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ESC GUIDELINES

Practical Instructions for the 2018 ESC Guidelines for the diagnosis and management of syncope

The Task Force for the diagnosis and management of syncope of the European Society of Cardiology (ESC)

Endorsed by: European Academy of Neurology (EAN), European Federation of Autonomic Societies (EFAS), European Federation of Internal Medicine (EFIM), European Union Geriatric Medicine Society (EUGMS), European Society of Emergency Medicine (EuSEM)

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Authors/Task Force Members: Michele Brignole* (Chairperson) (Italy), Angel Moya* (Co-chairperson) (Spain), Frederik J. de Lange (The Netherlands), Jean-Claude Deharo (France), Perry M. Elliott (UK), Alessandra Fanciulli (Austria),

*Corresponding authors: Michele Brignole, Department of Cardiology, Ospedali Del Tigullio, Via Don Bobbio 25, IT-16033 Lavagna, (GE) Italy. Tel: +39 0185 329 567, Fax: +39 0185 306 506, Email: mbrignole@asl4.liguria.it; Angel Moya, Arrhythmia Unit, Hospital Vall d'Hebron, P Vall d'Hebron 119-129, ES-08035 Barcelona, Spain. Tel: +34 93 2746166, Fax: +34 93 2746002, Email: amoyamitjans@gmail.com.

ESC Committee for Practice Guidelines (CPG) and National Cardiac Societies document reviewers: listed in the Appendix.
[1]Representing the European Academy of Neurology (EAN)
[2]Representing the European Society of Emergency Medicine (EuSEM)
[3]Representing the European Academy of Neurology (EAN)

ESC entities having participated in the development of this document:
Associations: European Heart Rhythm Association (EHRA)
Councils: Council on Cardiovascular Nursing and Allied Professions, Council for Cardiology Practice, Council on Cardiovascular Primary Care
Working Groups: Myocardial and Pericardial Diseases

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Document Reviewers: Adam Torbicki (CPG Review Coordinator) (Poland), Javier Moreno (CPG Review Coordinator) (Spain), Victor Aboyans (France), Stefan Agewall (Norway), Riccardo Asteggiano (Italy), Jean-Jacques Blanc (France), Natan Bornstein[1] (Israel), Serge Boveda (France), Héctor Bueno (Spain), Haran Burri (Switzerland), Antonio Coca (Spain), Jean-Philippe Collet (France), Giorgio Costantino[2] (Italy), Ernesto Díaz-Infante (Spain), Victoria Delgado (The Netherlands)Faas Dolmans (The Netherlands), Oliver Gaemperli (Switzerland), Jacek Gajek (Poland), Gerhard Hindricks (Germany), Josef Kautzner (Czech Replublic), Juhani Knuuti (Finland), Piotr Kulakowski (Poland), Ekaterini Lambrinou (Cyprus), Christophe Leclercq (France), Philippe Mabo (France), Carlos A. Morillo (Canada), Massimo Francesco Piepoli (Italy), Marco Roffi (Switzerland), Win K. Shen (USA), Iain A. Simpson (UK), Martin Stockburger (Germany), Peter Vanbrabant[3] (Belgium), Stephan Windecker (Switzerland), and Jose Luis Zamorano (Spain)

The disclosure forms of all experts involved in the development of these Guidelines are available on the ESC website http://www.escardio.org/guidelines.

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Web Contents: Web Practical Instructions

1. Practical Instructions for section 3.1: glossary of uncertain terms

The literature on syncope and associated conditions can be confusing because of a lack of consistency. The meaning of some terms has become obscured, and new terms were introduced to compete with older, often equally adequate ones. Regional differences exist in the interpretation of various words. This glossary is provided to clarify the nomenclature and improve consistency with the European Society of Cardiology (ESC) definitions of syncope and related concepts.

1.1 Blackout

The word 'blackout' seems to be used mostly in the UK, where it corresponds with transient loss of consciousness (TLOC)—as in the ESC sense—as proven by the title of the UK National Institute for Health and Care Excellence guideline: "*Transient loss of consciousness ("blackouts") in over 16s (CG109)*". In the introduction, the authors state that the medical term for 'blackout' is TLOC.

'Blackout' suggests that it has an origin in the loss of vision that people may experience just before unconsciousness in syncope. The fact that retinal hypoperfusion can be noticed suggests that retinal function is lost ahead of cerebral function, due to intracranial pressure or other retinal perfusion characteristics. Such loss of vision does not occur in other TLOC causes and is not universal in syncope, so blackout in its literal sense does not fit syncope or TLOC well.

- Blackout is too regional and imprecise to be used in a scientific setting; however, it may be useful in communication with patients.

1.2 Breath-holding spells

Breath-holding spells concern attacks of TLOC in infants. Two types are usually recognized: pallid and cyanotic. The pallid type concerns bradycardia or asystole triggered by fear and pain,[1] so these attacks represent cardioinhibitory vasovagal syncope (VVS). There is no appreciable contribution of respiration to the pathophysiology of these attacks.[1] Hence, for pallid breath-holding spells, the name 'breath holding' is a misnomer. In the cyanotic type, respiration plays a crucial role: attacks start with the child being hurt or startled, after which respiration ceases in expiration.[2] The circulation may become impaired secondarily, in turn causing unconsciousness. This unique pathophysiological pattern is not known in older children or adults. Both pallid and cyanotic types may occur in the same child, implying a susceptibility towards abnormal autonomic reflex activity, either inhibiting the circulation or the respiration.

The term 'breath holding' may be taken to mean that children do so voluntarily, which is not the case in these two forms. Some

children may hold their breath voluntarily, but it is almost certainly impossible to lose consciousness this way.

- Pallid breath-holding spells concern cardioinhibitory VVS in small children; respiration is not involved in the pathophysiology. Instead of breath-holding spells, terms such as cardioinhibitory VVS are advocated to reduce confusion.
- Cyanotic breath-holding spells represent a unique form of TLOC in small children in which a reflex action produces involuntary expiratory apnoea followed by secondary circulatory events.

1.3 Convulsive syncope

Convulsion means violent contractions of muscles; in neurological terminology, an individual abrupt involuntary movement is called myoclonus. Myoclonus in syncope occurs when the electroencephalogram (EEG) is slow but not flat.[3] Myoclonus occurs often enough in syncope to state that the mere presence of myoclonus is not sufficient evidence for an epileptic seizure. That distinction instead depends on the synchrony, rhythmicity, and probably the number of the movements: in syncope, there are few such movements and many (20–100) in generalized seizures.

- The term convulsive syncope does not imply epileptic seizures. The presence of myoclonus in syncope does not imply severe hypoperfusion or any specific cause for syncope, so adding the word convulsive to syncope has no clear advantage.

1.4 Drop attacks

The term 'drop attacks' may be used as a description of sudden falls, occurring without clear warning signs or symptoms and without an obvious external cause such as stumbling over an object. Patients may describe a fall as a 'drop attack'; usually they have no awareness of loss of consciousness (LOC). Such episodes should be classified as unexplained or non-accidental falls rather than drop attacks.

In the purely descriptive sense, drop attacks do not imply any specific cause. However, the term is also used for no less than three specific disorders: in epilepsy it can be used to describe atonic seizures; in Menière's disease it may be used for sudden falls without vertigo; and one variant describes a specific syndrome of unknown origin in which middle-aged and elderly women suddenly fall while walking, usually to their knees, without LOC.[4]

- The term 'drop attack' may be used as a non-specific descriptor of falls but does not constitute a diagnosis.
- In the context of falls, the term 'unexplained' or 'non-accidental falls' is preferred over 'drop attacks'.
- The term 'drop attacks' can be used to indicate a specific form of falling occurring in middle-aged and elderly women[4] for whom no other term seems appropriate.

1.5 Dysautonomia/dysautonomic

When used as part of 'familial dysautonomia' (Riley–Day syndrome), the term has a specific and clear meaning. However, beyond that context, dysautonomia is used for any abnormal function of the autonomic nervous system, bundling fundamentally different disorders such as neurogenic orthostatic hypotension (OH), reflex syncope, and postural orthostatic tachycardia syndrome (POTS). In some contexts, the word is reserved for a subset of the disorders encompassing autonomic medicine, i.e. disorders causing neurogenic OH.

- 'Dysautonomia' has a clear place in the term 'familial dysautonomia' (Riley–Day syndrome).
- For scientific use, specific terms indicating disorders or groups of disorders that share a common pathophysiology are preferred over the non-specific term 'dysautonomia'.
- Disorders characterized by an abnormally decreased function of the autonomic nervous system, mostly causing neurogenic OH, are preferably labelled 'autonomic failure'.

1.6 Faint

The noun 'faint' may be a colloquial synonym for 'syncope', but in that context, is probably used more often for VVS than for 'syncope regardless of cause'. The verb 'to faint' has the same connotations.

- The verb 'to faint' and noun 'faint' are too imprecise to be used in a scientific context, but may be useful to facilitate communication with patients.

1.7 Hyperventilation syncope

The role of hyperventilation in syncope is complex: hyperventilation reduces cerebral blood flow through vasoconstriction, but also (through negative intrathoracic pressure) increases venous return with positive effects. The net effect on the systemic and cerebral circulation in various causes of syncope is imperfectly known. Note that the term 'hyperventilation syndrome' is included in the Diagnostic Statistical Manual Fifth Edition, but the symptoms are much closer to panic attacks than to syncope. Hence, emotional and circulatory effects linked to hyperventilation may play a role in evoking syncope, but there is too little evidence to regard hyperventilation as the major cause.

- There is no reason to recognize 'hyperventilation syncope' as a specific entity.

1.8 Neurally mediated syncope

Neurally mediated syncope is a synonym for 'reflex syncope'. Like 'reflex syncope', it emphasizes the role of the autonomic nervous system in the disruption of normal circulatory control. Unlike 'reflex syncope', it does not emphasize the role of a trigger in eliciting syncope. Note that syncope due to OH might literally also fit the phrase 'neurally mediated syncope'; in practice, it is reserved for reflex syncope.

- Neurally mediated syncope is accepted as a synonym of reflex syncope.

1.9 Neurocardiogenic syncope

The term neurocardiogenic syncope occurs in the literature either as an alternative for reflex syncope or for VVS, making it ambiguous. The term 'vasovagal' is older, simpler, more common, and more apt, as it stresses both the vasodepressive ('vaso. . .') and cardioinhibitory ('. . .vagal') effector pathways. Reflex syncope is preferred over 'neurocardiogenic' for similar reasons. Moreover, the word 'neurocardiogenic' does not clearly indicate what the 'neuro' and 'cardio' parts represent; the term apparently ignores the vasodepressive mechanism.

- There is no need for more synonyms for reflex syncope or VVS, so 'neurocardiogenic' should be replaced by one of these terms.

1.10 Neurological syncope

The phrase 'neurological syncope' is rarely defined. When encountered, its use suggests that 'syncope' was not used in the ESC sense but in a much wider sense, probably corresponding to TLOC. Although the autonomic nervous system is involved in reflex syncope, syncope due to OH, and even in cardiovascular syncope, there is no need to label any expression of this involvement as 'neurological'.

- There is no need for the term 'neurological syncope'; specific terms should be used instead.

1.11 Postural orthostatic tachycardia syndrome

POTS is also called 'postural tachycardia syndrome'. The word 'postural' is not limited to any specific posture, whereas 'orthostatic' specifically means standing upright (originating from the Greek words for upright and standing). There is little chance of misunderstanding, as the abbreviations of both forms of the name are 'POTS' (sometimes 'PoTS'), and all descriptions and definitions stress standing as a factor provoking complaints and tachycardia.

- As 'orthostatic' in POTS stresses the upright position, this variant is preferred over 'postural tachycardia syndrome'.

1.12 Psychogenic syncope

Patients may exhibit signs of unconsciousness even when somatic brain function is normal. Spells of apparent unconsciousness without gross body and limb movements are most often called 'psychogenic pseudosyncope' (PPS). The term stresses what the attacks look like (i.e. syncope) but are not (i.e. pseudo), while stating their origin (i.e. psychogenic). During such attacks, there is no cerebral hypoperfusion, so 'syncope' is incorrect.

- The term psychogenic syncope is pathophysiologically incorrect. PPS is the preferred term for the form of psychogenic TLOC that outwardly resembles syncope.

1.13 Reflex anoxic seizure

The term 'reflex anoxic seizure' designates syncopal attacks in infants, particularly those with myoclonus. The use of 'seizure' in 'reflex anoxic seizures' was not intended to imply epilepsy, but only to describe an attack without any specific pathophysiological connotations. However, for many, the word seizure is strongly associated with epilepsy. As such attacks in children are often mistaken for epilepsy through superficially similar signs, their terminology should prevent confusion as much as possible. Also see 'breath-holding spells'.

- The phrase 'reflex anoxic seizures' denotes reflex syncope in small children. To avoid confusion with epileptic seizures, specific terms such as 'VVS in infants' are preferred.

1.14 Seizures

For some, the word seizure refers to attacks that may include epilepsy as well as syncope. The term 'psychogenic non-epileptic seizures' (PNES) also suggests that seizures are not limited to epileptic seizures. Still, for many people, seizures suggest epileptic attacks. If the meaning is ambiguous, there is a risk of mistaking syncope for epilepsy.

- To avoid confusion between syncope and epileptic seizures, it is best not to use 'seizure' in a wide sense that includes syncope.
- Use of the term 'epileptic seizures' is advocated whenever confusion is possible.

1.15 Vasodepressor/vasodepressive syncope

In the older literature, the term 'vasodepressor/vasodepressive syncope' was used as an alternative for VVS. The distinction between the two effector pathways of reflex syncope means that its current meaning is restricted to one such pathway, the other being cardioinhibitory. Note that 'vasodepressor' in the context of reflex syncope refers to an abnormal decrease of sympathetic vasoconstriction, the effect of which is vasodilatation.

- 'Vasodepressor' is best used to denote a pathophysiological mechanism of reflex syncope, and 'vasodepressor syncope' only for reflex syncope without bradycardia.

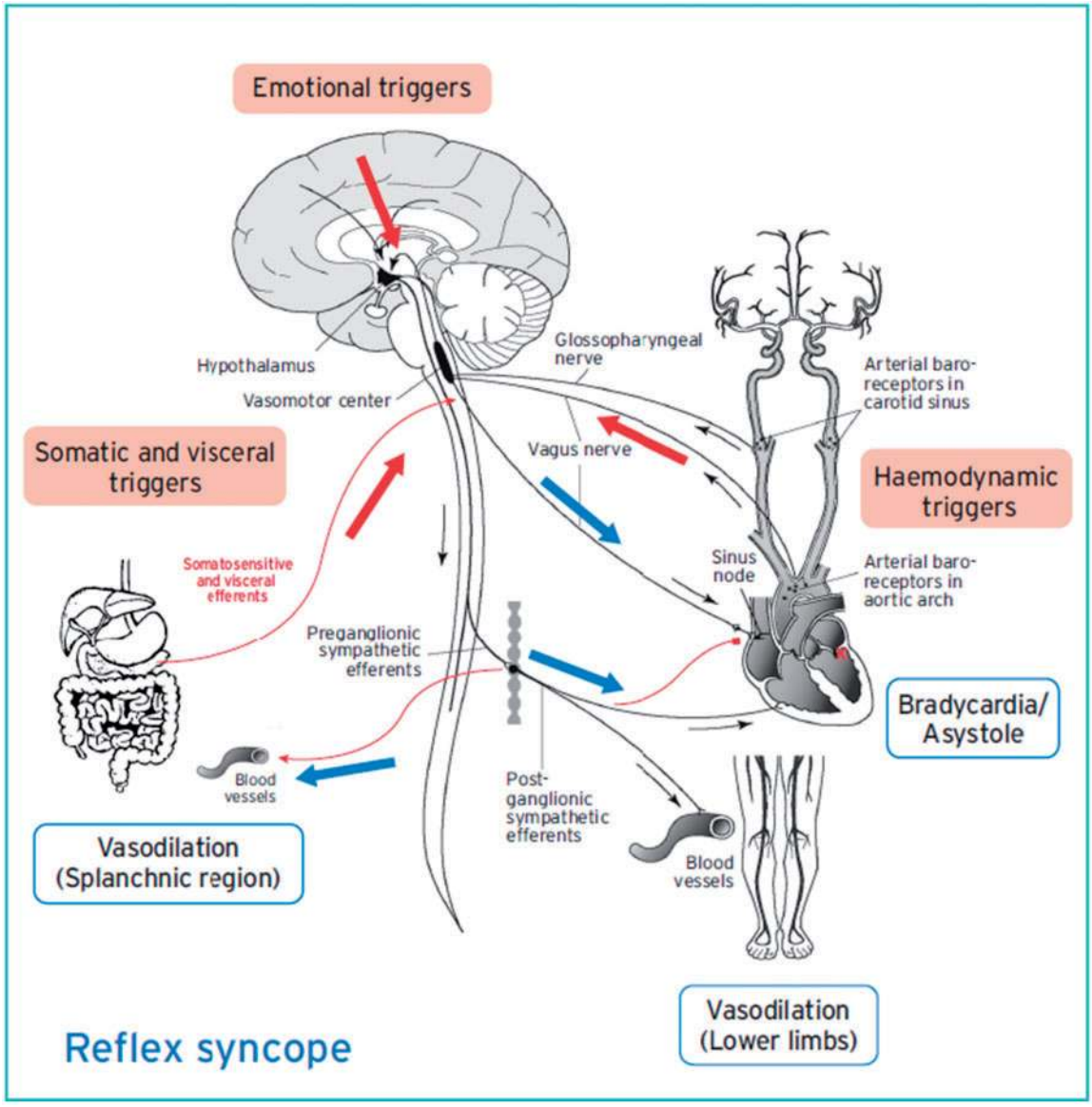
2. Practical Instructions for section 3.2.: classification, pathophysiology, epidemiology, prognosis, quality of life, and costs

2.1 Pathophysiology

2.1.1 Reflex syncope

In reflex syncope, the afferent pathways (shown in red in *Web Figure 1*) transfer information from the circulatory and visceral receptors to the brain. Haemodynamic instability (evidenced by central hypovolaemia, hypotension, and/or tachycardia), gastrointestinal symptoms, pain, and other triggers can activate the reflex. Higher brain functions such as emotional triggers can also facilitate activation of the reflex or trigger it directly. The main efferent components of the reflex (shown in blue in *Web Figure 1*) are bradycardia or asystole, as well as dilation of capacitance vessels in the splanchnic region and lower limbs, with consequent hypotension. The combination of vasodepressive effects and bradycardia to varying degrees results in manifestations such as vasodepressor, cardioinhibitory, or mixed reflex syncope.

