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ESC GUIDELINES

Guidelines on Management (Diagnosis and Treatment) of Syncope — Update 2004[☆]

The Task Force on Syncope, European Society of Cardiology[☆☆]

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Preamble

Guidelines and Expert Consensus documents aim to present all the relevant evidence on a particular issue in order to help physicians to weigh the benefits and risks of a particular diagnostic or therapeutic procedure. They should be helpful in everyday clinical decision-making.

A great number of Guidelines and Expert Consensus Documents have been issued in recent years by the European Society of Cardiology (ESC) and by different organisations and other related societies. This profusion can put at stake the authority and validity of guidelines, which can only be guaranteed if they have been developed by an unquestionable decision-making process. This is one of the reasons why the ESC and others have issued recommendations for formulating and issuing Guidelines and Expert Consensus Documents.

In spite of the fact that standards for issuing good quality Guidelines and Expert Consensus Documents are well defined, recent surveys of Guidelines and Expert Consensus Documents published in peer-reviewed journals between 1985 and 1998 have shown that methodological standards were not complied with in the vast majority of cases. It is therefore of great importance that guidelines and recommendations are presented in formats that are easily interpreted. Subsequently, their implementation programmes must also be well conducted. Attempts have been made to determine whether guidelines improve the quality of clinical practice and the utilisation of health resources.

The *ESC Committee for Practice Guidelines (CPG)* supervises and coordinates the preparation of new *Guidelines* and *Expert Consensus Documents* produced by Task Forces, expert groups or consensus panels. The chosen experts in these writing panels are asked to provide disclosure statements of all relationships they may have which might be perceived as real or potential conflicts of interest. These disclosure forms are kept on file at the European Heart House, headquarters of the ESC. The Committee is also responsible for the endorsement of these Guidelines and Expert Consensus Documents or statements.

The Task Force has classified and ranked the usefulness or efficacy of the recommended procedure and/or treatments and the Level of Evidence as indicated in the tables below:

Classes of recommendations

Class I	Evidence and/or general agreement that a given diagnostic procedure/ treatment is beneficial, useful and effective;
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the treatment;
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy;
Class IIb	Usefulness/efficacy is less well established by evidence/opinion;
Class III[a]	Evidence or general agreement that the treatment is not useful/effective and in some cases may be harmful.

[a] Use of Class III is discouraged by the ESC.

Levels of Evidence	
Level of Evidence A	Data derived from multiple randomized clinical trials or meta-analyses
Level of Evidence B	Data derived from a single randomized clinical trials or non-randomized studies
Level of Evidence C	Consensus of opinion of the experts and/or small studies, reprospective studies, registries

Scope of the document

The purpose of this document is to provide specific recommendations on the diagnostic evaluation and management of syncope. The document is divided into four parts: (1) classification, epidemiology and prognosis; (2) diagnosis; (3) treatment; and (4) special issues in evaluating patients with syncope. Each part reviews background information and summarizes the relevant literature. The details of pathophysiology and mechanisms of various aetiologies were considered to lie outside the scope of this document. Although the document encompasses many of the important aspects of syncope, the panel recommendations focused on the following main questions:

1. What are the diagnostic criteria for the causes of syncope?
2. What is the preferred approach to the diagnostic work-up in various subgroups of patients with syncope?
3. How should patients with syncope be risk stratified?
4. When should patients with syncope be hospitalized?
5. Which treatments are likely to be effective in preventing syncopal recurrences?

Method

The methodology for writing this document consisted of literature reviews and consensus development by the panel assembled by the European Society of Cardiology. The European Society of Cardiology guidelines for the management (diagnosis and treatment) of syncope were published in August 2001 [1]. Since then, numerous clinical trials and observational studies have been published or presented, some of which alter the recommendations made in the original document.

Therefore, the Task Force on Syncope of the European Society of Cardiology met in August 2002 and developed a comprehensive outline of the issues that needed to be revised in the document. Subgroups of the panel were formed and each was assigned the task of reviewing the literature on specific topics and of developing a draft summarizing the issue. Each subgroup was to perform literature searches on MEDLINE and to supplement the search by documents from their personal collections. The panel reconvened in September 2003, reviewed the draft documents, made revisions whenever appropriate and developed the consensus recommendations. The panel discussed each recommendation and arrived at consensus by obtaining a majority vote. When there was divergence of opinion, this was noted. Since the goal of the project was to provide specific recommendations for diagnosis and management, guidelines are provided even when the data from the literature was not definitive. It must be pointed out that most of the recommendations are based on consensus expert opinion. All the members of the panel reviewed final drafts and approved the final document.

With respect to the initial document, the following sections (and recommendations) were widely revised in the 2004 update:

- Classification of transient loss of consciousness
- Epidemiological and prognostic considerations
- Initial evaluation and diagnostic flow
- Prolonged electrocardiographic monitoring
- Electrophysiological study
- ATP test
- Ventricular signal averaged electrocardiogram, T wave alternans
- Exercise testing
- Neurological and psychiatric evaluation
- Treatment of neurally-mediated (reflex) syncope
- Syncope in the older adult
- Syncope in paediatric patients
- Driving and syncope
- Glossary of terms.

Furthermore, since the strategies for the assessment of syncope vary widely among physicians and among hospitals in Europe, we recognised the need to coordinate the evaluation of syncope. We sought to define ESC standards for the management of syncope and we proposed a model of organization for the evaluation of the syncope patient. A new section was thus added to the document on this topic.

A major issue in the use of diagnostic tests is that syncope is a transient symptom and not

a disease. Typically patients are asymptomatic at the time of evaluation and the opportunity to capture a spontaneous event during diagnostic testing is rare. As a result, the diagnostic evaluation has focused on physiological states that could cause loss of consciousness. This type of reasoning leads, of necessity, to uncertainty in establishing a cause. In other words, the causal relationship between a diagnostic abnormality and syncope in a given patient is often presumptive. Uncertainty is further compounded by the fact that there is a great deal of variation in how physicians take a history and perform a physical examination, the types of tests requested and how they are interpreted. These issues make the diagnostic evaluation of syncope inordinately difficult. Consequently, there is a need for specific criteria for diagnosis from history and physical examination, and clear-cut guidelines for choosing tests, test abnormalities and how to use the results in establishing a cause of syncope. This document has tried to provide specific criteria by using the literature as well as a consensus of the panel.

A further concern about tests used for evaluation of the aetiology of syncope is that measurements of test sensitivity are not possible because of a lack of reference or gold standard for most of the tests employed for this condition. Since syncope is an episodic symptom, a reference standard could be an abnormality observed during a spontaneous event. This is possible, for instance, if syncope occurred concurrently with an arrhythmia detected by an implantable loop recorder. However, most of the time decisions have to be made based on the patient's history or abnormal findings during asymptomatic periods. To overcome the lack of a gold standard, the diagnostic yield of many tests in syncope has been assessed indirectly by evaluating the reduction of syncopal recurrences after administration of the specific therapy suggested by the results of the tests which were diagnostic.

A major problem with the literature on syncope is that it has been defined variably in the past. Definitions did not always include a restriction that transient loss of consciousness should be due to cerebral hypoperfusion, with the result that many other causes of loss of consciousness could also be interpreted as 'syncope', including concussion, vertebrobasilar TIAs and epilepsy, or even stroke, hardly ever even associated with unconsciousness. In many cases it was not clear whether 'syncope' was interpreted in this very wide sense, here 'transient loss of consciousness' (TLOC), or was used in the restricted sense as in these guidelines. Obviously, mixing epilepsy, concussion or even stroke with syncope proper seriously detracts from the value of epidemiological and prognostic estimates.

The literature on syncope testing is largely composed of case series, cohort studies, or retrospective analyses of already existing data. The impact of testing on guiding therapy and reducing syncopal recurrences is difficult to discern from these methods of research without randomization and blinding. Because of these issues, the panel performed full reviews of the literature for diagnostic tests but did not use predefined criteria for selection of articles to be reviewed. Additionally, the panel did not feel that an evidence-based summary of the literature was possible.

In assessing treatment of syncope, this document reviews the few randomised-controlled trials that have been reported. For various diseases and disorders with known treatments (e.g., orthostatic hypotension, sick sinus syndrome) those therapies are reviewed and recommendations are modified for patients with syncope. Most studies of treatment have used a non-randomized design and many even lack a control group. The interpretation of these studies is very difficult but their results were used in summary recommendations of treatment.

The strength of recommendations has been ranked as follows:

- Class I, when there is evidence for and/or general agreement that the procedure or treatment is useful. Class I recommendations are generally those reported in the sections labelled as 'Recommendations' and in the tables.
- Class II, when usefulness of the procedure or treatment is less well established or divergence of opinion exists among the members of the Task Force.
- Class III, when the procedure or treatment is not useful and in some cases may be harmful.

The strength of evidence supporting a particular procedure/treatment option has been ranked as follows:

- Level of Evidence A=Data derived from multiple randomized clinical trials or meta-analyses
- Level of Evidence B=Data derived from a single randomized trial or multiple non-randomized studies
- Level of Evidence C=Consensus Opinion of experts.

When not expressed otherwise, evidence is of type C

Part 1. Classification, epidemiology and prognosis

Definition

Syncope (derived from the Greek words, 'syn' meaning 'with' and the verb 'kopto' meaning 'I cut' or more appropriately in this case 'I interrupt') *is a symptom, defined as a transient, self-limited loss of consciousness, usually leading to falling. The onset of syncope is relatively rapid, and the subsequent recovery is spontaneous, complete, and usually prompt [2—5]. The underlying mechanism is a transient global cerebral hypoperfusion*.

In some forms of syncope there may be a premonitory period in which various symptoms (e.g., light-headedness, nausea, sweating, weakness, and visual disturbances) offer warning of an impending syncopal event. Often, however, loss of consciousness occurs without warning. Recovery from syncope is usually accompanied by almost immediate restoration of appropriate behaviour and orientation. Retrograde amnesia, although believed to be uncommon, may be more frequent than previously thought, particularly in older individuals. Sometimes the post-recovery period may be marked by fatigue.

An accurate estimate of the duration of syncope episodes is rarely obtained. However, typical syncopal episodes are brief. Complete loss of consciousness in vasovagal syncope is usually no longer than 20 s in duration. In one videometric study of 56 episodes of shortlasting severe cerebral hypoxia in adolescents induced by instantaneous deep fall in systemic pressure using the 'mess trick' syncope occurred in all without any premonitory symptoms and myoclonic jerks were present in 90 percent; the syncope duration averaged 12 s (range 5—22) [4]. However, rarely syncope duration may be longer, even lasting for several minutes. In such cases, the differential diagnosis between syncope and other causes of loss of consciousness can be difficult [5].

Pre-syncope or near-syncope refers to a condition in which patients feel as though syncope is imminent. Symptoms associated with pre-syncope may be relatively non-specific (e.g., 'dizziness'), and tend to overlap with those associated with the premonitory phase of true syncope described earlier.

Brief overview of pathophysiology of syncope

Specific factors resulting in syncope vary from patient-to-patient, but several general principles are worthy of note.

In healthy younger individuals with cerebral blood flow in the range of 50—60 ml/100 g tissue/min — that represents about 12—15 percent of resting cardiac output — minimum oxygen requirements necessary to sustain consciousness (approximately 3.0—3.5 ml O_2/100 g tissue/min) are easily achieved [6]. However, in older individuals, or those with underlying disease conditions, the safety margin for oxygen delivery may be more tenuous [7,8].

Cerebral perfusion pressure is largely dependent on systemic arterial pressure. Thus, any factor that decreases either cardiac output or total peripheral vascular resistance diminishes systemic arterial pressure and cerebral perfusion pressure [9]. In regard to cardiac output, the most important physiological determinant is venous filling (pre-load). Therefore, excessive pooling of blood in dependent parts of the body or diminished blood volume may predispose to syncope. Cardiac output may also be impaired due to bradyarrhythmias, tachyarrhythmias, or valvular disease. In terms of peripheral vascular resistance, widespread and excessive vasodilatation may play a critical role in decreasing arterial pressure (a main cause of fainting in the reflex syncopal syndromes). Vasodilatation also occurs during thermal stress. Impaired capacity to increase vascular tone during standing is the cause of orthostatic hypotension and syncope in patients taking vasoactive drugs and in patients with autonomic neuropathies [10]. Cerebral hypoperfusion may also result from an abnormally high cerebral vascular resistance. Low carbon dioxide tension is probably the main cause, but sometimes the cause remains unknown.

A sudden cessation of cerebral blood flow for 6—8 s has been shown to be sufficient to cause complete loss of consciousness [2]. Experience from tilt testing showed that a decrease in systolic blood pressure to 60 mmHg is associated with syncope [11]. Further, it has been estimated that as little as a 20 percent drop in cerebral oxygen delivery is sufficient to cause loss of consciousness [2]. In this regard, the integrity of a number of control mechanisms is crucial for maintaining adequate cerebral oxygen delivery, including: (a) cerebrovascular 'autoregulatory' capability, which permits cerebral blood flow to be maintained over

a relatively wide range of perfusion pressures; (b) local metabolic and chemical control which permits cerebral vasodilatation to occur in the presence of either diminished pO_2 or elevated $pC0_2$; (c) arterial baroreceptor-induced adjustments of heart rate, cardiac contractility, and systemic vascular resistance, which modify systemic circulatory dynamics in order to protect cerebral flow; (d) and vascular volume regulation, in which renal and hormonal influences help to maintain central circulating volume.

Whatever the mechanism, a transient global cerebral hypoperfusion to critical values induces a syncopal episode. Risk of failure is greatest in the elderly or critically ill patients [5,11]. Ageing alone has been associated with diminution of cerebral blood flow [7]. Additionally, certain common disease states may diminish cerebral blood flow protection. For example, hypertension has been associated with a shift of the autoregulatory range to higher pressures, while diabetes alters the chemoreceptor responsiveness of the cerebrovascular bed [8].

Classification

Syncope must be differentiated from other 'non-syncopal' conditions associated with real or apparent transient loss of consciousness (Fig. 1). Tables 1.1 and 1.2 provide a pathophysiological classification of the principal known causes of transient loss of consciousness. The subdivision of syncope is based on pathophysiology as follows:

- 'Neurally-mediated (reflex) syncope' refers to a reflex response that, when triggered, gives rise to vasodilatation and/or bradycardia; however the contribution of each of these two factors to systemic hypotension and cerebral hypoperfusion may differ considerably. The triggering events might vary considerably in individual patients. The 'classical vasovagal syncope' is

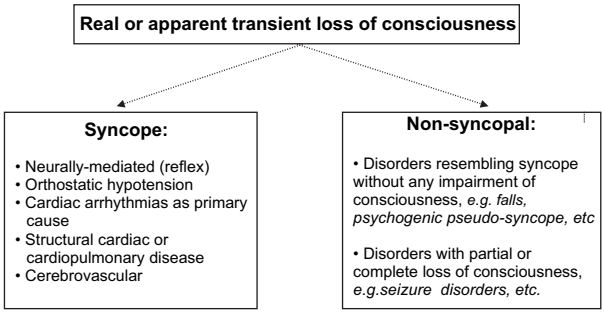

Figure 1 Classification of transient loss of consciousness.

Table 1.1 Causes of syncope

Neurally-mediated (reflex)
- Vasovagal syncope (common faint)
  - classical
  - non-classical
- Carotid sinus syncope
- Situational syncope
  - acute haemorrhage
  - cough, sneeze
  - gastrointestinal stimulation (swallow, defaecation, visceral pain)
  - micturition (post-micturition)
  - post-exercise
  - post-prandial
  - others (e.g., brass instrument playing, weightlifting)
- Glossopharyngeal neuralgia

Orthostatic hypotension
- Autonomic failure
  - primary autonomic failure syndromes (e.g., pure autonomic failure, multiple system atrophy, Parkinson's disease with autonomic failure)
  - secondary autonomic failure syndromes (e.g., diabetic neuropathy, amyloid neuropathy)
  - post-exercise
  - post-prandial
- Drug (and alcohol)-induced orthostatic syncope
- Volume depletion
  - haemorrhage, diarrhoea, Addison's disease

Cardiac arrhythmias as primary cause
- Sinus node dysfunction (including bradycardia/tachycardia syndrome)
- Atrioventricular conduction system disease
- Paroxysmal supraventricular and ventricular tachycardias
- Inherited syndromes (e.g., long QT syndrome, Brugada syndrome)
- Implanted device (pacemaker, ICD) malfunction
- drug-induced proarrhythmias

Structural cardiac or cardiopulmonary disease
- Cardiac valvular disease
- Acute myocardial infarction/ischaemia
- Obstructive cardiomyopathy
- Atrial myxoma
- Acute aortic dissection
- Pericardial disease/tamponade
- Pulmonary embolus/pulmonary hypertension

Cerebrovascular
- Vascular steal syndromes

Table 1.2 Causes of non-syncopal attacks (commonly misdiagnosed as syncope)

Disorders without any impairment of consciousness
• Falls
• Cataplexy
• Drop attacks
• Psychogenic pseudo-syncope
• Transient ischaemic attacks (TIA) of carotid origin
Disorders with partial or complete loss of consciousness
• Metabolic disorders, including hypoglycaemia, hypoxia, hyperventilation with hypocapnia
• Epilepsy
• Intoxications
• Vertebro-basilar transient ischaemic attack

mediated by emotional or orthostatic stress and can be diagnosed by history taking. 'Carotid sinus syncope' is defined as syncope which, by history, seems to occur in close relationship to accidental mechanical manipulation of the carotid sinuses, and which can be reproduced by carotid sinus massage. 'Situational syncope' refers to those forms of neurally-mediated syncope associated with specific scenarios (e.g., micturition, coughing, defaecating, etc.). Often, however, neurally-mediated reflex syncopes have 'non-classical' presentations. These forms are diagnosed by minor clinical criteria, exclusion of other causes for syncope (absence of structural heart disease) and positive response to tilt testing or carotid sinus massage. Examples of non-classical vasovagal syncope include episodes without clear triggering events or premonitory symptoms.

- 'Orthostatic hypotension' refers to syncope in which the upright position (most often the movement from sitting or lying to an upright position) causes arterial hypotension. This occurs when the autonomic nervous system is incapacitated and fails to respond to the challenges imposed by upright posture. A second major cause is 'volume depletion' in which the autonomic nervous system is itself not deranged, but is unable to maintain blood pressure due to decreased circulating volume. Note that vasovagal syncope can also be provoked by standing (e.g., soldiers fainting on parade), but these events are grouped under 'neurally-mediated (reflex) syncope'.
- 'Cardiac arrhythmias' can cause a decrease in cardiac output, which usually occurs irrespectively of circulatory demands.
- 'Structural heart disease' can cause syncope when circulatory demands outweigh the impaired ability of the heart to increase its output.
- 'Steal' syndromes can cause syncope when a blood vessel has to supply both part of the brain and an arm.

Several disorders may resemble syncope in two different ways. In some, consciousness is truly lost, but the mechanism is something other than cerebral hypoperfusion. Examples are epilepsy, several metabolic disorders (including hypoxia and, hypoglycaemia) and intoxications. In several other disorders, consciousness is only apparently lost; this is the case in 'psychogenic pseudo-syncope', cataplexy and drop attacks. In psychogenic pseudo-syncope patients may pretend to be unconscious when they are not. This condition can be seen in the context of factitious disorders, malingering and conversion. Finally, some patients may voluntarily trigger true syncope in themselves to attract attention, as a game, or to obtain some other advantage. Table 1.2 lists the most common conditions misdiagnosed as the cause of syncope. A differentiation such as this is important because the clinician is usually confronted with patients with sudden loss of consciousness (real or apparent) which may be due to causes not associated with decreased cerebral blood flow such as seizure and/or conversion reaction.

Note that the term 'syncope' should only be used when cerebral hypoperfusion was at least likely to have caused the loss of consciousness. If this is not the case, and no other cause is at least probable, then the term 'transient loss of consciousness' should be used to avoid limiting the scope of diagnostic thinking (see the 'glossary of terms').

A major limitation of this classification is the fact that more than one pathophysiological factor may contribute to the symptoms. For instance, in the setting of valvular aortic stenosis or left ventricular outflow tract obstruction, syncope is not solely the result of restricted cardiac output, but may be in part due to inappropriate neurally mediated reflex vasodilation and/or primary cardiac arrhythmias [12]. Similarly, a neural reflex component (preventing or delaying vasoconstrictor compensation) appears to play an important role when syncope occurs in association with certain brady- and tachyarrhythmias [13—15].

Epidemiological considerations

Numerous studies have examined epidemiological aspects of syncope and delineated the multiple potential causes of syncope. However, some reports

have focused on relatively select populations such as the military or tertiary care medical centres or solitary medical practices. For example, a survey of 3000 United States Air Force personnel (average age 29 years) revealed that 27% had experienced a syncopal spell during their lifetime [16]. Application of these findings to medical practice is limited not only by the nature of the environment in which patients were enroled, but also the variable manner in which symptoms were evaluated.

In terms of studies examining a broad population sample, the Framingham Study (in which biennial examinations were carried out from 1971 to 1998 in 7814 free-living individuals) 822 (10.5%) reported at least one syncopal event during an average of 17 years [17]. The incidence of a first report of syncope was 6.2 per 1000 person-years. Assuming a constant incidence rate over time, the authors calculated a 10-year cumulative incidence of syncope of 6%; this means a 42% prevalence of syncope during the life of a person living 70 years. However, the incidence was not constant, but increased more rapidly starting at the age of 70 years. Indeed, it was 11 per 1000 person-years for both men and women at the age of 70—79 and 17 per 1000 person-years for men and 19 per 1000 person-years for women at the age ≥ 80.

