Neurally-mediated reflex syncope: diagnosis and treatment
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Chapter 1

Introduction and outline
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Transient loss of consciousness (T-LOC) can be caused by various traumatic and non-traumatic clinical disorders, ranging from potentially lethal to relatively benign.\textsuperscript{1, 2} Non-traumatic episodes of T-LOC caused by a reduction of blood flow to the brain are called ‘syncope’\textsuperscript{1, 3-5} Syncope is characterized by a rapid onset, short duration and spontaneous complete recovery.\textsuperscript{1, 3, 4} Syncopal causes of T-LOC are often categorized into three major subgroups: (neurally mediated) reflex syncope, syncope due to orthostatic hypotension and cardiac syncope (Figure 1).\textsuperscript{1, 4}

Reflex syncope is the most common cause of T-LOC.\textsuperscript{2} A diagnosis of reflex syncope is obtained in 30-45% of patients presenting with T-LOC at the emergency department.\textsuperscript{6, 7} Reflex syncope is caused by reflex vasodilatation and/or bradycardia, resulting in systemic arterial hypotension and cerebral hypoperfusion.\textsuperscript{1} Although the exact pathophysiological mechanisms leading to an episode of reflex syncope are poorly understood,\textsuperscript{8} a significant number of predisposing factors or triggers have been identified.\textsuperscript{9} Based on these predisposing factors, reflex syncope can be further classified into different subtypes: vasovagal syncope (VVS), situational syncope, carotid sinus syncope, and atypical forms (Figure 1).\textsuperscript{1, 4} VVS, the common faint, is by far the most common form of reflex syncope.\textsuperscript{2, 4, 6, 7, 10, 11} VVS is mediated by acute pain, fear, or prolonged standing.\textsuperscript{9, 12} Triggers can differ between episodes of VVS in one person.\textsuperscript{4, 9, 12} Most patients with VVS experience their first syncope before 30 years of age.\textsuperscript{13, 14}
Reflex syncope associated with swallowing, coughing, micturition, or defecation is called ‘situational syncope’.\(^1\)\(^,\)\(^4\)\(^,\)\(^9\), while reflex syncope occurring upon mechanical manipulation of the carotid sinuses in the neck is called ‘carotid sinus syncope’.\(^1\)\(^,\)\(^15\) The classic, but rare, examples of a spontaneous carotid sinus syndrome include fainting while shaving the neck, turning the neck, or wearing a tight collar\(^4\). In laboratory circumstances, carotid sinus massage will induce abnormal slowing of heart rate and hypotension in these patients.\(^1\) Based on the predominant response to carotid sinus massage, carotid sinus hypersensitivity can be further classified into vasodepressor, cardio-inhibitory and mixed suptypes.\(^15\) Reflex syncope occurring upon uncertain or even apparently absent triggers is called ‘atypical’.\(^1\) In these cases, the diagnosis is usually based on tilt-table testing or a positive response during carotid sinus massage and the exclusion of other causes of T-LOC.\(^1\)

Patients diagnosed with reflex syncope have a mortality similar to that of people who have not experienced T-LOC.\(^2\) Mortality is increased in patients with cardiac and neurological causes of T-LOC.\(^2\) Since treatment options and mortality differ depending on the likely cause of T-LOC, it is of vital importance to make a clear distinction between reflex syncope and other causes of T-LOC. This is not straightforward as there can be considerable overlap in symptoms and in triggers between various causes of T-LOC. Below, a number of relevant issues in the diagnosis and treatment of patients with T-LOC are discussed.
Diagnosing patients presenting with T-LOC

The medical history, in combination with the physical examination and an ECG, plays a key role in diagnosing patients presenting with T-LOC. Based on this initial evaluation, attending physicians can make a diagnosis in 63% of patients, with a diagnostic accuracy of 91%. For this evaluation, attending physicians rely on information pertaining to personal characteristics, signs, symptoms and triggers of different causes of T-LOC as well as on their respective prevalence.

