center for syncope. We reviewed patient records and studied attack frequency, factors affecting attack frequency, health care use and quality of life using a questionnaire. We explored influences on attack freedom and attack frequency in the six months before follow-up for age, sex, education level, duration until diagnosis, probability of diagnosis, additional syncope and acceptance of diagnosis.

**Results**

47 out 57 PPS cases could be traced, of these 35 (74%) participated. Twelve (34%) were attack free for at least six months. The median time from diagnosis to follow-up was 50 months (range 6-103 months). Communicating and explaining the diagnosis resulted in immediate reduction of attack frequency ($p=0.007$) from the month before diagnosis (median one attack, range 0-156) to the month afterwards (median one attack, range 0-16).

In the six months before follow-up the number of admissions decreased from 19/35 to 0/35 ($p=0.002$). The use of somatic and mental health care shifted towards the latter ($p<0.0001$). Quality of life at follow-up (SF-36) showed lower scores for six of seven domains compared to matched Dutch control values; quality of life was not influenced by attack freedom.

**Conclusion**

After communicating the diagnosis in PPS, attack frequency decreased and health care use shifted toward mental care. Low quality of life underlines that PPS is a serious condition.

## Introduction

The three main groups of apparent transient loss of consciousness (TLOC) are syncope, epileptic seizures and psychogenic attacks.[1] Psychogenic TLOC consists of 'psychogenic non-epileptic seizures' (PNES), resembling epileptic seizures, and 'psychogenic pseudosyncope' (PPS), resembling syncope. The prevalence of PNES is 2-33 per 100,000 people. [2] In tertiary epilepsy clinics, PNES accounts for 20-30% of patients.[3-5] While patients with PNES and PPS probably suffer from the same psychiatric disorder,[8,9] they are seen by different specialties which may affect diagnosis, therapy and prognosis.[8]

Patients with PPS typically lie immobile and unresponsive with closed eyes during attacks. Attacks last longer and are more frequent than in syncope.[6,7] The diagnosis rests on history taking from patients and eyewitnesses, and on documenting an event with a tilt table test[6,7] or home video recording.[7] Such documented attacks must be recognized by patients and eyewitnesses as the same as habitual ones.[5] The diagnosis of both PPS and PNES must not rest on exclusion but on positive evidence.[5,8] The absence of PPS in large syncope series[9] suggests that PPS is not always recognized, as does the paucity of PPS research compared to PNES.[6,10]

The prognosis of PNES is generally better for those who are young, are more highly educated, and who have a short delay between the first event and the diagnosis.[11-13] A comprehensive PNES study showed that 26% of patients receiving psychotherapy were attack free after 42 months, with another 40% having a 50% reduction of attack frequency.[14] Follow-up studies in PNES have shown that not only attack frequency, but also quality of life, use of health care facilities and employment are important indicators.[14-17] We did not find any studies on the prognosis of PPS, and therefore studied the prognosis in a cohort of PPS patients taking these aspects into account.

## Methods

### Patients

We searched the database of the tertiary syncope outpatient department of the Leiden University Medical Center (LUMC) from 2007 to 2015 for possible PPS cases who were at least 18 years old at follow-up. Patients were seen by a neurologist (JGvD) experienced in syncope and PPS. The diagnosis rested on history taking of patients and eyewitnesses and on event documentation using tilt table testing, home video recording or, rarely, home blood pressure recording. The explanation of the nature of PPS conformed to PNES procedures,[6,7] stressing that attacks happen involuntarily, that patients were taken seriously and were not 'mad', and that the attacks signaled an underlying psychological problem.

Terms such as 'psychological' were used and not avoided. Patients were seen after one or two weeks to repeat the explanation, address questions and discuss therapeutic options. If attacks did not resolve, patients received advice to seek psychiatric or psychological help. As patients came from a wide area, the choice of a suitable therapist was left to their general practitioner or the referring specialist. In earlier years contact was ended after advocating psychiatric therapy, but later on contact was maintained until psychotherapy was underway.[18]

## Standard Protocol Approvals, Registrations, and Patient Consents

The study protocol was approved by the local institutional review ethical board. We sent potential participants an informational letter and asked them to fill in a questionnaire on paper or online. DPS and MJO contacted patients by telephone to provide additional information and to encourage a response until patients completed the questionnaire or further attempts seemed futile. All participants gave informed consent.

## Patient inclusion

DPS, RDT and JGvD studied case records using diagnostic criteria adapted from PNES criteria;[8] the adaptation meant we ignored interictal EEG findings and in their place stressed ictal heart rate and blood pressure. The history had to contain positive features of PPS such as closed eyes during attacks, a long duration and high frequency.[9] Attack documentation required recording an event recognized as typical by patients or relatives during a tilt table test, comprising continuous blood pressure, ECG, EEG and video,[6,7,19] or ictal home video or blood pressure recording. Cases with a positive history and attack documentation were classified as 'definite', those with a positive history without documentation as 'probable'. The final inclusion criterion was that the diagnosis had been explained as stated above.

## Study data

The following information was noted: age, sex, frequency of events in one month both before and after diagnosis, duration from the first PPS attack until diagnosis, the additional presence of syncope, earlier consultation of medical specialists and psychologists, and hospital admission or emergency department visits for these attacks.

The questionnaire asked for duration since last attack and attack frequency in the last week, month and six months. We defined 'attack free' as no attack in the last six months. Questions addressing health care use included frequency of visits to general practitioners, emergency departments, medical specialists and psychologists and the number of admissions for PPS in the last six months before follow-up.

We investigated patients' reception of the diagnosis, asking whether patients had felt to have been treated with respect, had felt offended by the psychological nature of attacks and whether they agreed with the explanation at time of diagnosis and at follow-up, all of which were noted as 'agree', 'no opinion' and 'disagree'.

Other questions concerned marital status, housing situation, education level and employment. We used the Dutch version of the Short Form Health Survey 36 (SF-36) to assess quality of life.[20]

## Data analysis

We compared baseline variables between participants, i.e. those who completed the questionnaire, and non-participants who did not. As attack frequency and various other variables had skewed distributions we favored nonparametric analyses. We examined an immediate effect of diagnosing PPS on attack frequency by comparing attack frequency in the months before and after explanation of the diagnosis. The main analysis of attack frequency concerned a comparison between the number of attacks in the month before diagnosis and that in the month before follow-up, using Wilcoxon's paired signed rank test, and between the proportions of attack free and not attack free participants, using Fisher's exact test.