Among the elderly confined to long-term care institutions, the annual incidence may be as high as 6% with a recurrence rate of 30% [18]. Several reports indicate that syncope is common presenting problem in the health care settings accounting for 3% to 5% of emergency room visits and 1% to 3% of hospital admissions [19—21]. Other studies in specific populations provide insight into the relative frequency with which syncope may occur in certain settings. Several of these reports may be summarized as follows:

- 15% of children before the age of 18 [22]
- 25% of a military population aged 17—26 [23]
- 20% of air force personnel aged 17—46 [24]
- 39% of young medical students (median age of 21 years) with a prevalence in females twice as high than in males [25]
- 16% during a 10-year period in men aged 40—59 [26]
- 19% during a 10-year period in women aged 40—49 [26]
- 23% during a 10-year period in elderly people (age $>$ 70) [18].

However, the majority of these individuals probably do not seek medical evaluation.

In summary, even if some variability in prevalence and incidence of syncope is reported, the majority of studies suggest that syncope is a common problem in the community, long-term care institutions, and in health care delivery settings.

Prognostic evaluation

Mortality

In the Framingham study [17], the participants with syncope from any cause, compared with those who did not have syncope, had 1.31 increased risk of 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. Patients with cardiac syncope had the highest risk of death from any cause (hazard ratio of 2.1) and cardiovascular events (hazard ratio of 2.66). Studies in the 1980s showed that one-year mortality of patients with *cardiac syncope* was consistently higher (ranging between 18 and 33%) than patients with non-cardiac cause (0—12%) or unexplained syncope (6%) [19,20,27—29]. One-year incidence of sudden death was 24% in patients with a cardiac cause compared with 3—4% in the other two groups [28,29]. When adjustments were made for differences in baseline rates of heart and other diseases, cardiac syncope was still an independent predictor of mortality and sudden death [28,29]. However, a more recent study [30] directly compared the outcomes of patients with syncope with matched control subjects without syncope. Although patients with cardiac syncope had higher mortality rates compared with those of non-cardiac or unknown causes, patients with cardiac causes did not have a higher mortality when compared with their matched controls that had similar degrees of heart disease. This study showed that presence of structural heart disease was the most important predictor of mortality. In a selected population of patients with advanced heart failure and a mean ejection fraction of 20%, the patients with syncope had a higher risk of sudden death (45% at 1 year) than those without (12% at 1 year); admittedly, the risk of sudden death was similarly high in patients with either supposed cardiac syncope or syncope from other causes [31].

Structural heart disease is a major risk factor for sudden death and overall mortality in patients with syncope. The association of syncope with aortic stenosis has long been recognised as having an average survival without valve replacement of 2 years [32]. Similarly, in hypertrophic cardiomyopathy, the combination of young age, syncope at diagnosis, severe dyspnoea and a family history of sudden death best predicted sudden death [33]. In arrhythmogenic right ventricular dysplasia,

patients with syncope or symptomatic ventricular tachycardia have a similarly poor prognosis [34]. Patients with ventricular tachyarrhythmias have higher rates of mortality and sudden death but the excess mortality rates depend on underlying heart disease; patients with severe ventricular dysfunction have the worst prognosis [35]. Some of the cardiac causes of syncope do not appear to be associated with increased mortality. These include most types of supraventricular tachycardias and sick sinus syndrome.

A number of subgroups of patients who have an excellent prognosis can be identified:

- *Young healthy individuals without heart disease and normal ECG*. The 1-year mortality and sudden death rates in young patients (less than 45 years of age) without heart disease and normal ECG is low [36]. Although comparisons have not been made with age and sex matched controls, there is no evidence that these patients have an increased mortality risk. Many of these patients have neurally mediated syncope or unexplained syncope.
- *Neurally mediated syncope*. A large number of cohort studies in which the diagnosis has been established using tilt testing show that the mortality at follow-up of patients with neurally mediated syncope is near 0% [37]. Most of these patients had normal hearts. None of these studies report patients who died suddenly. In the Framingham study [17], there was no increased risk of cardiovascular morbidity or mortality associated with vasovagal (including orthostatic and medication-related) syncope during an average 17-year follow-up.
- *Orthostatic hypotension*. The mortality rates of patients with orthostatic hypotension depend on the causes of this disorder. Some causes (e.g., volume depletion, drug induced) are transient problems that respond to treatment and do not have long-term consequences. Other diseases causing primary and secondary autonomic failure have long-term consequences and may potentially increase mortality depending on the severity of the underlying disease. In elderly patients with orthostatic hypotension, the prognosis is largely determined by co-morbid illnesses.

Syncope of unknown cause is a heterogeneous group at intermediate risk. The definition of unexplained syncope largely depends on the diagnostic accuracy employed. An approximately 5% first year mortality in patients with unexplained syncope has been a relatively consistent observation in the literature [19,20,28,29,38]. As referred to earlier [17], the participants with syncope of unknown cause, compared with those who did not have syncope, had 1.31 increased risk of death. The group of patients with unknown syncope, in general, is heterogeneous probably including patients with a benign cause of syncope as well as those with an undiagnosed cardiac cause. The consequence is that this group shows an intermediate risk between the cardiac and neurally-mediated groups. The remaining challenge is how to identify those who are at high risk of death although the presence or the absence of structural heart disease seems to be an important determinant of risk. Although the mortality is largely due to underlying co-morbidity, such patients continue to be at risk of physical injury, and may encounter employment and lifestyle restrictions.

Recurrences

Approximately 35% of patients have recurrences of syncope at 3 years of follow-up; 82% of recurrences occur within the first 2 years [29,39]. Predictors of recurrence of syncope include having had recurrent syncope at the time of presentation (four or more episodes in one study [39]) or a psychiatric diagnosis [39—41]. In one study [42], more than five lifetime episodes gave a 50% chance of recurrence in the following year. In another study [40], age ≥ 45 years was also associated with higher rates of syncopal recurrence after controlling for other risk factors. After positive tilt table testing the patients with more than six syncopal spells had a risk of recurrence of $>50\%$ over 2 years [43].

Recurrences are not associated with increased mortality or sudden death rates, but patients with recurrent syncope have a poor functional status similar to patients with other chronic diseases.

Risk stratification

One study has developed and validated a clinical prediction rule for risk stratification of patients with syncope [36]. This study used a composite outcome of having cardiac arrhythmias as a cause of syncope or death (or cardiac death) within 1 year of follow-up. Four variables were identified and included age ≥ 45 years, history of congestive heart failure, history of ventricular arrhythmias, and abnormal ECG (other than non-specific ST changes). Arrhythmias or death within 1 year occurred in 4—7% of patients without any of the risk factors and progressively increased to 58—80% in patients with three or more factors [34]. The

critical importance of identifying cardiac causes of syncope is that many of the arrhythmias and other cardiac diseases are now treatable with drugs and/or devices.

Physical injury
Syncope may result in injury to the patient or to others such as may occur when a patient is driving. Major morbidity such as fractures and motor vehicle accidents were reported in 6% of patients and minor injury such as laceration and bruises in 29%. There are no data on the risk of injury to others. Recurrent syncope is associated with fractures and soft-tissue injury in 12% of patients [39].

Quality of life
A study that evaluated the impact of recurrent syncope on quality of life in 62 patients used the Sickness Impact Profile and found functional impairment similar to chronic illnesses such rheumatoid arthritis, low back pain, and psychiatric disorders [44]. Another study on 136 patients with unexplained syncope found impairment on all five dimensions measured by the EQ-5D instrument, namely Mobility, Usual activities, Self-care, Pain/discomfort, Anxiety/depression. Furthermore there was a significant negative relationship between frequency of spells and overall perception of health [42].

Economic implications
Patients with syncope are often admitted to hospital and undergo expensive and repeated investigations, many of which do not provide a definite diagnosis. In a study, performed in 1982, patients often underwent multiple diagnostic tests despite which a cause of syncope was established in only 13 of 121 patients [45]. With the advent of newer diagnostic tests (e.g., tilt testing, wider use of electrophysiological testing, loop monitoring) it is likely that patients are undergoing a greater number of tests at considerably higher cost. In a recent study, based on administrative data from Medicare, there were estimated to be 193,164 syncope hospital discharges in 1993 in the USA [46]. The cost per discharge was calculated to $4132 and increased to $5281 for those patients who were readmitted for recurrent syncope. This figure underestimates the true total cost associated with syncope because many patients with syncope are not admitted to hospital for either investigation or therapy. In the UK [47] the overall cost per patient was £611, with 74% attributed to the costs of hospital stay alone. Cost per diagnosis of patients admitted to hospital was £1080.

Part 2. Diagnosis

The diagnostic strategy based on the initial evaluation

Fig. 2 shows a flow diagram of an approach to the evaluation of transient loss of consciousness (TLOC).

Initial evaluation
The starting point for the evaluation of syncope is a careful history and physical examination including orthostatic blood pressure measurements. In most young patients without heart disease a definite diagnosis of neurally mediated syncope can be made without any further examination. Apart from this case, a 12-lead ECG should usually be part of the general evaluation of patients. This basic assessment will be defined as *Initial evaluation*.

Three key questions should be addressed during the initial evaluation:

- Is loss of consciousness attributable to syncope or not?
- Is heart disease present or absent?
- Are there important clinical features in the history that suggest the diagnosis?

Differentiating true syncope from other 'non-syncopal' conditions associated with real or apparent transient loss of consciousness (TLOC) is generally the first diagnostic challenge and influences the subsequent diagnostic strategy (see classification in Part 1 and Table 2.1). The symptoms surrounding the loss of consciousness accurately discriminate between seizures and syncope [48]. Apart from the prognostic importance of the presence of heart disease (see Part 1, prognostic stratification), its absence excludes a cardiac cause of syncope with few exceptions. In a recent study [49], heart disease was an independent predictor of cardiac cause of syncope, with a sensitivity of 95% and a specificity of 45%; by contrast, the absence of heart disease allowed exclusion of a cardiac cause of syncope in 97% of the patients. Finally, accurate history taking alone may be diagnostic of the cause of syncope or may suggest the strategy of evaluation (see Part 2, initial evaluation). It must be pointed out that syncope may be one of the accompanying symptoms which occur at the presentation of

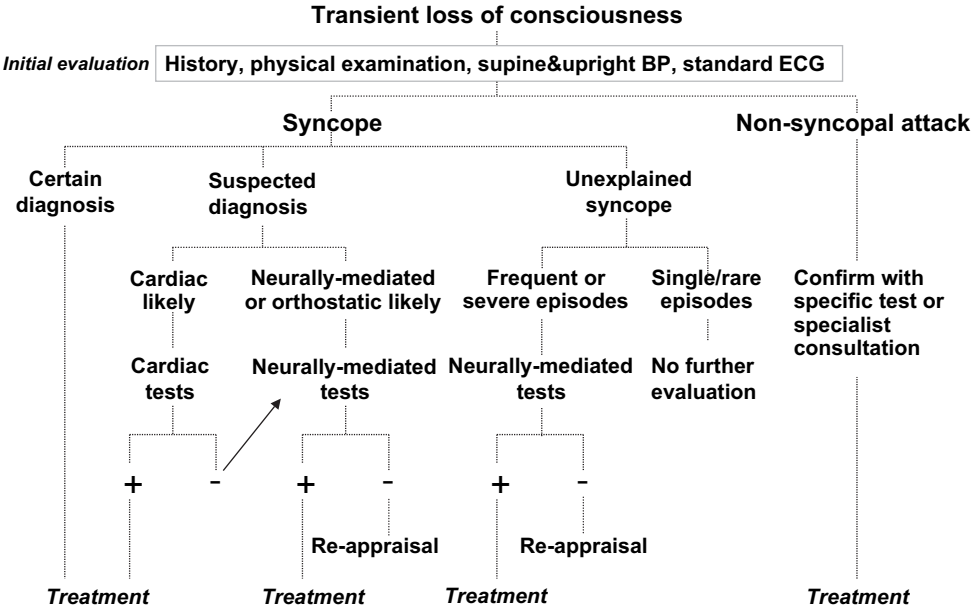

Figure 2 The flow diagram proposed by the Task Force on Syncope of an approach to the evaluation of loss of consciousness based on the initial evaluation. *Instruction for the use of the flow diagram*. Differentiating true syncope from other 'non-syncopal' conditions associated with real or apparent transient loss of consciousness is generally the first diagnostic step and influences the subsequent diagnostic strategy. For the classification of syncope refer to Table 1.1 and for the classification of non-syncopal attacks refer to Table 1.2. The conditions in which the results of the initial evaluation are diagnostic of the cause of syncope and no further evaluation is required are listed as recommendations in the section on ''The initial evaluation''. The features which suggest cardiac or neurally-mediated cause of syncope are listed in Tables 2.2 and 2.3. Among cardiac investigations, echocardiography, prolonged electrocardiographic monitoring, stress test, electrophysiological study and implantable loop recorder are most useful. Among neurally-mediated investigations, tilt test, carotid sinus massage and implantable loop recorder are most useful. When a cardiac diagnosis cannot be confirmed, neurally-mediated tests are usually performed. Once the evaluation, as outlined, is completed and no cause of syncope is determined, re-appraisal of the work-up may be needed. BP = blood pressure; ECG = electrocardiogram.

certain diseases, such as aortic dissection, pulmonary embolism, acute myocardial infarction, outflow tract obstruction, etc. In these cases, priority must be given to specific and immediate treatment of the underlying condition. Those issues are not addressed by this report.

The initial evaluation may lead to certain or suspected diagnosis or no diagnosis (here termed as unexplained syncope).

Certain diagnosis

Initial evaluation may lead to a certain diagnosis based on symptoms, signs or ECG findings. The recommended diagnostic criteria are listed in the section under Initial Evaluation. Under such circumstances, no further evaluation of the disease or disorder may be needed and treatment, if any, can be planned.

Suspected diagnosis

More commonly, the initial evaluation leads to a suspected diagnosis, when one or more of the features listed in Tables 2.2 and 2.3 are present. The recommended diagnostic work-up is listed in the section under Initial evaluation. A suspected diagnosis needs to be confirmed by directed testing If a diagnosis is confirmed by specific testing, treatment may be initiated. On the other hand, if the diagnosis is not confirmed, then patients are considered to have unexplained syncope and are evaluated as follows.

Unexplained syncope

The initial evaluation may lead to no diagnosis (here termed as unexplained syncope). The strategy of evaluation varies according to the severity and frequency of the episodes. In patients with unexplained syncope the likely diagnosis is neurally-mediated. The tests for neurally mediated syncope consist of tilt testing and carotid massage. The majority of patients with single or rare episodes in this category probably have neurally mediated syncope and tests for confirmation are usually not necessary. If it is not clear that it was syncope, the term transient loss of consciousness (TLOC) is preferable and reappraisal is warranted.

Table 2.1 Important historical features

Questions about circumstances just prior to the attack
- Position (supine, sitting or standing)
- Activity (rest, change in posture, during or after exercise, during or immediately after urination, defaecation, cough or swallowing)
- Predisposing factors (e.g., crowded or warm places, prolonged standing, post-prandial period) and of precipitating events (e.g., fear, intense pain, neck movements)

Questions about onset of the attack
- Nausea, vomiting, abdominal discomfort, feeling of cold, sweating, aura, pain in neck or shoulders, blurred vision, dizziness

Questions about the attack (eyewitness)
- Way of falling (slumping or kneeling over), skin colour (pallor, cyanosis, flushing), duration of loss of consciousness, breathing pattern (snoring), movements (tonic, clonic, tonic-clonic or minimal myoclonus, automatism) and their duration, onset of movement in relation to fall, tongue biting;

Questions about the end of the attack
- Nausea, vomiting, sweating, feeling of cold, confusion, muscle aches, skin colour, injury, chest pain, palpitations, urinary or faecal incontinence

Questions about the background
- Family history of sudden death, congenital arrhythmogenic heart disease or fainting
- Previous cardiac disease
- Neurological history (Parkinsonism, epilepsy, narcolepsy)
- Metabolic disorders (diabetes, etc.)
- Medication (antihypertensive, antianginal, antidepressant agent, antiarrhythmic, diuretics and QT prolonging agents)
- (In case of recurrent syncope) Information on recurrences such as the time from the first syncopal episode and on the number of spells

Table 2.2 Clinical features suggestive of specific causes of real or apparent loss of consciousness

Neurally-mediated syncope
- Absence of cardiological disease
- Long history of syncope
- After sudden unexpected unpleasant sight, sound, smell or pain
- Prolonged standing or crowded, hot places
- Nausea, vomiting associated with syncope
- During the meal or in the absorptive state after a meal
- With head rotation, pressure on carotid sinus (as in tumours, shaving, tight collars)
- After exertion

Syncope due to orthostatic hypotension
- After standing up
- Temporal relationship with start of medication leading to hypotension or changes of dosage
- Prolonged standing especially in crowded, hot places
- Presence of autonomic neuropathy or Parkinsonism
- After exertion

Cardiac syncope
- Presence of definite structural heart disease
- During exertion, or supine
- Preceded by palpitation
- Family history of sudden death

Cerebrovascular syncope
- With arm exercise
- Differences in blood pressure or pulse in the two arms

Syncope-like disorders (see text)

Re-appraisal

Once the evaluation, as outlined, is completed and no cause of syncope is determined, re-appraisal of the work-up is needed since subtle findings or new historical information may change the entire differential diagnosis. Re-appraisal may consist of obtaining details of history and re-examining patients as well as review of the entire work-up. If unexplored clues to possible cardiac or neurological disease are apparent, further cardiac and neurological assessment is recommended. In these circumstances, consultation with appropriate speciality services may be needed. An additional consideration is psychiatric illness. Psychiatric assessment is recommended in patients with frequent recurrent syncope who have multiple other somatic complaints and initial evaluation raises concerns for stress, anxiety and possible other psychiatric disorders.

Diagnostic yield and prevalence of causes of syncope

Data from seven population based studies [19,20,27,29,41,50,51] showed that the history and physical examination identified a potential cause of syncope in 726 (45%) of 1607 patients whose primary disorder can be diagnosed. However, the diagnostic criteria for vasovagal syncope, which represent the most frequent cause of loss of consciousness, have been varied among studies. While some studies have used precipitating events for diagnosing vasovagal syncope, others have used only the presence of prodromal symptoms which may lack specificity.

The diagnostic yield of electrocardiography and rhythm recordings obtained in the emergency

Table 2.3 ECG abnormalities suggesting an arrhythmic syncope

- Bifascicular block (defined as either left bundle branch block or right bundle branch block combined with left anterior or left posterior fascicular block)
- Other intraventricular conduction abnormalities (QRS duration $\geq$ 0.12 s)
- Mobitz I second degree atrioventricular block
- Asymptomatic sinus bradycardia (<50 beats/min), sinoatrial block or sinus pause $\geq$ 3 s in the absence of negatively chronotropic medications
- Pre-excited QRS complexes
- Prolonged QT interval
- Right bundle branch block pattern with ST-elevation in leads V1—V3 (Brugada syndrome)
- Negative T waves in right precordial leads, epsilon waves and ventricular late potentials suggestive of arrhythmogenic right ventricular dysplasia
- Q waves suggesting myocardial infarction

department is low, ranging between 1% and 11% (mean 7%) [19,27,29,51]. The most common diagnoses included ventricular tachycardia, bradyarrhythmias and, less commonly, acute myocardial infarction.

Similarly routine blood tests (blood count and tests for electrolyte and glucose level) rarely yield diagnostically useful information. They usually confirm a clinical suspicion of hypoglycaemia, when loss of consciousness is associated with confusion, salivation, tremors, hunger, hyperadrenergic state and serum glucose value is <40 mg/dl. Syncope due to acute severe anaemia and bleeding may be diagnosed by clinical features and confirmed by a complete blood count.

The cause of syncope remains unknown despite a complete work-up in a substantial proportion of patients. For example, in five studies [19,27,29,50,51], performed in the 1980s, the cause of syncope could not be determined in 34% of cases (range 13—41%) and in four recent studies [49,52—54] the cause of syncope could not be determined in 20% of cases (range 17.5—26%).

The prevalence of the causes of syncope has been evaluated in six population-based studies of unselected patients [19,27,29,41,50,51] for a total of 1499 patients, performed in the 1980s. The most common cause was neurally-mediated and orthostatic hypotension which accounted for 381 cases (37%). The second most common cause was cardiac which accounted for 246 cases (17%) with a primary arrhythmic mechanism being responsible in 195 (13%). Neurological and psychiatric causes were found in 150 cases (10%). In four recent studies [49,52—54], for a total of 1640 patients, neurally-mediated and orthostatic hypotension accounted for 917 cases (56%). The second most common cause was cardiac which accounted for 233 cases (14%) with a primary arrhythmic mechanism being responsible in 182 (11%). Neurological and psychiatric causes were found in 155 cases (9%). Thus, the percentage of neurally-mediated syncope increased and that of unexplained syncope decreased compared with the older studies. In more recent studies there was a more extensive use of carotid sinus massage and tilt testing [49]. This suggests that when specific tests are used, reflex syncope or autonomic failure are even more frequent and that carotid sinus massage and tilt testing are useful to discover those particular forms when the history alone is not diagnostic.

Initial evaluation

The following section provides specific recommendations about how to use the history, physical examination and ECG for making certain or presumptive diagnoses of syncope.