Most episodes of syncope occur in the upright posture. Basic to the understanding of syncope is the concept of central blood volume (i.e. the reservoir of blood available in the four cardiac chambers and in the pulmonary and great thoracic vessels). A low central blood volume due to venous pooling below the diaphragm is a main causative factor in syncope, as the heart can never pump out more blood than flows in.[5] The key circulatory adjustments to the upright posture are the constriction of arterioles and venous capacitance vessels in the splanchnic area, and an increase in skeletal and abdominal muscle

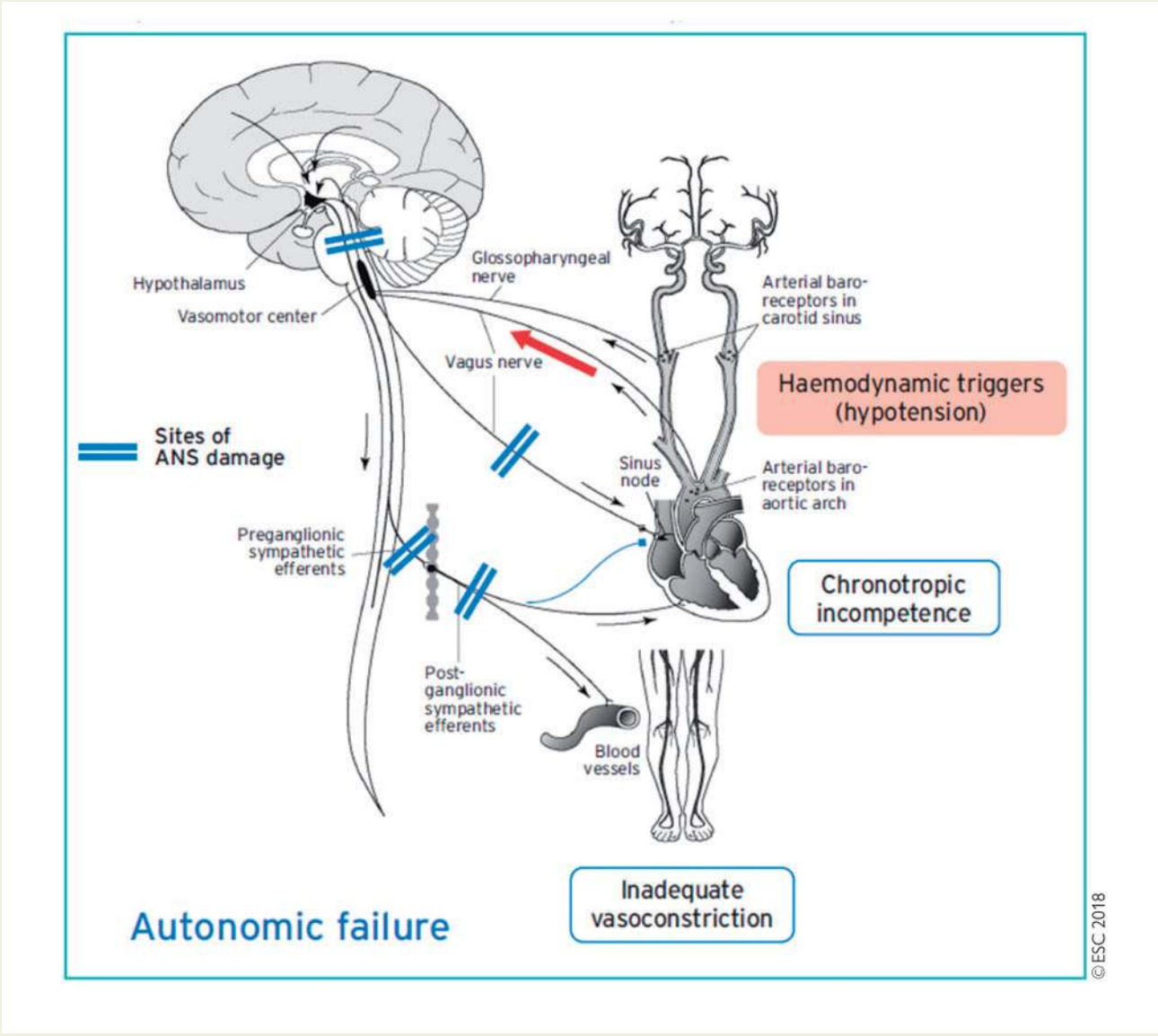


Web Figure 1 The mechanism of reflex syncope: anatomical view. Afferent pathways (shown in red) transfer information from the circulatory and visceral receptors to the brain. Arterial baroreceptors are in the aortic arch and the carotid sinus; these are stretch receptors that are activated when distended 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 are bradycardia/asystole, and the dilation of vasoconstrictor vessels and capacitance vessels in the splanchnic bed.

tone causing an increase in venous return. Control of vasomotor function by the arterial baroreflex is the key in rapid hemodynamic adjustments to the upright posture.

The pathophysiology of orthostatic VVS deserves mention. In it, syncope is preceded by a period of 4–6 min in which the blood pressure (BP) is unstable and decreases slightly.[6] Baroreceptor malfunctioning may disorganize the discharge activity of vascular sympathetic fibres, thus leading to ineffective vasoconstrictor activity before syncope.[7] This is caused by a progressive decrease in cardiac output, presumably due to venous pooling of blood below the diaphragm. The decrease in cardiac output is more important than the decrease in total peripheral resistance, which does not decrease in all subjects and may even increase.[6,8–11] Peripheral resistance may only decrease before syncope in vasodepressive but not 'pure' cardioinhibitory syncope.[12] These progressive circulatory changes finally trigger the reflex in which cardioinhibition and vasodepression (i.e. vasodilatation) play their role.[13–15]

Finally, efferent mechanisms other than simple sympathetic inhibition may account for reflex syncope, including the recently suggested



Web Figure 2 The mechanism of autonomic failure (orthostatic hypotension). The afferent pathway (shown in blue) transfers information from the arterial baroreceptors in the carotid arteries and aortic arch to the vasomotor centre in the medulla oblongata. The efferent pathway (shown in red) regulates two basic cardiovascular responses: heart rate and vascular tone. ANS = autonomic nervous system; HR = heart rate.

increased activity of the norepinephrine transporter protein. This would clear noradrenaline more rapidly, reducing vasoconstriction.[16]

2.1.2 Orthostatic hypotension and other syndromes of orthostatic intolerance

In syncope due to OH, functional and structural impairments of the autonomic nervous system lead to an inadequate increase in peripheral resistance and heart rate (HR) upon standing. In primary and secondary autonomic failure, cardiovascular sympathetic fibres are unable to increase total peripheral vascular resistance in the upright posture. Gravitational stress, in combination with vasoconstrictor, chronotropic, and inotropic failure, results in venous pooling of blood below the diaphragm and a decrease in venous return and carbon dioxide, resulting in a low BP.

Web Figure 2 depicts the afferent pathway (shown in red), which transfers information from the arterial baroreceptors in the carotid arteries and aortic arch. The information reaches the vasomotor centre in the medulla oblongata. The efferent pathway (shown in blue) regulates two basic cardiovascular responses: HR and vascular tone. An increase in vascular tone is key, the HR increase is not an important contributor. Degeneration of autonomic nuclei within the central nervous system and/or peripheral autonomic denervation may lead to the hallmark of autonomic failure, OH, and finally syncope.[17]

The circulatory autonomic causes of orthostatic intolerance include classical OH, initial OH, delayed OH, POTS, and VVS, which in this context can be called orthostatic VVS.[18,19] Syndromes of orthostatic intolerance that may cause syncope are presented in *Web Table 1*.

Web Table 1 **Syndromes of orthostatic intolerance that may cause syncope**

Syndrome	Ancillary test for diagnosis	Time from upright position to abnormal BP response	Pathophysiology	Most frequent symptoms	Most frequent associated conditions
Initial OH	Beat-to-beat BP on active standing test (lying to standing)	0–15 seconds	Transient mismatch between cardiac output and total peripheral resistance	Light-headedness, dizziness, visual disturbances a few seconds after standing up (syncope rare)	Young, asthenic subjects; old age, drug-induced (alpha-blockers)
Classical OH	Active standing test; TTT	<3 minutes	Impaired increase in total peripheral resistance and HR in autonomic failure resulting in pooling of blood; alternately, severe volume depletion	Dizziness, light-headedness, fatigue, weakness, visual and hearing disturbances,	Frailty, drug-induced (any vasoactive drugs and diuretics), autonomic failure, hypovolaemia
Delayed OHsometimes followed by reflex syncope	TTT; active standing test	>3 minutes	Pathophysiology uncertain. Progressive fall in venous return and low cardiac output are likely	Prolonged prodromes (dizziness, light-headedness, fatigue, weakness, visual and hearing disturbances, low back pain, neck or precordial pain) that may be followed by reflex syncope	Frailty, incipient autonomic failure, drug-induced (any vasoactive drugs and diuretics), comorbidity
Orthostatic vasovagal syncope	TTT	Usually prolonged standing	Vasovagal reflex due to progressive pooling of blood with final vasodepressive and/or cardioinhibitory pathways, often preceded by autonomic activation	Autonomic activation (nausea, pallor, sweating) precedes syncope	More common in women. Orthostatic VVS may be associated with chronic orthostatic intolerance
POTS	Active standing test; or TTT	<10 minutes Abnormal HR response	Inappropriate HR increase without concomitant BP fall. Likely mechanisms: severe deconditioning, immune-mediated processes, excessive venous pooling and hyperadrenergic state.	Orthostatic intolerance (light- headedness, palpitations, tremor, weakness, blurred vision, and fatigue). Syncope is rare and usually elicited by vasovagal reflex activation.	Young women overrepresented, recent infection or trauma, joint hypermobility syndrome

BP = blood pressure; HR = heart rate; OH = orthostatic hypotension; POTS = postural orthostatic tachycardia syndrome; VVS = vasovagal syncope; TTT = tilt-table test.

- Classical OH is defined as a sustained decrease in systolic BP ≥20 mmHg, diastolic BP ≥10 mmHg, or a sustained decrease in systolic BP to an absolute value <90 mmHg within 3 min of active standing or head-up tilt of at least 60 degrees.[18] In cases of supine hypertension, a systolic BP drop ≥30 mmHg should be considered. Orthostatic HR increase is blunted in neurogenic OH [usually <10 beats per minute (b.p.m.)], because autonomic HR control is impaired. In contrast, the orthostatic HR increase is preserved, or even enhanced, in OH due to hypovolaemia. Classical OH may be symptomatic or asymptomatic. Symptoms depend more on the absolute BP level than the magnitude of the fall.[20] Their occurrence likely also depends on a key role of cerebral autoregulation.[21] The severity of symptoms varies widely among patients, which has therapeutic implications. Classical OH is associated with increased mortality and cardiovascular disease prevalence.[22]
- Initial OH is characterized by a BP decrease on standing of >40 mmHg for systolic BP and/or >20 mmHg for diastolic BP within 15 s of standing.[18] BP then spontaneously and rapidly returns to normal, so the period of hypotension and symptoms is short (<40 s) but may still cause syncope. Recent findings indicate that the rate at which BP climbs after an initial fall on standing up has important prognostic consequences: impaired recovery represents a negative prognostic factor in the elderly.[23,24]
- Delayed OH is defined as OH occurring beyond 3 min of head-up tilt or active standing.[18] It is characterized by a slow progressive decrease in BP. The absence of bradycardia helps to differentiate delayed OH from reflex syncope. However, the progressive

decrease in central blood volume caused by delayed OH may induce reflex syncope. Delayed OH is not uncommon in elderly persons, in whom it is attributed to stiffer hearts, sensitive to a decrease in preload and impairment of compensatory vasoconstrictor reflexes.[17,25] It may also represent a mild form of classical OH, especially if associated with Parkinsonism or diabetes.[26,27]

- POTS: some patients, mostly young women, present with severe orthostatic intolerance (light- headedness, palpitations, tremor, generalized weakness, blurred vision, and fatigue) and a marked orthostatic HR increase (>30 b.p.m., or >120 b.p.m. within 10 min of standing or head-up tilt in the absence of OH. In patients of 12–19 years of age, HR increase should be >40 b.p.m.[18] VVS may sometimes follow. POTS is frequently associated with deconditioning, recent infections, chronic fatigue syndrome, joint hypermobility syndrome, and a spectrum of non-specific symptoms such as headache and chest pain. The pathophysiology is debated and likely heterogeneous: deconditioning, immune-mediated processes, excessive venous pooling, and a hyperadrenergic state have been proposed.[28,29]

The BP fall of orthostatic VVS differs from that in classical OH. In VVS the BP drop starts several minutes after standing up and the rate of BP drop accelerates until people faint, lie down, or do both. Hence, low BP in orthostatic VVS is short-lived. In classical OH, the BP drop starts immediately on standing and the rate of drop decreases, so low BP may be sustained for many minutes.[30]

History taking in patients with orthostatic intolerance may reveal the following:[28,31]

(1) Dizziness, light-headedness, weakness, fatigue, and or lethargy.
(2) Palpitations (may refer to abnormal beats in cardiac syncope, but also to sinus tachycardia in reflex syncope, OH, and POTS).
(3) Pallor, sweating, and/or nausea: autonomic activation (reflex syncope).
(4) Pain in the neck and shoulder region (coat hanger pain), low back pain, or precordial pain (classical OH, mostly autonomic failure).
(5) Hearing disturbances: impaired hearing, crackles, tinnitus, and/or sounds as if from a distance (all causes).
(6) Visual disturbances: blurring, enhanced brightness, loss of colour, tunnel vision, and finally loss of vision (all causes).
(7) Syncope.

These symptoms typically develop upon standing, are relieved by sitting or lying, and may be worse in the morning, with heat exposure, and after meals or exertion.

2.1.3 Cardiac syncope

Primary bradyarrhythmias such as sick sinus syndrome, atrioventricular (AV) block, and tachyarrhythmias (supraventricular or ventricular) are the most common causes of cardiac syncope. Patients with structural heart disease (myocardial infarction or hypertrophic cardiomyopathy) may also present with syncope, usually due to arrhythmia. Pulmonary embolism is a frequently underdiagnosed cause in patients hospitalized for syncope.[32]

2.1.3.1. Arrhythmias

Arrhythmias are the most common cardiac cause of syncope. They all cause syncope through a critical decrease in cardiac output, but there are multiple contributory factors: the type of arrhythmia (supraventricular or ventricular), ventricular rate (too low or too high), left ventricular (LV) function, posture, and adequacy of vascular compensation. The latter includes baroreceptor-mediated vasoconstrictor reflexes induced by a sudden hypotension.[33,34]

In sick sinus syndrome, the sinoatrial node is dysfunctional, either because of abnormal automaticity or sinoatrial conduction abnormalities. In this situation, syncope is due to long pauses caused by sinus arrest or sinoatrial block and a failure of the escape mechanism, and may also be reflex in origin.[35]

As a rule, severe forms of acquired AV block (Mobitz II block, 'high grade', and complete AV block) are most closely related to syncope. In these cases, the cardiac rhythm may become dependent on subsidiary or escape (often unreliable) pacemaker sites such as nodal or idioventricular rhythm.

Syncope or presyncope may occur at the onset of paroxysmal tachycardia, before vascular compensation develops.[33,34] Consciousness is, in general, restored before tachycardia terminates, but unconsciousness may persist, especially when ventricular rate is high or ventricular activity is ineffective.

Several drugs can cause bradyarrhythmias and tachyarrhythmias. Drugs prolonging the QT interval may promote torsade de pointes in association with bradycardia and pauses [acquired long QT syndrome (LQTS)], particularly in a setting of low potassium and magnesium level. In contrast, in congenital LQTS, arrhythmias often follow a sudden adrenergic rise due to exercise, arousal, sudden auditory stimuli, or an abrupt fright. QT-prolonging drugs belong to different categories, e.g. antiarrhythmics, vasodilators, psychotropics, antimicrobials, and non-sedating antihistamines. More is known about inherited LQTS than about drug-induced LQTS. This Task Force recommends checking dedicated and up-to-date websites (www.crediblemeds.org and www.brugadadrugs.org).

2.1.3.2. Structural heart and great vessel diseases

Structural cardiovascular diseases can cause syncope when circulatory demands outweigh the impaired ability of the heart to increase cardiac output. Syncope is of great concern when associated with fixed or dynamic obstruction to LV outflow. Nonetheless, syncope is often not solely the result of restricted cardiac output: it may be due in part to a vasovagal reflex, OH, or arrhythmia. Similarly, pulmonary embolism may not infrequently be accompanied by reflex syncope. Involvement of a reflex mechanism in pulmonary embolism has been hypothesized to explain syncope in these patients, even if the extent of pulmonary arterial obstruction is very limited and unlikely to cause severe haemodynamic compromise directly.[36] Furthermore, arrhythmias, particularly ventricular, are frequently important causes of syncope in structural heart disease such as myocardial infarction or hypertrophic cardiomyopathy. Thus, the mechanism of syncope may be multifactorial. However, even when syncope in cardiac disease may be primarily due to a reflex, these events should be categorized as cardiac syncope, to stress the need to correct the underlying structural disease, if possible.

2.2 Epidemiology

2.2.1 Prevalence of syncope in the general population

TLOC events of suspected syncopal nature are extremely frequent in the general population.[37] An epidemiological study performed in the state of Utah[38] showed that the yearly prevalence of syncope resulting in medical evaluation was 9.5 per 1000 inhabitants, with 1 in

10 patients hospitalized. The majority of individuals with syncope probably do not seek medical evaluation. Only a small fraction of patients seek a specialist consultation and an even smaller proportion is referred to the emergency department (ED) (*Web Table 2*). The first-time incidence of syncope by age is bimodal.[39–41] Its prevalence is very high in patients aged 10–30 years, is uncommon in adults with an average age of 40 years, and peaks again in patients aged >65 years. In the Framingham study,[40] the 10-year cumulative incidence of syncope was 11% for both men and women aged 70–79 years, and 17% and 19%, respectively, for men and women aged ≥80 years. Overall, it is estimated that approximately half of the general population will have one syncopal event during their lifetime (*Web Figure 3*).

2.2.2 Prevalence of the causes of syncope

The prevalence of the causes of syncope differs depending on the age and clinical settings in which the patient is evaluated (see *Supplementary Data Tables 1 and 2*). However, some general comments are possible:

- Reflex syncope is the most frequent cause of syncope in any setting and at all ages.
- Cardiac syncope is the second most common cause. The number of patients with a cardiac cause varies widely between studies; higher frequencies are observed in emergency settings mainly in older subjects, and in settings orientated towards cardiology. Cardiac syncope is extremely rare in children, teenagers, and young adults.
- In patients <40 years, OH is a rare cause of syncope; it is frequent in very elderly patients.
- Non-syncopal TLOC events are more frequent in emergency referrals and reflect the multifactorial complexity of these patients.
- While reflex syncope is by far the most frequent cause of TLOC in the young, multiple causes are often present in the elderly, and the medical history may be less reliable than in the young.

2.3 Prognosis

2.3.1 Syncope severity

The reason for defining 'severe syncope' is that having such an assignment can aid patient care as well as stratify patients for scientific purposes. There are two reasons to label syncope as severe:

(1) The first concerns the 'causal risk' of syncope, i.e. the risk associated with the underlying disease. Cardiac syncope is associated with high morbidity and considerable mortality, meaning that any syncope due to a proven cardiac cause is classified as severe syncope, even if the actual episode was short-lived and had no adverse effects.