We explored influences on attack frequency in the six months before follow-up and on attack freedom for age, sex, education level, and duration until diagnosis, probability of diagnosis, presence of syncope and reception of the diagnosis. To analyze effects on attack frequency we used Spearman's rho for quantitative variables (e.g. age, duration until diagnosis), and the Mann-Whitney test for dichotomous variables (e.g. sex). To analyze effects on attack freedom (yes/no) we used the Mann-Whitney, Chi-square and Fisher's exact tests.

Answers concerning reception of the diagnosis were dichotomized resulting in 'disagree' and 'agree', ignoring the category 'no opinion'.

We compared somatic and mental health care use before and six months after diagnosis. We compared the subset of patients of working age (25-65 years) to 2015 employment data from 'Statistics Netherlands' (www.CBS.nl). We compared the expected number of patients not working to the actual number not working, taking into account the patient group's age and sex composition (Fisher's exact test).

We compared the eight domains of the SF-36 to published Dutch control values, taking age and sex into account.[20] We calculated individual patient z-scores per domain by first calculating the difference between a patient value and the control group mean for

the correct sex and age group, and then dividing that by the control group's standard deviation. We used Student's t-test to investigate whether mean patient z-scores differed from zero, i.e. whether their mean scores differed from age- and sex-corrected control values. We also compared mean z-scores per domain between attack free and not-attack free groups.

No attempts were made to impute any missing data. We used SPSS-20 and Matlab for statistical analysis. A significance threshold of $p<0.01$ was used .

# Results

## Baseline data

### *Participants and non-participants*

Fifty-seven participants fulfilled PPS criteria (48 definite, nine probable). Ten cases were lost to follow-up. Of the remaining 47 cases 12 (25.5%) did not reply (Figure 1), leaving 35 participants. The participant and nonparticipant groups did not differ in age, sex, and attack frequency in the month before diagnosis, duration until diagnosis, and probability of the diagnosis. (Table 1)

**Table 1. Comparison of participants and non-participants**

| | **Participants (n=35)** | **Non participants (n=12)** | **p-value** |
|---|---|---|---|
| Median age (range) | 36.0 (14-74) | 35.0 (17-59) | 0.92 (M-W) |
| Sex (M:F) | 11:24 | 2:10 | 0.46 (FET) |
| Median attack frequency in one month before diagnosis (range) | 2.0 (0-16) | 1.0 (0-10) | 0.33 (M-W) |
| Probability of diagnosis (d: definite; p: probable) | d: 33, p: 2 | d: 9, p: 3 | 0.062 (Chi) |
| Median duration until diagnosis in months (range) | 24.0 (0-288) | 42.0 (0-216) | 0.33 (M-W) |

M-W: Mann-Whitney test; FET: Fisher's exact test; Chi: chi-square test

### *Participant baseline data*

Most participants were female (24/35, 69%). The median age was 36 years (range 14-74 years). The median delay to diagnosis was 24 months (range 0-288). Almost all patients (33/35, 94%) had a definite diagnosis of PPS; two had 'probable PPS'. The median attack frequency in the month before diagnosis was two (range 0-16).

***Health care use***

Patients had on average each seen 1.49 somatic specialties and 0.14 mental health care providers (i.e. a psychologist or psychiatrist) in the six months before diagnosis. The number of previous admissions for PPS was unknown in five patients; of the remaining 30 cases, 19 had been admitted in the year before diagnosis (54%).

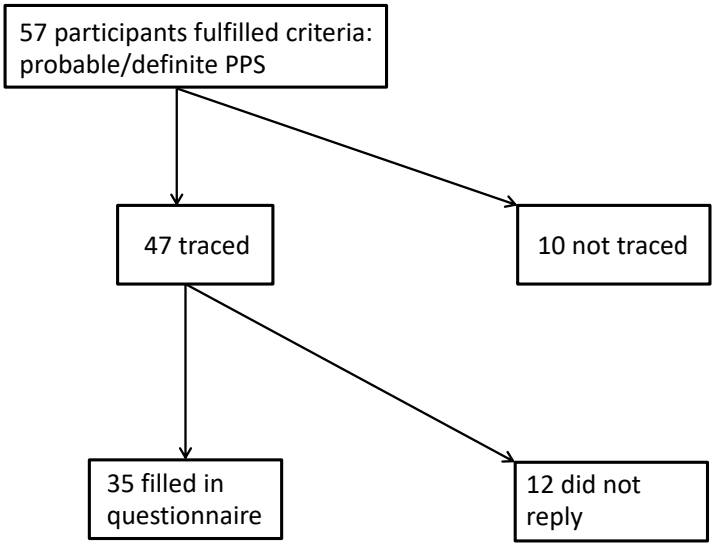


**Figure 1. Flowchart explaining the amount of responders, non-responders and non-traceable participants in relation with the initial participants.**

PPS: psychogenic pseudosyncope

## Follow-up analysis

***Attack frequency***

Data on attack frequency in the first month after diagnosis were available for 21 cases. Their median frequency had decreased (p=0.007) from the month before diagnosis (median one, range 0-156; mean 4.0+4.9 attacks) to the month afterwards (median one, range 0-16; mean 1.7+3.5).

The median time from diagnosis to follow-up was 50 months (range 6-103 months). The median attack frequency in the last month of follow-up was 0 attacks/ month (range 0-35), which was lower than in the month before diagnosis (p=0.006). At follow-up twelve patients were attack free.

***Factors affecting attack frequency***

Age did not influence attack frequency in the last six months of follow-up (p=0.9), and did not differ between those who were attack free and those who were not (p=0.25). Likewise, sex neither affected attack frequency (p=0.33) nor attack freedom (p=1.0). Education level did not affect attack frequency (p=0.9) nor attack freedom (p=0.14). The duration between the first attack and diagnosis did not affect attack frequency (p=0.74) or attack freedom (p=0.33). This also held for the presence of syncope, both for attack frequency (p=0.66) and for attack freedom (p=1.0).