History and physical examination

The history alone may be diagnostic of the cause of syncope or may suggest the strategy of evaluation. The clinical features of the presentation are most important, especially the factors that might predispose to syncope and its sequelae. Some attempts have been made to validate the diagnostic value of the history in prospective and case-control studies [5,27,41,48,49,55,56].

The important parts of the *history* are listed in Table 2.1. They are the key features in the diagnostic work-up of patients with syncope. When taking a history, all the items listed in Table 2.1 should be carefully sought.

Apart from being diagnostic, the history may guide the subsequent evaluation strategy. For example, a cardiac cause is more likely when syncope is preceded by palpitations or occurs in the supine position or during exercise. Conversely, a neurally-mediated mechanism is likely when predisposing factors, precipitating events and accompanying symptoms are present and the patient has recurrent syncopal episodes over several years.

Physical findings that are useful in diagnosing syncope include cardiovascular and neurological signs and orthostatic hypotension. For example, the presence of a murmur or severe dyspnoea is indicative of structural heart disease and of a cardiac cause of syncope. Table 2.2 lists how to use the history and physical findings in suggesting various aetiologies.

Baseline electrocardiogram

An initial ECG is most commonly normal in patients with syncope. When abnormal, the ECG may disclose an arrhythmia associated with a high likelihood of syncope, or an abnormality which may predispose to arrhythmia development and syncope. Moreover, any abnormality of the baseline ECG is an independent predictor of cardiac syncope or increased mortality, suggesting the need for pursuing evaluation for cardiac causes in these patients. Equally important, a normal ECG is associated with a low risk of cardiac syncope as the cause, with a few possible exceptions, for example in case of syncope due to a paroxysmal atrial tachyarrhythmia.

Arrhythmias that are considered diagnostic of the cause of syncope are listed below. More commonly, the baseline ECG leads to a *suspected* cardiac arrhythmia, which needs to be confirmed by directed testing (Table 2.3).

Recommendations. Diagnosis: diagnostic criteria based on the initial evaluation

Class I:
The results of the initial evaluation (history, physical examination, orthostatic blood pressure measurements and ECG) are diagnostic of the cause of syncope in the following situations:

- Vasovagal syncope is diagnosed if precipitating events such as fear, severe pain, emotional distress, instrumentation or prolonged standing are associated with typical prodromal symptoms
- Situational syncope is diagnosed if syncope occurs during or immediately after urination, defaecation, cough or swallowing
- Orthostatic syncope is diagnosed when there is documentation of orthostatic hypotension associated with syncope or presyncope. Orthostatic blood pressure measurements are recommended after 5 min of lying supine, followed by measurements each minute, or more often, after standing for 3 min. Measurements may be continued for longer, if blood pressure is still falling at 3 min. If the patient does not tolerate standing for this period, the lowest systolic blood pressure during the upright posture should be recorded. A decrease in systolic blood pressure ≥ 20 mmHg or a decrease of systolic blood pressure to <90 mmHg is defined as orthostatic hypotension regardless of whether or not symptoms occur [57]
- Cardiac ischaemia related syncope is diagnosed when symptoms are present with ECG evidence of acute ischaemia with or without myocardial infarction, independently of its mechanism.[a]
- Arrhythmia related syncope is diagnosed by ECG when there is:
  - Sinus bradycardia <40 beats/min or repetitive sinoatrial blocks or sinus pauses >3 s
  - Mobitz II 2nd or 3rd degree atrioventricular block
  - Alternating left and right bundle branch block
  - Rapid paroxysmal supraventricular tachycardia or ventricular tachycardia
  - Pacemaker malfunction with cardiac pauses.

[a] Note. In the case of ischaemic syncope, the mechanism can be cardiac (low output or arrhythmia) or reflex (Bezold—Jarish reflex), but management is primarily that of ischaemia.

Recommendations. Diagnostic work-up based on the initial evaluation

When the mechanism of syncope is not evident, the presence of suspected or certain heart disease is associated with a higher risk of arrhythmias and a higher mortality at 1 year. In the patients with clinical features suggesting cardiac syncope listed in Tables 2.2 and 2.3 cardiac evaluation is recommended. Cardiac evaluation consists of echocardiography, stress testing, prolonged ECG monitoring (Holter, external or implantable loop recorder as appropriate) and electrophysiological study. If cardiac evaluation does not show evidence of arrhythmia as a cause of syncope, evaluation for neurally mediated syncope is recommended in those with recurrent or severe syncope.

In patients without suspected or certain heart disease, evaluation for neurally mediated syncope is recommended for those with recurrent or severe syncope. The tests for neurally mediated syncope consist of tilt testing and carotid massage and, if negative, prolonged ECG monitoring and implantable loop recorder. The majority of patients with single or rare episodes in this category probably have neurally mediated syncope and tests for confirmation are usually not necessary.

Specific indications

- Basic laboratory tests are only indicated if syncope may be due to loss of circulating volume, or if a syncope-like disorder with a metabolic cause is suspected.
- In patients with suspected heart disease, echocardiography, prolonged electrocardiographic monitoring and, if non-diagnostic, electrophysiological studies are recommended as first evaluation steps.
- In patients with palpitations associated with syncope, electrocardiographic monitoring and echocardiography are recommended as first evaluation steps.

- In patients with chest pain suggestive of ischaemia before or after loss of consciousness, stress testing, echocardiography, and electrocardiographic monitoring are recommended as first evaluation steps.
- In young patients without suspicion of heart or neurological disease and recurrent syncope, tilt testing and, in older patients, carotid sinus massage are recommended as first evaluation steps.
- In patients with syncope occurring during neck turning, carotid sinus massage is recommended at the outset.
- In patients with syncope during or after effort, echocardiography and stress testing are recommended as first evaluation steps.
- In patients with signs of autonomic failure or neurological disease a specific diagnosis should be made.
- In patients with frequent recurrent syncope who have multiple other somatic complaints and initial evaluation raises concerns for stress, anxiety and possible psychiatric disorders, psychiatric assessment is recommended.
- When the mechanism of syncope remains unclear after full evaluation, an implantable loop recorder is indicated in patients who have the clinical or ECG features suggesting an arrhythmic syncope listed in Tables 2.2 and 2.3 or a history of recurrent syncopes with injury.

Echocardiogram

Echocardiography is frequently used as a screening test to detect cardiac disease in patients with syncope. Although numerous published case reports have suggested an important role of echocardiography in disclosing the cause and/or mechanism of syncope, larger studies have shown that the diagnostic yield from echocardiography is low in the absence of clinical, physical or electrocardiographic findings suggestive of a cardiac abnormality [59—61]. In patients with syncope or pre-syncope and normal physical examination, the most frequent (from 4.6% to 18.5% of cases) finding is mitral valve prolapse [59]. This may be coincidental as both conditions are common. Other cardiac abnormalities include valvular diseases (most frequently aortic stenosis), cardiomyopathies, regional wall motion abnormalities suggestive of myocardial infarction, infiltrative heart diseases such as amyloidosis, cardiac tumours, aneurysms, atrial thromboembolism and other abnormalities [62—66]. Even if echocardiography alone is only seldom diagnostic, this test provides information about the type and severity of underlying heart disease which may be useful for risk stratification. If moderate to severe structural heart disease is found, evaluation is directed toward a cardiac cause of syncope. On the other hand, in the presence of minor structural abnormalities detected by echocardiography, the probability of a cardiac cause of syncope may not be high, and the evaluation may proceed as in patients without structural heart disease.

Examples of heart disease in which cardiac syncope is likely include:

- cardiomyopathy with episodes of overt heart failure
- systolic dysfunction (ejection fraction $<40\%$)
- ischaemic cardiomyopathy following an acute myocardial infarction
- right ventricular dysplasia
- hypertrophic cardiomyopathy
- congenital heart diseases
- cardiac tumours
- outflow tract obstruction
- pulmonary embolism
- aortic dissection.

Recommendations

Indications	Diagnosis
Class I: • Echocardiography is recommended in patients with syncope when cardiac disease is suspected in order to stratify the risk by assessing the cardiac substrate.	Class I: • Echocardiography only makes a diagnosis in severe aortic stenosis and atrial myxoma.

Carotid sinus massage

It has long been observed that pressure at the site where common carotid artery bifurcates produces a reflex slowing in heart rate and fall in blood pressure. In some patients with syncope, especially those >40 years, an abnormal response to carotid massage can be observed. A ventricular pause lasting 3 s or more and a fall in systolic blood pressure of 50 mm/Hg or more is considered abnormal and defines the carotid sinus hypersensitivity [67,68].

The carotid sinus reflex arc is composed of an afferent limb arising from the mechanoreceptors of the carotid artery and terminating in midbrain centres, mainly the vagus nucleus and the vasomotor centre. The efferent limb is via the vagus

nerve and the parasympathetic ganglia to the sinus and atrioventricular nodes and via the sympathetic nervous system to the heart and the blood vessels. Whether the site of dysfunction resulting in a hypersensitive response to the massage is central at the level of brainstem nuclei or peripheral at the level of carotid baroreceptors is still a matter of debate [68—70].

Methodology and response to carotid sinus massage

Carotid sinus massage is a tool used to disclose carotid sinus syndrome in patients with syncope.

Protocol

In most studies the carotid sinus massage is performed in the supine position; in others, it is performed in both supine and upright positions (usually on a tilt table). Continuous electrocardiographic monitoring must be used. Continuous blood pressure monitoring, for which a non-invasive measurement device is best suited, should also be used as the vasodepressor response is rapid and cannot be adequately detected with devices which do not measure continuous blood pressure. After baseline measurements, the right carotid artery is firmly massaged for 5—10 s at the anterior margin of the sternocleomastoid muscle at the level of the cricoid cartilage. After one or two minutes a second massage is performed on the opposite side if the massage on one side failed to yield a 'positive' result. If an asystolic response is evoked, to assess the contribution of the vasodepressor component (which may otherwise be hidden) massage is usually repeated after intravenous administration of Atropine (1 mg or 0.02 mg/kg body weight). Atropine administration is preferred to temporary dual chamber pacing as it is simple, non-invasive, and easily reproducible [71]. The response to carotid sinus massage is generally classified as cardioinhibitory (i.e., asystole), vasodepressive (fall in systolic blood pressure) or mixed. The mixed response is diagnosed by the association of an asystole of ≥ 3 s and a decline in systolic blood pressure of ≥ 50 mmHg on rhythm resumption from the baseline value.

There are two widely used methods of carotid sinus massage. In the first method, massage is performed only in the supine position and pressure is applied for no more than 5 s. A positive response is defined as a ventricular pause ≥ 3 s and/or a fall in systolic blood pressure ≥ 50 mmHg. Pooled data from four studies performed in elderly patients with syncope show a positive response rate of 35% (235 of 663 patients) [72—75]. However, abnormal responses are also frequently observed in subjects without syncope. For example, an abnormal response was observed in 17—20% of patients affected by various types of cardiovascular diseases [76], and in 38% of patients with severe narrowing of the carotid arteries [77]. Moreover, the diagnosis may be missed in about one third of cases if only supine massage is performed [78,79].

In the second method, reproduction of spontaneous symptoms is required during carotid massage (80). Eliciting symptoms requires a longer period of massage (10 s) and massage performed in both supine and upright positions [81,82]. A positive response was observed in 49% of 100 patients with syncope of uncertain origin [83] and in 60% of elderly patients with syncope and sinus bradycardia [84], but only in 4% of 101 control patients without syncope pooled from three studies [82—84]. In an intrapatient comparison study [82], the 'method of symptoms' appears to carry a higher positivity rate (49% vs 41%) in patients with syncope and a lower positivity rate (5% vs 15%) in patients without syncope than the first method. In a large population of 1719 consecutive patients with syncope unexplained after the initial evaluation (mean age 66 ± 17 years), carotid sinus hypersensitivity was found in 56% and syncope was reproduced in 26% of cases [85]. Among the positive tests, the response was cardioinhibitory in 46%, mixed in 40% and vasodepressor in 14%. The positivity rate increased with age, ranging from 4% in patients <40 years to 41% in patients >80 years. The test was positive only in the upright position in 49% of patients.

Whatever method is used, increasing importance has been given to the execution of the massage also in the upright position, usually using a tilt table [78,79,85,86]. Other than a higher positivity rate compared with supine massage only, the importance of performing upright massage is due to the better possibility of evaluating the magnitude of the vasodepressor component and of reproducing symptoms. Underestimated in the past, actually a vasodepressor component of the reflex is present in most patients with an asystolic response [86]. A correct determination of the vasodepressor component of the reflex is of practical importance for the choice of therapy. Indeed, pacemaker therapy has been shown to be less effective in mixed forms with an important vasodepressor component rather than in dominant cardioinhibitory forms [71,72].

In conclusion, carotid sinus syndrome is a frequent cause of syncope, especially in the elderly. The syndrome is misdiagnosed in half of the cases

if the massage is not performed in the upright position.

Reproducibility
A concordance between abnormal and normal responses during a second carotid sinus massage was reported in 93% of cases [76]. In another study [81], a pause >3 s was repeatedly reproduced in all patients who were referred for implantation of pacemaker because of severe carotid sinus syndrome.

Complications
The main complications of carotid sinus massage are neurological [87]. In three studies, neurological complications were reported respectively in: 7 among 1600 patients (5000 massages) with an incidence of 0.45% [87], 11 in 4000 patients (16,000 massages) with an incidence of 0.28% [88], and in 3 among 1719 patients with an incidence of 0.17% [85].

Even if these complications are rare, carotid massage should be avoided in patients with previous transient ischaemic attacks or strokes within the past 3 months (except if carotid Doppler studies excluded significant stenosis) or in patients with carotid bruits [87]. Rarely carotid massage may elicit self-limited atrial fibrillation of little clinical significance [67,72]. Since asystole induced by the massage is self-terminating shortly after the end of the massage, no resuscitative measures are usually needed.

Personnel
As it carries potential hazards, the test should be performed by physicians who are aware that complications, especially neurological, may occur.

Relationship between carotid sinus massage and spontaneous syncope
The relationship between carotid sinus hypersensitivity and spontaneous, otherwise unexplained, syncope has been demonstrated by pre-post comparative studies, two controlled trials, and a prospective observational study (Level B). Pre-post comparisons were made by analysing the recurrence rates of syncope in patients treated by pacing in several non-randomized studies [89,90]. These studies show fewer recurrences at follow-up. One non-randomized comparative study of patients receiving a pacemaker and untreated patients showed syncope recurrence rates to be lower in paced than non-paced patients [91]. Brignole et al. [81] undertook a randomized study in 60 patients; 32 patients were assigned to the pacemaker arm and 28 to the 'no treatment' group. After a mean follow up of 36±10 months, syncope recurred in 9% of pacemaker group versus 57% in the untreated patients ($p<0.0002$). Finally, in patients implanted with a pacemaker designed to detect asystolic episodes, long pauses (≥ 6 s) were detected in 53% of the patients during 2 years of follow-up, suggesting that a positive response to carotid massage predicts the occurrence of spontaneous asystolic episodes [92].

Recommendations

Indications and methodology	Diagnosis
Class I • Carotid sinus massage is recommended in patients over age 40 years with syncope of unknown aetiology after the initial evaluation. If there is a risk of stroke due to carotid artery disease, massage should be avoided. • Electrocardiographic monitoring and continuous blood pressure measurement during carotid massage is mandatory. Duration of massage for a minimum of 5 and a maximum of 10 s is recommended. Carotid massage should be performed with the patient both supine and erect.	Class I • The procedure is considered positive if syncope is reproduced during or immediately after massage in presence of asystole longer than 3 s and/or a fall in systolic blood pressure of 50 mm of Hg or more. A positive response is diagnostic of the cause of syncope in the absence of any other competing diagnosis.

Tilt testing

Background
On moving from supine to erect posture there is a large gravitational shift of blood away from the chest to the distensible venous capacitance system below the diaphragm. This shift is estimated to total one half to one litre of thoracic blood and the bulk of the total change occurs in the first 10 s. In addition, with prolonged standing, the high capillary transmural pressure in dependent parts of the body causes a filtration of protein-free fluid into the interstitial spaces. It is estimated that this results in about a 15–20% (700 ml) decrease in plasma volume in 10 min in healthy humans [10].

As a consequence of this gravitationally induced blood pooling and the superimposed decline in plasma volume, the return of venous blood to the heart is reduced resulting in a rapid diminution of cardiac filling pressure and thereby in a decrease in stroke volume. Despite decreased cardiac output, a fall in mean arterial pressure is prevented by a compensatory vasoconstriction of the resistance and the capacitance vessels in the splanchnic, musculo-cutaneous, and renal vascular beds. Vasoconstriction of systemic blood vessels is the key factor in the maintenance of arterial blood pressure in the upright posture. Pronounced heart rate increases are insufficient to maintain cardiac output [10]. The rapid short-term adjustments to orthostatic stress are mediated exclusively by the neural pathways of the autonomic nervous system. During prolonged orthostatic stress, additional adjustments are mediated by the humoral limb of the neuroendocrine system [10]. The main sensory receptors involved in orthostatic neural reflex adjustments are the arterial mechanoreceptors (baroreceptors) located in the aortic arch and carotid sinuses. Mechanoreceptors located in the heart and the lungs (cardiopulmonary receptors) are thought to play a minor role. Reflex activation of central sympathetic outflow to the systemic blood vessels can be reinforced by local reflex mechanisms like the venoarteriolar reflex. The skeletal muscle pump and the respiratory pump play an important adjunctive role in the maintenance of arterial pressure in the upright posture by promoting venous return. The static increase in skeletal muscle tone induced by the upright posture opposes pooling of blood in limb veins even in the absence of movement of the subject [8]. Failure of the above discussed compensatory adjustments to orthostatic stress is thought to play a predominant role in a large number of patients with syncope. This forms the basis for the use of tilt testing in the evaluation of patients with syncope. There is a large body of literature on the mechanisms involved in vasovagal syncope induced by tilt testing. Yet many unanswered questions remain regarding the multiple potential causes and the underlying pathophysiology. The panel did not consider an extensive review of pathophysiology as one of the goals of the consensus process. Excellent reviews are available [93—96].

Tilt test protocols

In 1986 Kenny et al. [97] observed an abnormal response to tilt test in 10 of 15 patients with syncope of unknown origin. This response consisted of hypotension and/or bradycardia. They also performed the test in 10 healthy controls without previous syncope, and an abnormal response was provoked in only one. In this study, the authors used an inclination of 60° during 60 min of tilt duration. Since then, tilt testing has been used extensively by many authors proposing different protocols for diagnostic, investigational and therapeutic purposes. Tilt testing protocols have varied with respect to many factors including the angle of tilting, time duration and the use of different provocative drugs.

In 1991, Fitzpatrick et al. [98] showed that the use of a bicycle saddle with the legs hanging free for tilt testing gave a low specificity when compared with footboard support. They also showed that tilting at an angle of less than 60° resulted in a low rate of positive responses. Analysing the time to positive responses, they reported a mean time of 24 ± 10 min and proposed 45 min of passive tilting as an adequate duration for the test since this incorporated the mean duration to syncope plus two standard deviations. This method is widely known as the Westminster protocol. They reported a rate of positive responses in patients with syncope of unknown origin of 75% and a specificity of 93%.

In 1989, Almquist et al. [99] and Waxman et al. [100] used intravenous isoprenaline tilt testing. In the study of Almquist [99], after 10 min of passive tilt test without drugs, patients were returned to the supine position and isoprenaline infusion at initial doses of 1 μg/min was administered. When patients achieved a stable increase in heart rate they were tilted again. This manoeuvre was repeated at increasing doses up to 5 μg/min. With this protocol 9 of 11 patients with syncope of unknown origin and negative electrophysiological study showed hypotension and/or bradycardia, whereas such responses were found in 2 of 18 control subjects. In 1992, Kapoor et al. [101] using an isoprenaline tilt test at 80°, in which the drug was administered in progressive doses from 1 to 5 μg/min, without returning the patient to the supine position before each dose increase, reported a low specificity (between 45% and 65%). In 1995, Morillo et al. [102] and Natale et al. [103] proposed a 'shortened' low-dose isoprenaline tilt testing, in which, after 15—20 min of baseline tilt at 60—70°, incremental doses of isoprenaline designed to increase average heart rate by about 20—25% over baseline (usually $\leq$3 μg/min) were administered without returning the patient to the supine position in one study, or returning to the supine position in the other. With this

protocol, the rate of positive responses was of 61% with a specificity of 92—93%.

