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Syncope : an integrative physiological approach

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General introduction

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*“Li quens Rollant, quant il veit mort ses pers,
E Oliver, qu'il tant poeit amer,
Tendrur en out, cumencet a plurer.
En sun visage fut mult desculurez.
Si grant doel out que mais ne pout ester;
Voeillet o nun, a tere chet pasmet.
Dist l'arcevesque: “Tant mare fustes ber!”*

*The count Rollanz, when dead he saw his peers,
And Oliver, he held so very dear,
Grew tender, and began to shed a tear;
Out of his face the colour disappeared;
No longer could he stand, for so much grief,
Will he or nill, he swooned upon the field.
Said the Archbishop: "Unlucky lord, indeed!"^l*

La chanson de Roland (c. 1090)

English translation of Charles Scott Moncrief (London, 1919)

Symptoms and signs of syncope

Syncope is an extremely common symptom with a life time prevalence of 30 to 40% in the general population.^{52,81,212} Syncope has been defined as a transient, brief and self-limited loss of consciousness due to global cerebral hypoperfusion.²⁹ This specific pathophysiology sets syncope apart from other conditions causing transient loss of consciousness (TLOC), such as epilepsy. The most important physiological event leading to syncope is arterial hypotension, but high cerebral vascular resistance, high cerebral (venous) pressure or hypoxia may also contribute.^{160,219,236} In an acute circulatory arrest it usually takes 6-8 seconds before consciousness is lost.^{85,202,264} In the EEG this phase is represented by bilateral slow waves, which in turn fairly abruptly make way for a complete flattening of the EEG.^{27,85} The threshold to syncope appears to depend on age, with the lowest threshold in early childhood.²³⁶ Loss of consciousness is usually preceded by prodromal features such as blurred vision (greying or blacking out due to hypoperfusion of the retina), buzzing in the ears or light-

headedness.^{59,85,109,202,223} In addition, in specific subtypes of syncope signs of autonomic activation may be noted including facial pallor, nausea, pupillary dilatation, and excessive sweating.^{3,84,151,186} Prodromal signs may permit the patient to predict an oncoming attack and sometimes thereby to prevent loss of consciousness, such as by lying down. Other effective manoeuvres to abort an impending faint include body tensing, squatting, or sitting with the head between the knees.^{253,269} The duration of loss of consciousness in syncope is usually no longer than 20 seconds, but this may be longer, especially if the subject is kept upright while unconscious. Syncope may cause the subject to fall with either flaccid or stiff limbs.¹⁴⁸ Myoclonic jerks were frequently (90%) observed in healthy subjects who intentionally provoked syncope using the 'fainting lark'.¹⁴⁸ In this study the jerks were almost exclusively arrhythmic and asynchronous and always occurred after the individual had fallen down. However, jerking movements do not occur in 90% of all syncope attacks: in fainting blood donors, such movements were seen in 46% of patients.¹⁸⁶ Furthermore, eyewitnesses observed abnormal movements in only 13% of patients with typical vasovagal syncope.³ Prolonged tonic spasms in extension may occur in syncope and should not be misdiagnosed as epilepsy.^{85,202,236,264} Adding to diagnostic complexity true epileptic seizures may be induced by syncope.^{114,235} During loss of consciousness in syncope the eyes are open and upward eye deviation or downbeat nystagmus may be noted.^{84,149,152,236} In addition, turning of the head to one side may occur.^{85,148,202,236} Subsequent recovery of consciousness is spontaneous and complete. Afterward, the patient may appear pale and complain of headache and a feeling of weakness or fatigue.^{84,151,219} In some patients facial flushing is observed when they regain consciousness, indicating a very rapid recovery of blood pressure as seen in some cases of arrhythmias (labelled Adams-Stokes attacks) but also in some cases of reflex syncope.²⁷¹ Urinary incontinence may occur in syncope and so does faecal incontinence, although the latter should be considered rare.^{109,152,186} Occasionally, tongue biting may be caused by a syncopal event, but if so it is usually restricted to the tip of the tongue in contrast to the lateral lacerations caused by epileptic seizures.^{14,148}