***Reception of the diagnosis***

Most patients felt they had been treated respectfully: 29 agreed (83%), three disagreed, three had no opinion). Eight had felt offended, 22 had not, while five had no opinion. Fifteen agreed with the psychological explanation at the time of diagnosis, while 13 did not, with seven 'no opinion'. At follow-up, 18 agreed, 11 did not, while six neither agreed nor disagreed. We used the dichotomized form of these answers to explore a relation with attack frequency and attack freedom: no effects were found. For example, of the 18 who agreed at follow-up that their attacks had a psychological explanation, 11 were not attack free, against 8 of 11 who did not agree (p=0.4).

***Health care use***

No patient had visited an emergency department or had been admitted for PPS in the six months before follow-up. This differed from the year before diagnosis (19/35 admissions) after correcting for the difference in duration of the periods (Fisher's exact test, p=0.002).

In the year before diagnosis, patients had together seen 52 somatic specialists and 5 mental health care providers (psychologists or psychiatrists), or 57 health care providers in all. Corresponding numbers in the six months before follow-up were 6 and 14, i.e. 20 health care providers in all. After correction for the difference in duration, the proportion of somatic to mental health care providers had shifted over time towards more mental health care use (p<0.0001).

***Social status and employment***

The number of patients who were married or having a relationship was the same before diagnosis as at follow up (24/35, 69%). At follow-up, 9 of 24 patients of working age did not work. The expected unemployment rate for a group with this age and sex composition was 7.0%, leading to an expected number of patients not working of 1.67 patient. After rounding the latter number to two, the actual proportion of those not working and working (9:15) was compared to the expected proportion (2:22). Although more patients did not work then expected, this difference was not significant (p=0.036).

*Quality of life (SF-36)*

Due to an entry error the last four questions concerning the 'general health' domain were missing from the online version (n=19) of the questionnaire. Quality of life is shown in Tables 2 and 3. Patient scores differed for seven of the eight domains from Dutch normal values corrected for age and sex. Mean domain scores did not differ between attack free and not-attack free patients, although values were worse for those who were not attack free for all eight domains (Figure 2).

**Table 2. Quality of Life (SF-36)**

| Domain | Patients | Corrected normal | Difference | z Score | t Test p-value |
|---|---|---|---|---|---|
| Physical functioning | 68.4 ± 29.4 | 86.5 | -18.1 ± 26.5 | -1.15 ± 1.71 | 0.0004 |
| Role physical | 50.0 ± 44.6 | 79.1 | -29.0 ± 42.9 | -0.94 ± 1.47 | 0.0006 |
| Role emotional | 65.7 ± 46.1 | 81.5 | -15.8 ± 45.9 | -0.51 ± 1.42 | 0.0406 |
| Vitality (energy) | 46.0 ± 24.8 | 67.9 | -21.9 ± 24.3 | -1.22 ± 1.36 | <0.0001 |
| Mental health | 60.0 ± 25.6 | 76.0 | -16.0 ± 25.9 | -1.04 ± 1.63 | 0.0006 |
| Social functioning | 54.3 ± 27.8 | 84.9 | -30.6 ± 27.2 | -1.51 ± 1.41 | <0.0001 |
| General health | 41.3 ± 25.4 | 72.5 | -31.1 ± 23.3 | -1.65 ± 1.27 | <0.0001 |
| Body pain | 54.0 ± 31.2 | 75.3 | -21.3 ± 30.6 | -1.00 ± 1.50 | 0.0004 |

Mean values (SD) are given for the eight domains of the SF-36 questionnaire. All domains range from 0 to 100, with higher values for better quality of life. The 'corrected normal' shows the mean values of a hypothetical group, in which each subject had the same age and sex and the patient group, but whose value for each domain represents the mean of the control value for that age and sex: it represents age and sex-corrected normal values. The 'difference' represents mean group differences from control values, and the z-scores represent how much patient values differ from control values in units of SD of control values. The p-values show whether mean z-scores differ from zero. For seven domains patients have lower quality of life than controls.

**Table 3. Quality of life as a function of attack freedom**

| Domain | Not attack free n=23 | Attack free n=12 | Between groups p-value |
|---|---|---|---|
| Physical functioning | 61.3 ± 30.4 | 82.1 ± 22.8 | 0.107 |
| Role physical | 41.3 ± 43.7 | 66.7 ± 43.1 | 0.196 |
| Role emotional | 63.8 ± 47.0 | 69.4 ± 46.0 | 0.871 |
| Vitality (energy) | 40.7 ± 25.9 | 56.3 ± 19.9 | 0.176 |
| Mental health | 55.7 ± 25.2 | 68.3 ± 25.3 | 0.290 |
| Social functioning | 51.1 ± 28.9 | 60.4 ± 25.5 | 0.616 |
| General health | 36.9 ± 24.7 | 49.8 ± 25.6 | 0.311 |
| Body pain | 47.8 ± 30.6 | 65.8 ± 30.0 | 0.313 |

Mean values for the attack free and not attack free groups are shown for all eight SF-36 domains. The p-value represents results of a t-test. Although mean values were lower for the group that continued to have attacks for all domains, none of the differences was significant.