In 1994, Raviele et al. [104] proposed the use of intravenous nitroglycerin infusion. With their protocol, 21 of 40 (53%) patients with syncope of unknown origin had positive responses with a specificity of 92%. Ten of 40 patients (25%), had progressive hypotension without bradycardia. This response was classified as an exaggerated response consisting of an excessive hypotensive effect of the drug. More recently, Raviele et al. [105] have used sublingual nitroglycerin instead of an intravenous infusion. After 45 min of baseline tilting, 0.3 mg of sublingual nitroglycerin was administered. With this protocol, the overall rate of positive responses in patients with syncope of unknown origin was 51% (25% with baseline tilt test and 26% after nitroglycerin administration) with a specificity of 94%. An exaggerated response was observed in 14% of patients and 15% of controls. The main advantage of sublingual nitroglycerin is that venous cannulation is not needed for the protocol. Oraii et al. [106], Raviele et al. [107] and Graham et al. [108] have compared the isoprenaline test with the nitroglycerin test, with similar rates of positive responses and specificity, but with a lower rate of side effects with nitroglycerin. The optimal duration of the unmedicated phase before the administration of sublingual nitroglycerin has not been fully established. Bartoletti et al. [109] compared the effect of an unmedicated phase of 45 min versus 5 min on the overall positive rate of the nitroglycerin test. The test with the short passive phase was associated with a significant reduction in the rate of positive responses, and they concluded, that at least some baseline unmedicated tilt testing is needed. Recently, many authors have used a shortened protocol using 400 μg nitroglycerin spray sublingually after a 20 min baseline phase. Pooled data from three studies [110—112] using this protocol, in a total of 304 patients, showed a positive response rate of 69% which was similar to the positive rate of 62% observed in another 163 patients from three studies [109,112—113] using a passive phase duration of 45 min and 400 μg nitroglycerin spray administration. With this protocol, specificity remained high, being 94% in 97 controls [110—112]. Thus a 20 min passive phase before nitroglycerin administration appears to be an alternative to the more prolonged 45 min passive phase. This method is known as the Italian protocol. Sensitivity and specificity values are also similar in the older patients but the older patients have more exaggerated responses than younger [114]. The difficulty of a clear cut distinction between exaggerated and positive responses partly gives an explanation of the lower specificity values reported by some recent reports [108,115].

Clomipramine, a central serotoninergic agent, is another provocative agent. The drug is given intravenously administered during the first 5 min of tilting at a dose of 5 mg (1 mg/min). Following this, the patients remain in the upright position for a further 15 min or until syncope occurs [116,117]. Thus the test is time-saving. Its sensitivity ranged between 64% and 83%, the specificity was 93%. Further experience is needed before the test can become widely accepted.

Other drugs used as provocative agents during tilt testing include isosorbide dinitrate [118,119], edrophonium [120,121], and adenosine; the latter is discussed in another section.

Irrespective of the exact protocol, some general measures may be suggested when tilt testing is performed. Many of the following rules were published in 1996 as an expert consensus document [122]. The room where the test is performed should be quiet and with dim lights. The patients should fast for at least 2 h before the test. The patients should be in a supine position 20—45 min before tilting. This time interval was proposed to decrease the likelihood of a vasovagal reaction in response to venous cannulation [123,124]. With the protocols that do not use venous cannulation, time in supine position before tilting can be reduced to 5 min. Continuous beat-to-beat finger arterial blood pressure should be monitored non-invasively. Invasive measurements of arterial blood pressure can affect the specificity of the test, especially in the elderly [123] and in children [124]. Although intermittent measurement of pressure using a sphygmomanometer is less desirable, it is an accepted method of testing and is widely used in clinical practice, especially in children. The tilt table should be able to achieve the upright position smoothly and rapidly and to reset to the supine position quickly ($<$10 s) when the test is completed in order to avoid the consequences of prolonged loss of consciousness. Only tilt tables with footboard support are appropriate for syncope evaluation. An experienced nurse or medical technician should be in attendance during the entire procedure. The need for a physician to be present throughout the tilt test procedure is less well established because the risk to patients of such testing is very low. Therefore, it is sufficient that a physician is in proximity and immediately available should a problem arise.

Recommendations. Tilt test protocols

Class I
- Supine pre-tilt phase of at least 5 min when no venous cannulation is performed, and at least 20 min when cannulation is undertaken.
- Tilt angle is 60—70°.
- Passive phase of a minimum of 20 min and a maximum of 45 min.
- Use of either intravenous isoproterenol/isoprenaline or sublingual nitroglycerin for drug provocation if passive phase has been negative. Drug challenge phase duration of 15—20 min.
- For isoprenaline, an incremental infusion rate from 1 up to 3 μg/min in order to increase average heart rate by about 20—25% over baseline, administered without returning the patient to the supine position.
- For nitroglycerin, a fixed dose of 400 μg nitroglycerin spray sublingually administered in the upright position.
- The end-point of the test is defined as induction of syncope or completion of the planned duration of tilt including drug provocation. The test is considered positive if syncope occurs.

Responses to the tilt test

Experience from tilt testing showed that in general the vasovagal reaction lasts roughly 3 min or less before causing loss of consciousness [125,126]. A decrease in systolic blood pressure to below 90 mmHg is associated with symptoms of impending syncope [127,128] and to below 60 mmHg is associated with syncope [11,127]. Prodromal symptoms are present in virtually all cases of tilt-induced vasovagal syncope, which occurs, on average, 1 min after the onset of prodromal symptoms [127,128]. During the prodromal phase, blood pressure falls markedly; this fall frequently precedes the decrease in heart rate, which may be absent at least at the beginning of this phase [126—128].

In 1992, Sutton et al. [125], using the details of haemodynamic responses to tilt testing, proposed a classification of the positive responses, which has recently been modified [126]. This classification is shown in Table 2.4.

Since the decision to terminate tilting influences the type of responses [129], some authors propose to interrupt tilting at the precise occurrence of loss of consciousness with simultaneous loss of postural tone [126]. Premature interruption underestimates and delayed interruption overestimates the cardioinhibitory response and exposes the patient to the consequences of prolonged loss of consciousness. However, a consensus does not exist in this regard and many physicians consider a steadily falling blood pressure accompanied by symptoms sufficient to stop the test.

Some authors [104,105,126,130] have analyzed the behaviour of blood pressure and heart rate during the period of upright position which precedes the onset of the vasovagal reaction. Different patterns have been recognized. To summarize, two of these are the most frequent. The typical pattern is characterized by an initial phase of rapid and full compensatory reflex adaptation to the upright position resulting in a stabilization of blood pressure and heart rate (which suggests normal baroreflex function) to the time of an abrupt onset of the vasovagal reaction. The patients with this pattern are largely those young and healthy; they have a long history of several syncopal episodes; in many cases the first syncopal episodes occurred in the teenage years; secondary trauma is infrequent. This pattern, also-called 'Classic', is felt to represent a 'hypersensitive' autonomic system that over-responds to various stimuli. Conversely, a different pattern is frequently observed that is characterized by inability to obtain a steady-state adaptation to the upright position and, therefore, a progressive fall in blood pressure and heart rate occurs until the onset of symptoms. The cause of symptoms in this case seems to be a compromised capability to adapt promptly to some external influences ('hyposensitive' autonomic function). Different subtypes have been described with slight differences between them. The patients affected are dominantly old and many have associated diseases; they have a short history of syncope with few episodes per patient; syncopal episodes begin late in life, suggesting they are due to the occurrence of some underlying dysfunction. This pattern resembles that seen in patients with autonomic failure and suggests that an overlap between the typical vasovagal syncope and more complex disturbances of the autonomic nervous system exists. Tilt testing can be useful to discriminate between these two syndromes.

Role of tilt test for assessing the effectiveness of the treatment

In order to use tilt testing effectively in the evaluation of the therapeutic options, two conditions are needed: a high reproducibility of the test and responses to tilt testing that are predictive of outcomes at follow-up. The reproducibility of tilt testing has been widely studied [131—135]. The overall reproducibility of an initial negative response (85—94%) is higher than the reproducibility of an initial positive response (31—92%). In addition, data from controlled trials

showed that approximately 50% of patients with a baseline positive tilt test became negative when the test was repeated with treatment or with placebo [136—138]. The mechanism of tilt-induced syncope was frequently different from that of the spontaneous syncope recorded with the implantable loop recorder [139]. Moreover, acute studies were not predictive of the long-term outcome of pacing therapy [140]. These data show that the use of tilt testing for assessing the effectiveness of different treatments has important limitations (Level A).

Recommendations

Indications	Diagnosis
Class I Tilt testing is indicated for diagnostic purposes: • In case of unexplained single syncopal episode in high risk settings (e.g., occurrence of, or potential risk for, physical injury or with occupational implications), or recurrent episodes in the absence of organic heart disease, or, in the presence of organic heart disease, after cardiac causes of syncope have been excluded. • When it will be of clinical value to demonstrate susceptibility to neurally-mediated syncope to the patient.	**Class I** • In patients without structural heart disease, tilt testing can be considered diagnostic, and no further tests need to be performed when spontaneous syncope is reproduced. • In patients with structural heart disease, arrhythmias or other cardiac causes should be excluded prior to considering positive tilt test results as evidence suggesting neurally mediated syncope.
Class II Tilt testing is indicated for diagnostic purposes: • When an understanding of the haemodynamic pattern in syncope may alter the therapeutic approach • For differentiating syncope with jerking movements from epilepsy • For evaluating patients with recurrent unexplained falls • For assessing recurrent presyncope or dizziness.	**Class II** • The clinical meaning of abnormal responses other than induction of syncope is unclear.
Class III • Assessment of treatment • A single episode without injury and not in a high risk setting • Clear-cut clinical vasovagal features leading to a diagnosis when demonstration of a neurally mediated susceptibility would not alter treatment.	

Complications

Head up tilt test is a safe procedure and the rate of complications is very low. Although asystolic pauses as long as 73 s have been reported [141] the presence of such prolonged asystole during a positive response cannot be considered a complication, since this is an end point of the test. Rapid return to supine position as soon as syncope occurs is usually all that is needed to prevent or to limit the consequences of prolonged loss of consciousness; raising the legs immediately is advised in cases of prolonged syncope; brief resuscitation manoeuvres are seldom needed. Case reports have documented life-threatening ventricular arrhythmias with isoprenaline in the presence of ischaemic heart disease [142] or sick sinus syndrome [143]. No complications have been published with the use of nitroglycerin. Minor side effects are common and include palpitations with isoprenaline and headache with nitroglycerin. Atrial fibrillation can be induced during or after a positive tilt test and is usually self-limited [144].

Electrocardiographic monitoring (non-invasive and invasive)

ECG monitoring is a procedure for diagnosing intermittent brady- and tachyarrhythmias. However, the technology of ECG monitoring currently has serious limitations.

Indications

Patients with very infrequent syncope, recurring over months or years, are unlikely to be diagnosed

by conventional Holter monitoring, since the likelihood of symptom-ECG correlation is very low. Consideration should be given to conventional event recording in such patients, but this technique has important logistical limitations that might prevent a successful ECG recording during syncope. Patients with syncope often have significant arrhythmia, infrequent recurrences, and sudden loss of consciousness and recover quickly. In such circumstances where the interval between recurrences is measured in months or years, consideration should be given to implantable ECG loop recorder. As a general rule ECG monitoring is indicated only when there is a high pre-test probability of identifying an arrhythmia responsible of syncope. These conditions are those listed in Tables 2.2 and 2.3.

In-hospital monitoring in syncope

In-hospital monitoring (in bed or telemetric) is warranted only when the patient is at high risk of life-threatening arrhythmias. A few days of ECG monitoring may be of value in patients with clinical features or ECG abnormalities suggesting an arrhythmic syncope such as those listed in Tables 2.2 and 2.4, especially if the monitoring is applied immediately after a syncopal episode. Although in such circumstances the diagnostic yield of ECG monitoring may be only as high as 16% [145], it is justified by the need to avoid immediate risk to the patient.

Holter monitoring in syncope

Most ECG monitoring in syncope is undertaken with external 24 h Holter recorders connected to the patient via external wiring and adhesive ECG patches.

Advantages include: it is a non-invasive test; there is beat-to-beat acquisition; device costs are low and there is relatively high fidelity over short time-periods.

Limitations include: patients may not tolerate adhesive electrodes or electrodes may not remain adherent throughout monitoring or during an event.

Presenting symptoms may not recur during monitoring. The vast majority of patients have a syncope-free interval measured in weeks, months or years, but not days and, therefore, symptom-ECG correlation can rarely be achieved with Holter monitoring. In an overview [146] of the results of eight studies of ambulatory monitoring in syncope, only 4% of patients (range between 1% and 20%) had correlation of symptoms with arrhythmia. The true yield of conventional ECG monitoring in syncope may be as low as 1—2% in an unselected population [147—149]. Admittedly, in 15% of patients, symptoms were not associated with arrhythmia. Thus in these patients, a rhythm disturbance could potentially be excluded as a cause of syncope.

An asymptomatic arrhythmia detected by Holter monitoring is often used to make a diagnosis by inference, but, without symptom-ECG correlation, there is potential for ECG findings to be inappropriately maximised leading to unnecessary therapy, e.g., pacemaker implantation in a patient with vasodepressor syncope. Alternatively, there is potential for symptoms to be inappropriately minimised by physicians if Holter monitoring fails to yield any evidence of an arrhythmia.

Holter monitoring in syncope is therefore cheap in terms of set-up costs, but expensive in terms of cost-per-diagnosis. Whilst unnecessary analysis of asymptomatic tapes might be avoidable by analysis only of symptomatic tapes. Such a strategy would require further provision of very large numbers of tape-recorders, greatly increasing the cost.

Holter monitoring in syncope may be of more value if symptoms are very frequent. Daily single or multiple episodes of loss-of-consciousness might increase the potential for symptom-ECG correlation. However, experience in these patients suggests that many have psychogenic blackouts. Undoubtedly, in such patients, true negative findings of Holter monitoring may be useful in confirming the underlying cause.

External loop recorder in syncope

Conventional event recorders are external devices equipped with fixed electrodes through which an ECG can be recorded by direct application to the chest wall. Provided the patient can comply at the time of symptoms, a high-fidelity recording can be made. Recordings can be prospective or retrospective (loop recorders) or both. Some recorders have long-term cutaneous patch connections, making a good skin contact for recordings less crucial. Prospective external event recorders have a limited value in syncope because the patient must be able to apply the recorder to the chest during the period of unconsciousness and activate recording. In one study [150], external retrospective loop recorders showed relatively higher diagnostic yield in syncope, 25% of enroled patients having syncope or pre-syncope recorded during the monitoring period up to 1 month, but comparisons with Holter monitoring are not possible because the study used highly selected patients with relatively high recurrence of syncope. However, since patients usually do not comply for more than a few weeks, with this instrument, symptom-ECG correlation cannot be achieved when the syncopal recurrence rate is less frequent. In a recent study [151],

external loop recorder was not useful for diagnosis of syncope in patients with 3±4 episoders (more than 2) of syncope during the previous 6 months, no overt heart disease and negative tilt testing.

Implantable loop recorder in syncope

The implantable ECG event monitor (implantable loop recorder) is placed subcutaneously under local anaesthesia, and has a battery life of 18—24 months. High fidelity ECG recordings can be made. The device has a solid-state loop memory, and the current version can store up to 42 min of continuous ECG. Retrospective ECG allows activation of the device after consciousness has been restored. Automatic activation is also available in case of occurrence of predefined arrhythmias.

Advantages of the implantable loop recorder include: continuous loop high-fidelity ECG recording for up to 24 months; a loop memory which allows activation after consciousness is restored; removal of logistical factors which prevent good ECG recording during symptoms; and a potential for a high yield in terms of symptom-ECG correlation because of the high likelihood of recording during recurrence of presenting symptoms.

Disadvantages include: the need for a minor surgical procedure; the lack of recording of any other concurrent physiological parameter, e.g., blood pressure; the high cost of the implantable device.

The implantable loop recorder carries a high upfront cost. However, if symptom-ECG correlation can be achieved in a substantial number of patients within 12 months of implantation, then analysis of the cost per symptom-ECG yield could show that the implanted device may be more cost-effective that a strategy using conventional investigation [152—154].

In the initial clinical experience Implantable Loop recorder was used for diagnosis in patients with unexplained syncope at the end of unsuccessful full conventional work-up. In a small series of highly selected patients, symptom-ECG correlation was achieved in 88% of patients within a mean of 5 months of implantation [152]. In a larger series [153], correlation between symptoms (syncope or pre-syncope) and ECG was achieved in 59% of 85 patients within a mean of 10 months of implantation. Syncope-ECG correlation was achieved in 27% of patients and presyncope-ECG correlation in 32%; presyncope was much less likely to be associated with an arrhythmia than syncope and did not prove to be an accurate surrogate for syncope in establishing a diagnosis (Level B). Pooled data from four studies [139,152,153,155] for a total of 247 patients with unexplained syncope at the end of a complete conventional investigation show that a correlation between syncope and ECG was found in 84 patients (34%); of these 52% had a bradycardia or asystole at the time of the recorded event, 11% had tachycardia and 37% had no rhythm variation.

One further study [154] randomized 60 patients with unexplained syncope to 'conventional' testing with external loop recorder and tilt and electrophysiological testing or to prolonged monitoring with the implantable loop recorder. The results were that a strategy of implantation of the loop recorder in an initial phase of the work-up is more likely to provide a diagnosis than conventional testing (52% vs 20%) (Level B). However, patients at high risk of life-threatening arrhythmias, as were those with an ejection fraction $<35\%$, were excluded.

From the initial experience in patients with unexplained syncope, it appears that the implantable loop recorder might become the reference standard to be adopted when an arrhythmic cause of syncope is suspected but not sufficiently proven to allow treatment based on aetiology. There are several areas of interest that merit further clarification:

- patients in whom epilepsy was suspected but the treatment has proven ineffective [156];
- patients with recurrent unexplained syncope without structural heart disease when the understanding of the exact mechanism of spontaneous syncope may alter the therapeutic approach [139];
- patients who have a diagnosis of neurally-mediated syncope when the understanding of the exact mechanism of spontaneous syncope may alter the therapeutic approach [139];
- patients with bundle branch block in whom a paroxysmal AV block is likely despite a complete negative electrophysiological evaluation [157];
- patients with definite structural heart disease and/or non-sustained ventricular tachyarrhythmias in whom a ventricular tachyarrhythmia is likely despite a completed negative electrophysiological study [158];
- patients with unexplained falls [159].

ECG monitoring in syncope — where in the workup?

The role of ECG monitoring in syncope cannot be defined in isolation. Physicians may be guided by the results of clinical history, physical examination and objective testing, for example, by tilt testing. Under some situations where the clinical evidence strongly suggests a diagnosis of reflex syncope, ECG monitoring may be deemed unnecessary. This is especially the case if symptoms are infrequent.

Under these circumstances, Holter monitoring is particularly unlikely to yield a diagnosis, and there implantable monitoring is now considered. However, future technology may allow recording of multiple signals in addition to the ECG and will place emphasis on the features of spontaneous episodes as they correlate with cardiac rhythm, rather than provoked syncope. Knowledge of what transpires during a spontaneous syncopal episode is the gold standard for syncope evaluation. For this reason it is likely that implantable monitors will become increasingly important in syncope and that their use will be anticipated in the diagnostic flow instead or before many other conventional investigations. However, in patients with important structural heart disease that expose them to a high risk of life-threatening arrhythmias, an electrophysiological study should precede the use of ECG monitoring systems. Although the documentation of a bradyarrhythmia concurrent with a syncopal episode is considered diagnostic, nevertheless sometimes further evaluation may be necessary in order to discriminate between an intrinsic cardiogenic abnormality and a neurogenic mechanism; this latter seems to be the most frequent cause of paroxysmal bradyarrhythmias [159].

Recommendations

Indications	Diagnosis
Class I • In-hospital monitoring (in bed or telemetric) is warranted when the patient has important structural heart disease and is at high risk of life-threatening arrhythmias (see section 'Need for hospitalization'). • Holter monitoring is indicated in patients who have the clinical or ECG features suggesting an arrhythmic syncope such as those listed in Tables 2.2 and 2.3 and very frequent syncopes or pre-syncopes, (e.g., ≥ 1 per week). • When the mechanism of syncope remains unclear after full evaluation, implantable loop recorder is indicated in patients who have the clinical or ECG features suggesting an arrhythmic syncope such as those listed in Tables 2.2 and 2.3) or a history of recurrent syncope with injury.	**Class I** • ECG monitoring is diagnostic when a correlation between syncope and an electrocardiographic abnormality (brady- or tachyarrhythmia) is detected. • ECG monitoring excludes an arrhythmic cause when there is a correlation between syncope and no rhythm variation. • In the absence of such correlations additional testing is recommended with possible exception of: — ventricular pauses longer than 3 s when awake — periods of Mobitz II or 3rd degree atrioventricular block when awake — rapid paroxysmal ventricular tachycardia.
Class II • Holter monitoring may be useful in patients who have the clinical or ECG features suggesting an arrhythmic syncope such as those listed in Tables 2.2 and 2.3 in order to guide subsequent examinations (i.e., electrophysiological study). • External loop recorder may be indicated in patients who have the clinical or ECG features suggesting an arrhythmic syncope such as those listed in Tables 2.2 and 2.3 and inter-symptom interval ≤ 4 weeks. • Implantable loop recorder may be indicated: — In an initial phase of the work-up instead of completion of conventional investigations in patients with preserved cardiac function who have the clinical or ECG features suggesting an arrhythmic syncope as those listed in Tables 2.2 and 2.3. — To assess the contribution of bradycardia before embarking on cardiac pacing in patients with suspected or certain neurally-mediated syncope presenting with frequent or traumatic syncopal episodes.	**Class II** • Presyncope may not be an accurate surrogate for syncope in establishing a diagnosis and, therefore, therapy should not be guided by presyncopal findings.
Class III ECG monitoring is unlikely to be useful in patients who do not have the clinical or ECG features suggesting an arrhythmic syncope as those listed in Tables 2.2 and 2.3 and therefore it should not be performed.	