The causes of syncope can be classified according to the underlying mechanisms (Table 1). The four mechanisms there may be grouped in two major pathophysiological categories: decreased cardiac output including cardiac syncope and hypovolemia and disturbed regulation of resistance and capacitance vessels including autonomic failure and reflex syncope. It should however be understood that there are often multiple causes at work. For instance, decreased cardiac output due to hypovolemia during diarrhea may contribute to both

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Table 1 Classification of syncope

A. <u>Insufficient pumping action of the heart</u>	
-Arrhythmia	<i>Examples: paroxysmal (supra)ventricular tachycardia, long QT syndrome</i>
-Structural cardiac disease	<i>Examples: valvular disease, obstructive cardiomyopathy</i>
B. <u>Insufficient vascular tone, leading to orthostatic hypotension</u>	
-Autonomic failure	
Primary	<i>Examples: multiple system atrophy, pure autonomic failure</i>
Secondary	<i>Examples: diabetic and other neuropathies</i>
Drugs	<i>Examples: antidepressants, alpha-adrenergic blockers</i>
C. <u>Insufficient circulatory volume: hypovolemia</u>	
<i>Examples: Addison's disease, diuretics, hemorrhage</i>	
D. <u>Inappropriate neural control over the circulation: reflex syncope (= neurally-mediated syncope)</u>	
<i>Examples: vasovagal syncope, carotid sinus syndrome, miction syncope</i>	

vasovagal syncope and orthostatic hypotension in autonomic failure.

The autonomic nervous system abnormality in reflex syncope differs fundamentally from that in autonomic failure: in autonomic failure, the autonomic nervous system initiates a normal action but fails to deliver a response of sufficient magnitude, while in reflex syncope the action itself is inappropriate, consisting of vasodilation and/or bradycardia, indicating both sympathetic withdrawal and vagal hyperactivity. Further subtypes may be added to each category. For example, the group of reflex syncope (synonym: “neurally-mediated syncope”) can be subdivided according to triggering events: head rotation or pressure on the carotid sinus is a precipitant in the carotid sinus syndrome, coughing in cough syncope, micturition in micturition syncope etc.

Pathophysiology of vasovagal syncope

Vasovagal syncope is by far the most common form of syncope.^{29,52,81} 'Vasovagal syncope' is sometimes used as a synonym for reflex syncope, and sometimes as reflex syncope evoked by

specific triggers such as pain, emotional stress or the sight of blood. As in all reflex syncope loss of consciousness is due to sympathetically mediated vasodilation and/or vagally mediated bradycardia. A peak in the incidence of vasovagal syncope is found in adolescence with a marked female preponderance.^{81,224} The natural history is extremely variable: some subjects experience only a single episode, while others have frequent episodes during their lives.⁸¹ Vasovagal syncope is probably unique for humankind as it does not appear to occur spontaneously in animals.²⁵⁰ It is unclear, however, how an external stimulus can elicit the vasovagal reflex, hereby causing a temporary cessation of the circulation. Although the efferent pathway of the vasovagal reflex (sympathetic withdrawal and/or vagal hyperactivity) is well understood, the afferent part remains elusive. Central hypovolemia appears to be the common physiological denominator of many triggers to vasovagal syncope. A classical example is initiation of the vasovagal reflex by the reduction of circulating volume by bloodletting. The Bezold-Jarisch reflex or the “empty heart” theory was for a long time the prevailing model to explain vasovagal syncope. The reflex loop includes venous pooling (preload reduction), activation of cardiac mechanoreceptors, transmission via C fibers (i.e., vagal afferents), central integration (nucleus of the tractus solitarius) and efferent discharge culminating in vasodilation or bradycardia, or both. However, apart from many experimental findings there are two important clinical observations that plead against the Bezold-Jarisch theory.⁹⁹ Firstly, the heart is usually not empty at the time of syncope; syncope may even occur without any decrease of cardiac chamber size, thus making the assumption of mechanical stimulation of ventricular walls very unlikely.¹⁸⁸ Secondly, the occurrence of vasovagal syncope after heart transplantation, i.e., in patients with ‘denervated’ hearts, raised serious doubts whether ventricular receptors are of importance to trigger syncope.^{74,181} Hence, mechanisms other than the activation of ventricular receptors may be implicated in the vasovagal response to hypovolemia. Baroreflex dysfunction or alterations in neurohumoral control may play a role, although firm data are still lacking.¹⁸³ Alternatively, the afferent part of the vasovagal reflex originates in the brain. In dogs, the stimulation of hypothalamic centres involved in the defence reaction has been found to evoke bradycardia and hypotension.¹³⁵ With the advent of fMRI the understanding of central autonomic pathways in humans has increased considerably the last few years. The dorsal anterior cingulate cortex has been identified as a distinct region modulating the sympathetic cardiovascular response to effortful cognitive tasks.⁶¹ Furthermore, more insight has been gained into the cortical network related to baroreceptor unloading. Baroreceptor unloading as induced by lower body