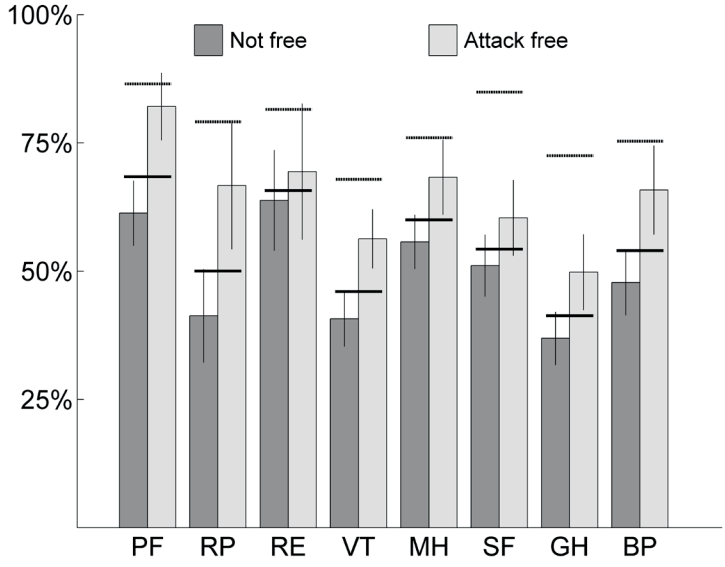


**Figure 2. Attack freedom and quality of life.**

The eight domains of the SF-36 are shown for those who are and who are not attack free. The horizontal dotted lines above the bars indicate normal values per domain corrected for age and sex. Vertical bars indicate mean values for those who were not attack free (n=23) and those who were (n=12). Vertical lines show standard errors. The horizontal bold lines indicate the mean value per domain for the entire PPS group (n=35).

PF: Physical Functioning; RP: Role Physical; RE: Role emotional; VT: vitality (energy); MH: mental health (emotional wellbeing); SF: social functioning; GH: general health; BP: body pain

## Discussion

The main result of this first PPS follow-up study was a reduction in the number of attacks, both expressed as attack frequency and as attack freedom: at the follow-up of over four years, one third (12/35) were attack free. Other important findings were that conveying the diagnosis resulted in an immediate decrease in attacks in the first month after diagnosis. At follow-up, the number of hospital admissions had decreased and the nature of health care use had shifted from somatic to mental health care. Patients tended to have a higher than expected unemployment rate. Quality of life was low, both for those who were attack free and who were not.

The positive effects in our study are largely in line with PNES studies showing that a clear explanation may lead to a reduction of attacks,[13,21,22,23] and a reduction of emergency service use.[13] We confirm that communication of the diagnosis can cause an immediate reduction of attack frequency.[13,24,25] Fifty-seven percent had syncope besides PPS,

conforming to PNES results, in which 10-30% of patients also have epilepsy. The incidence of syncope among PPS patients seems higher than that of epilepsy among PNES patients, possibly due to syncope being much more prevalent than epilepsy.

The analysis did not reveal some relations reported for PNES, such as a poor prognosis for those with a long duration between the first attack and diagnosis.[11, 24, 26] This might be due to the relatively short duration in our PPS group: the median duration was 24 months (mean 46 months), contrasting with the typically longer mean duration for PNES of 6-7 years. [13] We did not find a worse prognosis for higher age[11, 27] or for women.[13] We suspect that the lack of these relations represents sampling effects, as such relations are not universally found in PNES either. We also did not find a relation between how well the diagnosis was received and attack frequency. Intriguingly, this also held for the question whether patients accepted the psychological nature of PPS. Hence, acceptance of the psychological nature does not seem to be a prerequisite for attack freedom, nor does its absence imply that attacks must continue.

The number of admissions decreases and health care use shifted from somatic to psychiatric care. The rate of unemployment did not differ from Dutch values corrected for age and sex, but was higher (37.5%) than expected (7%). The lack of significance is probably due to the restriction to those of working age, reducing the sample size of the remaining group (n=24).

Quality of life was remarkably poor compared to sex- and age-matched Dutch control data. Quality of life was not higher in those who were attack free than in those who were not. The overall poor quality of life and lack of a clear relation with attack freedom suggests that the underlying psychological problems impair quality of life more than the mere presence of attacks. This emphasizes the opinion derived from PNES studies that attack frequency should not be the sole parameter of follow-up: quality of life may well be the most relevant outcome parameter.



The study contained no control group and took place in a tertiary referral center, with a likely bias towards difficult cases and, presumably for that reason, a high rate of PPS (8-10% of cases). We had made no attempt to standardize psychological treatment, because patients came from across the Netherlands, making long-term treatment in our hospital impractical. Hence, only the diagnostic process, the explanation of the diagnosis and the early follow-up were standardized. The lack of a standardized treatment may have impaired treatment efficacy.

The low quality of life emphasizes that PPS represents a considerable burden to patients. Although we did not aim to calculate the burden to society, our results concerning

employment and medical consumption suggest that that burden too is considerable. At follow-up, attack frequency was reduced and there was a shift away from somatic towards psychiatric health care use. The outcome may well be worse for PPS patients who remain undiagnosed or who are not directed towards psychiatric health care.

We feel that all those diagnosing syncope should be aware of PPS, in particular those working in dedicated syncope units.[28] Much like specialized epilepsy units attract a concentration of PNES cases, so a high rate of PPS is a corollary of tertiary syncope care. Neurologists and cardiologists who see PPS patients may tend to shy away from communicating a psychiatric diagnosis, out of fear of offending patients. In this study, words such as 'psychological' were consistently used, and yet the vast majority of patients (83%) felt to have been treated with respect. This suggests that this fear is not warranted, provided adequate time is taken to communicate the diagnosis; hence, we urge somatic specialists seeing PPS patients to overcome their reticence in communicating the diagnosis, as otherwise they are likely to do their patients a disservice.

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# CHAPTER VIII

# Summary, general discussion & future perspectives (EN)

# Samenvatting en discussie (NL)

# Summary, general discussion & future perspectives

This thesis described several aspects of syncope in the wider context of transient loss of consciousness (TLOC). The various aspects ranged from classification to details of pathophysiology, all aiming to obtain a better understanding of pattern recognition of the different forms of TLOC, with a focus on syncope.

An unambiguous definition of syncope is important for care, research and teaching purposes.[8] Unfortunately, many published definitions defined 'syncope' as a broad category, in fact equating it with the later concept of TLOC.[7] The ESC-classification from 2001 was the first to formally distinguish between 'transient loss of consciousness', i.e. disorders sharing unconsciousness of short duration with a rapid and spontaneous recovery and 'syncope', the form of TLOC that is due to cerebral hypoperfusion. Adding the cerebral hypoperfusion element set syncope apart from other forms of TLOC, mostly epileptic seizures and psychogenic attacks.[4] We provided short descriptions of different forms of syncope and other forms of TLOC in **chapter II,** focusing on the pathophysiological logic of the classification.