Table 2.4 Classification of positive responses to tilt testing (modified from ref. [126])

- *Type 1 Mixed*. Heart rate falls at the time of syncope but the ventricular rate does not fall to less than 40 beats/min or falls to less than 40 beats/min for less than 10 s with or without asystole of less than 3 s. Blood pressure falls before the heart rate falls.
- *Type 2A Cardioinhibition without asystole*. Heart rate falls to a ventricular rate less than 40 beats/min for more than 10 s but asystole of more than 3 s does not occur. Blood pressure falls before the heart rate falls.
- *Type 2B Cardioinhibition with asystole*. Asystole occurs for more than 3 s. Blood pressure fall coincides with or occurs before the heart rate fall
- *Type 3 Vasodepressor*. Heart rate does not fall more than 10% from its peak at the time of syncope.
- *Exception 1. Chronotropic incompetence* No heart rate rise during the tilt testing (i.e., less than 10% from the pre tilt rate).
- *Exception 2. Excessive heart rate rise (Postural Orthostatic Tachycardia Syndrome or POTS)*. An excessive heart rate rise both at the onset of the upright position and throughout its duration before syncope (i.e., greater than 130 beats/min)

Electrophysiological testing

Transoesophageal electrophysiological study

The role of the non-invasive or transoesophageal electrophysiological examination is limited to screening for fast supraventricular tachycardia due to atrioventricular nodal reentrant tachycardia or atrioventricular reentrant tachycardia in patients with normal resting ECG and a history of syncope associated with palpitations and to the evaluation of sinus node dysfunction in patients with syncope suspected to be due to bradycardia. It can also be used for risk evaluation in patients with pre-excitation, although a normal refractory period of the accessory pathway cannot rule out a risk of atrial fibrillation with a fast ventricular response [161].

Invasive electrophysiological study

The diagnostic efficacy of the invasive electrophysiological study is — like all test procedures — highly dependent on the degree of suspicion of the abnormality (pre-test probability), but also on the applied protocol, and the criteria used for diagnosing the presence of clinically significant abnormalities.

The diagnostic yield

Electrophysiological studies use endocardial and (in the coronary sinus) epicardial electrical stimulation and recording to disclose abnormalities that suggest a primary arrhythmia as the cause of syncope. However, only few studies have used Holter monitoring or implantable devices to confirm the results of the electrophysiological study. The true diagnostic yield of the electrophysiological study is therefore only partly known.

Four studies [160,162—164] have compared the findings of a positive electrophysiological study with the arrhythmia documented during a spontaneous syncopal episode by ECG monitoring. In the study by Fujimura et al. [162], the utility of electrophysiological study was questioned because its result suggested the correct diagnosis only in 15% of patients, who had syncope due to transient bradycardia. However, in that study pharmacological provocation was not used, a very conservative criterion for significant sinus node dysfunction (SNRT $>$ 3000 ms) was used, and bradycardiac syncope due to an abnormal vagal reflex was not excluded. Indeed, when neurally-mediated syncope was excluded, Brignole et al. [160] showed that the presence of abnormal sinus node or His-Purkinje function (at baseline or after ajmaline provocation) disclosed the correct diagnosis in 86% of cases with spontaneous syncope due to sinus arrest or paroxysmal AV block, respectively. The results of the latter study have been corroborated in subsequent reports on patients with either electrocardiographic monitoring performed before electrophysiological study or by a bradycardia detecting pacemaker after an electrophysiological study [165,166]. Importantly, unrelated ventricular tachycardia and fibrillation and atrial tachyarrhythmias were induced in 24% and in 20% of patients in the Fujimura and Brignole studies, tachycardias that mistakenly might have been designated as the cause of syncope. In patients with syncope due to atrial or ventricular tachyarrhythmias, Lacroix et al. [163] showed that, while an electrophysiological study reproduced the spontaneous arrhythmia in 13 of 17 cases, a non-specific atrial or ventricular arrhythmia was also induced in 31 of 44 cases. Finally, Moasez et al. [164] showed that sustained monomorphic ventricular tachycardia on Holter monitoring was a strong predictor of induction of the same arrhythmia by electrophysiological study in syncopal patients, in concordance with many other studies on monomorphic ventricular tachycardia in patients with ischaemic heart disease (see below).

Predictors of positive results

In an overview of eight studies including 625 patients with syncope undergoing electrophysiological study Linzer et al. [167] assessed the association between

organic heart disease and an abnormal test result. Ventricular tachycardia was induced in 21%, and abnormal indices of bradycardia were found in 34% of patients with organic heart disease or an abnormal standard ECG. The corresponding figures were 1 and 10%, respectively, in patients with an apparently normal heart ($p<0.001$ for both comparisons). Thus, positive results at electrophysiological study occur predominantly in patients with evidence of organic heart disease (Level B).

Suspected intermittent bradycardia

The pre-test probability of a transient symptomatic bradycardia is relatively high when there is an asymptomatic sinus bradycardia (<50 beats/min) or sinoatrial block and syncope is occurred suddenly, without premonitory symptoms, is independent of posture and physical activity, is short-lasting, and is followed by rapid recovery. Sinus node disease/sick sinus syndrome is present when symptoms and sinus bradycardia or pauses occur simultaneously as proven by ECG monitoring ('gold standard'). Sinus node dysfunction can be demonstrated by abnormal sinus cycle variations on resting ECG, chronotropic incompetence on exercise testing, and by prolonged sinus node recovery time (SRT or SNRT) or sino-atrial conduction time (SACT) on electrophysiological study. The assessment of sinus node refractoriness is clinically not yet proven useful [168,169]. The major concern lies in limited sensitivity with all above mentioned methods, while specificity is high. There is no generally accepted protocol for evaluating sinus node function. SACT cannot always be assessed in patients with proven sinus node disease [170], and recovery time assessment is therefore usually preferred. A prolonged sinus node recovery time reflects abnormal sinus node automaticity, sinoatrial conduction, or both [171]. The sensitivity of SNRT >1500—1720 ms and/or CSNRT (SNRT corrected for heart rate) >525 ms is approximately 50—80%, while the specificity is >95% [169]. The value of including assessment also after administration of atropine and propranolol for inhibition of autonomic tone is accepted for distinguishing between intrinsic and extrinsic sinus node dysfunction [169], but its diagnostic value is still debated. According to two studies [165,172] pharmacological challenge has a place in increasing the sensitivity of the electrophysiological study, when the baseline study is inconclusive. Complete autonomic blockade of the sinus node activity can be achieved by administration of intravenous propranolol (0.2 mg/kg body weight) and intravenous atropine sulphate (0.04 mg/kg body weight) according to the seminal work by Jose and Collison, defining the so-called intrinsic heart rate [173]. Normal values for intrinsic heart rate can be determined by using a linear regression equation, which relates predicted intrinsic heart rate (IHRp) to age; IHRp = 118.1 − (0.57 × age) [173]. The sensitivity of IHRp is very low for diagnosing sinus node dysfunction. Initially the same dosages were used for distinguishing between intrinsic and extrinsic sinus node dysfunction when assessing sinus node recovery time [174,175], and later modified to 75% by Tonkin et al. [176]. From a diagnostic point of view it seems sufficient to use propranolol 0.1 mg/kg body weight and atropine 0.02 mg/kg body weight, since higher doses might cause adverse effects, at least in patients older than 60 years [165].

The prognostic value of a prolonged sinus node recovery time is largely unknown. One observational study, however, showed a relationship between the presence of prolonged recovery time at electrophysiological study and the effect of pacing on symptoms [177]. Recently Menozzi et al. [178] addressed a related issue in a small prospective study, showing that the patients with a CSNRT of ≥ 800 ms had an eight times higher risk of syncope than patients with a CSNRT below this value. The panel discussed the criteria for SNRT as a diagnostic tool for syncope but could not arrive at a consensus because of the lack of other prospective data evaluating the diagnostic value of this test. The following diagnostic criteria are widely used for defining sinus node dysfunction: 1.6 or 2 s for SNRT [171,179] or 525 ms for CSNRT [177]. In one study [179], marked prolongation of SNRT (longer than 3 s) was suggested to increase the possibility that sinus node dysfunction may be responsible for syncope. It is opinion of the panel that, in presence of a SNRT >2 s or CSNRT >1 s, sinus node dysfunction may be the cause of syncope.

Syncope in patients with bundle branch block (impending high degree AV block)

The most alarming ECG sign in a patient with syncope is probably alternating complete left and right bundle branch block, or alternating right bundle branch block with left anterior or posterior fascicular block, suggesting trifascicular conduction system disease and intermittent or impending high degree AV block. The 'trifascicular' concept, introduced by Rosenbaum [180], is still the most clinically useful, albeit a simplification. Also patients with bifascicular block (right bundle branch block plus left anterior or left posterior fascicular block, or left bundle branch block) are at higher risk of developing high degree AV block. A significant problem in the evaluation of syncope

and bifascicular block is the transient nature of high degree AV block and, therefore, the long periods required to document it by ECG [181].

Two factors were shown to increase the risk for AV block: a history of syncope and a prolonged HV interval. The risk of developing AV block increased from 2% in patients without syncope to 17% in patients with syncope [182]. The prognostic value of the HV interval was prospectively studied by Scheinman et al. [183]; the progression rate to AV block at 4 years was 4%, 2%, and 12%, respectively, for patients with an HV interval of <55 ms (normal), 55—69 ms, and ≥ 70 ms; in patients with an HV interval ≥ 100 ms it was even higher, 24%. This pioneering work on bundle branch block, published in the 1980s, did not use pharmacological stress testing and the progression to high degree AV block was not followed by sensitive detectors of AV block progression such as a bradycardia detecting pacemaker. The figures provided are, therefore, likely to represent estimates at the lower end of the range.

In order to increase the diagnostic yield of the electrophysiological evaluation incremental atrial pacing and pharmacological provocation were added. The development of intra- or infra His block at incremental atrial pacing [181,184—187] is highly predictive of impending AV block, but is rarely observed and has low sensitivity. For example, in the study by Gronda et al. [188] on 131 patients, an HV prolongation of >10 ms was observed in 6% and 2nd degree AV block in 5% of cases. Complete AV block developed in 40% of these patients during a mean follow-up of 42 months. In the study by Dini et al. [189], on 85 patients, pacing induced AV block in 7% with progression to complete AV block in 30% within 2 years. Acute intravenous pharmacological stress testing of the His-Purkinje system has been performed with several class IA antiarrhythmic substances: ajmaline, at a dosage of 1 mg/kg [188—190], procainamide at a dosage of 10 mg/kg [191], and disopyramide at a dosage of 2 mg/kg [166]. Importantly, not only should the occurrence of high degree AV block during spontaneous rhythm be sought, but also any intra- or infra- His block at incremental atrial pacing or after short sequences of ventricular pacing [166]. In five studies [181,188,189] evaluating the diagnostic value of pharmacological stress testing for a total of 333 patients, high-degree AV block was induced in 50 (15%) of the patients. During the follow-up ranging between 24 and 63 months, 68% (range 43—100) of these patients developed spontaneous AV block. Thus, the induction of AV block during the test is highly predictive of subsequent development of AV block. The prognostic value of a pharmacologically prolonged HV interval to a value of ≥ 120 ms or $>50\%$ of the baseline value without induction of AV block has also been evaluated but its utility is less certain. In three studies [181,188,189] AV block progression was observed in 18%, 29% and 75% of positive patients. Untreated high degree AV block carries an adverse prognosis. It is, therefore, important to reach a high diagnostic accuracy. By combining the above mentioned parts of the electrophysiological protocol, it was possible to identify most of the patients who developed high degree AV block; for example, the positive predictive value was 87% in the study of Gronda et al. [188] and 80% in that of Bergfeldt et al. [181] (Level B). On the other hand, in patients with negative electrophysiological studies, Link et al. [192] observed development of permanent AV block in 18% (after 30 months) and Gaggioli et al. [193] in 19% (at 62 months) and intermittent or stable atrioventricular block was documented by an implantable loop recorder in 33% of patients (within 15 months) [157]. Finally, pacemaker therapy resulted in effective suppression of syncopal recurrences in almost all patients and was significantly better than no pacing, thus indirectly confirming the usefulness of the electrophysiological study [183,184,190].

Importantly, a high incidence of total deaths and sudden death was observed in patients with bundle branch block. In pooled data from 9 studies for a total of 1761 patients the total mortality was 28% at 40 months and 32% of deaths were sudden [181—183,187,190,193—195]. However, neither syncope nor a prolonged HV interval was associated with a higher risk of death [182,194], and pacemaker therapy did not decrease this risk [183]. The mechanism of sudden death is therefore supposedly due to a ventricular tachyarrhythmia or electromechanical dissociation rather than a bradyarrhythmia. A sustained ventricular tachyarrhythmia is frequently inducible in patients with bundle branch block by means of programmed ventricular stimulation, having been observed in 32% of a total of 280 patients (pooled data from four studies [187,190,195,196]. In one study [195], sustained monomorphic ventricular tachyardia was exclusively induced in patients with previous myocardial infarction. Nevertheless, inducibility was of the same magnitude in patients with and without a history of syncope and clinical events during follow-up were not predicted by programmed ventricular stimulation [155—196].

In conclusion, in patients with syncope and bifascicular block, an electrophysiological study is highly sensitive in identifying patients with

intermittent or impending high degree AV block (Level B) though a negative electrophysiological investigation cannot rule-out paroxysmal AV block as the cause of syncope (Level B). This block is the likely cause of syncope in most cases, but not of the high mortality rate observed in these patients. Indeed, the high total and sudden mortality seems mainly related to underlying structural heart disease and ventricular tachyarrhythmias (Level B). Unfortunately, ventricular programmed stimulation does not seem to be able correctly to identify these patients and the finding of inducible ventricular arrhythmia should therefore be interpreted with caution.

Suspected tachycardia

Supraventricular tachycardia presenting as syncope without accompanying palpitations is probably rare [187]. Both non-invasive (transoesophageal) and invasive electrophysiological studies may be used to evaluate the haemodynamic effects of an induced tachycardia, especially if combined with administration of isoprenaline or atropine.

Ventricular tachycardia may present as syncope with or without palpitations or other accompanying symptoms. The major concern with programmed electrical stimulation as part of an electrophysiological study for inducing clinically significant ventricular arrhythmia is its varying sensitivity (and specificity) in different clinical settings [198] and the lack of a standard protocol [199] (Table 2.5). Generally speaking, programmed electrical stimulation is thought to be a sensitive tool in patients with chronic ischaemic heart disease (previous myocardial infarction) and susceptibility for a spontaneous monomorphic ventricular tachycardia. Applying the opposite perspective, the induction of a monomorphic ventricular tachycardia is thought to be a specific event that should guide therapy. For example, in the ESVEM trial [200], syncope, associated with induced ventricular tachyarrhythmias at electrophysiological testing, indicated high risk of death, similar to that of patients with documented spontaneous ventricular tachyarrhythmias. The specificity of induction of ventricular tachycardia has been questioned in patients with syncope and bifascicular block [195]. The specificity of the induction of polymorphic ventricular tachycardia and ventricular fibrillation probably depends on the clinical setting. On one hand, in coronary artery disease and syncope, the follow-up of patients with and without inducible ventricular fibrillation demonstrated no difference in survival between the two groups [201]. On the other hand, the induction of polymorphic ventricular arrhythmias seems to have a predictive value in patients with the Brugada syndrome [202,203], in survivors of cardiac arrest with significant coronary artery disease undergoing coronary bypass surgery and in idiopathic ventricular fibrillation [204,205].

Table 2.5 Minimal suggested electrophysiological protocol for diagnosis of syncope

- Measurement of sinus node recovery time and corrected sinus node recovery time by repeated sequences of atrial pacing for 30—60 s with at least one low (10—20 beats/min higher than sinus rate) and two higher pacing rates[a]
- Assessment of the His-Purkinje system includes measurement of the HV interval at baseline and His-Purkinje conduction with stress by incremental atrial pacing. If the baseline study is inconclusive, pharmacological provocation with slow infusion of ajmaline (1 mg/kg i.v.), procainamide (10 mg/kg i.v.), or disopyramide (2 mg/kg i.v.) is added unless contraindicated
- Assessment of ventricular arrhythmia inducibility performed by ventricular programmed stimulation at two right ventricular sites (apex and outflow tract), at two basic drive cycle lengths, (100 or 120 beats/min and 140 or 150 beats/min), with up to two extrastimuli[b]
- Assessment of supraventricular arrhythmia inducibility by any atrial stimulation protocol

[a] When sinus node dysfunction is suspected autonomic blockade may be applied, and measurements repeated.
[b] A third extrastimulus may be added. This may increase sensitivity, but reduces specificity. Ventricular extrastimulus coupling intervals below 200 ms also reduce specificity.

The predictive value of non-inducibility depends on the aetiology and severity of the underlying heart disease, e.g., ischaemic or non-ischaemic heart disease. In patients with coronary artery disease and preserved cardiac function, non-inducibility at electrophysiological study predicted a low risk of sudden death and ventricular arrhythmias [192]. A study [158] has evaluated the predictive value of a negative electrophysiological study in 35 patients with overt heart disease at risk of ventricular arrhythmia, as these were patients with previous myocardial infarction or cardiomyopathy with moderately low values of ejection fraction (mean 47 ± 17) or non-sustained ventricular tachycardia who had received the implantation of a loop recorder. During the follow-up, syncopal recurrences never were due to tachyarrhythmia which was documented only in one patient and caused presyncope. Interestingly, the induction of polymorphic ventricular tachycardia or fibrillation during electrophysiological study (that was considered as a negative result) was of no value for

predicting syncopal events and, in particular, ventricular tachyarrhythmias. Thus, in the absence of a severe pump dysfunction, the negativity of the electrophysiological study, predicts a low risk of ventricular tachyarrythmias.

Conversely, programmed ventricular stimulation has a low predictive value in patients with non-ischaemic dilated cardiomyopathy [31] and one study [206] of patients with unexplained syncope treated with implantable cardioverter defibrillators (ICD) showed a high incidence of tachyarrhythmic episodes during the follow-up despite an initial negative electrophysiological study. In another study [207] of selected patients affected by idiopathic dilated cardiomyopathy who received an ICD, there was a high incidence of appropriate shocks both in the inducible and in non-inducible sustained monomorphic ventricular tachycardia groups.

The advent of ICDs with improved documentation of arrhythmic events offers a safe and sensitive tool for the follow-up in different high-risk populations. Eight studies [206—213] have evaluated the utility of ICDs in highly selected patients with syncope. Link et al. [208] reported on 50 patients who had an appropriate — due to ventricular tachycardia/fibrillation — device discharge rate of 22% at 1 year and 50% at 3 years' follow-up. Among the 33 patients of the study by Militianu et al. [209], an appropriate discharge of the device occurred in 36% over a period of 17 months. In these two studies, the population was heterogeneous, including patients with ischaemic and non-ischaemic cardiomyopathy, and the induction of ventricular fibrillation was also considered a positive result. In three studies concerning patients affected by coronary artery disease programmed ventricular stimulation was useful in risk stratification [210—212]. In the study by Mittal et al. [210], which evaluated 67 consecutive patients with coronary artery disease, mostly with a prior myocardial infarction and a depressed ejection fraction (mean $37 \pm 13\%$), sustained monomorphic ventricular tachycardia was inducible in 43% of cases. During a follow-up of more than 1 year, 41% of inducible patients received an appropriate device discharge, and only one had a syncopal relapse, which was not related to the ventricular arrhythmia. However, the total mortality for patients with inducible tachycardia was significantly higher than for non-inducible patients, the actuarial 2-year survival rates being 84% and 45% respectively. Andrews et al. [211], performed a retrospective case-control study in which 22 patients with unexplained syncope and inducible ventricular tachycardia were compared with a matched group of 32 patients with documented syncopal ventricular tachycardia. Almost all the patients had coronary artery disease with severe systolic dysfunction (mean ejection fraction 30%). After 1 year, a similar incidence of ICD discharges occurred in the 2 groups (57% vs 50%), suggesting that electrophysiological testing can identify patients with severe coronary artery disease at risk of life-threatening arrhythmias. Pires et al. [212] observed, in 178 patients with unexplained syncope, inducible ventricular tachycardia/fibrillation for the most part and coronary artery disease, who were treated with ICDs, a high recurrence of ventricular tachyarrhythmias (55% at 2 years), high correlation (85%) between recurrent syncope and ventricular arrhythmia and low mortality, which was comparable with the results in similar patients with documented sustained ventricular tachycardia/fibrillation. Conversely, in three other studies concerning patients affected by non-ischaemic dilated cardiopathy programmed ventricular stimulation was not useful in risk stratification [206,207,213]. Knight et al. [206], in patients with non-ischaemic dilated cardiopathy with severe systolic dysfunction (mean ejection fraction of 26%), performed a similar small retrospective case-control study. Fourteen consecutive patients with unexplained syncope and a negative electrophysiological study were compared with a matched group of 19 patients with a documented cardiac arrest due to ventricular tachyarrhythmia. After 2 years, the same incidence of ICD discharges occurred in the 2 groups (50% vs 42%) and the relapses of syncope or presyncope were primarily due to ventricular fibrillation. The patients with more severe cardiomyopathy (ejection fraction of 20%) were more likely to receive an appropriate shock. Thus, in patients with very severe non-ischaemic cardiomyopathy, risk stratification on a clinical basis seems superior to that based on the results of an electrophysiological study. Improved survival with ICD in respect of conventional therapy has been observed in the study of Fonarow et al. [213] in patients with non-ischaemic advanced heart failure referred for heart transplantation (mean ejection fraction of 21%). Actuarial survival at 2 years was 85% in the 25 patients managed with an ICD and 67% in the 122 patients without. No patient with an ICD had sudden death and an appropriate shock discharge occurred in 40% of these. Finally, Brilakis et al. [207], in a selected group of 17 patients of a total of 54 affected by idiopathic dilated cardiomyopathy who received an ICD, the incidence of appropriate shocks at 1 year was 47% and 40%, respectively, in the inducible and in non-inducible sustained monomorphic ventricular tachycardia.