(2) The second principle concerns the 'consequential risk' of syncope. This concerns the impact that syncope has on a patient's life, through physical trauma, disruption of school and work activity, driving, and personal consequences:
   - Physical trauma mostly occurs when there are no warning symptoms, or these are of such a short duration that they do not allow a patient time to take adequate action to prevent a fall or other adverse consequence. Having suffered previous syncope-related trauma counts strongly.
   - Disruption of schooling is present when syncope causes enough absence to cause the patient to fail grades or additional schooling is needed to prevent this from occurring.
   - Work disruption occurs when the nature of the occupation makes even a single episode hazardous, or if patients are no longer allowed to work directly because of syncope.
   - Driving: when national regulations mean that a patient with syncope is not allowed to drive for a period of time this counts as a substantial consequence.
   - Personal consequences concern depression, as well as significant disruption regarding the ability to take part in family activities or societal activities causing significant personal suffering.

2.3.2 Risk of death and life-threatening events

Individuals with syncope have been reported to have a 1.31 increased risk for death from any cause, 1.27 for non-fatal myocardial infarction or death from coronary heart disease, and 1.06 for fatal or non-fatal stroke compared with controls.[40] Several prognostic markers have been identified (see *Supplementary Data Table 3*). In general:

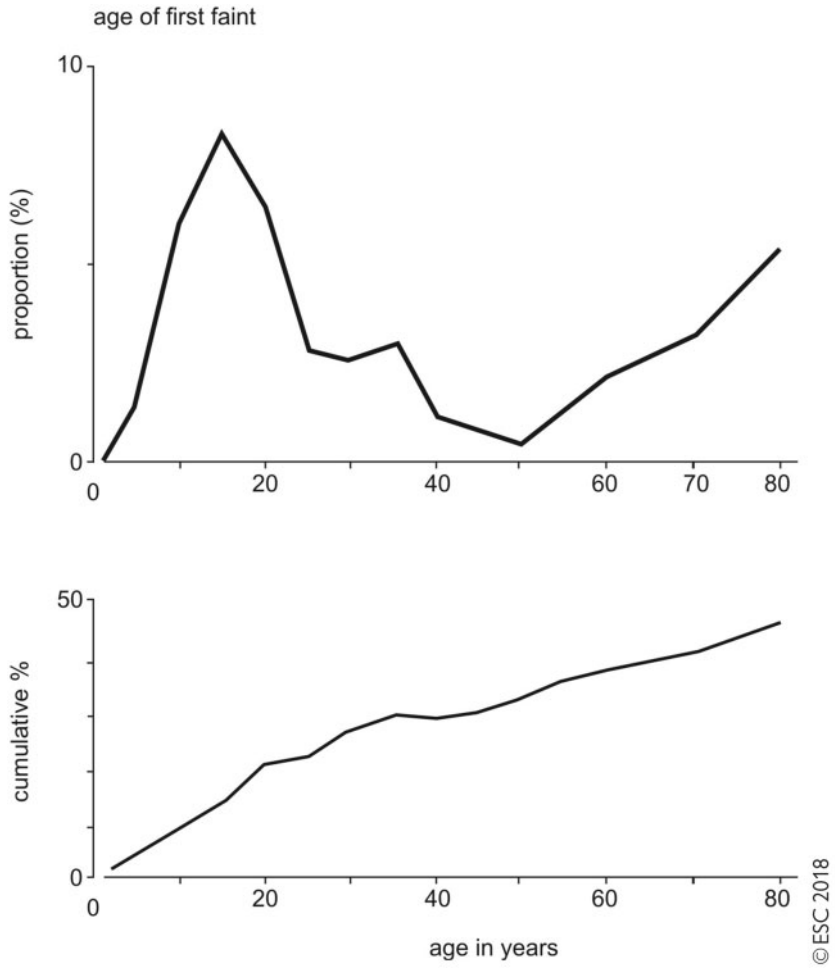
- Poor outcomes, including death, are related to the severity of the underlying disease rather than to syncope itself.[40,42,43]
- Structural heart disease[44–48] is the major risk factor for sudden cardiac death and overall mortality in patients with syncope. In patients with severe heart failure with an implantable cardioverter defibrillator or cardiac resynchronization therapy, syncope is associated with appropriate defibrillator discharge and predicts a higher mortality than similar patients without syncope.[49,50]
- In OH, the risk of death, coronary artery disease, heart failure, and stroke is two-fold as high as that of the general population, largely caused by the greater severity of comorbidities.[22,51]
- Conversely, young patients in whom structural or electrical heart disease have been excluded have an excellent prognosis.[40]

2.3.3 Recurrence of syncope and risk of physical injury

In a recent systematic review, the incidence of syncope relapse increased linearly from 0.3% at 30 days to 22% at 2 years of follow-up.[52]

Web Table 2 **Syncope frequency depends on the setting in which the measurement is made Adapted from Olde Nordkamp *et al.*[37] and Malasana *et al.*[38]**

Setting	Incidence (per 1000 subject-years)	Relative frequency (compared with 100 patients with syncope)
General population	18–40	100
Seeking any medical evaluation	9.3–9.5	25–50
Referred for specialty evaluation	3.6	10–20
Referred to emergency department	0.7–1.8	2–10



Web Figure 3 Distribution of age and cumulative incidence of first episodes of syncope in the general population from subjects aged ≤80 years The data from subjects aged 5–21 years come from a study by Ganzeboom *et al.*[39], from subjects <5 years from a study by Lombroso and Lerman[41], and from subjects aged 20–80 years from a study by Soteriades *et al.*[40]

The number of episodes of syncope in the 1–2 years preceding clinical evaluation is the strongest predictor of recurrence.[53] Conversely, sex, severity of presentation, presence of structural heart disease, and tilt-test response have little or no predictive value.[53,54]

Recurrent syncope is associated with fractures and soft-tissue injury in 12% of patients.[55] In the ED, minor trauma was reported in 29.1% and major trauma in 4.7% of cases; the highest prevalence (43%) was observed in older patients with carotid sinus hypersensitivity.[56] In the elderly, morbidity secondary to syncope includes loss of confidence, depression, fear of falling, fractures, and subsequent institutionalization.[57]

2.3.4 Risk of syncope during driving

Among patients with a history of syncope, the prevalence of recurrence of syncope during driving spans from 3–9.8%.[58,59] The risk of syncope-mediated car accidents is less than 1%/year.[59] In highly symptomatic subjects with VVS, the estimated risk of a severe harm during driving was even lower than that observed in the general population.[60] In patients with life-threatening ventricular arrhythmias enrolled in the Antiarrhythmics versus Implantable Defibrillators (AVID) trial,[61] symptoms suggestive of tachyarrhythmia recurred frequently while driving, but they were unlikely to lead to motor vehicle accidents (0.4% per patient-year). The risk might be increased in the 2–4 months following an implantable cardioverter defibrillator shock due to a higher probability of subsequent shocks.[62] Thus, patients with syncope are surprisingly safe to drive.

Nevertheless, a history of syncope may be regarded as an indirect risk factor for driving accidents. Indeed, the 2-year incidence rate of motor vehicle crashes was almost twice as high in patients with a first-time diagnosis of syncope from an ED or hospital (2.1%/year) compared with the general population (1.2%/year).[63] Thus, syncope should be considered as one of several factors when assessing fitness to drive.[63]

In conclusion, the absolute risk of driving accidents due to syncope is low. In addressing the problem of driving resumption after a syncope spell, physicians should first stratify the clinical risk of the patient and the likely chance for a syncope recurrence. This applies to both private and commercial driving independently of local driving regulations that might

differentiate private from commercial driving, which may differ among various European countries. Common principles of syncope risk stratification may include an assessment of prodromal symptoms, frequency, intensity, and duration, and their relationships with posture and environmental conditions. Provoking factors should also be taken into account.

Several consensus documents have been published by the ESC and other entities in the past two decades.[64–70] Taking advantage of those documents and the new literature, this Task Force proposes the advice detailed in *Web Table 3*.

2.3.5 Risk of syncope during work

Syncope at work is a rare event and its impact in terms of injury is usually benign.[71] However, as syncope is associated with a loss of postural tone, even a benign vasovagal episode can be hazardous in high-risk working environments. Thus, in people with syncope, it is necessary to stratify the *occupational risks* of syncope recurrence, particularly if the time of exposure to hazardous conditions is significant.[65,72] Referral to occupational physicians may be recommended in these circumstances.

2.4 Impact on quality of life

Recurrent syncope has effects on quality of life and the degree of impairment is proportional to syncope frequency. In patients with six or more lifetime syncopal spells, there was a negative relationship between the frequency of spells and overall perception of health, which was not evident in those with a history of fewer than six lifetime spells.[73] Adults presenting with TLOC in a tertiary syncope facility had a worse score on all quality-of-life scales of the generic Short Form-36 than the general population. The disease-specific syncope functional status questionnaire indicated mean impairment in 33% of the listed activities, such as driving.[74] Female sex, a high level of comorbidity, the number of episodes of syncope, the presence of presyncope, and a neurological or psychogenic diagnosis were associated with poorer quality of life. Quality of life usually improves over time.[75]

2.5 Hospitalization and economic issues

Although a comparison of costs between studies is difficult due to differences in methods of calculation and between healthcare systems in different countries, it is generally believed that the management of syncope is expensive because syncope is frequent in the general population, and it inevitably results in high direct clinical (i.e. the need for multiple tests and specialist visits) and indirect social costs.[76,77]

In general, 1–1.5% of referrals to the ED are for syncope; of these, about 50% are hospitalized (*Supplementary Data Table 4*). Hospitalization costs account for >75% of the total costs, and most hospitalizations are

Web Table 3 Advice for driving in patients with syncope

Disorder causing syncope	Group 1 (private drivers)	Group 2 (professional drivers)
Cardiac arrhythmias		
Untreated arrhythmias	Unfit to drive	Unfit to drive
Cardiac arrhythmia, not life-threatening, medical treatment	After successful treatment is established	After successful treatment is established
Cardiac arrhythmia, life-threatening (e.g. inheritable disorders), medical treatment	After successful treatment is established	Permanent restriction
Pacemaker implant	After 1 week	After appropriate function is established (first post-implant visit)
Catheter ablation	After successful treatment is established	After successful treatment is established
Implantable cardioverter defibrillator implant	After 1 month. The risk may increase in the few months following an implantable cardioverter defibrillator shock (3 months)	Permanent restriction
Structural cardiac/cardiopulmonary		
	After appropriate function is established	After appropriate function is established
Orthostatic hypotension (neurogenic)		
Syncope while sitting	After successful treatment is established	After successful treatment is established
Reflex syncope		
Single/mild	No restrictions unless it occurred during driving	No restriction unless it occurred during driving or without prodromes
Recurrent and severe	After successful treatment is established	After successful treatment is established. Particular caution if it occurred during driving or without prodromes
Unexplained syncope		
	No restrictions unless absence of prodrome, occurrence during driving, or presence of severe structural heart disease. If yes, after diagnosis and appropriate therapy is established	After diagnosis and appropriate therapy is established

Group 1: private drivers of motorcycles, cars, and other small vehicles with and without a trailer.
Group 2: professional drivers of vehicles over 3.5 tons or passenger-carrying vehicles exceeding eight seats excluding the driver. Drivers of taxicabs, small ambulances, and other vehicles form an intermediate category between the ordinary private driver and the vocational driver and should follow local legislation.
Important remark. The observation period for the assessment of therapy efficacy should generally be longer in group 2.

unnecessary.[78] Among the patients who present to the ED for syncope, 0.8% die and an average of 3.6% have some serious outcome within the next 7–30 days (*Supplementary Data Table 4*). Therefore, only a small minority will potentially benefit from urgent hospitalization.

One of the main objectives of a specialized syncope unit is to reduce costs through the reduction of unnecessary hospitalizations and the appropriate use of diagnostic tests.[76] This issue is developed in section 9 in the main manuscript.

3. Practical Instructions for section 4.1.: initial evaluation

3.1 Medical history taking as a diagnostic test

The medical history of a patient with TLOC can be seen as a diagnostic test with very different test characteristics, depending on how and by whom the information from the patient is obtained and analysed. History taking, if properly performed, is a powerful diagnostic tool, which in most cases proves to be the only 'test' necessary other than physical examination and an electrocardiogram (ECG) in patients with TLOC.[79]

Assessing the efficacy of the 'history' as a diagnostic test has aspects of physiological reasoning. There is no independent gold/reference standard to diagnose syncope. As a solution to the lack of a straightforward reference in conditions such as TLOC/syncope, dedicated long-term follow-up, preferably with an expert review committee, can be used as a test of reliability of diagnosis, relying on ancillary testing and/or additional information during follow-up, including recurrences and health status.[80,81]

In one multicentre study,[82] using long-term follow-up as a reference for the yield of the initial evaluation by the attending physicians, the sum of certain (100% certain) and highly likely (80–100% certain) initial diagnoses ranged from 50–80%. The overall diagnostic accuracy of the initial evaluation was also high, at 91%. Dangerous diagnoses were not missed.

3.2 Explanation of the clinical features of transient loss of consciousness

TLOC is characterized by four specific characteristics: short duration, abnormal motor control, loss of responsiveness, and amnesia for the period of LOC. The specific characteristics of TLOC that aid diagnosis are outlined in *Web Table 4*:

- TLOC is certain when all four clinical features are present.
- TLOC is ruled out when any one of the following is true: motor control was normal for the entire event, responsiveness was intact for the entire event, or the patient has recollection of events during the entire event.
- The absence of awareness that consciousness was lost does not rule out TLOC.
- If there is no eyewitness, TLOC was likely present when there is a clear gap in memory during which a fall occurred.
- A fall without amnesia is most often not TLOC; however, syncope, especially in the elderly, can occur without awareness that consciousness was lost. Presyncope in the elderly may cause falls.

The criteria for TLOC are based exclusively on the patient's history and eyewitness accounts because such events are usually not witnessed by medically trained persons. As the diagnosis of TLOC is based on history taking and not on an examination at the time, the criteria cannot ensure that consciousness was truly lost, only that it appeared lost. Hence, TLOC includes disorders with a somatic LOC, i.e. syncope and epileptic seizures, as well as their psychogenic mimics. Syncope, mostly due to VVS, vastly outnumbers the other conditions.

Web Table 4 Explanation of the clinical features of transient loss of consciousness[a]

Clinical feature	Comments
Short duration of LOC[b]	Based on often-unreliable accounts from the patient and eyewitness • When measured reliably, a duration of 5 minutes represents the limit of TLOC • When estimated, longer times may be mentioned
Abnormal motor control • Fall (loss of postural control)[c] • Abnormal high (stiff) or low (flaccid) muscle tone • Absence of normal limb movement • Presence of abnormal movement	Fall requires both patient history and eyewitness accounts: • A fall is more likely due to LOC if there is no recollection of the fall itself and no evidence of protective measures such as extending the hands. The other aspects of motor control require an eyewitness account: • Stiffness and flaccidity are apparent from the way of falling and the posture once supine; limb, neck, or trunk muscle tone can be felt by eyewitness • Absence of normal movement is established through observation • Abnormal movements may include muscle jerks, abnormal posture of limbs, the face or head, the breathing pattern, eye opening, making sounds or incontinence
Loss of responsiveness	Requires action by an eyewitness • No response to speech • No or abnormal response to touch or pain
Amnesia for period of unconsciousness	Requires patient history (sometimes eyewitness account)

LOC = loss of consciousness; TLOC = transient loss of consciousness.
[a]'Transient' implies that the features of transient loss of consciousness resolve completely.
[b]A short duration here concerns motor elements, amnesia, and responsiveness only; concomitant symptoms such as fatigue or sleepiness may last for much longer periods.
[c]A fall cannot be assessed when a patient is already supine or when circumstances prevented falling, such as sitting in a car or armchair. A fall on its own does not guarantee loss of consciousness.

4. European Society of Cardiology guideline checklists of historical clues to diagnose transient loss of consciouness

The items listed in the five tables below have been gathered from several sources. Note that for most of the items, not enough information is available to evaluate their utility in terms of sensitivity and specificity. This scheme assumes the classification of TLOC as used by the ESC.

4.1 Triggers before the attack

Web Table 5.1 Checklists of historical clues to diagnose transient loss of consciousness

Historical clue	Possible diagnosis	References, comments, definition
Supine position (awake)	- Cardioinhibitory VVS through pain or fear - Arrhythmia - PPS and PNES	Epilepsy[83] Cardiac[84]
During normal sleep	- Epilepsy - Arrhythmia - If prodrome of VVS causing awakening + syncope thereafter: "sleep syncope"	Epilepsy[83,85] Sleep syncope[86,87]
Sitting	- All causes (including "orthostatic VVS" and classical OH)	For VVS[88,89]
Standing for some period	- All causes - If TLOC occurs only while standing: OH, orthostatic VVS	
Couple of steps after standing up or straightening from bending or squatting position	Initial OH and classical OH	Initial OH[90]
Micturition, defaecation	Situational reflex syncope (note: defaecation and diarrhoea may act as triggers for VVS but also as symptoms of VVS)	Micturition[91–93] Defaecation[93,94]
Coughing	Situational syncope (usually prolonged intensive coughing, often in smokers with lung disease)	[95–98]
Swallowing	Situational syncope (usually oesophageal disease)	[99]
Laughing out loud, telling jokes, unexpectedly meeting an acquaintance	Cataplexy (ask about excessive daytime sleepiness)	[100]
Laughter	Situational reflex syncope (very rare)	[101,102]
During and after eating	- All causes (a specific circumstance)- Only during/after eating (15 minutes): postprandial hypotension, particularly in the elderly and with autonomic failure- If preferentially during meals: arrhythmia/Brugada syndrome	Postprandial hypotension[103,104]
Head movements, pressure on the neck, shaving	Spontaneous type of carotid sinus syncope	[105]
Fear, pain, instrumentation	Classical VVS	[90]
During physical exercise	- Cardiac structural- Cardiac arrhythmic: AV block, LQTS1, catecholaminergic VT- May occur in autonomic failure- VVS in very young/teenagers	Effort[84]
Directly after cessation of physical exercise	- Post-exercise hypotension in middle-aged and elderly people: autonomic failure - Young people: VVS, particularly in trained athletes	AF[106,107] VVS[108,109]
During arm exercise	Steal syndrome (very rare)	[110]
Palpitations	- Cardiac: tachyarrhythmia - Postural tachycardia in VVS, POTS	[111] Syncope vs. seizure[112]
Strong emotions other than fear (e.g. argument)	- Cataplexy - Arrhythmia: catecholaminergic polymorphic VT; also during exercise, in children and young adults	Cataplexy[100] Catecholaminergic polymorphic VT[113,114]
Startling (e.g. alarm clock)	- LQTS2 - Startle epilepsy	LQTS2[115] Epilepsy[116]
During fever	- VVS (more often) - Brugada syndrome	Many case reports but no systematic counts on syncope with/without fever
Flashing lights	Epilepsy with photosensitivity	[117,118]
Sleep deprivation	- Epilepsy - VVS	Epilepsy[83,119]
Heat/warmth/hot bath	- VVS - Classical OH	VVS[39] OH[120,121] Syncope vs. seizure[112]

AF = atrial fibrillation; AV = atrioventricular; LQTS = long QT syndrome; OH = orthostatic hypotension; PNES = psychogenic non-epileptic seizures; POTS = postural orthostatic tachycardia syndrome; PPS = psychogenic pseudosyncope; TLOC = transient loss of consciousness; VT = ventricular tachycardia; VVS = vasovagal syncope.