Within syncope, reflex syncope is the most common cause. The pathophysiology of reflex syncope encompasses both vasodepressor and cardioinhibitory mechanisms. Both mechanisms can cause syncope on their own, but in most cases both tend to occur together. The basis by which the vasodepressor response cause blood pressure to decrease remains controversial, but at present venous pooling in the lower part of the body is considered the primary cause of vasovagal due to standing, i.e. orthostatic VVS. This mechanism may be less important in other forms of reflex syncope.[6] The cardioinhibitory mechanism is probably of the same type in all forms of reflex syncope; it is effected through an increase in vagal tone with asystole as the most extreme expression. The presence of asystole might prompt physicians to consider pacemaker therapy to prevent syncope. However, the benefit of pacemaker therapy proved very limited in VVS.[1] Several large studies (ISSUE-3[2], SUP-2[3]) suggest that among patients with documented spontaneous asystole during VVS, pacing efficacy was primarily of value in those individuals without evident vasodepressor susceptibility.

**In chapter III** we investigated the relationship between the onset of asystole and transient loss of consciousness (TLOC) in tilt-induced reflex syncope and estimated how often asystole was the principal cause of TLOC. We divided patients with tilt-evoked VVS with asystole in three groups: asystole after onset of TLOC (group A), asystole within 3 seconds before TLOC (group B) and asystole starting more than 3 seconds before TLOC (group C). TLOC is very unlikely to be caused in the first two groups, conforming to one third of cases.

The median of the mean arterial pressure at the onset of asystole was higher when asystole occurred early (45.5 mm Hg, group C) than when it occurred late (32.0 mm Hg, groups A and B), which suggested that vasodepression was not prominent at the start of asystole in early asystole. In turn this opened the possibility that cardioinhibition was in fact the prime mechanism of syncope in those with early asystole. However, we could not prove that, as we were unable at the time to measure the relative importance of cardioinhibition and vasodepression when both act together. We later devised a method to do so, however,[6] opening the possibility to measure the importance of cardioinhibition in both early and late asystole. The clinical relevance of the study was that pacemaker aiming to abolish asystole would be unlikely to be beneficial in groups A and B, meaning one third of subjects with asystolic tilt-induced VVS. In addition, we reasoned that reliance on electrocardiography data alone is likely to overestimate the importance of asystole.

**In chapter IV** we illustrated the importance of history taking in two complex TLOC cases. The first concerned a patient with sleep syncope, a rare form of syncope which is probably rarely recognized by clinicians as a form of vasovagal syncope. It is characterized by a high vagal tone with cardioinhibition and frequently asystole. The patient commonly wakes up with abdominal discomfort during the night and loses consciousness shortly after awakening.

We also described the case of a patient with vasovagal syncope who also suffered from psychogenic pseudosyncope. This is a common combination that is frequently missed.

**In chapter V,** five patients with syncope caused by a complete AV-block while bending forward were discussed. The association of syncope and bending forward is in fact common, but the familiar order concerns syncope occurring during or after straightening following bending. These five patients, however, all experienced syncope while bending forwards. We concluded that they shared both features of intrinsic AV-block (AVB), e.g. ectopic beats before syncope and pre-existing conduction disturbances, and of a reflex AVB. e.g. triggers. The association of syncope during bending forward should suggest a search for an AVB because of its diagnostic and therapeutic consequences. All patients responded favourably to cardiac pacing. We found no literature reports concerning the association between bending forward and AVB.

**In chapter VI,** we conducted a review on the clinical value of the tilt table test. The tilt table test helps to establish whether episodes of transient loss of consciousness are due to syncope and, if so, it yields ictal patterns of blood pressure and heart rate that define the type of syncope. In most cases further diagnostic testing is not necessary. We discussed the different tilt test methods and indications for a tilt table test. In our opinion, medical physicians seeing patients with a form of TLOC should be familiar with the differential

diagnosis, if only to prevent misdiagnosis. It is well known that a misdiagnosis of epilepsy may bring significant clinical, socioeconomic and psychological burden.[5] While tilt table testing can become an important clinical neurophysiological tool for TLOC diagnosis, it should be seen as an important addition to history taking, never as an isolated procedure.

In **chapter VII** we determined the outcome of patients with psychogenic pseudosyncope (PPS) after communication of the diagnosis. We carried out a retrospective cohort study of patients referred between 2007 and 2015 to a tertiary referral center for syncope. We reviewed patient files and recorded attack frequency, factors affecting attack frequency, health care use, and quality of life using a questionnaire. We explored influences on attack freedom and attack frequency in the 6 months before follow-up.

We followed 35 patients. Communication and explaining the diagnosis resulted in immediate reduction of attack frequency from the month before diagnosis (median 1, range 0-156) to the month after (median 1, 0-16). In the six months before follow-up, the number of hospital admissions decreased significantly from 19 of 35 to 0 of 35 patients (p=0.002).

Quality of life at follow-up showed low scores of seven of eight domains compared to matched Dutch control values. An important conclusion from our study is that the attack frequency decreased immediately after communication of the diagnosis and that the use of health care shifted from somatic towards mental health care. The low quality of life underlines that PPS is a serious condition. The positive effects in our study are in line with studies on psychogenic non-epileptic attacks (PNEA), meaning that a clear explanation of the nature of the attacks may itself lead to an immediate attack reduction. The incidence of syncope besides PPS was high (57%) in our study. Interestingly, we did not find a relation between how well the diagnosis was received and attack frequency. The acceptance of the psychological nature of the attacks did not seem to be a prerequisite for attack freedom, nor did its absence imply that attacks did continue.

## Future perspectives

In recent years, the definition of both syncope and transient loss of consciousness appears to be used with increasing consistency. This will contribute to a better communication between clinicians, and will also increase the quality of future studies. It would be useful to quantify whether consistency indeed increased, for instance by repeating a study on the use of 'syncope' in top ten journals of different specialties.