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negative pressure causes activation of the right superior posterior insula, the fronto-parietal cortices and the left cerebellum and disinhibition of the bilateral anterior insula, orbito-frontal cortices, amygdala, midbrain, mediodorsal nucleus of the thalamus and the dorsal anterior cingulate cortex.¹³³ The question remains however if and how these autonomic pathways are involved in vasovagal syncope.

The complexity of the vasovagal reflex may be explained by the fact that the hemodynamic and neurohumoral profiles in patients with vasovagal syncope appear to be extremely heterogeneous.^{65,78,225,259,261} For example, the hemodynamic changes associated with syncope have been found to differ between²⁶¹ but also within⁶⁵ age groups and even within subjects.²⁰⁵ Further insight into the heterogeneity of vasovagal reflexes may prove fruitful to elucidate their pathophysiology.

Historical considerations

In this section we will briefly review the history of syncope with an emphasis on the evolution of clinical descriptions. Accounts on syncope can be found throughout literature, such as in the verses of the medieval epos *la Chanson de Roland* cited at the beginning of the chapter. Several Shakespearean characters faint from strong emotions.¹⁰⁶ In the play *Love's Labour's Lost* Rosaline exclaims: "Help! Hold his brows! He will swoon. Why look you pale?", and in *As you like it* Oliver comments on Rosalind's fainting: "Many will swoon when they do look at blood".²¹⁵

But as may be expected given the frequent occurrence of syncope, the first accounts on syncope in medical literature date much further back. For instance, in the famous *Corpus Hippocraticum*, commonly attributed to Hippocrates of Kos (c. 460-377 B.C.), the following aphorism is found 'Οι εκλυόμενοι πολλάκις και ισχυρως ανευ φανερης προφάσιος εξαπίνης τελευτώσιν' 'Those who faint (literally 'loosen') frequently and severely without obvious cause die suddenly.'⁸ From a modern point of view this aphorism refers to cardiac syncope, since cardiac syncope frequently lacks an obvious trigger and is associated with a poor prognosis.^{29,41,130,176} Hence, Hippocrates' aphorism probably offered a concise notion of the unfavourable prognosis of cardiac syncope.^{130,176}

Galen (c. 129-200), a prominent Greek physician from Pergamon and a follower of the Hippocratic school, provided more detailed descriptions of syncope. An advocate of phlebotomy as a treatment for high fever, and a physician to gladiators, Galen saw numerous patients

with severe blood loss, causing either syncope or death. Galen favoured phlebotomy as he believed that bloodletting could 'slaughter' the fever by cooling down the body. He wrote:

*"It is appropriate to take patients in this condition as far as loss of consciousness. I have seen some of them, from the chilling that invariably accompanies fainting, sweat from the whole body and pass faeces, after which they quickly recover from their disease. It is good, however, to pay attention to the diminution of the pulse, feeling it while the blood is still flowing, as is usually done in all patients who are phlebotomised, so that you will never negligently cause your patient death instead of loss of consciousness."*²⁵

Galen explained syncope as 'the dissolution and deterioration of vital powers'.²²⁷ Galen was the first to describe the vagal nerve, which he labelled the sixth cranial nerve, and its long course from the brain to thoracic, abdominal organs and the heart. He believed that syncope was a sign that the heart was weakened by an abnormal irritation, which fits the concept of inappropriate cardioinhibition in reflex syncope remarkably well.²²⁷ Galen postulated that syncope resulted from mutual suffering ('sympathy') of the stomach and the heart through the vagal nerve.^{227,228} However, he also related syncope to humoral concepts, such as combusive processes in the left ventricle. In Galen's writings accounts of syncope can be found under various headings, including leiopsychia and lipothymia.²⁰⁷ For example, his description of leiopsychia resembles today's concept vasovagal syncope elicited by pain:

*"Pain compelling the soul to move, brings symptoms of great fear. For people are pale and cold, they shiver and tremble, they have weak or absent pulse, and finally they die... When these kind of affections bring death, it is not surprising that they also bring leiopsychia."*¹²³

In medieval times, medicine was predominantly practised on the basis of the teachings of the Ancient Greeks.¹⁹⁸ Hence, the Galenic concept of the heart as an organ of heat production and respiration held authority for fifteen hundred years.²²⁷ Galen's views were challenged in the Renaissance by a new concern for scientific inquiry particularly through dissections. William Harvey (1578-1657) pursued investigations into the operations of the heart and opposed Galen's views. In *Exercitatio anatomica de motu cordis et sanguinis in animalibus* Harvey set forth his revolutionary theory asserting that the heart acted like a pump that forced blood to move throughout the body in a circular manner.¹⁹⁸ Accordingly, Harvey established the relation between the slow pulse rate and reduced blood flow in syncope:

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“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.”¹⁸⁵

A similar concept of syncope was formulated by the Italian philologist and physician Geronimo Mercuriale (1530-1606):

“Ubi pulsus sit rarus semper expectanda est syncope.”¹⁵⁹

It was not until the Enlightenment that the practice of autopsy emerged in medicine, and more light was shed on the pathological substrate of syncope. Giovanni Battista Morgagni (1682-1771) pathologist and prosecutor to Antonio Valsalva (1666–1723) elaborated more specifically on the clinical symptoms of syncope in his famous treatise *De sedibus, et causis morborum per anatomen indagatis*. By relating clinical case studies with post mortem discoveries, Morgagni sharpened clinical reasoning regarding syncope. On a 28-year-old man with unexpected fainting and sudden death he comments:

“For whatever was the matter in which the beginning of the last attack came on, and however the head and the nerves might conspire hitherto, there is nothing which greatly forbids us to suppose that it ended in syncope: and this is confirmed by the succeeding paleness of the face, nor rendered less probable by the exit of the faeces and urine, inasmuch as the relaxation of the sphincters is also, sometimes, common to syncope. Without doubt a great disorder was found in the heart.”¹⁸⁰

Morgagni not only recognised the heart as a possible origin of syncope, but also pointed towards the stomach, probably influenced by Galen. In the case of a priest with frequent syncope upon standing and gastric pains, he questions:

“But whence did it happen, that he was seized with those faintings when he stood, rather than at other times? Was it because no situation of body tires a man more than standing? Or was it from the weight of the very large omentum drawing down the stomach more at that time, which was already weak?”¹⁸⁰

He further remarks:

“If in this man also I cannot explain the cause of them without bringing some mention of the nerves, since nothing was found except in the brain and at the stomach, which we may conjecture this cause to have been; and the nerves being compressed at their origin, or irritated in any other place, are very frequently, and very evidently, the cause of swoonings. This appears from the great number of faintings with which

Figure 1 Herman Boerhaave (1668 –1738) addressing a large audience at the University of Leiden. Boerhaave was a prominent scientific physician and medical teacher of the Enlightenment.¹³¹



persons are seized, when suddenly disturbed by certain passions of the mind, or affected by very ill smells, or seized with the most cruel pains of the nervous part, and particularly of the stomach."¹⁸⁰

Herman Boerhaave (1668 –1738) a Dutch physician of world fame, also known for his contributions to the field of botany and chemistry, put less emphasis on role of nervous irritation or

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compression in syncope (Figure 1). In his oration *De usu ratiocinii mechanici in medicina* Boerhaave, a great admirer of the works of Isaac Newton, viewed the body in terms of mechanical structures. On syncope he comments:

“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 thought, 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.”¹³¹

Since Boerhaave believed that knowledge of pneumatics and hydraulics was crucial to the understanding of syncope, he argued that syncope could be wholly explained by mechanics.

