CHAPTER 1

General Introduction and Outline

GENERAL INTRODUCTION

Definition and clinical spectrum of syncope and hypotension

Syncope is defined as transient loss of consciousness (T-LOC) caused by global cerebral hypoperfusion, characterised by rapid onset, short duration and spontaneous complete recovery without persistent neurological deficits.[1-3] This means that blood flow to the brain as a whole is briefly insufficient.

Syncope is T-LOC with a mechanism. The definition distinguishes syncope from other forms of T-LOC.[1-3] In epileptic seizures, the mechanism is abnormal electrical activity in the brain. In functional syncope mimics, the event may clinically resemble syncope, but there is no global cerebral hypoperfusion. Metabolic disorders, i.e. biochemical disturbances, and structural disorders of the central nervous system may also cause loss or alteration of consciousness. These causes require a different diagnostic and therapeutic approach.[1-3]

In clinical practice, syncope forms part of a broader spectrum of hypotension related symptoms.[1,2] Hypotension means that blood pressure is too low to maintain cerebral perfusion at that moment. When blood pressure is insufficient to maintain adequate cerebral perfusion, symptoms may range from mild dizziness to complete loss of consciousness. Presyncope, or near-syncope, refers to symptoms such as light-headedness, blurred vision, weakness, nausea, sweating or a sensation of impending fainting, without complete loss of consciousness.[1,4-] In clinical practice, presyncope is most informative when the patient recognises these symptoms as resembling the prodrome of previous episodes with actual transient loss of consciousness.

For patients, presyncope may be almost as burdensome as syncope, because fear of fainting may lead to avoidance of work, driving, social activities or physical exertion.[4-6] This is particularly relevant in older adults, in patients with comorbidity and in frail patients, in whom presyncope, falls and functional decline often coexist.[4-6]

An important cause of hypotension-related symptoms is orthostatic hypotension. Orthostatic means posture-related: blood pressure falls on standing or during upright posture. Orthostatic hypotension is classically defined as a sustained fall in systolic blood pressure of ≥20 mmHg or in diastolic blood pressure of ≥10 mmHg within three minutes of standing or head-up tilt.[1,2,7] It may present as syncope, presyncope, falls or non-specific fatigue, and may coexist with reflex syncope.[1,2,8,9]

Symptomatic hypotension is a broader term for symptoms caused by intermittent or sustained low blood pressure.[1,2] Potential mechanisms include autonomic dysfunction, in which the autonomic nervous system responds inadequately to postural change; hypovolaemia, in which the circulating volume is reduced; medication effects; and reflex-mediated vasodilatation, in which blood vessels dilate and blood pressure falls.[1,2,7-9] These mechanisms may occur separately or in combination.

The clinical challenge is therefore not only to establish whether an episode represents syncope, but first to place the event within the broader classification of transient loss of consciousness. In this framework, syncope must be distinguished from epileptic seizures, functional or dissociative T-LOC, and other

mimics, because these conditions differ fundamentally in mechanism, prognosis and management. Once syncope is considered likely, the next step is to determine why cerebral perfusion temporarily became insufficient.[1,2] The underlying mechanism, for example reflex-mediated hypotension, orthostatic hypotension or a cardiac cause, determines which investigations are required, how risk should be assessed, which treatment is appropriate and what follow-up is needed.

Epidemiology and clinical burden

Syncope is very common. The most common one is the regular faint. Population-based studies show that the cumulative lifetime incidence, meaning the proportion of people who experience syncope at some point in life, is approximately 35–40%.[10] There is a first peak in adolescence and young adulthood, and a second increase in older age.[11] A substantial proportion of the population will therefore experience a syncopal episode, although only a subset will seek medical attention or require hospital care.[10-13]

In acute care and emergency settings, syncope or unexplained T-LOC is a relevant cause of unplanned presentations.[12,13] Admission rates vary considerably between healthcare systems and are often influenced by concern about cardiac causes, trauma, underlying disease, sudden death, or medico-legal considerations.[1,12-15] At the same time, only a minority of patients are ultimately found to have a life-threatening cause.[1,12-15] This imbalance between high healthcare utilisation, meaning extensive use of healthcare resources, and the relatively limited yield of serious diagnoses highlights the need for more efficient diagnostic and organisational strategies.[1,14,15]