This thesis showed that asystole during tilt-table testing occurred too late to be the cause of syncope in one third of cases. This suggests that a conventional 'fall back' pacemaker, that sets heart rate to a specific values such as 50 or 60 bpm, will not be useful in this group of patients. In the future it will hopefully be possible to make a better selection of patients who may benefit from a pacemaker and to refrain from subjecting others to a potentially harmful treatment. A potentially useful method would be to equip an implantable loop recorder with an additional device to measure body position. In this way, at least those who have already fallen before asystole starts will not receive a pacemaker. Such a device would also provide valuable information regarding the occurrence of 'late asystole' in daily life. Till now, we only have the results from tilt-induced VVS with asystole and we do not know whether this reflects the situation in daily life. A study with patients receiving an ILR could show whether the situation changes between attacks or if this is a consistent phenomenon.

In our study, we identified those with 'late asystole' because a pacemaker would be unlikely to be of much value. However, there is also a group of patients with 'early asystole', in whom it is not clear whether a pacemaker would be helpful because blood pressure dropped already significantly. In this group it would be extremely useful to predict whether a pacemaker could prevent syncope. This requires a method to quantify how much bradycardia contributed to low pressure, using a recently developed quantification method, allowing quantification of the separate effects of SV, HR and TPR on BP.[6]

As mentioned in chapter VI, reflex syncope is not claimed by any specialty and therefore remains a 'blind spot'. The overuse of diagnostic tools and delay in diagnosis is still huge. In our opinion, it is important that any specialist seeing patients with TLOC should be educated regarding its differential diagnosis. A neurologist should at least know the cardiac dangers signs of syncope, and a cardiologist should be able to recognise a generalised seizure using history taking. An educational program during medical training could fulfill this need.

In our study on psychogenic pseudosyncope, we found similar results as reported in studies on PNEA. In both groups the attack frequency and use of medical care significantly

decreased after diagnosis and explanation of the diagnosis. A quick diagnosis and thorough explanation procedure seems therefore very important. At present the psychiatric treatment of patients with psychogenic attacks is difficult because few somatic specialists, and indeed psychiatrists, show an overt interest in treating these patients. A renewed interest from both sides, as well as close cooperation between these groups is useful in a better treatment of patients with functional attacks but also in reducing the medical costs.

It is interesting that something as common as syncope is such a mystery for so many doctors. This is probably because the common 'faint' is a diagnosis everybody is familiar with, thereby creating the 'blind spot' for other illnesses. Hopefully creating attention for this blind spot will make physicians more alert, knowing when to do a diagnostic test but also when to leave such a test behind.

# Samenvatting en discussie (NL)

Dit proefschrift beschrijft verschillende aspecten van syncope in de bredere context van transient loss of consciousness (TLOC). De verschillende aspecten variëren van de classificatie tot de pathophysiologie, allemaal met als doel een beter begrip van de patroonherkenning van verschillende vormen van TLOC te krijgen waarbij de focus op syncope ligt.

Een ondubbelzinnige definitie van syncope is belangrijk voor patiëntenzorg, onderzoek en onderwijsdoeleinden.[8] Helaas zijn er vele publicaties waarbij syncope als een brede categorie wordt gedefinieerd waarbij eigenlijk het concept van TLOC wordt beschreven.[7] De ESC-classificatie van 2001 was de eerste welke een formeel onderscheid maakte tussen transient loss of consciousness, i.e. aandoeningen met bewusteloosheid van korte duur met snel en spontaan herstel, en syncope, de vorm van TLOC met cerebrale hypoperfusie. De toevoeging van cerebrale hypoperfusie aan de definitie onderscheidt syncope van andere vormen van TLOC, vooral epilepsie en psychogene aanvallen.[4]

In **hoofdstuk II** worden korte beschrijvingen van verschillende vormen van syncope en TLOC gegeven, waarbij de focus ligt op de pathophysiologische achtergrond van de classificatie.

Van de vormen van syncope is reflex syncope de meest voorkomende vorm. De pathophysiologie van reflex syncope omvat zowel vasodepressieve als cardioinhibitoire componenten. Deze mechanismes kunnen op zichzelf optreden maar treden in de meeste gevallen allebei op. De manier waarop de vasodepressieve respons voor een daling van de bloeddruk zorgt blijft een controversieel onderwerp, maar op dit moment wordt veneuze pooling van bloed in het onderste gedeelte van het lichaam als belangrijkste oorzaak gezien van vasovagale syncope door staan, i.e. orthostatische VVS. Dit mechanisme is mogelijk van minder belang in andere vormen van reflex syncope. [6]

Het cardioinhibitoire mechanisme is waarschijnlijk hetzelfde in alle vormen van reflex syncope; door een toename van de vagale tonus treedt een daling van de hartslag op met asystolie als meest extreme vorm. De aanwezigheid van asystolie tijdens syncope zorgt er vaak voor dat er overwogen wordt een pacemaker te plaatsen om syncope te voorkomen. Het nut van een pacemaker bij VVS is echter zeer beperkt.[1] Verschillende grote onderzoeken (ISSUE-3[2], SUP-2[3]) lieten zien dat bij patiënten met asystolie tijdens VVS een pacemaker vooral nuttig was als er geen duidelijke vasodepressieve component was.

In **hoofdstuk III** onderzochten we de relatie tussen het begin van de asystolie en TLOC bij kantelproef-geïnduceerde reflex syncope en schatten we hoe vaak asystolie de belangrijkste oorzaak van TLOC was. We deelden patiënten met kantelproef-geïnduceerde reflex syncope in drie groepen in; asystole na het begin van TLOC (groep A), asystolie binnen 3 seconden voor begin TLOC (groep B) en asystolie welke meer dan 3 seconden voor de start van TLOC begon (groep C). In de eerste twee groepen is het zeer onwaarschijnlijk dat TLOC veroorzaakt wordt door alleen asystolie, wat een derde van de gevallen betrof.