In patients with syncope so-called ‘prodromal’ or ‘pre-syncopal’ signs and symptoms occur when cerebral blood flow diminishes gradually. Difficulty in thinking and light-headedness occur early during a typical pre-syncopal episode. Next, loss of colour vision and blurring or darkening of vision usually occur. Sounds can seem to come from far away.

Syncope occurs if systolic blood pressure decreases to 40 mmHg or lower at heart level for at least 6 to 8 seconds. Upon loss of consciousness, loss of voluntary motor control occurs and patients fall down. The eyes are usually open and directed upwards or straight ahead. Additionally, if the hypotensive period is prolonged, myoclonic jerking and urinary incontinence may occur. Tongue biting is very rare in syncope. If it occurs, the tip of the tongue is usually involved, rather than the side as in epilepsy. During a syncopal episode, loss of consciousness usually lasts shorter than 20 seconds, since the supine position usually helps to restore venous return and thereby cardiac output, leading to a rise in systemic blood pressure and cerebral perfusion. Restoration of consciousness occurs quickly after resumption of cerebral perfusion; patients can subsequently think clearly and remember events. Fatigue and sleepiness might however persist for some time.

Though the clinical history is of vital importance in diagnosing patients presenting with T-LOC, obtaining a diagnosis can be difficult since the symptoms of the different types of syncope are often quite similar, with differences mainly caused by the rapidity of onset rather than the underlying cause. Episodes rarely occur in a hospital setting which means that physicians have to rely on identifying predisposing factors and descriptions of symptoms and signs from patients and witnesses. An eyewitness’ account of a single episode of T-LOC should be interpreted with caution since salient features were found to be often overlooked or inaccurately recalled. Because of all of the factors mentioned above, properly developed and validated diagnostic tools could facilitate the diagnostic process in patients presenting with T-LOC.
The prevalence of different causes of T-LOC has been shown to depend on both age and gender.\textsuperscript{6, 12, 23, 24} In a group of medical students (median age 21 years), 39% reported to have experienced at least one episode of T-LOC in their life. In women, the percentage was almost twice that in men (47 versus 24%).\textsuperscript{12} Most of these episodes involved stresses or conditions that affect orthostatic blood pressure regulation, making reflex syncope the most likely cause of T-LOC in these young subjects. In this age-group the lifetime cumulative incidence of epilepsy (0.5%) and cardiac causes of T-LOC were much lower.\textsuperscript{18, 25} A similar pattern was found for patients aged 35 to 60 years of age, although episodes of T-LOC were less common in this age group.\textsuperscript{14} In patients of 65 years or above, episodes of T-LOC again become more common, reflex syncope was still found to be the most frequent cause of T-LOC (54%).\textsuperscript{26} However, cardiac causes of T-LOC and for instance orthostatic hypotension occur much more frequently in elderly patients compared to younger patients.\textsuperscript{6, 27-29} Since reflex syncope tends to occur more often in younger patients and women, the prevalence of prodromal signs, symptoms and triggers could also be higher in these patients. If so, information about age and gender in addition to information about prodromal signs, symptoms and triggers can be of use in diagnosing patients presenting with T-LOC.

To facilitate diagnostic decision-making upon initial evaluation, several tools have been developed.\textsuperscript{1} The Calgary Syncope Symptom Score (Calgary Score) attempts to differentiate VVS from other causes of T-LOC based on history.\textsuperscript{30} In the internal validation, the Calgary Score was reported to have a high sensitivity (89%) and specificity (91%).\textsuperscript{30}

**Treating patients with reflex syncope**

Treatment of reflex syncope is directed at reducing the number of (pre-)syncopal recurrences and improving quality of life. The syncope management guideline of the European Society of Cardiology recommends non-pharmacological treatment as first line of treatment for patients diagnosed with reflex syncope.\textsuperscript{1} This treatment includes lifestyle measures and physical counterpressure manoeuvres, such as leg crossing and hand grip and arm tensing.\textsuperscript{1} Patients with cardio-inhibitory carotid sinus syncope and patients with other forms of reflex syncope not responding to non-pharmacological treatment are usually prescribed pharmacological and/or pacemaker treatment.\textsuperscript{1} If reflex syncope is associated with blood phobia and/or psychiatric complaints, psychological counselling might be considered.\textsuperscript{31}
**Non-pharmacological treatment**