4.2 At the onset of the attack

Web Table 5.2 Checklists of historical clues to diagnose transient loss of consciousness: at the onset of the attack

Historical clue	Possible diagnosis	References, comments, definition
Change in vision: seeing dark spots, loss of colour vision (rare).Change in hearing: sounds coming as if from a distance, buzzing or ringing in the ears	Syncope: symptoms of cerebral hypoperfusion, so not related to cause of syncope	[122]
Nausea, sweating, pallor	Reflex syncope: autonomic activation	Sweating (syncope vs. epilepsy)[112]
Pain in shoulders and neck ("coat hanger pattern")	Classical OH: ischaemia of local muscles	[123,124]
Shout at onset of attack ("ictal cry")	Epilepsy	[125]
Rising sensation from abdomen	- Epileptic aura - Rising abdominal sensation occurs in VVS, not often	Epilepsy[126] VVS[122]
Rising sensation from abdomen, unpleasant smell or taste, or other phenomena specific to subject but recurring in attacks	Epileptic aura	[127,128] Déjà vu/jamais vu (pro seizure)[112]

OH = orthostatic hypotension; VVS = vasovagal syncope.

4.3 During the attack (eyewitness account)

Web Table 5.3 Checklists of historical clues to diagnose transient loss of consciousness: during the attack (eyewitness account)

Historical clue	Possible diagnosis	References, comments, definition
Fall:		
Keeling over, stiff	- Tonic phase epilepsy - Syncope less often (all causes)	[129]
Flaccid collapse	- Syncope (all variants) - Atonic epilepsy (rare, children)	[129] Atonic seizures[130]
Movements[a]:		
Mere presence:	limited utility for differentiating syncope from epilepsy; details needed	
Beginning before the fall (partial, one-sided)	Epilepsy	-
Beginning after the fall	- Epilepsy - Syncope	-
Symmetrical, synchronous	Epilepsy	-
Asymmetrical, asynchronous	Syncope, may rarely be epilepsy	-
Beginning at onset of unconsciousness	- Epilepsy - Syncope (usually some seconds later)	Syncope[3]
Beginning after onset of LOC	Syncope	Syncope[3] (mean ~20 seconds)
Duration LOC <30 seconds	If measured, syncope far more likely than epilepsy	Seizure: mean 74 seconds,[131] mean 90 seconds[132] Syncope[3]
Duration of LOC >1 minute	- If measured, epileptic seizure more likely than syncope - PNES	Seizure[131] Syncope[3]
Duration of LOC >5 minutes	- PPS - PNES	PNES vs. seizure[85,133,134] PPS[135]
Few movements (10 or so)	Syncope far more likely than epilepsy	
Many movements ("100", "cannot count")	- Epilepsy - PNES	
Restricted to one limb or one side	- Epilepsy - Syncope	-
Pelvic thrusting	- PNES - Frontal lobe seizures, rare in temporal lobe seizures	[136,137] In children: very rare[134]
Repeated waxing and waning in intensity and changes in nature of movement	PNES	[85]

LOC = loss of consciousness; PNES = psychogenic non-epileptic seizures; PPS = psychogenic pseudosyncope.

[a]The word "clonic" is in everyday use restricted to epilepsy, while the word "myoclonus" is used for the movements in syncope as well as for certain types of epilepsy and to describe postanoxic movements. The word "convulsions" is best reserved for epilepsy. "Myoclonic jerks" has little connotation with a specific cause, and it is preferable to avoid making unwarranted conclusions.

4.4 Other aspects

Web Table 5.4 Checklists of historical clues to diagnose transient loss of consciousness: other aspects

Historical clue	Possible diagnosis	References, comments, definition
Oral automatisms (chewing, smacking, blinking)	- Epilepsy - Syncope (often, but very rarely noticed)	Syncope[3]
Cyanotic face	- Epilepsy -Cardiac syncope	VVS vs. arrhythmic syncope[138]
Eyes open	-Epilepsy -Syncope (only closed in shallow and short-lasting syncope)	seizure vs. PNES[139]
Eyes closed during unconsciousness	-PPS -PNES -Concussion	PPS[135] PNES[140–142]
Tongue bitten	-Epilepsy more likely than syncope if lateral side of tongue (uni- or bilateral) -Syncope very rare, then tip of tongue -Does not differentiate PNES from epilepsy -Accidental falls can also cause tongue laceration	Trauma[143] Epilepsy vs. syncope[112,144,145] Epilepsy vs. PNES[146]
Urinary incontinence	Does not differentiate epileptic seizures and syncope, nor epileptic seizures and psychogenic TLOC	[147]
Paresis, ataxia, brain stem signs	Vertebrobasilar TIA	[148]
Sterterous (snoring) breathing	-Epileptic seizure more likely than PNES -Syncope only short (~10 seconds) in deep hypoperfusion	Seizure[85] Syncope[3]
Head turning	-Epileptic seizures (prolonged) -Syncope with deep hypoperfusion (<30 seconds)	Syncope vs. seizure[3,112]
Sudden severe headache. Later vomiting, nuchal rigidity	Subarachnoid haemorrhage	[149]
Apparent LOC lasts 10–30 minutes	-Not TLOC! -PNES or PPS (more properly "pseudocoma") -LOC due to trauma, metabolic causes, etc.	[135]
Eye fluttering	PNES more likely than epileptic seizure	[139]
Bruises and other injuries	All causes (including PPS, PNES)	PNES[150]

LOC = loss of consciousness; PNES = psychogenic non-epileptic seizures; PPS = psychogenic pseudosyncope; TIA = transient ischaemic attack; TLOC = transient loss of consciousness; VVS = vasovagal syncope.

4.5 After the attack

Web Table 5.5 Checklists of historical clues to diagnose transient loss of consciousness: after the attack

Historical clue	Possible diagnosis	References, comments, definition
Nausea, sweating, pallor	-Reflex syncope: autonomic activation -Also stress response to TLOC of any cause	-
Clear-headed immediately on regaining consciousness	-Syncope -Epilepsy (extremely rare)	-
Disorientated and amazed for 5–10 seconds, memory restored at once afterwards	Syncope (typical, often not noted)	[3]
Confused, with memory problems for many minutes after regaining consciousness	Epilepsy	[112]
Sleep	-Epilepsy (initially stupor) -Reflex syncope (voluntary sleep, particularly children)	[151]
Aching muscles (not due to bruises)	Epilepsy, but also PNES	[152]
Chest pain	Cardiac: ischaemia	[153]
Crying	-Infants: all causes	PNES[85]

PNES = psychogenic non-epileptic seizures; PPS = psychogenic pseudosyncope; TLOC = transient loss of consciousness.

4.6 Antecedent disorders

Web Table 5.6 Checklists of historical clues to diagnose transient loss of consciousness: antecedent disorders

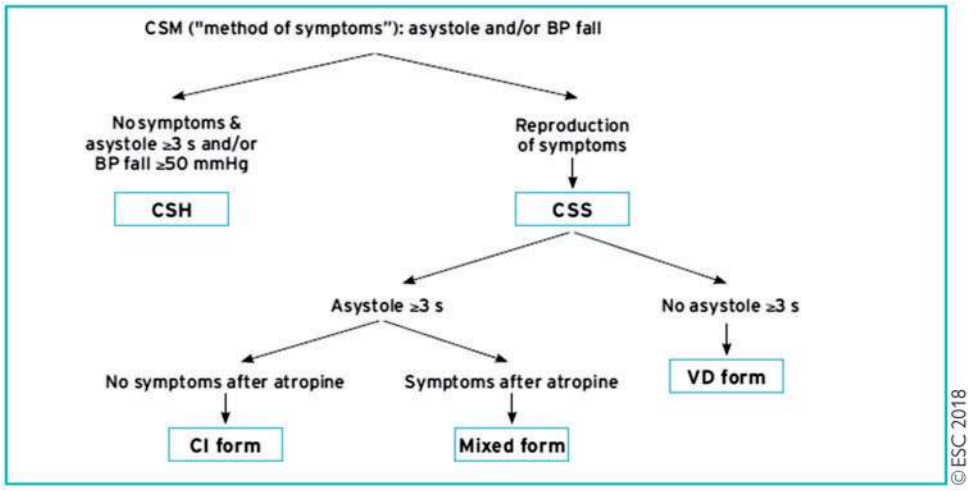
Historical clue	Possible diagnosis	References, comments, definition
Recent start or change of medication	-VVS (volume depletion, antihypertensives) -OH -Arrhythmia (long QT)	
History of heart disease	-Cardiac: arrhythmia or structural	-
Hypertension	-OH due to medication -OH in autonomic failure (if BP only measured supine or sitting)	
Parkinsonism	OH (autonomic failure: Parkinson's disease, multiple system atrophy)	154,155
Impotence and micturition problems for a few years	If OH present: autonomic failure	31
Orthostatic intolerance	-VVS -OH -POTS	By definition
History of epilepsy	Epilepsy	-
Structural brain damage	Epilepsy	-
Earlier possibly traumatizing events	-PNES -PPS (not obligatory!) -Other coincidental causes	156
Earlier psychosis, depression	OH due to antidepressive or antipsychotic drugs	157–160
Sudden death in family members <40 years of age	Genetic arrhythmia / cardiomyopathy / thoracic aortic dissection	161,162
Diabetes mellitus	- Cardiac syncope - OH (secondary autonomic failure) - (LOC due to hypoglycaemia: too long for TLOC)	OH[163]
Earlier VVS before 35 years of age	VVS more likely than arrhythmic syncope	138
No syncope before 35 years of age	VVS less likely	VT vs. VVS[164]
Family history of VVS	VVS much more likely (but background rate is one-third of population)	165–167
Recognition similar to VVS in youth	VVS much more likely	-

BP = blood pressure; LOC = loss of consciousness; OH = orthostatic hypotension; PNES = psychogenic non-epileptic seizures; POTS = postural orthostatic tachycardia syndrome; PPS = psychogenic pseudosyncope; TLOC = transient loss of consciousness; VT = ventricular tachycardia; VVS = vasovagal syncope.

5. Practical Instructions for section 4.2.1.: carotid sinus massage

The current definition of carotid sinus syncope requires the reproduction of syncope, i.e. the so-called 'method of symptoms',[168–172] in addition to the documentation of abnormal cardioinhibitory and/or vasodepressor reflex:

- Carotid sinus massage (CSM) is preferably performed during continuous ECG and non-invasive beat-to-beat BP monitoring.
- CSM consists of manual compression with the tips of the second, third, and fourth fingers of one hand at the site of the maximum carotid pulse,[173] between the angle of the jaw and the cricoid cartilage on the anterior margin of the sternocleidomastoid muscle, with the face rotated contralaterally. The massage is applied up and down the carotid artery on the right and then on the left side in the supine position, and then in the upright position for 10 s in each position, to allow symptoms to develop; the time between massages has to be long enough to allow HR and BP values to return to baseline. Thus, each patient undergoes up to four massages.
- Even if an asystolic pause is evoked by CSM, the possibility still exists that the patient may also exhibit a marked vasodepressor response. To assess the contribution of the vasodepressor component (which may otherwise be hidden), CSM is repeated after intravenous administration of 0.02 mg/kg of atropine. Atropine eliminates vagally induced asystolic pauses, thereby unmasking vasodepressor response.
- Carotid sinus hypersensitivity is diagnosed when CSM elicits abnormal cardioinhibition (i.e. asystole ≥3 s) and/or vasodepression (i.e. a fall in systolic BP >50 mmHg) (*Web Figure 4*). Carotid sinus syncope is established when spontaneous symptoms (syncope or presyncope) are reproduced in the presence of



Web Figure 4 Method of symptoms: classification of responses. BP = blood pressure; CI = cardioinhibitory; CSH = carotid sinus hypersensitivity; CSM = carotid sinus massage; CSS = carotid sinus syncope; VD = vasodepressor reflex.

bradycardia (usually >6 s) and/or hypotension. The isolated vasodepressor form is defined when CSM reproduces symptoms with a fall in systolic BP during at least one massage in the absence of asystole ≥3 s. In patients who have baseline asystole ≥3 s, the mixed form is diagnosed when symptoms persist after the elimination of asystole by means of atropine (*Web Figure 5*). In patients who have baseline asystole ≥3 s, the cardioinhibitory form is diagnosed when symptoms disappear after the elimination of asystole by means of atropine (*Web Figure 6*).

6. Practical Instructions for section 4.2.2.2: tilt testing

6.1 Method of tilt testing

It is recommended that the following method is adopted:[174–181]

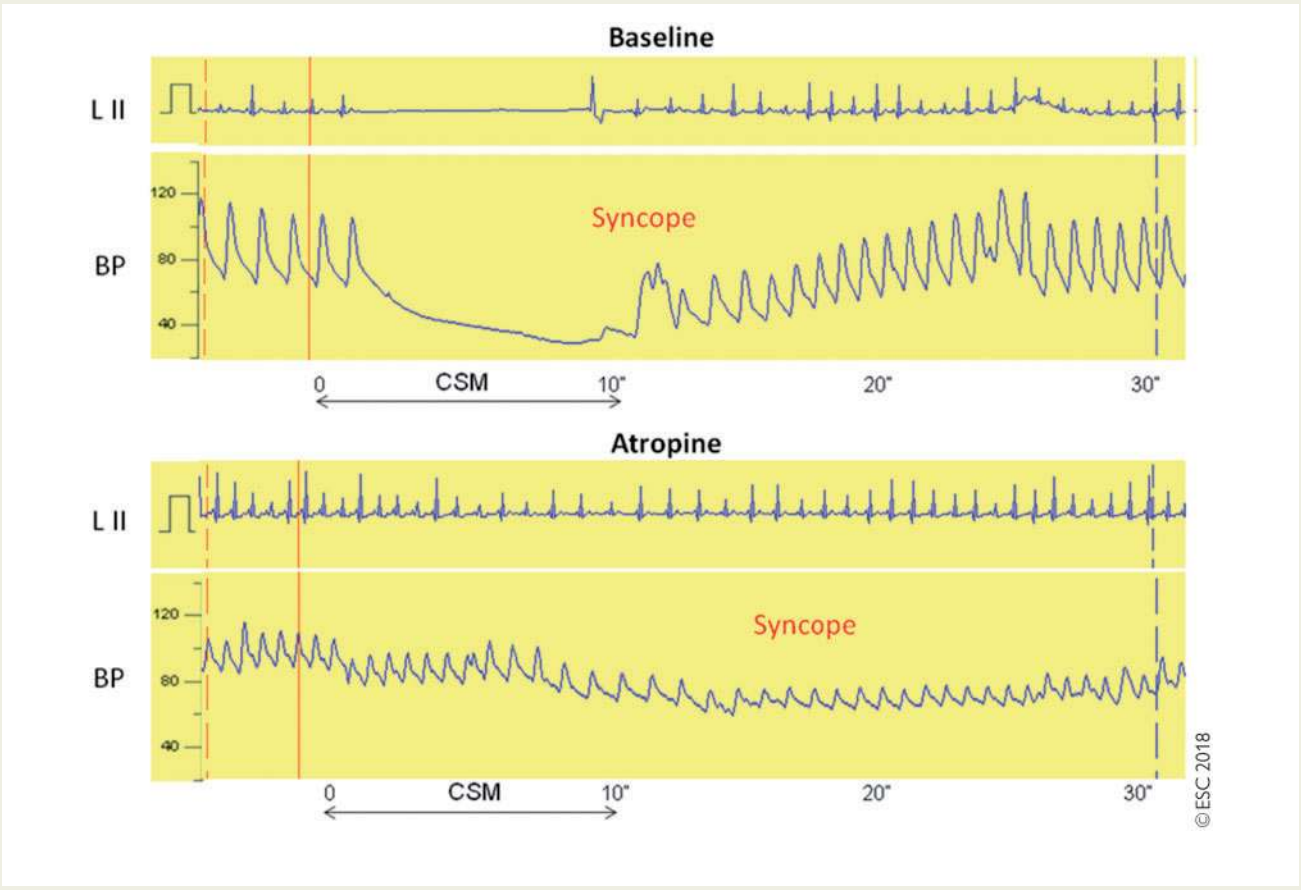
- Patients should be fasted for 2–4 h before the test.
- Ensure a supine pre-tilt phase of ≥5 min when there is no venous cannulation, and of ≥20 min when there is venous cannulation.
- Tilt angle between 60° and 70°.
- Passive phase of tilt of ≥20 min duration and a maximum of 45 min.
- Use either sublingual nitroglycerin or intravenous isoproterenol for drug provocation if the passive phase is negative. The duration of the drug-challenge phase is 15–20 min:
- for nitroglycerin challenge, a fixed dose of 300–400 μg sublingually administered with the patient in the upright position;
- for isoproterenol challenge, an incremental infusion rate from 1 μg/min rising to 3 μg/min to increase average HR by about 20–25% over baseline.
- The test should be continued until complete LOC occurs or completion of the protocol.
- Tilt tables have only one specific requirement: the tilt-down time should be short (<15 s) as longer times increase the duration of precipitated asystole.

Tilt testing is safe. There have been no reported deaths during the test. However, some rare life-threatening ventricular arrhythmias with isoproterenol in the presence of ischaemic heart disease have been reported.[182] No major complications have been published with the use of nitroglycerin. Minor side effects are common, and include palpitations with isoproterenol and headache with nitroglycerin. Atrial fibrillation can be induced during or after a positive tilt test and is usually self-limited.[34,183] Contraindications to the administration of isoproterenol include ischaemic heart disease, uncontrolled hypertension, LV outflow-tract obstruction, and significant aortic stenosis; caution should be used in patients with known arrhythmias.