De mediaan van de mean arterial pressure (MAP) aan het begin van de asystolie was hoger wanneer asystolie vroeg optrad (45.5 mm Hg, groep C) dan wanneer het laat optrad (32,0 mm hg, groep A en B), wat de suggestie wekt dat vasopdepressie niet prominent aanwezig was bij de start van asystolie in vroege asystolie. Aan de andere kant zou het dus wel zo kunnen zijn dat cardioinhibitie de belangrijkste oorzaak van syncope was in deze groep. Het was op dat moment echter niet mogelijk om de relatieve invloed van cardioinbitie en vasodepressie los te meten. In een vervolgstudie werd deze methode wel ontwikkeld[6], wat de mogelijkheid biedt om de invloed van cardioinhibitie op vroege en late asystolie te meten. De klinische relevantie van dit onderzoek is dat wanneer een pacemaker geplaatst wordt met als doel asystolie te voorkomen het onwaarschijnlijk is dat dit helpt in groep A en B, wat een derde van de patiënten met kantelproef-geïnduceerde reflex syncope betreft. Wanneer dus alleen wordt afgegaan op de gegevens van het ECG ontstaat er een overschatting van het belang van asystolie.

In **hoofdstuk IV** werd het belang geillustreerd van anamnese in twee complexe casus van TLOC. De eerste betrof een patiënt met slaap syncope, een zeldzame vorm van syncope die waarschijnlijk zelden herkend zal worden door clinici als een vorm van vasovagale syncope. Het wordt gekarakteriseerd door een hoge tonus van de nervus vagus met cardioinhibitie en in veel gevallen asystolie. De patiënt wordt meestal in de nacht wakker met buikpijn en verliest kort daarna het bewustzijn.
Daarnaast beschreven we de casus van een patiënt met vasovagale syncope welke ook last had van psychogene pseudosyncope. Dit is een veel voorkomende combinatie welke vaak gemist wordt.

In **hoofdstuk V** werden vijf patiënten met syncope veroorzaakt door een compleet AV-block beschreven tijdens bukken. De relatie tussen syncope en bukken is een veel voorkomende echter hierbij treedt syncope vooral op bij overeind komen. In dit geval trad syncope op tijdens voorover bukken. We concludeerden dat er zowel kenmerken van een intrinsiek AV-block (AVB), i.e ectopische slagen voor syncope en preexistente geleidingsstoornissen, als van een reflex AVB, zoals triggers, waren. De associatie tussen syncope en voorover bukken moet een trigger zijn om te zoeken naar een AVB gezien de

diagnostische en therapeutische consequenties. Alle vijf patiënten reageerden goed op pacemaker therapie. In de literatuur vonden we geen artikelen over de relatie tussen AVB en voorover bukken.

In **hoofdstuk VI** werd een review naar de klinische waarde van de kantelproef uitgevoerd. De kantelproef helpt bij de bevestiging of episodes van TLOC door syncope komen en als dat het geval is kan het door middel van ictale patronen van bloeddruk en hartslag ook duidelijkheid over het type syncope geven. In de meeste gevallen is verder diagnostisch onderzoek dan niet meer nodig. De verschillende methodes en indicaties van de kantelproef werden hier besproken. Naar onze mening moet clinici die patiënten met welke vorm van TLOC dan ook zien, bekend zijn met de differentiaal diagnose, alleen al om misdiagnose te voorkomen. Een misdiagnose van epilepsie kan significante psychologische en sociaaleconomische klachten geven.[5] De kantelproef moet gezien worden als een belangrijk klinisch neurophysiologisch hulpmiddel voor de diagnose van TLOC, maar het moet vooral als verlengstuk van de anamnese worden gezien, niet als vervanging hiervan.

In **hoofdstuk VII** onderzochten we de uitkomst van patiënten met psychogene pseudosyncope (PPS) nadat zij de diagnose hadden gekregen. Er werd een retrospectieve cohort studie uitgevoerd van patiënten verwezen tussen 2007 en 2015 naar een tertiair verwijscentrum voor syncope. We bekeken het patiëntendossier en verzamelden gegevens over aanvalsfrequentie, factoren welke de aanvalsfrequentie beïnvloedden, gebruik van gezondheidszorg en de kwaliteit van leven, welke middels een vragenlijst werd beoordeeld. We onderzochten factoren welke aanvalsvrijheid en aanvalsfrequentie beïnvloedden in de zes maanden voor follow-up. We volgden uiteindelijk 35 patiënten. Het vertellen van de diagnose en uitleg hierover resulteerde direct in een aanvalsreductie van de maand voor diagnose (mediaan 1, rang 0-156) tot de maand na diagnose (mediaan 1, 0-16). In de zes maanden voor follow-up nam het aantal ziekenhuisopnames significant af van 19 van de 35 patiënten naar 0 van de 35 patiënten (p=0.002). De kwaliteit van leven liet lage scores zien op zeven van de acht domeinen in vergelijking met gematchte Nederlandse controles. Een belangrijke conclusie van onze studie is dat de aanvalsfrequentie na het vertellen van de diagnose onmiddellijk daalde en dat het gebruik van gezondheidszorg zich verplaatste van somatische naar geestelijke gezondheidszorg. De slechte kwaliteit van leven laat zien dat PPS een serieuze aandoening is. De positieve effecten in ons onderzoek zijn in lijn met studies naar psychogene niet epileptische aanvallen, welke ook een forse afname van aanvallen laten zien na uitleg over de oorzaak van de aanvallen. De incidentie van syncope naast PPS was hoog in ons onderzoek (57%). Opvallend genoeg werd geen relatie gevonden tussen aanvalsreductie en acceptatie van de psychologische oorzaak van de aanvallen.

## Toekomstvisie (NL)

De laatste jaren wordt er steeds consistenter gebruikgemaakt van een eenduidige definitie voor syncope en transient loss of consciousness, ofwel TLOC. Dit draagt bij aan een betere communicatie tussen clinici wanneer zij het over deze groep aandoeningen hebben en zal de kwaliteit van toekomstige studies doen toenemen. In het verleden is het gebruik van de verschillende terminologie rondom TLOC al geëvalueerd, wat een inconsistent gebruik daarvan liet zien. Het zou nuttig zijn om een dergelijk onderzoek te herhalen met de huidige definities, om zo te beoordelen of het gebruik hiervan daadwerkelijk consistenter is.