The development of the sphygmograph (1860; Marey), sphygmomanometer (1896; Riva-Rocci) and electrocardiograph (1901; Einthoven) forms a conceptual turning point in the history of syncope.^{164,198} Until then, syncope was commonly attributed to a slow pulse rate causing a decrease of cardiac output. The notion of the fall of blood pressure as an added phenomenon had to wait until the discovery of blood pressure and its regulation. The availability of simultaneous recordings of blood pressure and heart rate allowed to tie in clinical observations with physiological changes. The carotid sinus syndrome was first described by the Prague physiologist Czermak (1828-1873) in 1866.¹⁴⁰ Using Marey's (1830-1904) wrist sphygmograph he documented carotid sinus hypersensitivity in himself while rubbing his carotid artery. Contrary to current insight he assumed that he was directly stimulating the vagal nerve being unaware of the existence of carotid baroreceptors, only to be discovered in 1927.¹⁴⁰ In 1933, Weiss (1898-1942) and Baker (1913-) provided the first comprehensive description of the carotid sinus syndrome.²⁶⁴ The term “vasovagal” was first put forward by Sir William Gowers (1845-1915) in 1907.⁹⁰ 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. Surprisingly, loss of consciousness was not part of his constellation of symptoms, although Gowers included unconsciousness in his observations on syncope in *The borderland of epilepsy*.¹⁸⁴ However, Lewis refuted the lack of objective measures in Gowers' concept of vasovagal attacks and redefined the term along pathophysiological lines.^{59,151} Lewis put forward the concept of vasovagal syncope in its current meaning to denote the association of vasodilatation and vagally mediated bradycardia. Unlike Gowers, Lewis related his clinical observations on soldiers who suffered from 'an irritable heart' during Word War I to simultaneous recordings of heart rate and blood pressure, resulting in vivid case histories:

*"December the 18th, 1916. The patient was sitting, and a few c.c. of blood had just been withdrawn from a vein in the arm and the needle had been removed. He began to feel queer, as though his "stomach had turned upside down;" he became dizzy; pallor was noticed; his head fell forward to his knees. He was at once placed in a long easy chair and further observed. By this time the pallor was intense and he was restless. The pulse was imperceptible, the heart sounds were distant, the rate of beating being 50 per minute; the action was for the most part regular, a single premature beat being noted. From time to time there were retching movements; the pupils were little, if at all, dilated; he was limp, mentally confused or actually unconscious for several minutes. A heavy sweat broke out over the forehead and spread over the chest and body; the pallor remained extreme; respiration was slow and sighing. The pulse was imperceptible for several minutes; as it returned the systolic blood pressure was registered (palpatory and auscultatory) at 60 mmHg. A little later the pressure fell to 55 and then to 50, the pulse varying in rate between 50 and 60. Five minutes after the onset some recovery was noted, the pulse had risen to 64 and the blood pressure to 80."*⁵⁹

The former house-physician to Lewis and eminent physiologist, Sir Edward Peter Sharpey-Schafer (1908-1963), carried on the tradition of bedside medicine.⁵ As an excellent clinical investigator and teacher, Sharpey-Schafer captured the quintessence of syncope by translating complex physiological events into ordinary clinical language.²¹⁹ Sharpey-Schafer combined clinical observations with invasive continuous blood pressure measurements and this enabled him to unravel the underlying mechanisms of various forms of syncope.²¹⁹ For example, until the advent of continuous blood pressure recordings, loss of consciousness from coughing was

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thought to be a form of epilepsy. Among his famous lectures at the Salpêtrière, Jean-Martin Charcot (1825-1893), the founder of modern neurology, coined these seizures *vertige laryngé*.⁴⁵ However, the documentation of the hemodynamic changes during loss of consciousness provided a definite proof for its syncopal nature.¹⁷⁰ Sharpey-Schafer further elaborated on cough syncope and attributed syncope to a decrease of vascular resistance, a theory that still holds sway.^{139,217} Other examples include his studies on the circulatory effects of dental instrumentation,²²⁰ hemorrhage,¹² trumpet playing,⁷³ squatting,²¹⁸ and the fainting lark or ‘mess trick’ (a procedure to voluntarily induce syncope).¹¹⁵