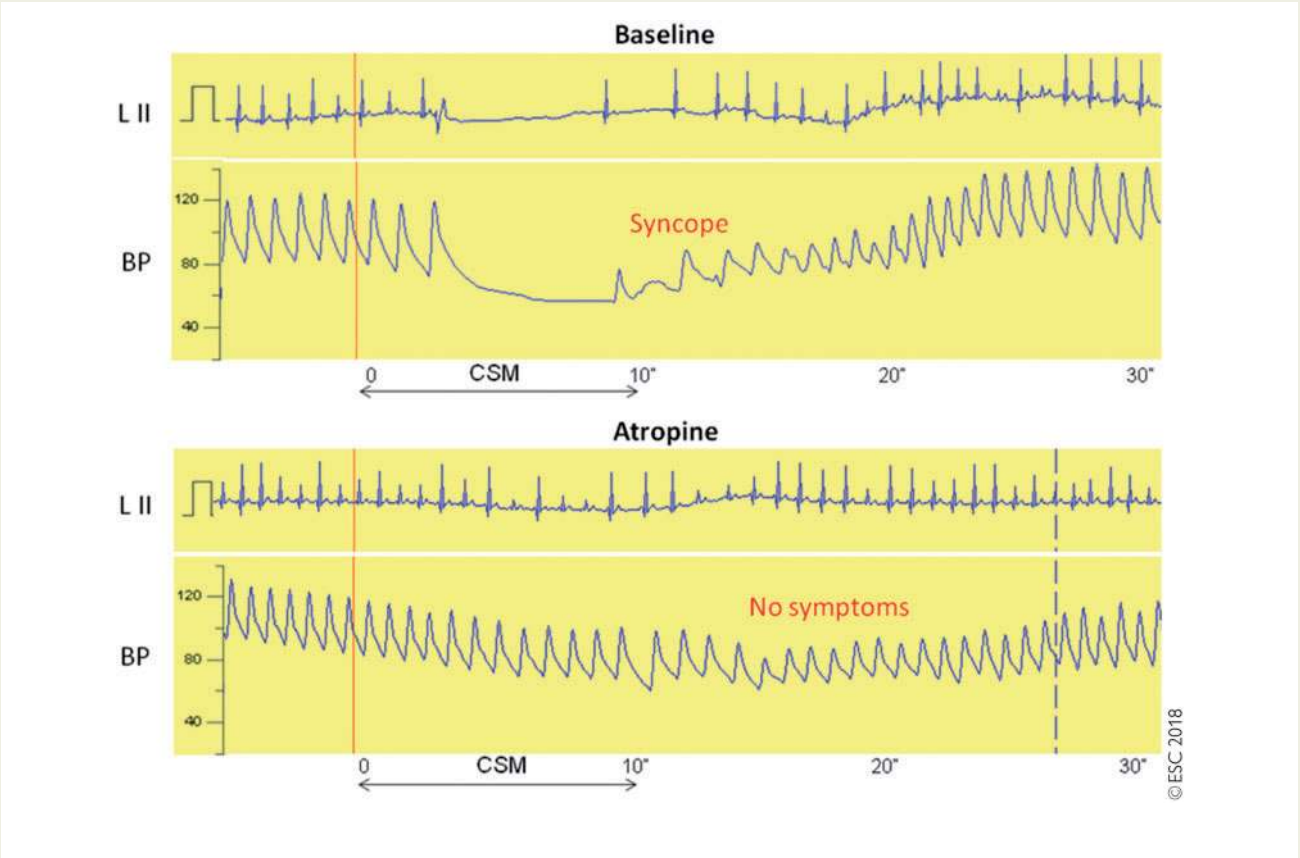
6.2 Classification of positive responses

In general, the vasovagal reaction lasts roughly 3 min or less before causing LOC.[180,184] A decrease in systolic BP to <90 mmHg is associated with symptoms of impending syncope[185,186] and to <60 mmHg is associated with syncope.[3,185] Prodromal symptoms are present in virtually all cases of tilt-induced VVS, which occurs, on average, 1 min after the onset of prodromal symptoms.[185,186] During the prodromal phase, BP falls markedly; this fall frequently precedes the decrease in HR, which may be absent at least at the beginning of this phase.[180,185,186] *Web Figure 7* shows the main events observed in tilt-induced reflex syncope based on the mean of 69 tests.[3] *Web Videos 1A* and *1B* (see Supplementary material online, Video 1A and 1B.) show clinical phenomena in relation to circulatory changes (plus EEG).

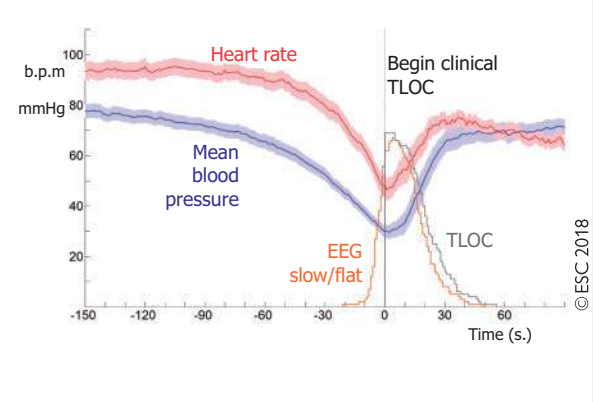
The temporal relationship between asystolic pause and LOC—assessed by means of video monitoring—has shown that an asystolic pause precedes LOC for 3–12 s in two-thirds of patients, whereas asystolic pause coincides or follows LOC in the others.[187] This finding might have practical implications for pacemaker therapy.



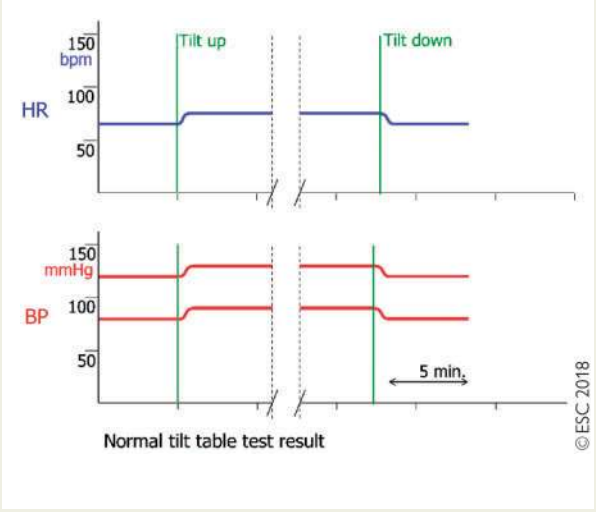
Web Figure 5 Mixed form of carotid sinus syndrome diagnosed by carotid sinus massage performed according to the 'method of symptoms'. Baseline (upper panel). The massage was performed during beat-to-beat, electrocardiograph (top trace), and systolic blood pressure (bottom trace) monitoring, with the patient on a tilt table in the upright 60° position. Arrows indicate the time of the beginning and end of massage, which was continued for 10 s. A 9.6-s asystole was induced soon after the beginning of the massage. The mean circulatory filling pressure decreased to approximately <40 mmHg after 10 s of carotid sinus massage; this was insufficient to preserve brain perfusion and caused syncope. Atropine (lower panel). To determine the relative contribution of the two components of the reflex, the cardioinhibitory component was suppressed by means of intravenous infusion of 0.02 mg/kg atropine and the massage was repeated. Systolic blood pressure fell to approximately 75 mmHg and the patient again had syncope after approximately 15 s. The vasodepressor component of the reflex, as well as the asystolic reflex, was therefore a major determinant of syncope in this patient, justifying classification as a mixed form. BP = blood pressure; CSM = carotid sinus massage; i.v. = intravenous; '' = seconds; L = lead.



Web Figure 6 Dominant cardioinhibitory form of carotid sinus syndrome diagnosed by carotid sinus massage performed according to the 'method of symptoms'. Baseline (upper panel). The massage was performed during beat-to-beat, electrocardiographic (top trace), and systemic BP monitoring (bottom trace), with the patient on a tilt table in the upright 60° position. Arrows indicate the time of the beginning and end of massage, which was continued for 10 s. A 6.2-s asystole was induced soon after the beginning of the massage. The mean circulatory filling pressure decreased to approximately 55 mmHg after 8 s of carotid sinus massage; this was insufficient to preserve brain perfusion and caused syncope. The vasodepressor reflex persisted longer than the cardioinhibitory reflex, with recovery to baseline values after 23 s. Atropine (lower panel). To determine the relative contribution of the two components of the reflex, the cardioinhibitory component was suppressed by means of intravenous infusion of 0.02 mg/kg atropine and the massage was repeated. Although systolic blood pressure fell to approximately 85 mmHg, syncope could not be reproduced, thus showing that the cardioinhibitory component of the reflex was the main determinant of syncope in this patient. BP = blood pressure; CSM = carotid sinus massage; i.v. intravenous; " = seconds; L = lead.



Web Figure 7 Main events observed in tilt-induced reflex syncope based on the mean of 69 tests.[3] Smoothed mean arterial blood pressure (blue line) and heart rate (red line) are shown. The shaded areas indicate mean ± 1 standard error. Data were centred around the clinically established onset of loss of consciousness ($t = 0$). Clinical loss of consciousness (grey line) shows how many subjects were unconscious as a function of time. Electroencephalogram (orange line) shows how many subjects had electroencephalogram changes (slow or flat) as a function of time. The vertical axis indicates mmHg for blood pressure, b.p.m. for heart rate, and numbers for the histograms. BP = blood pressure; b.p.m. = beats per minute; EEG = electroencephalogram; HR = heart rate; LOC = loss of consciousness; TLOC = transient loss of consciousness.



Web Figure 8 Normal tilt table test result. BP = blood pressure; b.p.m. = beats per minute; HR = heart rate.

6.3 Patterns of tilt table test results

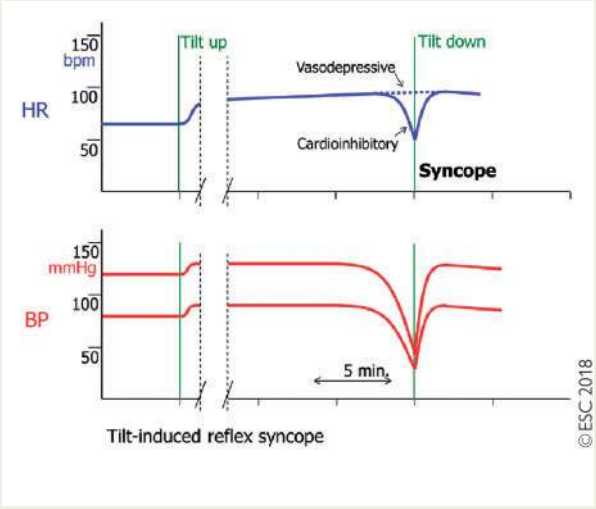
In the following figures, BP is shown in the bottom panel with separate lines for systolic and diastolic BP, expressed in mmHg. In the top panel, HR is shown as b.p.m. Time is indicated in minutes and axis ticks indicate 5 min. Results are first shown as schematic images, followed by example results. The example results are scaled to ensure that the scales for BP, HR, and time are the same in all figures.

6.3.1 Normal tilt table test results

After head-up tilt, no change in BP or a slight increase of ≤10% occurs (*Web Figure 8*). HR increases by ≤10% until patients are tilted back again.

6.3.2 Pattern of tilt-induced reflex syncope

At variable times after head-up tilt, BP starts to decrease slowly and slightly for several minutes (*Web Figure 9*). The rate of BP drop then increases, resulting in a 'convex' curve. HR usually increases gradually and slightly before syncope during tilt. HR then decreases, representing cardioinhibition. This decrease usually starts later than the BP decrease. The HR decrease, like BP, shows an increasing rate of drop. HR also decreases slightly in pure vasodepressive syncope. After tilting back, HR and BP increase quickly again. The core features of reflex syncope differentiating it from OH are a latency after head-up tilt, a 'convex' BP decrease, and a decrease in HR.



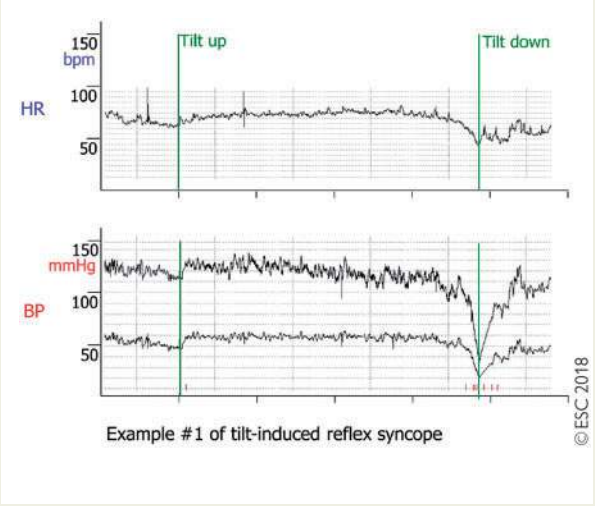
Web Figure 9 Pattern of tilt-induced reflex syncope. BP = blood pressure; b.p.m. = beats per minute; HR = heart rate.

6.3.3 Example #1 of reflex syncope

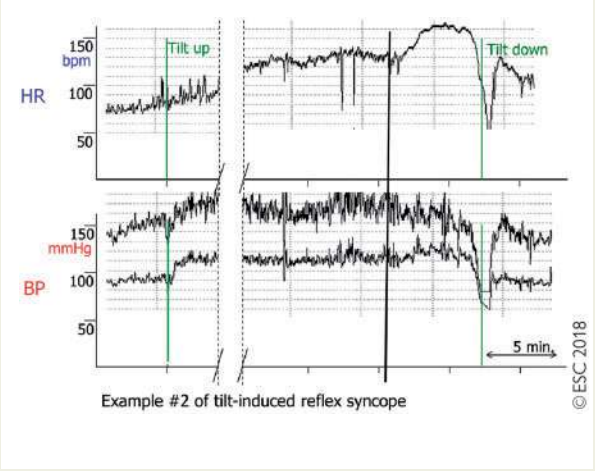
Note that the slow and slight decrease in BP occurs well before the BP decreases quickly (*Web Figure 10*). In this case, there is a limited HR decrease.

6.3.4 Example #2 of reflex syncope

Here, HR increases briefly when BP starts to decrease, but this makes way for a very steep decrease in HR, ending in asystole (*Web Figure 11*).



Web Figure 10 Example of result of tilt-induced reflex syncope. BP = blood pressure; b.p.m. = beats per minute; HR = heart rate.



Web Figure 11 Example of reflex syncope. BP = blood pressure; b.p.m. = beats per minute; HR = heart rate.

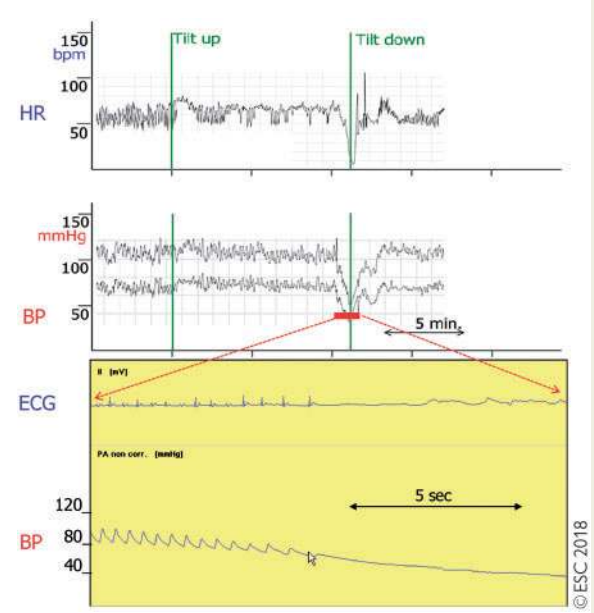
6.3.5 Example #3 of reflex syncope

In some cases, hardly any changes in BP or HR are seen before the accelerating decrease in BP causing syncope (*Web Figure 12*). Here, HR decreased along with BP, resulting in asystole (expanded in the bottom panel).

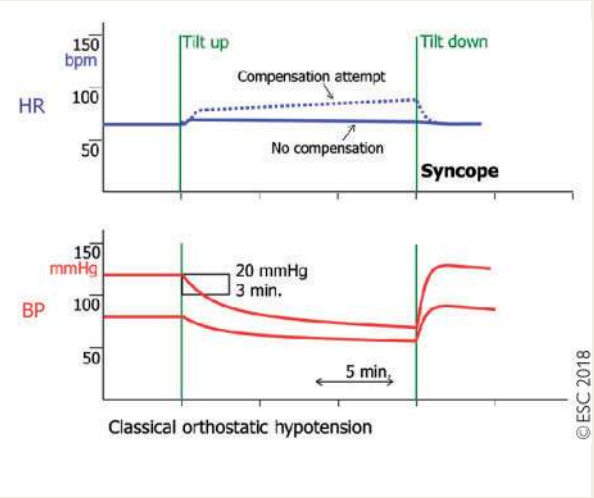
6.3.6 Pattern of classical orthostatic hypotension

Directly after head-up tilt, BP starts to decrease, with a decreasing rate of drop resulting in a 'concave' curve (*Web Figure 13*). BP may stabilize at a lower level or may continue to decrease during head-up tilt. The criteria for the systolic BP decrease used to recognize classical OH are indicated with a rectangle.

Note that after the first 3 min, BP may decrease considerably. If HR control is functional, HR will increase in an attempt to



Web Figure 12 Example of reflex syncope. BP = blood pressure; b.p.m. = beats per minute; ECG = electrocardiogram, lead II; HR = heart rate.

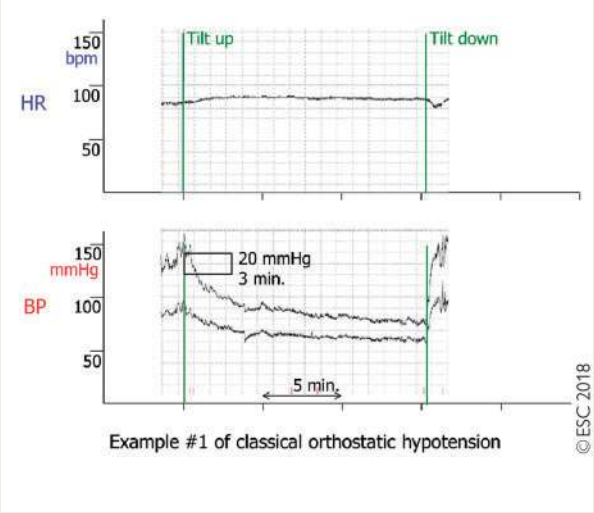


Web Figure 13 Pattern of classical orthostatic hypotension. BP = blood pressure; b.p.m. = beats per minute; HR = heart rate.

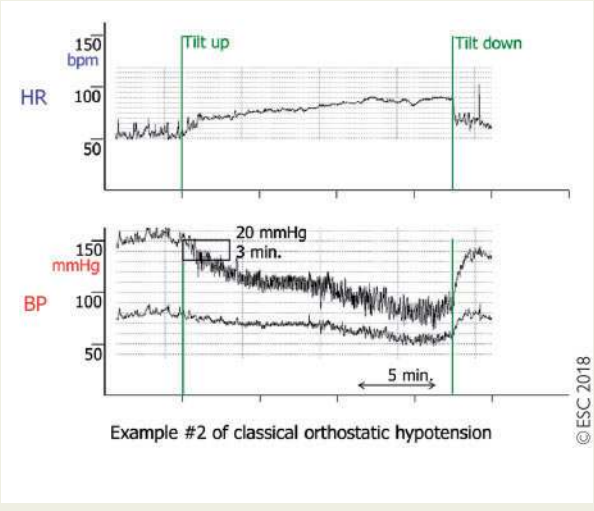
compensate for low BP. IF HR control is severely impaired, HR will not increase or only very little, and usually will not vary much between beats. The hallmarks of classical OH are no BP latency after head-up tilt, a (upwards) concave shape of the decrease, and if HR changes, it increases.

6.3.7 Example #1 of classical orthostatic hypotension

Note the concave shape of the BP curve and the lack of a significant HR increase: the lack of HR variability indicates impaired HR control (*Web Figure 14*). The recording was taken from a subject with neurogenic OH. Supine BP is high, which is common in neurogenic OH.



Web Figure 14 Example of classical orthostatic hypotension. BP = blood pressure; b.p.m. = beats per minute; HR = heart rate.



Web Figure 15 Example of classical orthostatic hypotension. BP = blood pressure; b.p.m. = beats per minute; HR = heart rate.