The burden of syncope extends beyond the event itself. Recurrent episodes are associated with impaired quality of life, restrictions in work and social activities, and increased anxiety in patients and relatives.[4-6,16-19] In older adults, syncope and falls are closely related, with overlapping mechanisms such as orthostatic hypotension, carotid sinus syndrome and medication-related hypotension.[1,2,7-9] Syncope-related injury, including fractures and head trauma, contributes to morbidity, meaning disease burden and complications, and to healthcare use.[1,2,1619] In addition, recurrent hypotensive symptoms may lead to activity avoidance and deconditioning, meaning loss of physical fitness due to inactivity, which may further increase underlying autonomic or haemodynamic vulnerability.[4-6,16-19]

The combination of high prevalence, recurrent morbidity and substantial healthcare utilisation justifies continued efforts to improve diagnostic accuracy, streamline care pathways and individualise treatment.[1,2,14,15]

Haemodynamic treatment and pharmacological stabilisation

In patients with recurrent symptoms due to hypotension, non-pharmacological strategies form the basis of treatment.[1,2] These include explanation and education, avoidance of triggers, volume expansion through adequate fluid and salt intake when appropriate, physical counterpressure manoeuvres and adjustment of hypotensive or vasodilating medication.[1,2] Volume expansion means increasing the circulating blood volume. Counterpressure manoeuvres are physical manoeuvres, such as leg crossing or tensing the arm and leg muscles, that may temporarily

increase blood pressure. Vasodilating medication widens the blood vessels and may therefore worsen hypotensive symptoms.

Recent haemodynamic studies have emphasised the relevance of blood pressure profiling and hypotensive susceptibility in patients with reflex syncope and orthostatic intolerance.[20-22] In a substantial subgroup, non-pharmacological measures are insufficiently effective or poorly tolerated.[1,2]

In such patients, pharmacological agents, meaning drug treatments, may be considered to stabilise blood pressure.[1,2] Fludrocortisone is a synthetic mineralocorticoid, a drug with effects similar to hormones that promote salt and water retention. It increases plasma volume, the fluid component of blood, by stimulating renal sodium and water retention.[1,2,23] Fludrocortisone is used in orthostatic hypotension and in selected patients with recurrent reflex syncope, particularly in those with low or normal blood pressure.[1,2,23] Potential adverse effects include supine hypertension, oedema and electrolyte disturbances.[1,2,23]

Midodrine is an orally active α_1-adrenergic agonist, a drug that stimulates vasoconstriction through α_1-receptors on blood vessels. This increases peripheral vascular resistance and venous return.[1,2,24,25] Peripheral vascular resistance refers to resistance in the small blood vessels, whereas venous return means the return flow of blood to the heart. Midodrine is used in orthostatic hypotension and in selected patients with severe reflex syncope with a dominant vasodepressor component, in which blood pressure fall is more prominent than bradycardia.[1,2,24,25] Adverse effects such as piloerection, pruritus, urinary retention and supine hypertension require careful monitoring.[1,2,24,25]

Ambulatory 24-hour blood pressure monitoring, in which blood pressure is measured over a full day outside hospital, has helped to define a hypotensive phenotype in reflex syncope and orthostatic intolerance as defined in recent studies.[2,21] This very simple diagnostic tool has gained new clinical value as diagnostic tool specifically in patients with reflex syncope. Patients with reflex syncope more often have a lower blood pressure profile and more systolic blood pressure drops.[20,21] Interventions aimed at increasing average 24-hour systolic blood pressure may reduce these blood pressure drops.[22]