A final milestone in the history of syncope was reached in the late 1970s when the non-invasive beat to beat blood pressure monitor was first introduced. The Finapres or volume-clamp technique was invented by Jan Peñaz and further developed by Karel Wesseling.¹¹⁷ This technological breakthrough formed a great impetus to physiological research and became a key instrument to investigate the circulation in almost any setting, even including space.⁷⁰ Non-invasive blood pressure monitoring did not only open new scientific avenues, but also enabled physicians to refine the clinical assessment of syncope. Ictal continuous blood pressure monitoring became an important tool to differentiate syncope from other conditions associated with real or apparent loss of consciousness and improved the clinical recognition of syncope due to rapid circulatory changes such as initial transient orthostatic hypotension. The availability of non-invasive continuous blood pressure monitoring thus hallmarks the advent of integrative physiology in clinical practice.

Aims of the thesis

Part I. Terminology of syncope

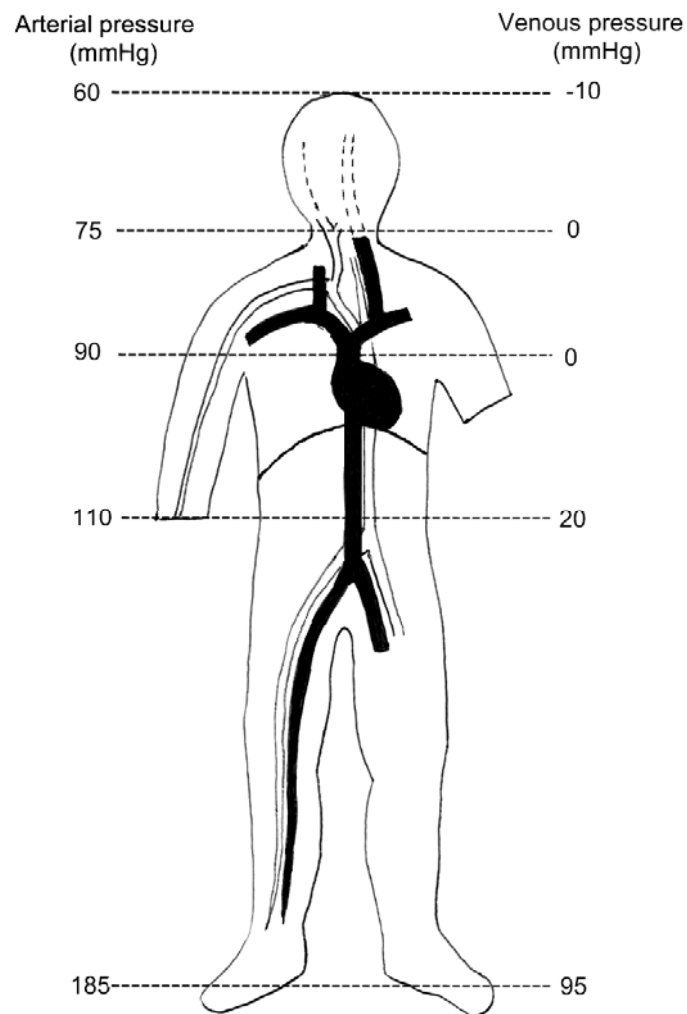
Various terms which may designate syncope are in use in everyday language, including, among many, in English *fit*, *faint*, *funny turn*, *funny do*, *swoon*, *blackout* or in the French language *petite mort*, *pâmoison*, *défaillance*, *évanouissement*, *perte de connaissance* and *tomber dans les pommes*.⁸⁴ The medical term syncope is derived from the ancient Greek verb ‘συγκόπτειν’ (syn-koptein) meaning ‘to cut short’, or probably more appropriately in this context ‘to interrupt’. Although syncope is most accurately defined as transient, brief and self-limited loss of consciousness due to global cerebral hypoperfusion,²⁹ less precise definitions are also common in the medical literature.^{e.g.15,22,38,48} Usually in such cases ‘syncope’ is defined as synonymous with transient loss of consciousness. The omission of the patho-

physiology of syncope causes such definitions of 'syncope' to include various forms of epilepsy, concussion, hypoglycaemic attacks, or subarachnoid haemorrhage. The inevitable risk is imprecise understanding of not only the pathophysiologic basis of syncope and related conditions but also their epidemiology and appropriate diagnostic evaluation. The aim of this part of the thesis is to investigate the scale of this problem. Chapter 1 systematically reviews definitions of syncope and related disorders in medical literature. The terms in use designating transient loss of consciousness in a Dutch emergency ward are evaluated in Chapter 2. In view of these findings a proposal of a pathophysiological classification of syncope is made in Chapter 3.