6.3.8 Example #2 of classical orthostatic hypotension

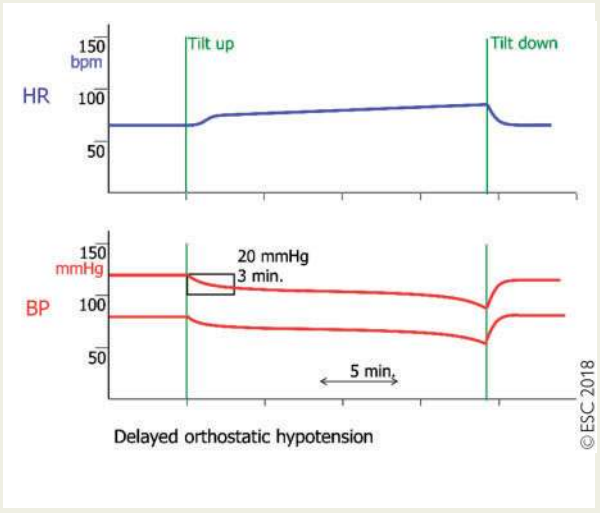
Supine BP is high in this patient with neurogenic OH (*Web Figure 15*). In contrast to the previous example, HR can still increase.

6.3.9 Pattern of delayed orthostatic hypotension

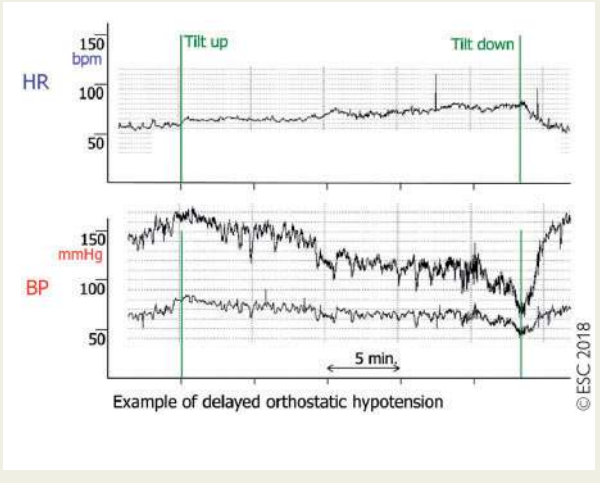
The shape of the decrease of HR and BP is more variable in delayed OH than in classical OH, and the rate of decrease may vary (*Web Figure 16*). The degree of HR compensation also varies.

6.3.10 Example of delayed orthostatic hypotension

In this example, BP decreases slightly in the first 3 min, but not enough to meet the demands for classical OH (*Web Figure 17*). In this



Web Figure 16 Pattern of delayed orthostatic hypotension. BP = blood pressure; b.p.m. = beats per minute; HR = heart rate.



Web Figure 17 Example of delayed orthostatic hypotension. BP = blood pressure; b.p.m. = beats per minute; HR = heart rate.

patient, this is followed by a slow decrease and finally a response that is reminiscent of reflex syncope.

6.3.11 Pattern of psychogenic pseudosyncope

PPS occurs with a variable interval after head-up tilt. However, it may occur within 1 or 2 min of head-up tilt (*Web Figure 18*). There are no decreases in BP and HR; usually both BP and HR increase several minutes before the event, reaching peak values during it.

6.3.12 Example of psychogenic pseudosyncope

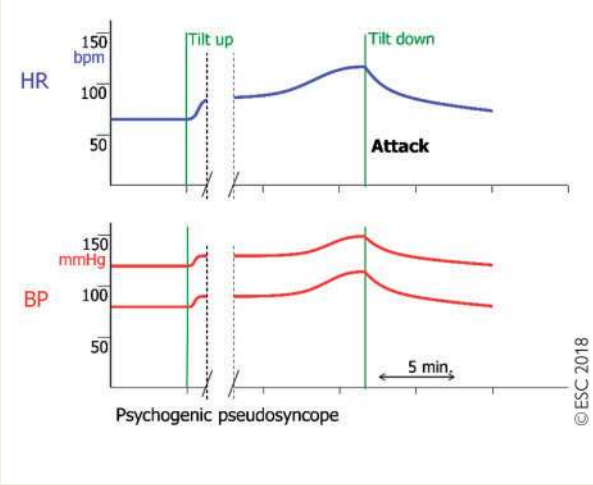
In this example, BP and HR start to increase about 2 min after head-up tilt and a clinical event occurred almost 5 min after head-up tilt (*Web Figure 19*). The marked variability in HR and BP after the event in this case was due to emotional upset.

6.3.13 Pattern of postural orthostatic tachycardia syndrome

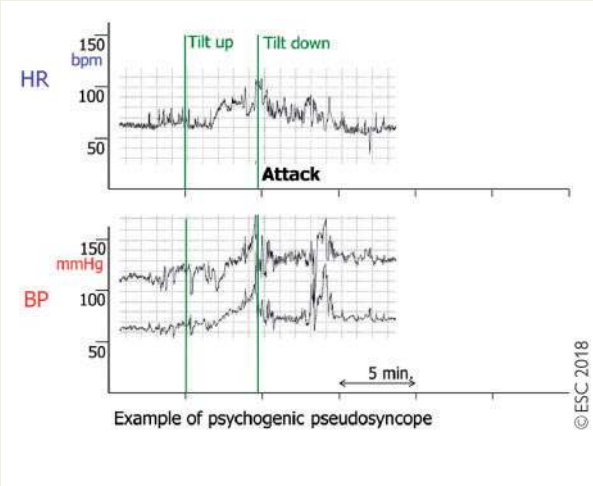
The HR criteria for POTS are indicated by a rectangle (*Web Figure 20*). POTS can only be diagnosed in the absence of OH.

6.3.14 Example of postural orthostatic tachycardia syndrome

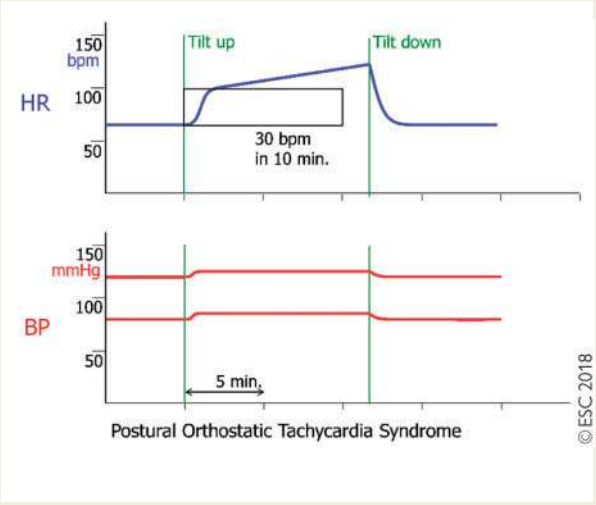
In this example, BP and HR increase quickly at first and then gradually keep increasing over about 15 min (*Web Figure 21*). There is no OH.



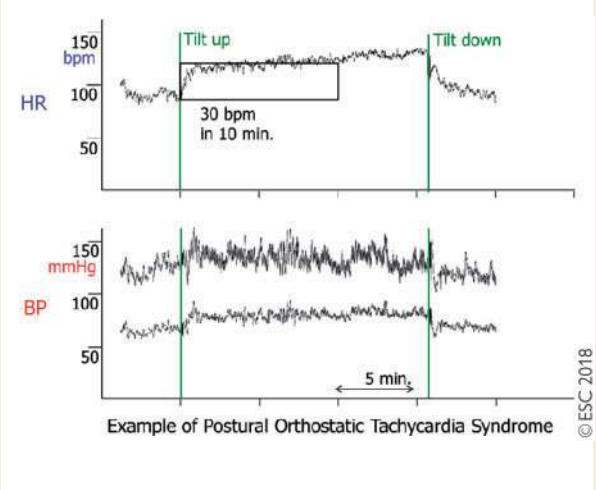
Web Figure 18 Pattern of psychogenic pseudosyncope. BP = blood pressure; b.p.m. = beats per minute; HR = heart rate.



Web Figure 19 Example of psychogenic pseudosyncope. BP = blood pressure; b.p.m. = beats per minute; HR = heart rate.



Web Figure 20 Pattern of postural orthostatic tachycardia syndrome. BP = blood pressure; b.p.m. = beats per minute; HR = heart rate.



Web Figure 21 Example of postural orthostatic tachycardia syndrome. BP = blood pressure; b.p.m. = beats per minute; HR = heart rate.

6.3.15 Example of video recording of reflex syncope
See Supplementary material online, *Video 1A and 1B*.

7. Practical Instructions for section 4.2.3: basic autonomic function tests

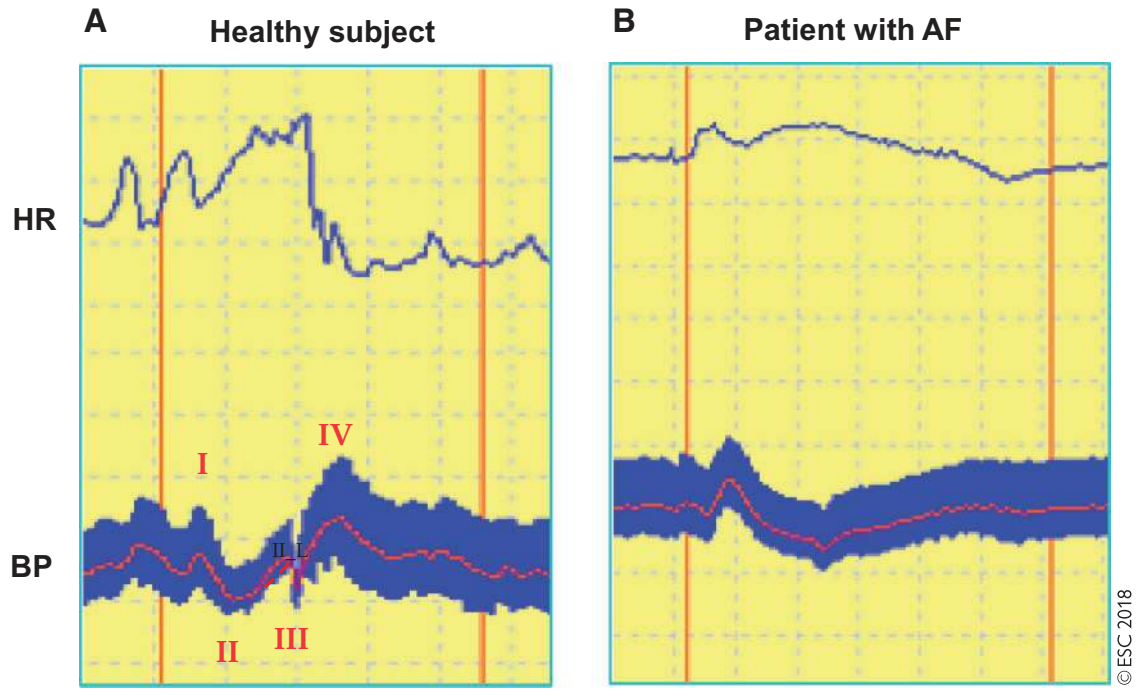
7.1 Method for performing and interpreting autonomic function tests properly

Autonomic function assessment, performed in a dedicated laboratory, aims to characterize cardiovascular sympathetic and parasympathetic autonomic function, and may identify autonomic failure as the underlying cause of syncope. No single autonomic function test can provide a comprehensive assessment of the autonomic nervous system, so different clinical questions may require a different battery of autonomic function tests.

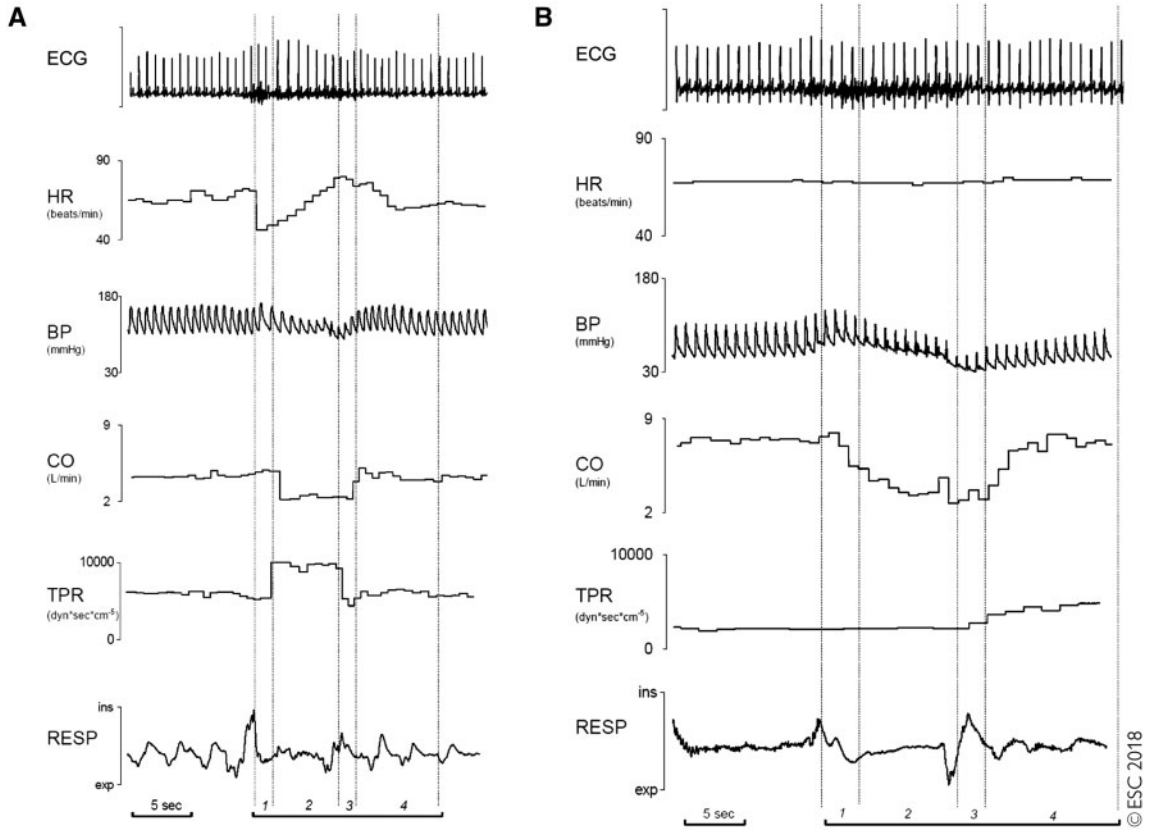
Autonomic function testing should be performed by a specialist trained in autonomic function testing and interpretation. The required equipment includes beat-to-beat BP and ECG monitoring, a motorized tilt table, 24-h ambulatory BP monitoring devices, and other specialized equipment depending on the range of testing. Tests should ideally be performed before noon in a quiet environment. The room should be temperature controlled, between 21–23°C. Patients should be fasted for 3 h before the test, and avoid nicotine and caffeine-, theine-, or taurine-containing drinks on the day of examination.

7.1.1 Valsalva manoeuvre

The four phases of the Valsalva manoeuvre are illustrated in *Web Figure 22A and 22B*. During the manoeuvre, the patient is asked to conduct a maximally forced expiration for 15 s against a closed glottis, i.e. with closed nose and mouth, or into a closed loop system with a resistance of 40 mmHg. The haemodynamic changes during the test should be monitored using beat-to-beat continuous non-invasive BP measurement and ECG. In the initial phase (phase I, first 2–3 s), BP slightly increases due to temporarily increased left ventricle filling. When intrathoracic pressure rises during the forced expiration (phase II), BP decreases due to strongly reduced venous return in normal individuals, cardiac output declines, and a compensatory HR increase occurs driven by the baroreceptor reflex. The hypotension evokes another autonomic compensatory response, i.e. an increase in the systemic vascular resistance (total peripheral resistance) driven by the sympathetic outflow to the vessels. Thus, both HR increase and vasoconstriction counteract hypotension. Finally, when the patient releases the air (phase III) and starts breathing normally (phase IV), the intrathoracic overpressure suddenly declines and a typical 'overshoot' in BP can be observed, while the HR normalizes.



Web Figure 22 Valsalva manoeuvre. (*A*) The four phases of a normal Valsalva response in a healthy subject. Phase I: the patient begins to inflate their lungs. Intra-thoracic pressure rises and transiently increases cardiac stroke volume (mechanical effect). Phase II: initially, a distinct blood pressure fall can be observed, as intrathoracic pressure increases and the venous return declines (early phase II); sympathetic outflow to the blood vessels increases and parasympathetic outflow to the heart decreases in late phase II. Phase III: the patient stops inflating their lungs; blood pressure falls briefly (mechanical effect, mirror of phase I). Phase IV: intrathoracic pressure returns to negative and enhances venous return to the heart; sympathetic vasoconstriction produces blood pressure 'overshoot', confirming preserved autonomic control of the cardiovascular system. Parasympathetic effect on the heart is rate decrease. (*B*) Pathological Valsalva response in autonomic failure. Absence of heart rate increase (phase II) and delayed blood pressure recovery (phase IV) are characteristic of cardiovascular autonomic denervation. AF = autonomic failure; BP = blood pressure; HR = heart rate.



Web Figure 23 Valsalva response. (*A*) Normal Valsalva response: initially, a distinct blood pressure fall can be observed as intrathoracic pressure increases and venous return declines (phase II). Reflex heart rate increase and vasoconstriction produce blood pressure 'overshoot' in late phase II and phase IV, confirming preserved autonomic control of the cardiovascular system. (*B*) Pathological Valsalva response in autonomic failure. Absence of HR increase (phase II) and delayed BP recovery (phase IV) are characteristic of cardiovascular autonomic denervation. BP = blood pressure; CO = cardiac output; ECG = electrocardiogram; exp = expiration; HR = heart rate; ins = inspiration; RESP = respiration; TPR = total peripheral resistance.

A case of normal Valsalva response is shown in *Web Figure 23A*. A case of pathological Valsalva response in autonomic failure is shown in *Web Figure 23B*. Absence of heart rate increase (phase II) and delayed blood pressure recovery (phase IV) are characteristics of cardiovascular autonomic denervation.

A case of pronounced hypotensive Valsalva response in situational syncope is shown in *Web Figure 24*.

7.1.1.1 Example of video recording of Valsalva manoeuvre

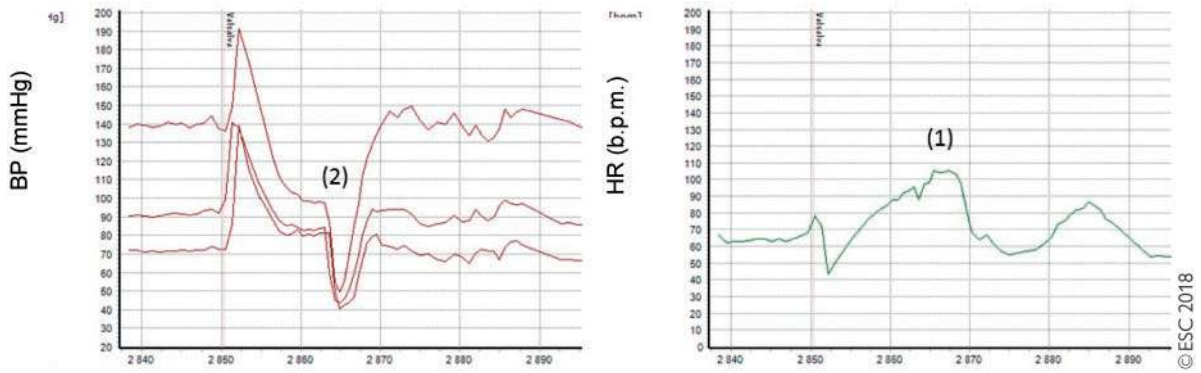
See Supplementary material online, *Video 2*. With thanks to Dr. Jean Pierre Ndayisaba, Innsbruck, A who contributed to Video production.