Education and reassurance regarding the benign nature of the condition are key elements of the non-pharmacological management of patients with reflex syncope.\(^1\) Patients are instructed to recognize warning symptoms, to avoid triggering circumstances, to increase their dietary fluid and salt intake, and to perform physical counterpressure manoeuvres.\(^1, 32-34\) Such manoeuvres have been shown to induce a significant increase in blood pressure during the phase of impending reflex syncope, helping to prevent or delay losing consciousness in most cases.\(^34-36\)

**Pharmacological treatment**

Many pharmacological agents have been proposed for treating more resistant forms of reflex syncope.\(^37\) Midodrine is an alpha\(_1\)-agonist that after absorption is rapidly metabolized to its active metabolite D-glymidodrine, which causes constriction of veins and arterioles.\(^37, 38\) In this way, venous pooling of blood is reduced, which may prevent the development of syncope.\(^37\) Other pharmacological agents to treat reflex syncope include beta-blockers, fludrocortison, serotonin re-uptake inhibitors, disopyramide and anticholinergic agents.\(^37\) Although multiple studies have been performed to assess the effectiveness of midodrine and other pharmacological agents, there are no data from large randomized, placebo controlled trials that show a long-term clinical benefit.\(^37\)

**Pacemaker treatment**

If significant bradycardia or asystole is detected, dual-chamber pacing is postulated to prevent reflex syncope by increasing the heart rate.\(^39\) In several non-randomized and/or non-blinded studies, syncopal recurrence was lower upon pacemaker treatment compared to no-pacemaker treatment.\(^40\) So far, these results have not been reproduced in properly blinded randomized trials.\(^39-41\) This is not surprising, if we consider that pacing may affect the cardio-inhibitory component of the reflex response, but will have no effect on the vasodepressor component, which is often dominant.\(^1\) In current syncope management guidelines, cardiac pacing is only recommended in case of spontaneous reflex syncope associated with severe bradycardia or asystole.\(^1, 39, 41\)

**Objectives**

This thesis focuses on key issues with respect to the diagnosis and treatment of reflex syncope.
The main objectives of this thesis are:

- To evaluate the importance of anthropomorphic characteristics and clues derived from history taking in diagnosing patients presenting with T-LOC.
- To study the short and long-term effectiveness of non-pharmacological treatment in patients with frequently recurring reflex syncope.
- To systematically review studies examining the efficacy of different pharmacological and pacemaker treatments for reflex syncope.
- To investigate the efficacy of midodrine treatment compared to placebo in patients with reflex syncope insufficiently responding to non-pharmacological treatment measures.

As the occurrence of different causes of T-LOC appears to be influenced by both age and gender, we wondered whether the respective signs, symptoms and triggers are also influenced by age and gender. We explored this in patients with reflex syncope (Chapter 2).

Using information on signs, symptoms and triggers of patients presenting with T-LOC, the Calgary Score has been designed to make a distinction between patients with vasovagal syncope and patients with other causes of T-LOC. We performed a validation study to assess the diagnostic performance of the Calgary Score in an external population. The results of this study are discussed in Chapter 3 of this thesis.

Since the effectiveness of several treatment options for specific patient groups diagnosed with reflex syncope is still unknown, we wondered whether non-pharmacological treatment would also be beneficial for patients with frequently recurring VVS. These findings are described in Chapter 4.

Several studies, mostly cross-sectional, have reported that patients with higher levels of psychological distress have more frequent syncopal recurrence, we investigated this hypothesis in the studies reported in Chapters 5 of this thesis.

A coherent evaluation of different kinds of pharmacological and pacemaker treatment for reflex syncope does not exist. To fill this gap, we systematically reviewed the available literature on this topic in Chapter 6.

For most patients with reflex syncope, pharmacological and pacemaker treatment are only relevant treatment options upon failure of non-pharmacological treatment. We investigated the effectiveness of midodrine treatment in patients in whom non-pharmacological treatment failed in Chapter 7.

The thesis ends with a summary of the main study findings and some concluding remarks.
Reference List