In conclusion, the outcome largely depends on the clinical features of the patients. It seems that only the inducibility of sustained monomorphic ventricular tachycardia and/or very depressed systolic function can predict a life-threatening arrhythmic syncope and, conversely, their absence may predict a more favourable outcome. Electrophysiological study with programmed electrical stimulation is an effective diagnostic test in patients with coronary artery disease, markedly depressed cardiac function and unexplained syncope (Level B). Its utility is more questionable in patients with non-ischaemic dilated cardiomyopathy (Level B). Patients who undergo implantation of an automatic defibrillator have a high incidence of spontaneous ventricular arrhythmia requiring device therapy, and suppression of syncopal recurrences (Level B). However, these results applied to a highly selected, high-risk population that might be not representative of the patients encountered in clinical practice.

Recommendations

Indications	Diagnosis
Class I • An invasive electrophysiological procedure is indicated when the initial evaluation suggests an arrhythmic cause of syncope such as those listed in Tables 2.2 and 2.3 (in patients with abnormal electrocardiography and/or structural heart disease or syncope associated with palpitations or family history of sudden death).	**Class I** • Normal electrophysiological findings cannot completely exclude an arrhythmic cause of syncope; when an arrhythmia is likely, further evaluations (for example loop recording) are recommended. • Depending on the clinical context, abnormal electrophysiological findings may not be diagnostic of the cause of syncope. • An electrophysiological study is diagnostic, and usually no additional tests are required, in the following cases: — sinus bradycardia and a very prolonged CSNRT (as discussed in the text) — bifascicular block and: — a baseline HV interval of $\geq$ 100ms, or — 2nd or 3rd degree His-Purkinje block is demonstrated during incremental atrial pacing, or — (if the baseline electrophysiological study is inconclusive) high-degree His-Purkinje block is provoked by intravenous administration of ajmaline, procainamide, or disopyramide — induction of sustained monomorphic ventricular tachycardia — induction of rapid supraventricular arrhythmia which reproduces hypotensive or spontaneous symptoms.
Class II	**Class II** The diagnostic value of an electophysiological study is less well established in case of:
• Diagnostic reasons: to evaluate the exact nature of an arrhythmia which has already been identified as the cause of the syncope.	• HV interval of $>$70 ms but $<$100 ms.
• Prognostic reasons: in patients with cardiac disorders, in which arrhythmia induction has a bearing on the selection of therapy; and in patients with high-risk occupations, in whom every effort to exclude a cardiac cause of syncope is warranted.	• Induction of polymorphic ventricular tachycardia or ventricular fibrillation in patients with Brugada syndrome, arrhythmogenic right ventricular dysplasia and patients resuscitated from cardiac arrest.
Class III • In patients with normal electrocardiograms and no heart disease and no palpitations an electrophysiological study is not usually undertaken.	**Class III** The induction of polymorphic ventricular tachycardia or ventricular fibrillation in patients with ischaemic or dilated cardiomyopathy has a low predictive value.

ATP test

Intravenous injection of adenosine triphosphate (ATP) has recently been proposed as a tool in the investigation of patients with unexplained syncope [214,215]. In predisposed patients with unexplained syncope, the stimulation of purinergic receptors, with a powerful dromotropic effect on the atrioventricular node [216], causes prolonged ventricular pauses due to atrioventricular block, which are considered as possibly responsible for spontaneous attacks. The action of ATP is due to its rapid catabolism to adenosine and the subsequent action of adenosine at purinoceptor sites.ATP and adenosine have similar effects in humans [216].

Protocol of the ATP test

The protocol proposed by Flammang [214] consists of the injection in a brachial vein of a bolus (<2 s) of 20 mg of ATP followed by a 20 ml flush of dextrose solution or dissolved in 10 ml of saline solution. During injection, patients remain supine with continuous electrocardiographic recordings just before and 2 min after drug administration. Blood pressure is monitored non-invasively. Due to possible bronchospastic reactions, the ATP test is contraindicated in patients with known asthma. Due to the risk of coronary steal, the test is also contraindicated in the patients with significant coronary disease. Other side effects are generally mild. Facial flush, shortness of breath, and chest pressure are the most frequently reported effects. Lightheadedness or syncope may also occur but are 'expected'. Rarely, short-duration self-limiting atrial fibrillation is initiated [215].

Interpretation of the result of the test is exclusively based on the duration of the cardiac 'pause'. A value of >6 s [215] or >10 s even if interrupted by some escape beats [204] is defined as abnormal (Level B). Such pauses were observed in about 5% of control subjects without syncope.

In patients with abnormal responses, reproducibility was roughly 80% both in the short and the long-term period [215,217].

Relationship between ATP test and spontaneous syncope

In patients with syncope of unknown origin, the ATP-test was abnormal in 28% and 41% of the patients in two series [214,215]. Moreover, in a small group of patients with syncope electrocardiographically documented to be caused by transient pause, Brignole et al. [215] found that ATP test reproduced atrioventricular block with a pause >6 s in 53% of the patients with documented spontaneous atrioventricular block but in none of those with sinus arrest. The interpretation of these studies is that some patients with unexplained syncope show an increased susceptibility to ATP testing in comparison with those without syncope and ATP testing is able to reproduce atrioventricular block (and suggest the mechanism) in patients with spontaneous paroxysmal atrioventricular block. However, the results were not confirmed in a small prospective follow-up study [218] which used an implantable loop recorder as an outcome measure. In that study indeed the mechanism of syncope was heterogeneous and an ATP-induced AV block predicted AV block as the mechanism of the spontaneous syncope only in a few patients; the outcome was benign and patients did not experience complications. The favourable outcome suggests implantation of a pacemaker or a loop recorder only when the clinical presentation is severe enough to require treatment.

Relationship between ATP and tilt testing

Both ATP and tilt testing were performed in patients with unexplained syncope in two studies [219,220]. Although some overlap of positive responses was observed, this was limited to no more than 20% of cases. Moreover, compared with the patients with isolated positive tilt test, those with isolated positive ATP were older, had a lower number of syncopal episodes, a shorter history of syncopal episodes, a lower prevalence of situational, vasovagal or triggering factors and a lower prevalence of warning symptoms. The results suggest that these two tests explored two different 'susceptibilities' leading to syncope under certain conditions. In a recent study [221], endogenous adenosine plasma levels were higher in patients with a positive tilt test than in patients with a negative test and they increased during tilt-induced syncope. These observations suggest that adenosine release may be involved in the trigger mechanism of syncope induced during tilt testing.

Other authors [222,223] have used adenosine as an alternative drug challenge during tilt testing based on the hypothesis that adenosine could be an important modulator in triggering a vasovagal response in susceptible patients but apparently without significant improvement over usual pharmacological challenges.

Recommendations

The test requires the rapid injection of a 20 mg bolus of ATP during electrocardiographic monitoring. Asystole lasting more than 6 s, or AV block lasting more than 10 s, is considered abnormal. ATP testing produces an abnormal response in some patients with syncope of unknown origin, but not in controls. ATP testing identifies a group of patients with otherwise unexplained syncope with definite clinical features and benign prognosis but possibly heterogeneous mechanism of syncope. Thus, specific treatment should be postponed until a definite mechanism of syncope can be obtained (Class II).

Ventricular signal-averaged electrocardiogram, T wave alternans

Ventricular late potentials represent areas of slow conduction that can promote the occurrence of ventricular arrhythmias. These low-amplitude signals can be detected on the surface electrocardiogram using a signal averaging technique if the area of slow conduction is activated late during ventricular depolarization [224].

It has been shown that the signal-averaged electrocardiogram might be useful (sensitivity 70—82%, specificity 55—91%) in identifying those patients with recurrent syncope in whom ventricular tachycardia may be the underlying mechanism [225,228]. Even if not specifically evaluated in patients with syncope, T-wave alternans seems to be a stronger predictor of ventricular tachyarrhythmias [229]. Therefore, the signal-averaged electrocardiogram and T wave alternans can serve as a non-invasive screening test for selecting patients with syncope who should undergo programmed ventricular stimulation. However, such patients are likely to need an electrophysiological study regardless of the results of the signal-averaged electrocardiogram because of a high risk of sudden death. Thus, the additional diagnostic benefit provided by the signal-averaged electrocardiogram or T-wave alternans may in fact be rather low.

The signal-averaged electrocardiogram may also be used as a non-invasive tool for detection of cardiac abnormality. An abnormal result of the test may indicate cardiomyopathy (arrhythmogenic right ventricular dysplasia or dilated cardiomyopathy) or cardiac involvement in systemic disorders (amyloidosis, systemic sclerosis, muscular dystrophy). The signal-averaged electrocardiogram may be particularly useful in the early stages of these diseases in those patients in whom other routine tests such as ECG or echocardiography are normal [230].

The methodology of signal-averaged electrocardiographic recording and analysis in patients with syncope is identical to that in patients with other conditions and should be performed according to the published standards [230].

Brugada syndrome is frequently associated with syncopal ventricular tachyarrhythmias. Some studies suggested that the presence of ventricular late potentials identifies those patients who have inducible ventricular tachyarrhythmias [231] or who have a history of syncope or aborted sudden death [232]. Two case reports suggested that T-wave alternans may identify patients with Brugada syndrome who are at risk of ventricular fibrillation [233,234]. However, a larger study did not confirm these preliminary findings [232].

Recommendations

There is general agreement that ventricular signal-averaged electrocardiogram and T-wave alternans are not diagnostic of the cause of syncope. In patients with syncope and no evidence of structural heart disease, these techniques may be useful for guiding the use of electrophysiological studies. Their systematic use is not recommended (Class III).

Exercise testing

Exercise-induced syncope is a rare finding, occurring in up to 5% of patients with unexplained syncope [45]. Exercise testing should be performed in patients who have experienced episodes of syncope during or shortly after exertion. It is generally recommended that exercise testing should be symptom-limited. However, some authors showed that a modified treadmill test with abrupt termination has a high diagnostic value (sensitivity 78%, specificity 95%, total predictive accuracy 86%) in disclosing the mechanism of exercise-related syncope [235]. Echocardiographic evaluation should precede the exercise test. Careful electrocardiographic and blood pressure monitoring should be performed during both the test and the recovery phase as syncope can occur during or immediately after exercise. These two situations should be separately considered. Indeed, syncope occurring during exercise may be cardiac, even if some case reports showed that it might be a manifestation of an exaggerated reflex vasodilatation [236,237]. Reflex syncope occurring during exercise is caused by marked hypotension without bradycardia [236,237]. By contrast, postexertional syncope is almost invariably due to autonomic failure or to a neurally-mediated mechanism [238,240,249] and is characterised by hypotension which can be

associated with marked bradycardia or asystole; it typically occurs in subjects without heart disease (Level B). It has been supposed that adrenaline plays an important role in the mechanisms leading to neurally mediated syncope associated with exercise [241]. Tilt testing has been used to diagnose neurally-mediated syncope, which may manifest as postexertional syncope [242]. The diagnostic yield of tilt testing is equally high in patients with exercise-related and exercise-unrelated neurally mediated syncope [235]. A failure of reflex vasoconstriction during exercise in splanchnic capacitance vessels and in forearm resistance vessels has been shown in patients with vasovagal syncope [236]. Syncope in athletes may be an important problem. However, in the absence of structural heart disease, syncope occurring during or immediately after exercise in athletes is a benign condition, with a good long-term outcome. The likely final diagnosis is neurally-mediated [243].

Tachycardia-related (phase 3) exercise-induced 2nd and 3rd degree atrioventricular block has been shown to be invariably located distal to the atrioventricular node and is an ominous finding of progression to stable chronic atrioventricular block. Resting electrocardiogram frequently shows an intraventricular conduction abnormality [244—246] (Level B).

Exercise testing is not particularly cost-effective when used in a general population with syncope. Its diagnostic yield was less than 1% in a population study [29]. However, when its use is limited to selected patients with exertional syncope, it may represent an important diagnostic test.

Recommendations

Indications	Diagnosis
Class I Patients who experience an episode of syncope during or shortly after exertion.	**Class I** • Exercise testing is diagnostic when ECG and haemodynamic abnormalities are present and syncope is reproduced during or immediately after exercise. • Exercise testing is diagnostic if Mobitz 2 second degree or 3rd degree AV block develop during exercise even without syncope.
Class III Use of exercise testing is not recommended in patients who do not experience syncope during exercise.	

Cardiac catheterization and angiography

Cardiac catheterization may consist of ventriculography to assess cardiac chambers morphology, coronary arteriography to visualise coronary anatomy and haemodynamics to assess blood flow and intravascular and intracardiac pressures. Because this is an invasive technique, it is rarely used as a screening test to detect cardiac disease in patients presenting with syncope.

The test may reveal coronary lesions causing ischaemia which may lead to syncope due to: wall motion disturbances and decrease in myocardial contractility; ischaemia-induced cardiac arrhythmias, asystole or complete heart block [247]; and ischaemia-induced vasovagal reaction [248]. It may also reveal coronary artery spasm or congenital abnormalities (single coronary artery, anomalous origin of right coronary artery or coronary arteriovenous fistula as a cause of syncope [249,250]. In case of suspected coronary spasm, the ergometrine test during coronary angiography may be indicated [251].

Recommendations

Indications
Class I In patients with syncope suspected to be due, directly or indirectly, to myocardial ischaemia, coronary angiography is recommended in order to confirm the diagnosis and to establish optimal therapy.
Class III Angiography alone is rarely diagnostic of the cause of syncope.

Neurological and psychiatric evaluation

Neurological evaluation

Neurological disorders feature in the diagnosis of syncope in three ways. Firstly, they may cause syncope as a result of a diseased and insufficient autonomic nervous system: autonomic failure. Secondly, some cerebrovascular disorders also cause syncope (mostly the 'steal' syndromes). Thirdly, several disorders feature in the differential diagnosis because they can cause a transient loss of consciousness (other than syncope), or because they cause 'attacks' that resemble loss of consciousness. These groups will be separately discussed.

Autonomic failure

In autonomic failure, the autonomic nervous system is incapable of meeting the demands of upright posture, causing orthostatic hypotension

and syncope. Its severity may be expressed as the length of time patients can remain standing before they have to sit down. There may be signs and symptoms showing autonomic malfunction of other organ systems. Impotence in men and disturbed micturition occur often, and can be assessed easily through history-taking. There are three groups of autonomic failure [252—253].

- *Primary autonomic failure* comprises primary degenerative diseases of the central nervous system. Three are numerically important; all three occur in middle age or later. In pure autonomic failure (PAF) other neurological systems are never affected, but in multiple system atrophy (MSA) Parkinsonian, pyramidal and/or cerebellar symptoms occur at some stage in the disease. Note that 'MSA' supplants three other disorders: Shy—Drager syndrome, striatonigral degeneration and olivopontocerebellar degeneration [253]. Finally, there may be a form of Parkinson's disease with autonomic failure, but the overlap with MSA makes recognition difficult. Although there are diagnostic guidelines or hints towards the clinical recognition of MSA [254—256] only pathological studies can reveal the true diagnosis.
- *Secondary autonomic failure* indicates damage to the autonomic nervous system caused by other diseases. This can occur through many disorders [252] but in numerical terms the most important disorders are probably diabetes mellitus, kidney or liver failure, and alcohol abuse.
- *Drug-induced autonomic failure* is important in terms of prevalence; main culprits are tricyclic antidepressives, phenothiazines, antihistamines, levodopa (Parkinson's disease) and MAO-inhibitors.

Generally, the pattern of autonomic failure does not depend in a clear manner on the primary disorder. Neurological evaluation is warranted in case of autonomic failure, apparent as orthostatic hypotension on its own or when accompanied by other autonomic signs or symptoms, such as impotence or disturbed micturition. The presence of other neurological signs, particularly Parkinsonism, that of sytemic diseases such as diabetes, or of certain drugs (antidepressives) help to distinguish between causes.

Cerebrovascular disorders
These are listed below.

- *Steal syndromes* occur when the arterial circulation to the arm is blocked, resulting in a shunt of blood though the cerebrovascular system, which then has to supply both (part of) the brain and the arm. This may cause insufficient perfusion of the brain stem (causing loss of consciousness) when the demands of the circulation in the arm exhaust the supply, i.e., during strenuous physical activity of the arm. Transient ischaemic attacks in a patient with steal only occur if there is atherosclerosis in other extracranial arteries as well. Symptoms attributed to vertebro-basilar steal include vertigo, diplopia, blurred vision and cranial nerve dysfunction as well as syncope and drop attacks. The chances that a transient loss of consciousness without any brainstem signs are due to subclavian steal are probably very small. A blood pressure difference between the arms may point towards the presence of a steal phenomenon. Complaints may be ascribed to steal with more likelihood if they are clearly associated with exercise of one arm. However, the presence of steal does not mean that any episode of loss of consciousness may be ascribed to it. Syncope may also occur during exertion due to cardiac causes, so care must be taken to assess whether the syncope in a steal syndrome is linked to activity of one arm.
- T*ransient ischaemic attacks* (TIAs) in the territory of one carotid artery do not cause loss of consciousness. Only TIAs in the vertebrobasilar circulation may theoretically do so, but other signs, such as ataxia, eye movement disorders, and vertigo then predominate. True loss of consciousness without any such features makes a TIA unlikely, and does not warrant ancillary investigation into the vertebrobasilar circulation.
- *Migraine* is probably associated with syncope, both outside attacks [257] and during an attack [258]. There is, however, little recent epidemiological research in this area, and the frequency of both disorders might cause a bias. It is not known whether the association has consequences for treatment of either condition. Vertebrobasilar migraine does cause a disturbance of consciousness, but attacks last too long to be confused with syncope, and they are accompanied by other neurological signs.

Non-syncopal attacks
The third group concerns disorders with non-syncopal or only apparent loss of consciousness.

- *Epilepsy* can (depending on the type) cause loss of consciousness. When witnessed by an

expert, tonic-clonic attacks are easy to recognize. Questions to distinguish between tonic-clonic seizures and syncope should be directed separately at patients and eye-witnesses (Table 2.6). The patient should be asked whether there were any promonitory signs. The typical textbook aura, consisting of a rising sensation in the abdomen, and/or an unusual unpleasant smell, are relatively rare [259]. Aura patterns are usually repetitive over time in patients, who will, therefore, learn to recognise them as such. The patient should be asked how he/she felt on regaining consciousness: confusion or sleepiness lasting more than a few minutes point to epilepsy, as do tongue biting, or muscle pains lasting for hours or days. Urinary incontinence is not useful for distinction. Witnesses should be asked to describe any movements. Unconsciousness without any movement makes epilepsy unlikely, but movements certainly do not exclude syncope (also improperly called 'convulsive syncope') [4], although the presence of any movement is often interpreted by both medical personnel and laymen as indicative of epilepsy. Syncopal movements are typically asynchronous and limited in scope (called 'myoclonic' in neurology), while a tonic posture concerns forceful extension of the extremities, and clonic movements (not called myoclonus) concern massive synchronous jerks of the arms and/or legs [4,5]. Mimicking the movements helps to make witnesses choose between the options. In syncope, movements occur as a result of brain ischaemia, and, therefore, occur after the patient has slumped to the floor. In epilepsy, clonic movements can occur before the fall, whereas the tonic posture can cause the patient to keel over like a falling log. In other forms of epilepsy, such as absence epilepsy in children and partial complex epilepsy in adults, consciousness is not so much lost as altered, and this does not lead to falls.

In general, the symptoms surrounding the loss of consciousness accurately discriminate between seizures and syncope [48]. Sometimes, in clinical practice, it is difficult to differentiate epilepsy from cardiovascular syncope occurring with myoclonic movements. Zaidi et al. [156] investigated the value of cardiovascular tests to diagnose

Table 2.6 When to suspect seizure at initial evaluation—the value of history for distinguishing seizure from syncope (adapted from ref. [5])

Clinical findings that suggest the diagnosis		
	Seizure likely	Syncope likely
Findings during loss of consciousness (as observed by an eyewitness)	• Tonic-clonic movements are usually prolonged and their onset coincides with loss of consciousness • Hemilateral clonic movement • Clear automatisms such as chewing or lip smacking or frothing at the mouth (partial seizure) • Tongue biting • Blue face	• Tonic-clonic movements are always of short duration (<15 s) and they start after the loss of consciousness
Symptoms before the event	• Aura (such as funny smell)	• Nausea, vomiting, abdominal discomfort, feeling of cold, sweating (neurally-mediated)[a] • Lightheadedness, blurring of the vision
Symptoms after the event	• Prolonged confusion • Aching muscles	• Usually short duration • Nausea, vomiting, pallor (neurally-mediated)

Other clinical findings of less value for suspecting seizure (low specificity)
- Family history
- Timing of the event (night)
- ''Pins and needle'' before the event
- Incontinence after the event
- Injury after the event
- Headache after the event
- Sleepy after the event

[a] Nausea and abdominal discomfort may be present also in partial complex seizure.

myoclonic syncope in 78 patients with apparent treatment-resistant epilepsy by means of tilt test, carotid sinus massage and long-term ECG monitoring with an implantable loop recorder. In total, an alternative diagnosis was found in 42% of cases: 19 developed profound hypotension or bradycardia during the tilt test, 1 had a typical vasovagal reaction during intravenous cannulation, 2 developed psychogenic symptoms during the tilt test, 7 had significant pauses during carotid sinus massage and 2 had prolonged bradycardia correlated precisely with seizures according to the implantable ECG loop recorder. They conclude that a cardiovascular evaluation may identify an alternative diagnosis in many patients with apparent epilepsy and should be considered early in the management of patients with convulsive blackouts. Conversely, from the loop recorder experience [139,153,154,158] a diagnosis of epilepsy was finally made even in a few patients in whom epilepsy had been excluded at the end of the conventional work-up.