7.1.2 Deep-breathing test

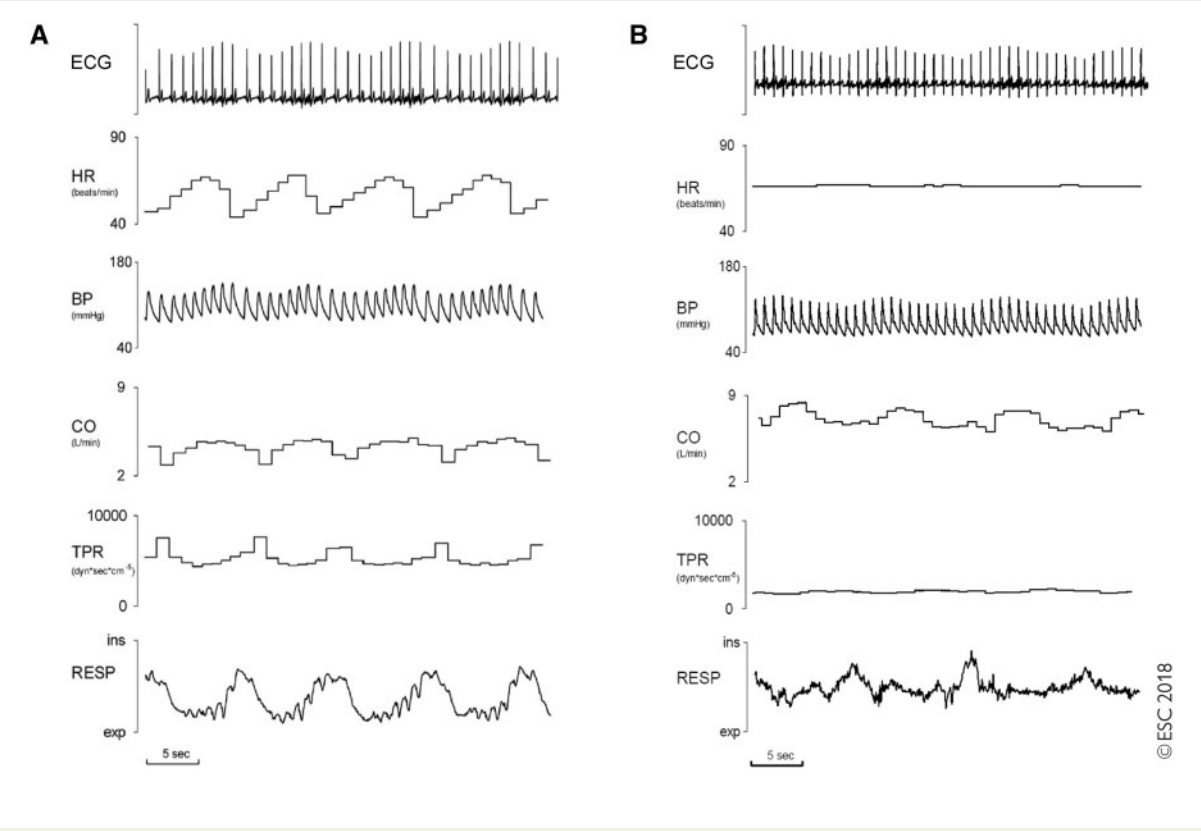
During the deep-breathing test, the patient is asked to breathe deeply at 6 breaths per minute for 1 min under continuous HR and BP monitoring. In healthy individuals, HR rises during inspiration and falls during expiration (*Web Figure 25A* and *Web Video 3*, see Supplementary material online, Video 3). This phenomenon, known as respiratory sinus arrhythmia, is modulated by cardiac parasympathetic (vagal) outflow. Similar fluctuations can be observed in BP, cardiac output, and total peripheral resistance. These oscillations are mechanically induced by the changes in transthoracic pressure produced by rhythmic respiratory activity. HR variability during deep breathing (also called the expiratory/inspiratory index, or E/I index) is ≥15 b.p.m. in healthy individuals aged >50 years. In patients with cardiovascular autonomic failure (*Web Figure 25B*), HR variability during deep breathing is blunted or even abolished due to degeneration of parasympathetic autonomic fibres to the heart. The absence of vascular sympathetic modulation can be inferred by the lack of oscillation in total peripheral resistance, whereas non-neural respiratory mediated fluctuations can be observed in BP and cardiac output.

7.1.2.1 Example of video recording of deep-breathing test

See Supplementary material online, *Video 3*. With thanks to Dr. Jean Pierre Ndayisaba, Innsbruck, A who contributed to Video production.



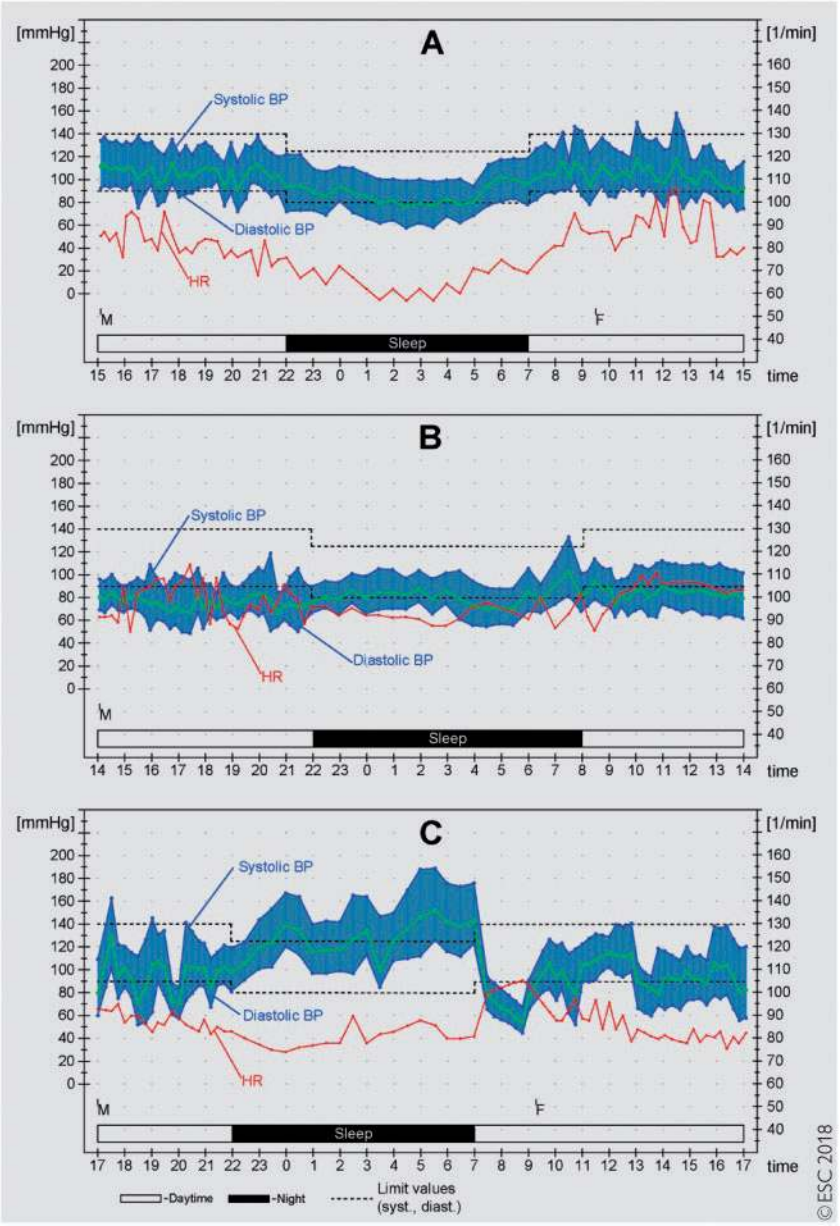
Web Figure 24 Pronounced hypotensive Valsalva response in situational syncope (cough, weightlifting, brass instrument playing, or singing). Normal heart rate response (1) is associated with a pronounced hypotension (2) and reproducible subjective symptoms (dizziness). BP = blood pressure; b.p.m. = beats per minute; Dia = diastolic; HF = heart failure; HR = heart rate; MAP = mean arterial pressure; Sys = systolic.



Web Figure 25 Deep-breathing test. (*A*) Deep-breathing test in a 59-year-old healthy proband. Note preserved heart rate modulation during the test. (*B*) Deep-breathing test in a 62-year-old patient with pure autonomic failure atrophy. Note that heart rate variability during the test is almost abolished. BP = blood pressure; CO = cardiac output; ECG = electrocardiogram; exp = expiration; HR = heart rate; ins = inspiration; RESP = respiration; TPR = total peripheral resistance.

7.1.3 Twenty-four-hour ambulatory blood pressure

In patients with autonomic failure, OH is frequently associated with a nocturnal 'non-dipping' or even 'reverse-dipping' BP pattern (*Web Figure 26*).



Web Figure 26 Nocturnal blood pressure patterns in 24-h ambulatory blood pressure monitoring. (*A*) Dipping (blood pressure falls >10% with respect to daytime). (*B*) Non-dipping (blood pressure falls <10% with respect to daytime). (*C*) Reverse dipping (BP increases with respect to daytime). Note exacerbation of hypotension in the early morning and after meals (at 2 p.m. and 8 p.m.) in this 57-year-old patient with multiple system atrophy. *Reproduced from Fanciulli et al., 2014*[188] *with permission from Springer Verlag Wien.* BP = blood pressure; diast. = diastolic; F = failed measurement; HR = heart rate; M = manual measurement; syst. = systolic.

8. Practical Instructions for section 4.2.4.7: implantable loop recorder

8.1 Classification of electrocardiographic recordings

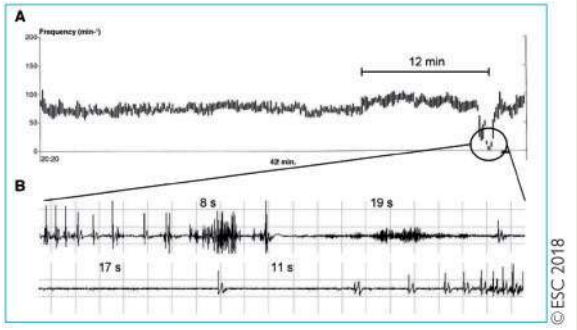
Figures taken from Brignole *et al.*[189,190]

Web Table 6 **Classification of electrocardiogram recordings with their probable related pathophysiology (adapted from the International Study on Syncope of Unknown Etiology classification)**[189–191]

Type	ECG classification	Suggested pathophysiology
Type 1. Asystole (R-R pause ≥3 seconds)	Type 1A. Sinus arrest: progressive sinus bradycardia or initial sinus tachycardia followed by progressive sinus bradycardia until sinus arrest *(see Web Figure 27)*	Probably reflex
	Type 1B. Sinus bradycardia plus AV block: progressive sinus bradycardia followed by AV block (and ventricular pause/s) with concomitant decrease in sinus rate *(see Web Figure 28)*	Probably reflex
	Type 1C. AV block: sudden onset AV block (and ventricular pause/s) with concomitant increase in sinus rate *(see Web Figures 29 and 30)*	Probably intrinsic (if SHD or bundle branch block) or idiopathic (if no SHD and low plasmatic adenosine)[190]
Type 2. Bradycardia	Decrease in HR >30% or <40 b.p.m. for >10 seconds *(see Web Figure 31)*	Probably reflex
Type 3. No (type 3A) or slight (type 3B) rhythm variations	Variations in HR <30% and HR >40 b.p.m *(see Web Figures 32 and 33)*	Uncertain
Type 4. Tachycardia. Increase in HR >30% or >120 b.p.m.	Type 4A. Progressive sinus tachycardia *(see Web Figures 34)*	Uncertain
	Type 4B. Atrial fibrillation	Cardiac arrhythmia
	Type 4C. SVT (except sinus)	Cardiac arrhythmia
	Type 4D. Ventricular tachycardia	Cardiac arrhythmia

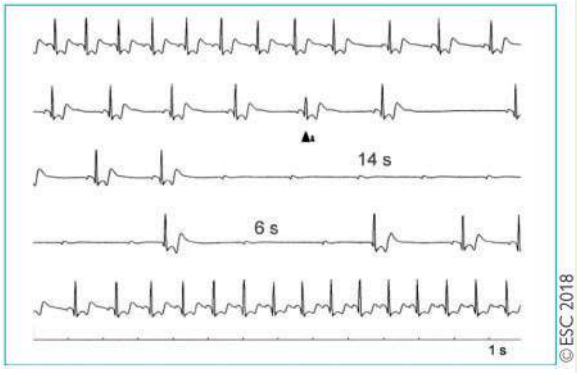
AV = atrioventricular; b.p.m. = beats per minute; ECG = electrocardiogram; HR = heart rate; ISSUE = International Study on Syncope of Unknown Etiology; SHD = structural heart disease; SVT = supraventricular tachycardia.

8.1.1 Type 1A, sinus arrest



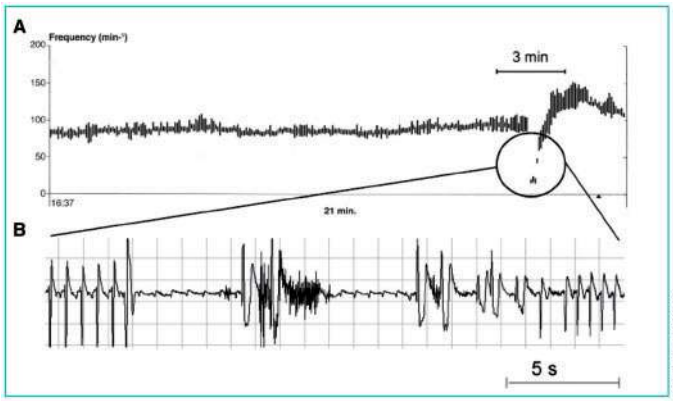
Web Figure 27 Type 1A, sinus arrest. (*A*) Heart rate trend during 42 min of loop recording. Initially, the heart rate is stable at approximately 70 b.p.m.; at the beginning of the episode the HR increases to 100 b.p.m., then decreases rapidly to a very low rate. (*B*) The expanded electrocardiogram at the time of syncope shows prolonged multiple pauses due to sinus arrest. The noise recorded during the pauses of 8 s and 19 s of asystole probably reflects jerking movements of the patient. The finding of initial sinus tachycardia with progressive sinus bradycardia frequently followed by sinus arrest has been regarded as highly suggestive of a neurally mediated mechanism. b.p.m. = beats per minute; ECG = electrocardiogram; HR = heart rate.

8.1.2 Type 1B, sinus bradycardia plus atrioventricular block

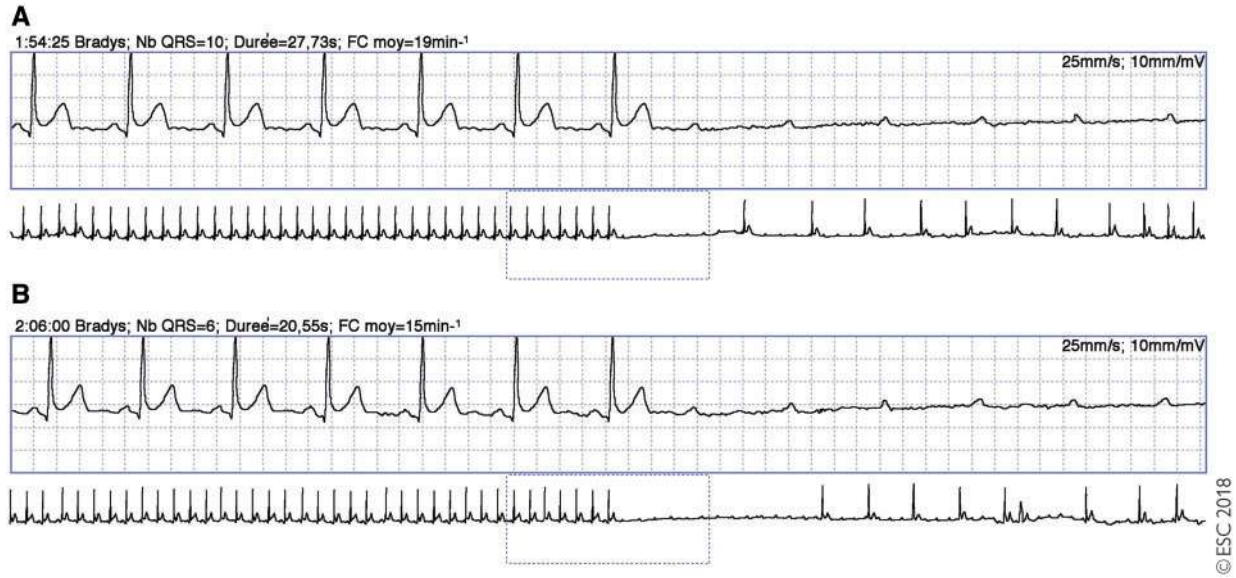


Web Figure 28 Type 1B, sinus bradycardia plus atrioventricular block. Progressive sinus bradycardia to <30 b.p.m. followed by atrioventricular block (and long ventricular pauses) with concomitant severe bradycardia. The association between atrioventricular block and sinus arrest suggests a neurally mediated mechanism. ▲ indicates the time when the patient activated the recording. AV = atrioventricular; b.p.m. = beats per minute.

8.1.3 Type 1C, atrioventricular block

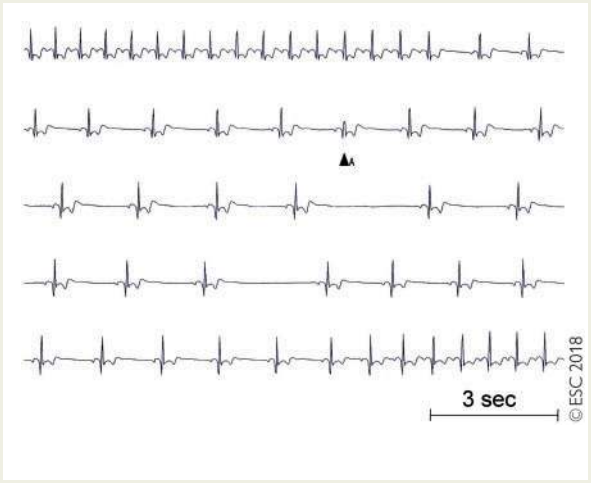


Web Figure 29 Type 1C, intrinsic atrioventricular block: patient with bundle branch block. (*A*) Heart rate trend during the whole 21-min loop recording. Initially, the heart rate is stable at approximately 80 b.p.m. and suddenly falls at the time of the syncope. (*B*) The expanded electrocardiogram shows blocked P waves with two main pauses of 5- and 6-s duration. The sinus rate increases during atrioventricular block. The noise recorded during the second pause probably reflects jerking movements of the patient. The onset of atrioventricular block (and ventricular pause) was sudden and was initiated and ended by ventricular premature extrasystole. This pattern is opposite to the finding of *Web Figures 27* and *28* and suggests a different mechanism, namely an intrinsic disease of the His-Purkinje system as observed in Stokes–Adams attacks. AV = atrioventricular; b.p.m. = beats per minute; ECG = electrocardiogram; HR = heart rate.