Dit proefschrift toonde aan dat een asystolie bij vasovagale syncope tijdens een kantelproef bij een derde van de patiënten pas na het begin van de wegraking optreedt. Het nut van een 'fall back' pacemaker, welke de hartslag op een specifieke waarde van bijvoorbeeld 50 of 60 slagen per minuut zet, lijkt bij deze groep patiënten afwezig.

Dit zal er hopelijk in de toekomst toe leiden dat er gerichter geselecteerd wordt naar de groep die wel baat bij een pacemaker kan hebben en zo kan een deel van de patiënten een potentieel schadelijke en niet effectieve therapie bespaard blijven. Een potentieel effectieve therapie zou het gebruik van een implantable loop recorder (ILR), op dit moment al gebruikt voor ritme monitoring, zijn die niet alleen het hartritme maar ook de lichaamspositie ten tijde van het begin van de asystolie kan meten. In dat geval zullen patiënten die al gevallen zijn voor de start van de asystolie geen pacemaker krijgen. Dit kan ook waardevolle informatie geven over asystolie bij VVS in het echte leven, aangezien tot op heden alleen resultaten bekend zijn van bij een kantelproef geïnduceerde asystolie; het is maar de vraag of dit een juiste afspiegeling is van syncope in het dagelijks leven. Een onderzoek bij patiënten met asystolie bij VVS die een ILR met lichaamspositie monitoring krijgen kan laten zien of het moment van de asystolie ten opzichte van de syncope altijd hetzelfde is, of dat dit wisselt.

In ons onderzoek keken we voor welke groep patiënten een pacemaker in ieder geval niet nuttig zou zijn. Er is echter ook een groep bij wie de asystolie wel voor de syncope begint, maar waarvoor het niet duidelijk is of een pacemaker zal helpen, omdat de bloeddruk op dat moment ook al fors gedaald is. In deze groep zou het interessant zijn om te zien in welke gevallen de pacemaker de wegraking toch voorkomt. Dit zou kunnen met een methode waarbij gekeken kan worden naar de bijdrage van bradycardie aan de lage bloeddruk. Met een recent ontwikkelde quantificatie methode kunnen de verschillende parameters van de bloeddruk, namelijk slagvolume, hartslag en totale perifere vaatweerstand en hun invloed op de bloeddruk apart beoordeeld worden.[6]

Zoals in hoofdstuk VI beschreven valt syncope niet duidelijk onder een specifiek specialisme en blijft het om die reden een 'blinde vlek'. Dit zorgt voor onnodig gebruik van aanvullend onderzoek. Naar onze mening is het daarom belangrijk dat iedere specialist die patiënten met wegrakingen ziet opgeleid is in de differentiaal diagnose van TLOC. Kortom; een neuroloog moet de alarmsymptomen van cardiale syncope kennen en een cardioloog moet weten wanneer een wegraking kan berusten op epilepsie of een functionele oorzaak. Een opleidingsprogramma gedurende de medische specialisatie is hiervoor uitermate geschikt.

In de follow-up van patiënten met psychogene pseudosyncope kwamen soortgelijke getallen naar voren als bij psychogenic non-epileptic attacks (PNEA) . Na het bespreken van de diagnose daalde de aanvalsfrequentie aanzienlijk en ook nam het gebruik van medische zorg fors af. Een snelle diagnose en duidelijke uitleg lijkt daarom zeer belangrijk.

Op dit moment is de psychiatrische begeleiding en behandeling van deze patiëntengroep beperkt aangezien weinig (somatisch) medisch specialisten en psychiaters zich hier op toegelegd hebben. Een betere samenwerking tussen deze twee groepen en meer aandacht voor deze patiëntenpopulatie kan bijdragen aan een betere prognose en daarnaast een reductie van de medische kosten.

Het is intrigerend dat syncope, wat zeer vaak voorkomt, voor veel dokters zoiets mysterieus blijft. Waarschijnlijk heeft dit te maken met het feit dat vasovagale syncope een diagnose is waar vrijwel iedereen bekend mee is, wat een blinde vlek oplevert voor andere oorzaken van syncope. Hopelijk zorgt bewustwording van deze 'blinde vlek' ervoor dat clinici weten wanneer wel en wanneer geen aanvullend onderzoek aan te vragen.

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# ADDENDUM

# A

List of abbreviations

Dankwoord

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# List of abbreviations

| | |
|---|---|
| BP | Blood pressure |
| EEG | Electroencephalography |
| ESC | European Society of Cardiology |
| ILR | Implantable loop recorder |
| LUMC | Leiden University Medical Centre |
| OH | Orthostatic hypotension |
| MAP | Mean arterial pressure |
| PNEA | Psychogenic non epileptical attack |
| PPS | Psychogenic pseudosyncope |
| SEIN | Stichting Epilepsy Instellingen Nederland |
| TLOC | Transient loss of consciousness |
| TTT | Tilt table test |
| VVS | Vasovagal syncope |

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## Over de auteur

Dirk Pieter Saal werd geboren op 26 mei 1983 te Alkmaar. Na het behalen van zijn middelbare school diploma (Murmellius Gymnasium, Alkmaar) ging hij in 2002 geneeskunde studeren aan de VU. Tijdens zijn studie nam hij deel aan onderzoek naar jeugdige zedendelinquenten bij De Bascule, kinder- en jeugdpsychiatrie in Amsterdam en ging hij tweemaal een periode naar Afrika (Ghana, 2006 en Tanzania, 2008). Hierna werd een oudste co-schap neurologie gelopen in het Spaarne Ziekenhuis (nu Spaarne Gasthuis) in Hoofddorp, waarna hij hier enige tijd als ANIOS werkte. In 2010 begon hij met de opleiding tot neuroloog in het LUMC (prof. R.A.C. Roos/ prof. J.J. van Hilten).
Tijdens zijn stage klinische neurofysiologie werd de basis gelegd voor het onderzoek bij prof. Gert van Dijk en dr. Roland Thijs, wat uiteindelijk tot dit proefschrift heeft geleid. Sinds 2016 is hij werkzaam als neuroloog in het Franciscus Gasthuis en Vlietland ziekenhuis (Rotterdam/Schiedam). Dirk woont samen met Agnes van Sonderen en hun dochters Juliette (2016) en Lizelot (2018) in Den Haag.

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