- There are many neurological reasons to fall, but only rarely are such falls accompanied by loss of consciousness. *Cataplexy* is an example: a partial or complete loss of muscular control occurs triggered by emotions, usually laughter [260]. Even when the patient appears to be wholly unconscious, there is a later full recollection of all events. Cataplexy most often occurs as part of narcolepsy; in fact, the combination of cataplexy with daytime sleepiness ensures the diagnosis of narcolepsy.
- *'Drop attack'* is an unclear entity. Definitions vary from the very expansive, encompassing syncope and most other causes to the more restrictive. The clearest use of the term concerns 'cryptogenic drop attacks' [261] describing middle-aged women (very rarely men) who suddenly drop on their knees without any apparent reason and warning, after which patients can get up immediately; because of this the disorder is also known as 'maladie des genoux bleus'. There is no loss of consciousness, or this is so short that it cannot be ascertained with certainty by patient or doctor. Commonly, patients remember landing on the floor. There are no associated signs or symptoms or signs of any kind. The disorder can exist unaltered for many years. There is no specific known cause for it. If used in this strict sense, the term has a specific meaning. The term is also used to describe atonic epileptic seizure in young children, but in such case the attack may be longer. Drop attacks was used also to describe episodes of falling in patients with Menière's disease. Short-lived disturbances of the vestibular system may have caused sudden disequilibrium, described as being 'pushed' by the patient. Finally some authors appear to use drop attack simply as a substitute for unexplained falling. If it is used in the wide sense, it obscures rather than elucidates a variety of diverse disorders, and hampers understanding.

Psychiatric evaluation

Psychiatric illness features in the discussion of syncope in two ways. Firstly, psychiatric drugs may cause orthostatic failure and thereby true syncope (phenothiazines, tricyclic antidepressives, monoamine oxidase inhibitors). These drugs are prescribed for major diseases such as schizophrenia and depression. If this is the cause of syncope, a change in drugs may be needed, to be overseen by a psychiatrist. Secondly, psychogenic pseudosyncope (simply put, pretended unconsciousness) may occur in completely different disorders, e.g., factitious disorder, malingering, panic attack and conversion. It should not be assumed that this second group of disorders (with pseudosyncope) occurs more often in patients with other psychiatric disease, prone to drug-induced true syncope. When pseudosyncope is witnessed by experts, attacks can easily be recognised as such. Otherwise, a careful search for other causes of syncope is needed since the presence of psychiatric disorders does not exclude other causes. Patients with pseudosyncope associated with psychiatric illnesses are young, with low prevalence of heart disease and have frequent recurrent syncope. Patients with conversion reactions (hysteria) may faint in the presence of a witness and may not have injury.

A high prevalence of psychiatric disorders (24%), especially anxiety and depressive states, is now suspected to play a role in the differential diagnosis of syncope based on findings in one study of patients with syncope referred to a tertiary medical centre [262]. Syncope had been unexplained in many of the patients and a large proportion of the patients who received treatment for their psychiatric disorder showed a marked diminution in syncope. More recently, a population-based study [42] showed a 35% prevalence of psychiatric disorders. The most common disorders were generalized anxiety (8.6%), panic disorder (4.3%) and major depression (12.2%). Psychiatric conditions such as conversion reactions can be

reproduced by a psychosomatic response to tilt-table testing (apparent syncope with normal vital signs) [263,264]. Two referral studies [263,264] showed a significant correlation between hyperventilation manoeuvres (resulting in near-syncope or syncope) and psychiatric causes of syncope. Unfortunately, 'syncope' was not always clearly defined, and psychiatric diagnoses were not always arrived at using predefined psychiatric criteria, leaving doubts as to the conclusions to be drawn.

Electroencephalography

In the early 1980s, electroencephalography (EEG) was one of the cornerstones of the workup for patients with syncope [265]. The possible contribution of the EEG is to disclose epileptiform abnormalities; there are no specific EEG findings for any loss of consciousness other that epilepsy. Accordingly, several studies [28,45,50,265–267] conclusively showed that electroencephalographic monitoring was of little use in unselected patients with syncope (Level B). Thus, electroencephalography is not recommended for patients in whom syncope is the most likely cause for a transient loss of consciousness; however, in patients in whom no likely cause was found (TLOC proper), or in whom epilepsy was the likely cause, an EEG is indicated.

Computed tomography and magnetic resonance imaging

No identifiable studies have specifically evaluated the use of brain imaging for patients with syncope. Early case series of such patients [19,28,45,50,251] found that computed tomography produced new information only in patients with focal neurological signs. Of 195 patients who were studied, the average yield of computed tomography was 4%; all patients who had positive scans had focal neurological findings or a witnessed seizure. It is therefore likely that at least some of these attacks did not concern syncope as used in these guidelines, but TLOC or probable epilepsy. The diagnostic utility of magnetic resonance imaging in syncope has not been studied. Thus, computed tomography and magnetic resonance imaging in uncomplicated syncope should be avoided (Level B). When physical or historical features of central nervous system dysfunction are present, imaging may be needed, based on a clinical neurological evaluation.

Neurovascular studies

Carotid TIAs are not accompanied by loss of consciousness. Therefore, no studies suggest that carotid Doppler ultrasonography is beneficial for patients with syncope.

Recommendations

Indications

Class I

- Neurological referral is indicated in patients in whom loss of consciousness cannot be attributed to syncope.
- In case of unequivocal syncope neurological referral is warranted when syncope may be due to autonomic failure or to a cerebrovascular steal syndrome.
- Psychiatric evaluation is recommended when symptoms suggest psychogenic pseudo-syncope or if true syncope is due to psychiatric medication, which may need to be altered.

Class III

- In all other patients with syncope, neurological and psychiatric investigations are not recommended.

Part 3. Treatment

General principles

The principal goals of treatment of the 'syncope patient' may be broadly classified into prevention of syncopal recurrences, and diminution of mortality risk. The need for initiating prophylactic treatment, and the relative importance of addressing one or both of these goals varies depending on many specific clinical circumstances, including:

- the level of certainty that the aetiology of the symptoms is known (see Part 2),
- an estimate of the likelihood that syncope will recur,
- the individual's anticipated syncope-associated mortality risk which is, for the most part, determined by the nature and severity of underlying cardiac and cardiovascular disease (see Part 1),
- the occurrence of, or potential risk for, physical or emotional injury associated with recurrent faints,
- the implications of syncope recurrence on occupation and avocation (i.e., individual economic and life-style issues),
- the public health risk, such as in the case of motor vehicle operators, pilots, etc., and
- an assessment of the effectiveness, safety, and potential adverse effects associated with

proposed therapies (in particular existing comorbidities in the patient being evaluated).

Neurally-mediated (reflex) syncope

Treatment goals: primarily prevention of symptom recurrence and associated injuries; improved quality of life.

In general, initial 'treatment' of all forms of neurally-mediated reflex syncope comprises education regarding avoidance of triggering events (e.g., hot crowded environments, volume depletion, effects of cough, tight collars, etc.), recognition of premonitory symptoms, and manoeuvres to abort the episode (e.g., supine posture). Additionally, if possible, strategies should address trigger factors directly (for example, suppressing the cause of cough in cough syncope). Despite the absence of randomized controlled trials for the treatment strategies outlined above, the value of these treatments is supported by basic physiological knowledge and small studies.

Additional treatment may be necessary in high risk or high frequency settings when:

- syncope is very frequent, e.g., alters the quality of life
- syncope is recurrent and unpredictable (absence of premonitory symptoms) and exposes patients at 'high risk' of trauma
- syncope occurs during the prosecution of a 'high risk' activity (e.g., driving, machine operator, flying, competitive athletics, etc.).

Treatment is not necessary in patients who have sustained a single syncope and are not having syncope in a high risk setting.

Vasovagal syncope

Despite the fact that vasovagal syncope is probably the most frequent of all causes of fainting, treatment strategies are as yet still based on an incomplete understanding of the pathophysiology of the faint. On the other hand, given the frequency with which the vasovagal syncope occurs, there is a wealth of clinical experience from which to draw. In the vast majority of cases, patients who seek medical advice after having experienced a vasovagal faint require, principally, reassurance and education regarding the nature of the condition. This assumption is derived from the knowledge of the benign nature of the disease. In particular, based on review of their medical history, patients should be informed of the likelihood of syncope recurrence. Initial advice should also include review of typical premonitory symptoms which may permit many individuals to recognize an impending episode and thereby avert a frank faint. Thus, avoiding venipuncture may be desirable when possible (e.g., not volunteering for blood donation), but psychological deconditioning may be necessary [268]. Additional common sense measures such as avoidance of volume depletion and prolonged exposure to upright posture and/or hot confining environments should also be discussed. In regard to these latter treatment concepts, formal randomized studies are not available, but physiological evidence and clinical experience are sufficient to warrant their inclusion here. Chronic vasodilator therapy given for concomitant conditions has been shown to enhance susceptibility to vasovagal syncope [269]. Thus, discontinuation or reduction of these drugs is advisable in susceptible patients.

When a more aggressive treatment strategy is needed, 'volume expanders' (e.g., increased dietary salt/electrolyte intake with fluids (e.g., 'sport' drinks, salt tablets)) or moderate exercise training [270—274] appear to be among the safest initial approaches (Level B).

Non-pharmacological 'physical' treatments are arising as a new front line treatment of vasovagal syncope. In highly motivated patients with recurrent vasovagal symptoms, the prescription of progressively prolonged periods of enforced upright posture (so-called 'tilt-training') may reduce syncope recurrence. However, this treatment is hampered by the low compliance of the patients to continue the training programme for a long period [275—278] (Level B). Two recent clinical trials [128,279] have shown that isometric counterpressure manoeuvres of the legs (leg crossing) or of the arms (hand grip and arm tensing) are able to induce a significant blood pressure increase during the phase of impending vasovagal syncope, which allows the patient to avoid or delay losing consciousness in most cases. This effect seems to be mediated largely by sympathetic nerve discharge and vascular resistance increase during manoeuvres and to mechanical compression of the venous vascular bed in the legs and abdomen. In the acute tilt study, both studies showed that the manoeuvres, initiated at the time of impending syncope, caused an abrupt rise in systemic blood pressure, which was already evident after a few seconds. Consequently, symptoms of impending syncope disappeared in many patients and remained unchanged in others, and syncope was aborted. This approach seems to be very helpful in real life. Indeed, during the clinical follow-up study, the patients were able to enact a counter-pressure

manoeuvre and to relieve symptoms in the vast majority of cases. The treatment is therefore easy to perform, reliable, safe and well accepted by the patients, who expressed good satisfaction (Level B).

Many drugs have been used in the treatment of vasovagal syncope (beta-blockers, disopyramide, scopolamine, clonidine, theophilline, fludrocortisone, ephedrine, etilefrine, midodrine, clonidine, serotonin reuptake inhibitors, etc.). In general, while the results have been satisfactory in uncontrolled trials or short-term controlled trials [280—293] with few exceptions [136,294], several long-term placebo-controlled prospective trials have been unable to show a benefit of the active drug over placebo [137—138,295—299] with one exception [300].

In vasovagal syncope beta-blockers, owing to their negative inotropic effect, have been supposed to lessen the degree of mechanoreceptor activation associated with abrupt fall in venous return and block the effects of elevated circulating adrenaline, but this theory has not been supported by facts. A rationale for use of beta-blockers is lacking in the other forms of neurally-mediated syncope and they may be detrimental in the dysautonomic syndromes. Beta-blockers may enhance bradycardia in the carotid sinus syndrome and in all other cardioinhibitory forms of neurally-mediated syncope. Beta-adrenergic blocking drugs have been claimed to be useful in many uncontrolled studies [280,282—286] or in one short-term controlled study [281], but have failed to be effective in five of six long-term follow-up controlled studies [295—299,301] and in one short-term controlled study [293]. Atenolol proved to be ineffective in preventing syncopal recurrences in a well designed double blind randomized controlled trial [299]: in the intention-to-treat analysis there was a trend towards a better outcome in patients treated with placebo ($p = 0.09$), especially in the tilt-negative subgroup and adverse events occurred more likely in the active arm patients ($p = 0.05$). Thus the evidence fails to support beta-blocker efficacy (Level A).

Since failure to achieve proper vasoconstriction of the peripheral vessels is common to all of these disorders, vasoconstrictive substances can be employed. Vasoconstrictor drugs are potentially more effective in orthostatic hypotension caused by autonomic dysfunction than in the neurally-mediated syncopes. Although effective, vasoconstrictor drugs used in the past (namely amphetamine-like methylphenidate and catecholamines) had several major adverse effects due to their potent effect on the central nervous system. Alternatives are the new alpha stimulating agents, midodrine and etilefrine. Etilefrine was studied as a segment of the randomized placebo-controlled double-blind VASIS trial [138]. The 126 patients had had a median of 4 syncopal episodes during the previous 2 years and had a positive response to tilt test. During the follow-up the patients were treated with etilefrine or placebo 25 mg twice a day; syncope recurred in 24% of patients and in 24% of controls and the time to first syncopal recurrence was also similar (106 days etilefrine versus 112 days placebo). These negative results were confirmed by another open label clinical randomized trial [297]; finally, a randomized acute tilt study [136] also failed to show a pathophysiological background for the efficacy of etilefrine. Thus, the evidence fails to support etilefrine efficacy (Level B).

Midodrine seemed to be effective in reducing symptoms (syncope and presyncope) and improving quality of life (evaluated by standardized questionnaires) during the short term in 2 small open label randomized trials [287,302] performed in patients affected by very frequent 'hypotensive' symptoms (>1 syncope/month); the spontaneous symptoms were reproduced during tilt test which showed a dominant vasodepressor response. Even if defined as 'neurocardiogenic', the clinical features of the patients of these studies seem different from those of the typical vasovagal syncope and of the VASIS-like patients and probably overlap with some forms of orthostatic hypotension. Vasoconstrictor drugs are potentially more effective in orthostatic hypotension than in the neurally-mediated syncopes. Midodrine was thoroughly investigated for orthostatic hypotension and was shown to be an effective treatment in some trials (see next section); the data to support the use of midodrine in vasovagal syncope are far less compelling.

Paroxetine has been shown to be effective in one placebo-controlled trial [300] which included a very large number of highly symptomatic patients in one institution, but failed to show a significant effect on baroreflex control of sympathetic nerve activity in a double-blind randomized 6-month follow study performed in healthy subjects [302]. Until the study is confirmed by others, use of this drug cannot be recommended.

Head-up tilt laboratory findings have generally reported that pacing fails to prevent syncope, although it may prolong the premonitory warning phase [303—307]. Nevertheless, pacing has been the subject of a number of both small single/multiple-centre observational studies [303—309]

demonstrating effectiveness in highly select patient populations. Pacing has been the subject of five major multicentre randomized controlled trials [140,310–313]: three unblinded gave positive results and two blinded gave negative results. In this regard, the strongest supportive evidence is provided in the published report of the North American Vasovagal Pacemaker Study (VPS) [310], and the pacemaker arm of the European VASIS trial [140]. In the randomized controlled Syncope Diagnosis and Treatment Study (SYDIT) [311], pacemaker was superior to the beta-blocker atenolol in preventing syncopal recurrences. The Second Vasovagal Pacemaker Study (VPS II) [312] and the Vasovagal Syncope and Pacing Trial (Synpace) [313] differed from the previous trials because the patients in the control arm had received a pacemaker implant that was switched off. Although there was a 30% reduction in syncope recurrence rate (95% CI −33% to 63%), the VPS II study failed to prove a significant superiority of pacemaker therapy. In the Synpace study syncope recurred in 50% of patients assigned to active pacemaker and in 38% of patients assigned to inactive pacemaker. Putting together the results of the five trials, 318 patients were evaluated; syncope recurred in 21% (33/156) of the paced patients and in 44% (72/162) of not paced patients ($p<0.000$). However, all the studies have weaknesses and further follow-up studies addressing many of these limitations (particularly the pre-implant selection criteria of the patients who might benefit from pacemaker therapy) need to be completed before pacing can considered an established therapy in other than a select group of patients with recurrent vasovagal syncope (Level B). It seems that pacing therapy might be effective in some but not in all patients. This is not surprising if we consider that pacing is probably efficacious for asystolic reflex but has no role to combat hypotension which is frequently the dominant reflex in neurally-mediated syncope. How to stratify the patients is still uncertain. A recent study using the implantable loop recorder as reference standard [139] showed that only about half of the patients had an asystolic pause recorded at the time of spontaneous syncope. The role of the implantable loop recorder for selecting patients who may benefit from cardiac pacing is presently under evaluation. Anyway, it must be underlined that the decision to implant a pacemaker needs to be kept in the clinical context of a benign condition which frequently affects young patients. Thus, cardiac pacing should be limited as a choice of last resort choice to a very selected small proportion of patients affected by severe vasovagal syncope.

Carotid sinus syndrome

Carotid sinus syndrome has long been recognized as a potential cause of syncope. However, in current clinical practice its importance is probably often underestimated. Controversy exists as to the frequency with which carotid sinus hypersensitivity is responsible for spontaneous syncopal episodes (i.e., carotid sinus syndrome). In part this controversy may be resolved by considering both 'spontaneous' and 'induced' carotid sinus syndrome separately. Thus, '*spontaneous carotid sinus syndrome*' may be defined as syncope which, by history, seems to occur in close relationship with accidental mechanical manipulation of the carotid sinuses, and which can often be reproduced by carotid sinus massage. Spontaneous carotid sinus syndrome is rare and accounts for only about 1% of all causes of syncope [80]. On the other hand, '*induced carotid sinus syndrome*', is more broadly defined, and may be accepted as being present even though a close relationship between manipulation of the carotid sinus and the occurrence of syncope is not demonstrated. Thus, induced carotid sinus syndrome is diagnosed in patients who are found to have an abnormal response to carotid sinus massage and an otherwise negative work-up for syncope. Regarded in this way, carotid sinus syndrome is much more frequent, being found in 26–60% of patients affected by unexplained syncope [72–75,83,84] (see Part 2). Moreover, carotid sinus syndrome may be responsible for many cases of syncope or unexplained 'falls' in older persons (see Part 4).

Treatment must be guided by the results of the carotid sinus massage. Cardiac pacing appears to be beneficial in carotid sinus syndrome (Level B) and is acknowledged to be the treatment of choice when bradycardia has been documented [71,81,92,314–319]. For the most part, dual-chamber cardiac pacing is preferred (Level B) [316–318], although it has been argued that single-chamber ventricular pacing may be sufficient in those relatively infrequent cases in which there is absence of both a marked vasodepressor component to the hypotension and so-called 'ventricular pacing effect' [71]. Medical therapy for carotid sinus syndrome has largely been abandoned [320,321]. There are as yet no randomized studies examining treatment of carotid sinus syncope in which hypotension is predominantly of vasodepressor origin. Certain therapies used for vasovagal syncope may be expected to be of some benefit; vasoconstrictors and salt are the most likely in this regard, but supine hypertension is a concern. Chronic vasodilator therapy given for concomitant conditions has been shown to enhance susceptibility to carotid

sinus syndrome [308]. Thus, discontinuation or reduction of these drugs is advisable in susceptible patients.

Situational syncope

Situational syncope refers to those forms of neurally-mediated syncope associated with specific scenarios (e.g., micturition, coughing, defaecating, arising from squatting etc.). In one way or another the mechanisms of the hypotension differ in each case. In certain cases (e.g., cough syncope, and syncope following micturition (so-called post-micturition syncope)) the condition appears to be primarily neural reflex mediated. In other conditions (e.g., straining, squatting) the mechanism appears to be largely unrelated to neural reflex activity. Nevertheless, since treatment strategies are similar it is reasonable to combine them here.

Treatment of most forms of neurally-mediated situational syncope relies heavily on avoiding or ameliorating the trigger event. In the case of 'trumpet blower's' syncope, identifying the trigger is straightforward, although its avoidance may have important economic and life-style implications for a dedicated musician. Similarly, the 'cough' trigger in cough syncope (for example, chronic obstructive pulmonary disease or asthma) is readily recognized, but suppressing it (the ideal treatment) is not easily accomplished. In other instances, it is impossible to avoid exposure to the trigger situation (e.g., unpredictable emotional upset or painful stimuli, bowel movement (defaecation syncope), bladder emptying (post-micturition syncope)). In conditions where trigger avoidance is not entirely feasible, certain general treatment strategies may be advocated, including: maintenance of central volume; protected posture (e.g., sitting rather than standing); slower changes of posture (e.g., waiting after a bowel movement before arising); recognition of increased risk when getting out of a warm bed. In specific conditions, certain additional advice may be helpful, such as use of stool softeners in patients with defaecation syncope, avoidance of excessive fluid intake (especially alcohol) just prior to bedtime in post-micturition syncope, and elimination of excessive cold drinks or large boluses of food or oesophageal spasm in 'swallow' syncope.

Patients with situational syncope often have a positive response to carotid sinus massage and/or tilt testing. In one study [83] the correspondence was 33% and 49% of cases, respectively. Consequently, it has been suggested that treatment of situational syncope can be guided by the responses of these tests, especially for the decision to implant a pacemaker. However, further study is needed to determine whether this is the case.