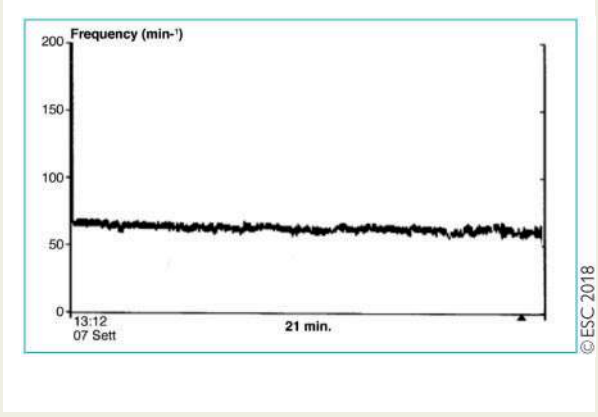
Web Figure 30 Type 1C, idiopathic (low-adenosine) atrioventricular block. Holter recording of two episodes of spontaneous syncope (*A* and *B*), which occurred a few minutes apart. The two episodes were very similar and were characterized by sudden-onset complete atrioventricular block without changes in P-P cycle length, which remained constant at 720 ms (top traces A and B), and long ventricular asystole of 7 and 11 s, respectively (bottom traces A and B). The patient had no structural heart disease, a normal electrocardiogram, and low values of plasmatic adenosine. Contrary to the case shown in *Web Figure 29*, atrioventricular block was never initiated by atrial, His, or ventricular premature extrasystole, increased heart rate (tachy-dependent atrioventricular block), or decreased heart rate (brady-dependent atrioventricular-block), all features that support a diagnosis of intrinsic atrioventricular block. AV = atrioventricular.

8.1.4 Type 2, bradycardia

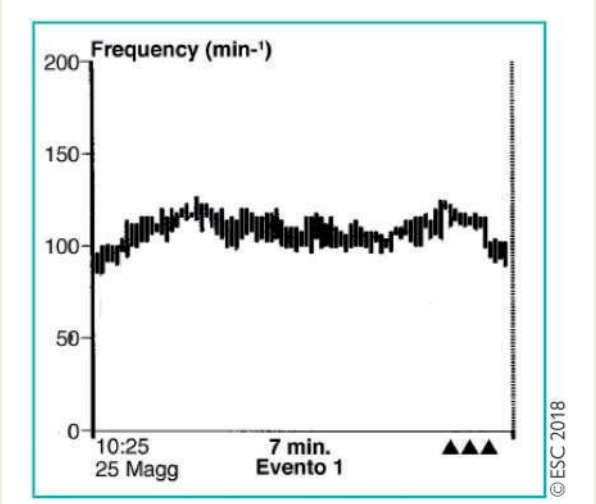


Web Figure 31 Type 2, bradycardia. The initial sinus tachycardia 90 b.p.m. is followed by progressive sinus bradycardia until <30 b.p.m. for >10 s. ▲ indicates the time when the patient activated the recording. b.p.m. = beats per minute.

8.1.5 Type 3, no or slight rhythm variations

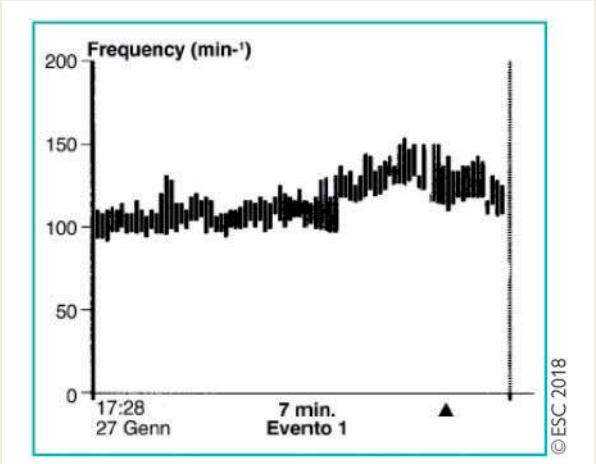


Web Figure 32 Type 3A. No variation in heart rate. Heart rate trend during 21 min of loop recording. Heart rate is approximately 60 b.p.m. and remains stable throughout the recording period. ▲ indicates the time when the patient activated the recording after resuming consciousness. The pattern of almost no variation in heart rate excludes the participation of a cardiac reflex in the genesis of the loss of consciousness; this means that reflex syncope is also unlikely, although it cannot be definitely ruled out. b.p.m. = beats per minute; HR = heart rate; LOC = loss of consciousness.



Web Figure 33 Type 3B. Slight variations (<10% variation in heart rate). Heart rate trend during 7 min of loop recording. Initially, the heart rate is approximately 90 b.p.m.; it progressively increases to 120 b.p.m. in a few minutes, then progressively decreases to 100 b.p.m. That value is reached roughly 1 min before multiple device activation by the patient (▲) and thus is likely to coincide with the loss of consciousness. The pattern of a progressive increase and then decrease in heart rate is similar to the pattern observed during tilt

8.1.6 Type 4, tachycardia



Web Figure 34 Type 4A progressive sinus tachycardia. Heart rate trend during 7 min of loop recording. Initially, the heart rate is approximately 100 b.p.m.; it then progressively increases up to 130 b.p.m., a value reached roughly 1 min before device activation by the patient (▲), and thus is likely to coincide with the loss of consciousness. The pattern of progressive heart rate increase is similar to a pattern observed in some patients during tilt testing; this pattern is characterized by progressive tachycardia and hypotension, and is variously defined as an 'excessive heart rate rise' or 'orthostatic intolerance'. This behaviour suggests that heart rate increases as part of an insufficient compensatory attempt and indicates a sympathetic arousal. b.p.m. = beats per minute; HR = heart rate; LOC = loss of consciousness.

9. Practical Instructions for section 5.2: treatment of reflex syncope

9.1 European Society of Cardiology information sheet for patients affected by reflex syncope

This information sheet has been written for patients (and their relatives and carers) who have been diagnosed with VVS. It is intended to explain their diagnosis and treatment.

What is syncope?

Syncope is one of several conditions in which a person loses consciousness for a short time, usually only a minute or two.

Syncope is caused by a reduction in the flow of blood to the brain. The brain then stops working, the person loses consciousness and falls, and will not know later what happened during that time.

There are several causes of syncope, such as problems with blood pressure or the heart, but vasovagal syncope (VVS) is the most common cause: one in four people will have at least one attack of VVS during their lives, but only 1 in 20 people will have at least five attacks, and even fewer will have many more attacks. Sometimes the diagnosis of VVS is easy, but sometimes it is not. In the latter, the attacks may at first look like epileptic seizures or a heart problem, in which case the person is seen by a neurologist or cardiologist who usually orders tests to investigate the brain and the heart.

The diagnosis of VVS

The diagnosis of VVS rests on specific clues from history taking, meaning that your doctor asks you what triggers the attacks and what happens to you during them. Typical triggers are pain, emotion, seeing blood or having a blood sample taken, and standing for some time. Other important clues are feeling nauseous, starting to sweat, or turning very pale before the attacks. During the attacks, people fall and, if they were upright, can hurt themselves. There can be a few movements of the face and limbs and the person may become incontinent. The unconsciousness typically lasts less than a minute and then the person quickly becomes fully conscious. However, many people feel very tired after the attack, and children especially may fall asleep. These clues are the most importance evidence that a person has VVS.

A 'tilt table test' can be used to test for VVS. This test tries to provoke an attack, so that doctors can monitor your blood pressure and heart rate during an attack and ask whether the attack is the same as a spontaneous one.

What happens in the body during VVS?

VVS is brought about by a brain reflex. When triggered, the reflex affects the circulation in two ways. First, blood vessels in the body open too widely, blood moves down in the body, and blood pressure drops. Second, the brain may 'tell' the heart to slow down and even to stop temporarily (this is not a heart disease, but a healthy heart receiving the wrong instruction). Either way, the circulation of blood decreases. The brain is affected first because it needs a lot of blood and because it is located at the top of the body, making it a more difficult place to pump blood to. Consciousness is lost when the brain stops working, and then the person falls down. However, lying down helps to get blood back to the brain and consciousness is quickly restored. This explains why lying down helps to prevent fainting: it helps to restore blood pressure and blood flow to the brain.

It is not known why some triggers, such as seeing blood, prompt the reflex. We do know that anything that reduces blood pressure or the amount of water in the body makes it easier to trigger the reflex, such as not drinking much, eating very little salt, sweating a great deal, diarrhoea, some drugs, warm places, and simply standing.

Preventing VVS

There are several things that you can do to prevent syncope. If you feel a spell coming on, lying down is best, with your feet in the air. Obviously, you cannot lie down everywhere, in which case you can sit down or do 'counter manoeuvres' (tricks that raise blood pressure). People who are prone to VVS should drink plenty of fluids and eat salt, as salt is needed to keep the water in the body (unless there are medical reasons to cut down on salt!). In most patients, these simple measures allow them to control the fainting tendency. In rare cases, doctors may try drugs to increase the volume of blood and blood pressure, and in very rare cases a pacemaker may be needed. This is a last resort when nothing else works and when it has been proven that the reflex makes the person's heart stop temporarily.

Box. Actions to take to avoid an impending attack of reflex syncope

(1) When you feel symptoms of syncope coming on, the best response is to lie down. If this is not possible, then sit down and do counter manoeuvres. The final warning symptom is when everything goes dark and you lose vision: then you only have seconds in which to prevent syncope.

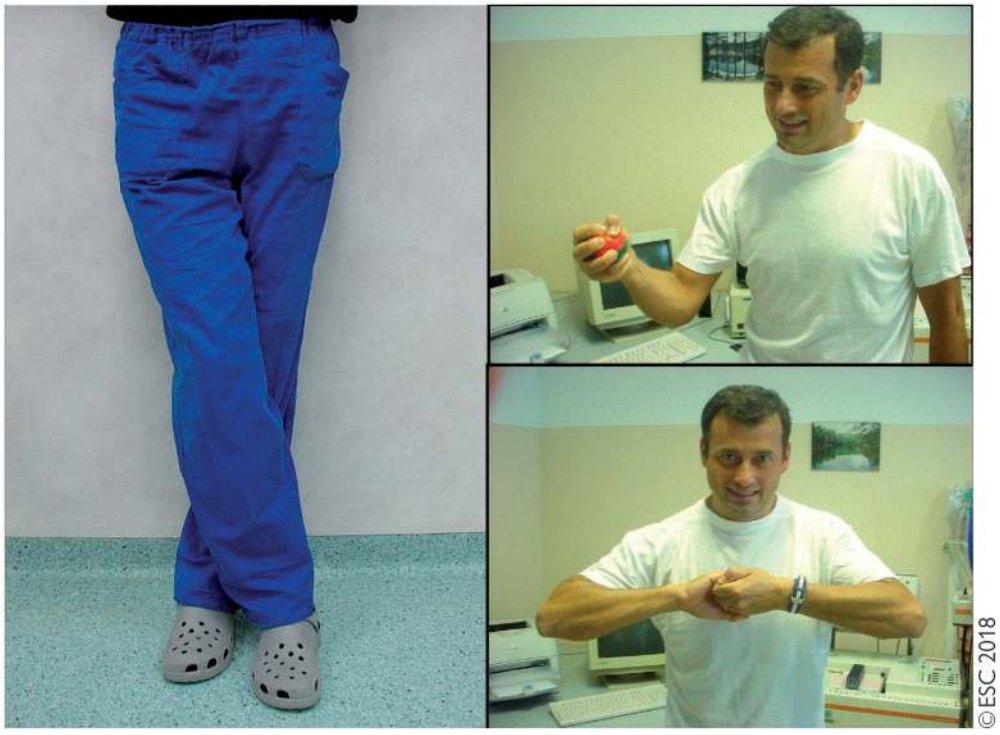
(2) Your doctor will have shown you how to do the counter manoeuvres. They all concern tensing large muscles in the body. One way is to press the buttocks together and straighten the knees forcefully; another is to cross your legs and press them together over their entire length. Others make fists and tense the arm muscles.

(3) Drink around 2 L of fluid a day and do not use salt sparingly (unless there are medical reasons not to!). A simple way to tell whether or not your fluid intake is high enough is to check the colour of your urine: if it is dark yellow there is little fluid in your body, so try to keep it very lightly coloured.

(4) Inform those in your immediate surroundings what to do during a spell: in typical spells there is no need to call a doctor or an ambulance. Of course, if you hurt yourself in the fall, this may change.

9.2 Counter-pressure manoeuvres

The most commonly used manoeuvres are leg crossing, hand gripping, and arm tensing[186,192] *(Web Figure 35)*. Patients with known susceptibility to neural reflex or orthostatic faints should be instructed to use these manoeuvres as preventive measures when they experience any



Web Figure 35 Most common counter-pressure manoeuvres: leg crossing, hand gripping, and arm tensing.

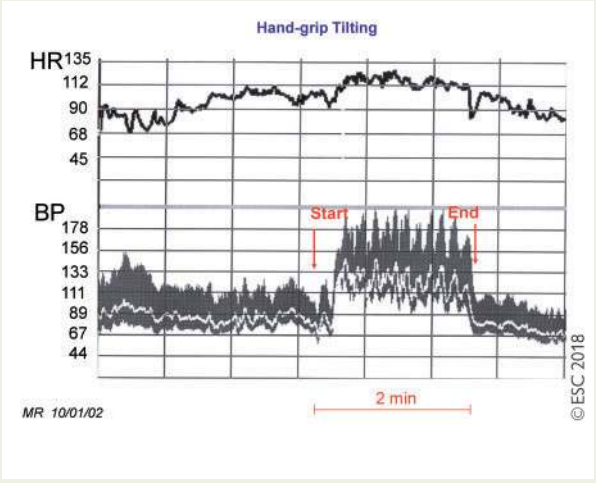
symptoms of impending fainting. Whichever of the manoeuvres is employed, they can increase blood pressure rapidly and significantly, thus aborting syncope for a sufficient period to permit the affected person to achieve a safe position (e.g. if driving, pull the car to the side of the road; if standing, sit or lie down) *(Web Figure 36)*.

Physical manoeuvres for interrupting reflex or orthostatic faints (*Web Figure 35*):

Leg crossing. Consists of leg crossing combined with maximum tensing of leg, abdominal, and buttock muscles for the maximum tolerated time or until complete the disappearance of symptoms. This procedure is sometimes described in the literature as leg crossing with muscle tensing. Leg crossing alone has also been shown to be useful but is less powerful in terms of preventing hypotension.

Hand gripping. Consists of the maximal squeezing of a rubber ball (approximately 5–6 cm in diameter) or a similar soft object taken in the dominant hand, for the maximum tolerated time or until the complete disappearance of symptoms (*Web Figure 36*).

Arm tensing. Consists of the maximum tolerated isometric contraction of the two arms achieved by gripping one hand with the other and at the same time abducting (pulling away) the arms for the maximum tolerated time or until the complete disappearance of symptoms.



Web Figure 36 Hand gripping. The start of the manoeuvre causes a rapid rise in blood pressure, which persists as long as the contraction is maintained; initially HR slightly increases and then slightly decreases. BP = blood pressure; HR = heart rate.

10. Practical Instructions for section 7: psychogenic transient loss of consciousness

European Society of Cardiology information sheet for patients affected by psychogenic pseudosyncope

This information sheet is aimed at patients with psychogenic pseudosyncope as well as their relatives or carers. It is intended to explain the diagnosis, treatment, and management of the condition.

What is psychogenic pseudosyncope?

Psychogenic pseudosyncope, or PPS, is one of the terms that doctors may use to describe your spells. Take a look at what the words mean on their own: 'syncope' means someone loses consciousness because the brain temporarily does not get enough blood. A good example of syncope is the 'common faint' (or vasovagal syncope, VVS), in which people faint when they see blood or stand for some time. Adding 'pseudo' means that the spells look like syncope but are not really. 'Psychogenic' means that the spells have a psychological origin. Together, the spells look as if someone loses consciousness because the brain does not get enough blood, but in reality, the cause is psychological. There are various other words for the psychological nature of the attacks, such as 'functional'.

What it does and does not mean

The 'psychological' part is difficult to understand. Certainly, people with PPS do not pretend to have attacks. Instead, the attacks happen to them—just as the common faint or a heart attack can happen—and all are beyond their control. Therefore, people with PPS should not be blamed for these attacks, nor should they blame themselves. People with PPS can suffer greatly from these spells: school, work, and social life suffer, with some becoming distressed and depressed. The problem must be taken seriously and addressed. Most people do not like to hear that they have a psychological problem; this is understandable. Even so, understanding what the attacks are is the first step to getting better.

People have such spells because of psychological stress. Sometimes patients with PPS know quite well that they are struggling with a problem, and sometimes they do not. Note that the spells rarely occur at actual moments of stress; most often they occur unexpectedly, without any trigger that doctors or patients can identify.

Diagnosing

Patients sometimes believe that doctors think a problem is psychological because the doctor cannot think of any other reason. But that is not how such a diagnosis is reached. Instead, specific features point towards PPS, just as for any diagnosis.

After the diagnosis

For some patients, getting the diagnosis is a relief: they finally know what they have. In some cases, just knowing what the problem is reduces the frequency of the spells, and the spells may even disappear altogether.

The spells indicate that something is causing stress, but not what it is. The causes differ greatly between patients, and in some cases, there is no obvious problem.

If the attacks do not go away a few months after the diagnosis, psychiatric or psychological help may be needed. The therapy will usually be a form of 'cognitive behavioural therapy', but the choice depends on the nature of the problem and the therapist. It is difficult to predict how well the patient will react to the therapy. This depends on many things, such as how serious the underlying problem is. If it is serious, having the spells may just be one expression of the problem, so there may be other symptoms.

Dealing with the attacks

After the diagnosis, patients and their relatives should understand that the spells are not a medical emergency: the heart and brain are not at any risk. There is no need to call a doctor or an ambulance for such spells (unless, obviously, the patient hurts themselves).

During the period in which patients receive psychological therapy, it may benefit the patient to speak with the doctor who made the diagnosis, to answer remaining or new questions.

Actions to take when there are attacks of PPS

- Relatives or colleagues should know what a typical attack looks like (usually patients look as if they are asleep but cannot be woken).
- Relatives or colleagues should know beforehand what to do during a typical attack.
- The attacks are not a medical emergency, so it is not necessary to call an ambulance.
- The attacks will pass by themselves, but some patience is required.
- Patients may be moved during an attack, if necessary.
- While waiting for the attack to end, patients may be put in a comfortable position, such as lying on their side with a pillow under the head.
- People close to the patient may stay next to the patient and comfort them when they recover, as they are then often emotionally distressed.

This sheet has been prepared in collaboration with Michela Balconi[a,c], Claudio Lucchiari[b], and Pier Luigi Baldi[c]

[a]Research Unit in Affective and Social Neuroscience, Catholic University of Milan, Milan, Italy

[b]Department of Philosophy, Università degli Studi di Milano, Milan, Italy

[c]Department of Psychology, Catholic University of Milan, Milan, Italy

11. Practical Instructions for section 9.2: the clinical nurse specialist in the syncope unit

See Supplementary material online, *Video 4*.

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