Organization of syncope care: from fragmented care to syncope units

Care for patients with syncope has historically often been fragmented, meaning that care is distributed across several specialties and healthcare settings.[1,2,26] Patients may present to emergency medicine, internal medicine, cardiology, neurology or geriatric medicine. When a fixed care pathway is lacking, this may lead to duplicate investigations, variable follow-up, delayed diagnosis and unnecessary hospital admissions.[1,2,14,15,26]

Syncope units have been developed to reduce this fragmentation.[26] A syncope unit is a specialised, multidisciplinary structure in which different specialties collaborate according to standardised protocols.[26] The aim is not to perform as many tests as possible in every patient, but to perform the initial syncope evaluation structured and, use additional investigations selectively and ensure safe follow-up.[1,2,26]

Structured syncope care has been shown to increase diagnostic yield, reduce unnecessary admissions and improve efficiency while maintaining patient

safety.[14,15,26] Diagnostic yield refers to the proportion of patients in whom a probable or definite explanation for the symptoms is ultimately found. For future syncope care, clear quality criteria, periodic evaluation and comparison between care pathways are therefore important to ensure that guideline recommendations translate into daily clinical practice.[1,2,14,15,26]

The emerging role of artificial intelligence in syncope

Artificial intelligence, and more specifically machine learning, is increasingly being investigated as a tool to support diagnosis, risk stratification and more efficient use of healthcare resources.[27,28] Machine learning means that algorithms identify patterns in large amounts of data and use these patterns to make predictions in new patients.[27,28]

Syncope is a relevant field for such approaches because the differential diagnosis is broad, risk varies considerably between patients and the available information often consists of a combination of symptoms, vital signs, ECG findings, medication and follow-up data.[28,29] In the future, AI may support triage, risk signalling, diagnostic decision-making and the structuring of syncope-unit workflows.[28,29]

At the same time, the use of AI in syncope requires caution. Models depend on the quality of input data, may reinforce existing bias in datasets and require external validation before they can be considered clinically reliable.[27-29] Diagnostic safety is particularly important in syncope, because missing cardiac syncope may have serious consequences.[29,30] AI should therefore currently be regarded as decision support within a clinician-led pathway, not as a replacement for clinical expertise.[29,30]

OUTLINE OF THIS THESIS

The overarching aim of this thesis is to optimise syncope care by examining organisation, diagnosis, artificial intelligence, provocation testing, haemodynamic treatment and patient-centred outcomes as interconnected components of an integrated care pathway.[1,2]

Part I focuses on the organisation and diagnostic structure of syncope care.

Chapter 2 evaluates guideline-based syncope units in the Netherlands and introduces the SU-19 score as a tool for assessing best-practice standards.[31]

Chapter 3 is an in dept analysis of the referral pattern in the FAST II cohort.[32]

Part II explores the role of artificial intelligence in syncope care.

Chapter 4 compares artificial intelligence with medical professionals using referral information.[30]

Chapter 5 evaluates artificial intelligence within the syncope-unit setting, using structured expert assessment and adjudicated final diagnoses as reference.[33] Together, these chapters assess the potential and limitations of artificial intelligence as diagnostic support.

Part III addresses bedside provocation, diagnostic methodology of diagnostic tests and the effect of blood pressure rising therapy on the haemodynamic stabilisation in patients with severe reflex syncope.

Chapter 6 reviews the practical methodology, indications and clinical interpretation of tilt table testing in the evaluation of syncope and orthostatic intolerance.

Chapter 7 presents the Six-Step-Method for carotid sinus massage.

Chapter 8 describes the haemodynamic effects of fludrocortisone and midodrine in patients with symptoms due to hypotension.[34-36]

Part IV deals with the clinical consequences of structured syncope care.

Chapter 9 whether guideline-based syncope evaluation and subsequent management are associated with consistent longitudinal improvements in syncope-specific and generic health-related quality of life across secondary and tertiary care settings, using the SFSQ, RAND-36 and SF-12.[37]

The thesis concludes with a summary of the main findings (**Chapter 10)**, followed by the general discussion and future perspectives (**Chapter 11)** and the Dutch summary (**Chapter 12)**.

The **appendices** include the list of publications, portfolio and acknowledgements.

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