Part II. Orthostatic fluid shifts

Upon standing 300 – 1000 ml of blood shifts to the lower parts of the body.^{168,230,257} The time course of orthostatic fluid shifts is characterised by a first fast increase due to filling of veins caused by a rise in hydrostatic pressure and a second slow phase due to fluid filtration through capillary walls.^{7,31,230} Gravitationally induced fluid shifts contribute to the marked differences in pressure in the body upon standing, with a substantial increase in arterial pressure below the heart and a decrease above it (Figure 2).⁹⁸ Despite these pressure changes, mean arterial pressure at the level of the neck is maintained in healthy humans mainly through rapidly acting neural reflex mechanisms causing constriction of the capacitance vessels.²⁷² In autonomic failure these systems fail and hypotension occurs upon standing. Orthostatic hypotension in autonomic failure is commonly ascribed to defective arterial vasoconstriction.²³⁰ In addition, excessive venous pooling is assumed to contribute to orthostatic hypotension. In spite of the attractive nature of the fluid shift hypothesis, evidence about the amount of venous pooling in the lower limbs in autonomic failure is contradictory. The aim of this part of the thesis is to evaluate the amount of orthostatic pooling in autonomic failure. In Chapter 4 a new non-invasive method is described to assess orthostatic fluid shifts. With this newly described method the amount of orthostatic pooling in patients with autonomic failure is compared with that of healthy controls in Chapter 5.

Figure 2 Arterial and venous pressures in an upright, motionless human. Gravitationally induced fluid shifts contribute to the marked differences in pressure in the body upon standing, with a substantial increase in arterial pressure below the heart and a decrease above it. Reproduced with permission from Hainsworth.⁹⁹



Part III. Effects of hyperventilation

Hyperventilation is frequently listed as one of the causes of syncope,^{15,48,129} but there is in fact no clear evidence that hyperventilation by itself can induce syncope.²⁹ Hyperventilation can indeed be involved in the chain of events preceding syncope,^{42,154,167} but its role is unclear: some authors have suggested that hyperventilation contributes to syncope,^{42,142} whereas others favoured a protective role.^{154,167} The aim of this part of the thesis is to elucidate the effects of hyperventilation on syncope and blood pressure control. In Chapter 6 the question is posed whether prolonged hyperventilation can cause syncope in healthy subjects. Chapter 7 elaborates on the effects of hyperventilation on blood pressure regulation as the reported effects of hyperventilation on blood pressure are conflicting: hyperventilation has been found to increase blood pressure,²⁴⁷ to reduce blood pressure,^{9,107,201} or to leave blood pressure unaffected.^{125,147,226} In order to identify factors affecting the blood response to hyperventilation, we dissected the effects of hypocapnic hyperventilation and isocapnic hyperventilation and evaluated the effects of acute vs. prolonged hyperventilation. Chapter 8 ties findings of the preceding chapters together by evaluating the potential of respiratory countermanoeuvres to combat orthostatic hypotension in autonomic failure.

Part IV. Clinical studies

This part contains various clinical studies. Chapter 9 describes a population-based study examining the association between migraine and syncope and related symptoms. Chapter 10 discusses the value of the eyewitness account in the evaluation of transient loss of consciousness, since, in contrast to the field of criminology, little is known about the accuracy of these observations in a medical context. Chapter 11 describes a patient with pure autonomic failure with stress-related complaints, probably through hypocapnia mediated hypotension. In Chapter 12 we discuss water drinking as a potential treatment for idiopathic exercise-related syncope. In Chapter 13 a patient is presented with rapidly sequential vasovagal syncope. Inspired by the similar occurrence of repeated epileptic seizures, the attacks are labelled a 'status vasovagalis'.