Recommendations

In general, initial treatment, e.g., education and reassurance, is sufficient.

Additional treatment may be necessary in high risk or high frequency settings when:

- syncope is very frequent, e.g., alters the quality of life
- syncope is recurrent and unpredictable (absence of premonitory symptoms) and exposes patients at 'high risk' of trauma
- syncope occurs during the prosecution of a 'high risk' activity (e.g., driving, machine operator, flying, competitive athletics, etc.)

Treatment is not necessary in patients who have sustained a single syncope and are not having syncope in a high risk setting.

It is valuable to assess the relative contribution of cardioinhibition and vasodepression before embarking on treatment as there are different therapeutic strategies for the two aspects. Even if evidence of utility of such an assessment exists only for the carotid sinus massage, it is recommended to extend this assessment also by means of tilt testing or implantable loop recorder.

Class I

- Explanation of the risk, and reassurance about the prognosis in vasovagal syncope.
- Avoidance of trigger events as much as possible and reducing magnitude of potential triggers when feasible (e.g., emotional upset) and causal situation in situational syncope.
- Modification or discontinuation of hypotensive drug treatment for concomitant conditions.
- Cardiac pacing in patients with cardioinhibitory or mixed carotid sinus syndrome.

Class II

- Volume expansion by salt supplements, an exercise programme or head-up tilt sleeping ($>10°$) in posture-related syncope.
- Tilt training in patients with vasovagal syncope
- Isometric leg and arm counter-pressure manoeuvres in patients with vasovagal syncope.
- Cardiac pacing in patients with cardioinhibitory vasovagal syncope with a frequency >5 attacks per year or severe physical injury or accident and age >40.

Class III

- The evidence fails to support the efficacy of beta-adrenergic blocking drugs. Beta-adrenergic blocking drugs may aggravate bradycardia in some cardioinhibitory cases.

Orthostatic hypotension

Treatment goals: prevention of symptom recurrence and associated injuries; improved quality of life.

Establishing the underlying diagnosis is crucial in patients with orthostatic hypotension [323]. The classification and the diagnosis of the syndromes of orthostatic hypotension have been treated in Part 2.

Drug-induced autonomic failure is probably the most frequent cause of orthostatic hypotension. The principal treatment strategy is elimination of the offending agent. Only in occasional patients is this not possible due to the essential nature of the responsible medication. Diuretics and vasodilators are the most important agents in this setting. Alcohol, apart from inducing an autonomic as well a somatic neuropathy, is also commonly associated with orthostatic intolerance. The mechanisms of the latter effect include both direct acute actions on central nervous system as well as central volume depletion. The principal treatment strategy is avoidance of the offending agent.

A working knowledge of the physiology and pathophysiology of blood pressure control is crucial in the management of patients with primary and secondary autonomic failure [11]. The main target for therapy should be reducing symptoms indicative of hypoperfusion of the brain (e.g., syncope, near-syncope, confusion, etc.). Treatment can improve orthostatic symptoms markedly even though the rise in systolic arterial blood pressure is relatively small (10—15 mmHg); bringing the mean arterial pressure up just enough to be once again within the auto regulatory zone can make a substantial functional difference [324]. In this regard, it is reasonable for all patients to receive advice and education on factors that influence systemic blood pressure, such as avoiding sudden head-up postural change (especially on waking), standing still for a prolonged period of time, prolonged recumbence during daytime, straining during micturition and defaecation, hyperventilation, high environmental temperature (including hot baths, showers, and saunas), severe exertion, large meals (especially with refined carbohydrates), alcohol and drugs with vasodepressor properties. Ambulatory blood pressure recordings may be helpful in identifying circumstances (e.g., time of the day) when blood pressure fluctuation is most severe. These recordings may also help identify supine/nocturnal hypertension in treated patients.

Additional treatment principles, used alone or in combination, are appropriate for consideration on an individual patient basis:

- chronic expansion of intravascular volume by encouraging a higher than normal salt intake and fluid intake of 2—2.5 litres per day [323,324]. Additional options include use of fludrocortisone in low dose (0.1—0.2 mg/day), and raising the head of the bed on blocks to permit gravitational exposure during sleep [324,329]. By way of a cautionary note, it is desirable to avoid supine/nocturnal hypertension as much as possible (Level B)
- reduce vascular volume into which gravitation induced pooling occurs by use of abdominal binders and/or waist height support stockings or garments [323,325]
- make use of portable chairs [326]
- small frequent meals with reduced carbohydrate content [323]
- introduce physical counter manoeuvres such as leg crossing and squatting [327,328]
- judicious exercise of leg and abdominal muscles, especially swimming [323].

In those circumstances when non-pharmacological methods are unsuccessful, drug treatment may be indicated as an additional measure. Drugs, however, may aggravate supine hypertension. Additionally, drug therapy is often less useful in the setting of hypotension during physical exercise or in warm surroundings [323]. The use of salt retaining steroids (i.e., principally fludrocortisone) is usually considered first [323,324,329]. Additional benefit may then be achieved with agents which increase peripheral resistance and reduce the tendency for gravitational downward displacement of central volume. Midodrine appears to be of particular interest given the rapidly expanding and generally positive experience (Level B) [325—332]. If the combination of fludrocortisone and sympathetic vasoconstrictor drugs does not produce the desired effect, then referral to medical centres specializing in the evaluation and treatment of autonomic failure should be considered. These centres may have access to investigational agents and/or may be more experienced in the use of drug combinations. Thus, desmopressin may be of value in those patients with nocturnal polyuria, octreotride in those with postprandial hypotension and erythropoietin in those with anaemia [323]. Cardiac pacing at relatively rapid rates has been reported, but has not been subject to rigorous study and

is not currently considered to be of value in treatment.

Recommendations

Class I

- Syncope due to orthostatic hypotension should be treated in all patients. In many instances treatment entails only modification of drug treatment for concomitant conditions.

Cardiac arrhythmias as primary cause

Treatment goals: prevention of symptom recurrence, improved quality of life, reduction of mortality risk.

Primary cardiac arrhythmias imply rhythm disturbances associated with intrinsic cardiac disease or other structural anomalies (e.g., accessory conduction pathways) and are among the most frequent causes of syncope. Intrinsic sinus node dysfunction (brady- and tachyarrhythmias), conduction system disturbances, and both supraventricular and ventricular tachycardias are included. The basis of syncope in these situations is multifactorial, including the rate of the arrhythmia, the status of left ventricular function, and the adequacy of vascular compensation (including the potential impact of neural reflex effects).

Sinus node dysfunction (including bradycardia/tachycardia syndrome)

Decisions regarding treatment strategy must of necessity consider the severity and nature of symptomatic arrhythmias, as well as the disease setting.

Recent insights suggest that, when syncope occurs in patients with sinus bradycardia, a disturbance of the autonomic nervous system is often a cause [15,84]. Thus, increased susceptibility to neurally-mediated bradycardia/hypotension, alone or in association with the intrinsic sinus-node dysfunction, is necessary to cause syncope. A reflex mechanism of syncope fits well with the unpredictable natural history of syncopal recurrences, and may in part explain why syncope recurs in about 20% of sick sinus syndrome patients during long-term follow-up despite adequate pacing [333].

In general, cardiac pacemaker therapy is indicated and has proved highly effective in patients with sinus node dysfunction when bradyarrhythmia has been demonstrated to account for syncope [334—339] (Class I, Level B). Permanent pacing will frequently relieve symptoms but may not affect survival, which is not related to the arrhythmia. Further, since a diagnosis of sinus node dysfunction is inherently associated with an inappropriate chronotropic response, the use of rate-adaptive pacing (especially atrial-based rate-responsive pacing) may be warranted for purposes of both minimizing exertion related lightheadedness or syncope.

In sinus node dysfunction, physiological pacing (atrial or dual-chamber) has been definitely shown to be superior to VVI pacing. Physiological pacing lowers risk of developing atrial fibrillation and systemic embolism (Class I, Level A) [337,338]. It may also improve quality of life by reducing symptoms of congestive heart failure, low cardiac output and angina pectoris, and thereby perhaps improve survival [335—338] (Class I, Level A). VVI or VVIR pacing should therefore be avoided in sick sinus syndrome.

Patients with sinus node dysfunction are often exposed to a wide range of drugs that may exacerbate or unmask underlying susceptibility to bradycardia and create pauses of sufficient duration to result in syncope. For example, cardiac glycosides, beta-adrenergic blockers, calcium channel blockers, and membrane-active antiarrhythmic agents (especially sotalol and amiodarone) are used to treat coexisting paroxysmal atrial tachyarrhythmias. Some of these same drugs, and many other bradycardia-promoting sympatholytic agents, are used to treat hypertension, a common problem in the generally older sinus node dysfunction population. Elimination of offending agents is an important element in preventing syncope recurrence. However, when substitution is not feasible, cardiac pacing may be necessary. Percutaneous cardiac ablative techniques for atrial tachyarrhythmia control have become of increasing importance in selected patients with the bradycardia-tachycardia form of the sick sinus syndrome, but are only infrequently used primarily for prevention of syncope.

AV conduction system disease

As a rule, it is the more severe forms of acquired AV block (that is, Mobitz type II block, 'high grade' and complete AV block) which are most closely associated with syncope. In these cases, the cardiac rhythm may become dependent on subsidiary (often unreliable) pacemaker sites. Syncope (reported in 38—61 percent [340,341]) occurs due to the often long delay before these pacemakers begin to 'fire'. In addition these subsidiary pacemaker sites typically have relatively slow rates (typically 25—40 beats/min); consequently, syncope or pre-syncope may be due to inadequate cerebral perfusion. Bradycardia also prolongs repolarization and predisposes to polymorphic

ventricular tachycardia, especially of the torsade de pointes type.

Apart from the use of atropine (or isoprenaline) in certain forms of transient AV block (e.g., that associated with neurally-mediated events including acute inferior wall myocardial infarction), cardiac pacing has replaced medical interventions in the treatment of syncope with symptomatic AV block. Although formal randomized controlled trials have not been performed, it is clear from several observational studies that pacing is able to improve survival in patients with heart block as well as prevent syncopal recurrences (Class I, Level B) [342—344]. A logical inference, but not proven, is that pacing may also be life-saving in patients with bundle branch block and syncope in whom the mechanism of the faint is suspected to be intermittent AV block. However, it is also critical to consider the possibility that ventricular tachyarrhythmias are responsible for loss of consciousness, since many patients who present with varying degrees of conduction system disease have significant concomitant left ventricular dysfunction.

Paroxysmal supraventricular and ventricular tachycardias

As a rule, supraventricular tachyarrhythmias are less frequently implicated as causes of syncope among patients referred for electrophysiological assessment of syncope of unknown origin. Conversely, the ventricular tachyarrhythmia tends to be a much more frequent and serious cause of syncope. The rate of the tachycardia, the volume status and posture of the patient at time of onset of the arrhythmia, the presence of associated structural cardiopulmonary disease, and the integrity of reflex peripheral vascular compensation are key factors determining whether hypotension of sufficient severity to cause syncope occurs. As a rule, if symptoms of syncope or near syncope do develop, it is at the onset of a paroxysmal tachycardia, before vascular compensation (i.e., vasoconstriction) can evolve. However, syncope may also occur at the termination of tachycardia if a pause ensues prior to restoration of a stable atrial rhythm. An important example of the latter scenario is in patients with paroxysmal atrial fibrillation and sinus node dysfunction. A neural reflex component (preventing or delaying vasoconstrictor compensation) may play an important role when syncope occurs in association with supraventricular tachyarrhythmias, especially when heart rate is not particularly high [13,14]. Similarly, drug effects may affect vascular compensation.

In the case of paroxysmal supraventricular tachyarrhythmias, there is little in the way of long-term follow-up studies examining the efficacy of conventional antiarrhythmic drug treatment when the presenting feature was syncope. Transcatheter ablation has become a very cost-effective treatment option and in paroxysmal supraventricular arrhythmia associated with syncope is probably the treatment of choice (Class I).

Syncope due to torsades de pointes is not uncommon and is, in its acquired form, the result of drugs which prolong the QT interval. Some of these drugs are listed in Table 3.1. Treatment is the immediate discontinuation of the suspected drug (Class I).

In the case of syncope due to ventricular tachycardia (VT), drug therapy may be useful in the setting of a normal heart or of heart disease with mild cardiac dysfunction. Early consideration is usually given to class 3 agents (particularly amiodarone), given its low proarrhythmic risk and generally well tolerated haemodynamic impact. However, in patients with depressed cardiac function, given the difficulty of assuring effective prophylaxis in this often high-risk patient population, the use of implantable pacemaker cardioverter-defibrillators (ICDs) is warranted.

Currently, ablation techniques are appropriate first choices in only a few forms of ventricular tachycardia, specifically right ventricular outflow tract tachycardia, bundle-branch reentry tachycardia, and so-called verapamil sensitive left ventricular tachycardias. Although multicentre trials of this strategy have not been undertaken, the evidence is compelling for pursuing ablation in the former tachycardia (i.e., right ventricle outflow tract), and reasonably strong in bundle-branch reentry (where an ICD may also be warranted in the setting of severe left ventricular dysfunction) and verapamil sensitive left ventricular tachycardia (fascicular tachycardia).

With regard to implantable devices for symptomatic ventricular tacharrhythmias, several prospective treatment trials provide evidence favouring ICD efficacy in terms of mortality risk compared with conventional pharmacological approaches. Although these studies did not directly target syncope patients, it is reasonable to extend the observations to those syncope patients in whom ventricular tachyarrhythmias and poor left ventricular function are identified. Furthermore, reports examining this issue in syncopal patients provide support for early ICD implantation [206—213]; their results are discussed in Part 2, electrophysiological study section. There are some situations, which are consistent with those reports, in which ICD therapy has been suggested to be useful to interrupt syncopal ventricular tachyarrhythmias and perhaps to increase survival (Table 3.2).

Table 3.1 Drugs that can prolong the QT interval and cause torsades de pointes (modified from ref. [345])

Antiarrhythmic agents
Class I
- Ajmaline[a]
- Disopyramide[a]
- Quinidine[a]
- Procainamide[a]
- Propafenone[a]

Class III
- Amiodarone[a]
- Azimilide[a]
- Dofetilide[a]
- Ibutilide[a]
- *N*-Acetylprocainamide (NAPA)[a]
- Sematilide[a]
- Sotalol[a]

Vasodilators/antianginal agents
- Bepridil[a]
- Lipoflazine[a]
- Prenylamine[a]

Psychoactive agents
- Amitryptiline[a]
- Clomipramine
- Cloral hydrate[a]
- Chlorpromazine[a]
- Citalopram[a]
- Desipramine[a]
- Doxepin[a]
- Droperidol[a]
- Fluphenazine
- Haloperidol[a]
- Imipramine[a]
- Lithium[a]
- Maprotiline
- Mesoridazine
- Nortryptiline
- Pericycline[a]
- Pimozide
- Prochlorperazine[a]
- Sertindole[a]
- Sultopride[a]
- Thioridazine[a]
- Timiperone
- Trifluoperazine[a]
- Zimeldine

Antimicrobial
- Amantadine[a]
- Clarythromycin[a]
- Chloroquine[a]
- Cotrimoxazole[a]
- Erythromycin[a]
- Fluconazole
- Grepafloxacin[a]
- Halofantrine[a]
- Ketoconazole[a]
- Pentamidine[a]
- Quinine[a]
- Spiramycine[a]
- Sparfloxacine

Non-sedating antihistamines
- Astemizole[a]
- Diphenhydramine[a]
- Ebastine
- Hydroxyzine
- Terfenadine[a]

Others
- Cisapride[a]
- Probucol[a]
- Terodiline[a]
- Vasopressin

These data derive from what is effectively a non-controlled review of the literature. Hence, some of these drugs have profound effects on QT prolongation and on induction of torsades de pointes, and others have minor effects whose documentation is questionable.
[a] Torsades de pointes reported.

Implanted device (pacemaker, ICD) malfunction

Infrequently, implantable pacing systems have been associated with provoking near-syncope or syncope. More often, however, syncope in such patients is unrelated to the device [345].

Table 3.2 Situations in which ICD therapy is likely to be useful

- Documented syncopal ventricular tachycardia or fibrillation without correctable causes (e.g., drug-induced) (Class I, Level A)
- Undocumented syncope likely to be due to ventricular tachycardia or fibrillation:
  - Inducible sustained monomorphic ventricular tachycardia with severe haemodynamic compromise, in the absence of another competing diagnosis as a cause of syncope (Class I, Level B)
  - Very depressed left ventricular systolic function in the absence of another competing diagnosis as a cause of syncope (Class II, Level B)
  - Established long QT syndrome, Brugada syndrome, arrhythmogenic right ventricular dysplasia, or hypertrophic obstructive cardiomyopathy, with a family history of sudden death, in the absence of another competing diagnosis for the cause of syncope (Class II)
  - Brugada syndrome or arrhythmogenic right ventricular dysplasia and inducible ventricular tachyarrhythmias with severe haemodynamic compromise in the absence of another competing diagnosis for the cause of syncope (Class II)

When syncope is attributable to the implanted device, it may occur as a result of pulse generator battery depletion or failure, or lead failure, in a pacemaker dependent patient. Device/lead replacement is indicated and eliminates the problem. Alternatively, certain patients may experience such symptoms as a result of 'pacemaker syndrome', a condition which itself incorporates many possible mechanisms for inducing hypotension. In the case of pacemaker syndrome [346], device re-programming to eliminate the problem is usually feasible although replacement is occasionally needed (e.g., replace a single chamber ventricular pulse generator with an atrial-based pacing system). ICDs may also be associated with syncope if they fail to diagnose and/or treat a symptom producing arrhythmia, or if effective treatment is delayed. Re-programming of the device generally resolves the problem. There are no large studies examining the effectiveness of the above noted treatments, but clinical experience suggests their adequacy (Class I).

Recommendations

Class I

- Syncope due to cardiac arrhythmias must receive treatment appropriate to the cause in all patients in whom it is life-threatening and when there is a high risk of injury.

Class II

- Treatment may be employed when the culprit arrhythmia has not been demonstrated and a diagnosis of life-threatening arrhythmia is presumed from surrogate data.
- Treatment may be employed when a culprit arrhythmia has been identified but is not life-threatening or presenting a high risk of injury.

Structural cardiac or cardiopulmonary disease

Treatment goals: prevention of symptom recurrence, reduction of mortality risk.

Structural cardiac or cardiopulmonary disease is often present in older syncope patients. However, in these cases it is more often the arrhythmias associated with structural disease that are the cause of the symptoms. In terms of syncope directly attributable to structural disease, probably the most common is that which occurs in conjunction with acute myocardial ischaemia or infarction. Other relatively common acute medical conditions associated with syncope include pulmonary embolism, and pericardial tamponade. The basis of syncope in these conditions is multifactorial, including both the haemodynamic impact of the specific lesion as well as neurally-mediated reflex effects. The latter is especially important in the setting of acute ischaemic events, exemplified by the atropine-responsive bradycardia and hypotension often associated with inferior wall myocardial infarction. Syncope is of considerable concern when it is associated with conditions in which there is fixed or dynamic obstruction to left ventricular outflow (e.g., aortic stenosis, hypertrophic obstructive cardiomyopathy). In such cases symptoms are often provoked by physical exertion, but may also develop if an otherwise benign arrhythmia should occur (e.g., atrial fibrillation). The basis for the faint is in part inadequate blood flow due to the mechanical obstruction. However, especially in the case of valvular aortic stenosis, neural reflex disturbance of vascular control is an important contributor to hypotension [12]. In hypertrophic cardiomyopathy, (with or without left ventricle outflow obstruction) neural reflex mechanisms may also play a role, but occurrence of atrial tachyarrhythmias (particularly atrial fibrillation) or ventricular tachycardia (even at relatively modest rates) are particularly important causes of syncopal events [65]. Other less common causes of syncope in this class include left ventricular inflow obstruction in patients with mitral stenosis or atrial myxoma, right ventricular outflow obstruction, and right-to-left shunting secondary to pulmonary stenosis or pulmonary hypertension. The mechanism of the faint may once again be multifactorial, with haemodynamic, arrhythmic, and neurally-mediated origins in need of evaluation.

In syncope associated with myocardial ischaemia, pharmacological therapy and/or revascularization is clearly the appropriate strategy in most cases. Similarly, when syncope is closely associated with surgically addressable lesions (e.g., valvular aortic stenosis, atrial myxoma, congenital cardiac anomaly), a direct corrective approach is often feasible. On the other hand, when syncope is caused by certain difficult to treat conditions such as primary pulmonary hypertension or restrictive cardiomyopathy, it is often impossible adequately to ameliorate the underlying problem. There are no data on the effect of reducing outflow gradient on relief of syncopal relapses in hypertrophic cardiomyopathy.

Recommendations

Class I

Treatment is best directed at amelioration of the specific structural lesion or its consequences.

Vascular steal syndromes

Subclavian steal is rare but is the most commonly recognized condition in this group. This may occur on a congenital [347] or acquired basis [348], with low pressure within the subclavian artery causing retrograde flow to occur in the ipsilateral vertebral artery (especially during upper arm exercise). The result is a diminution of cerebral blood flow. Syncope associated with upper extremity exercise in the setting subclavian steal syndrome (may warrant surgery or angioplasty). Direct corrective angioplasty or surgery is usually feasible and effective (Class I).

Metabolic

Metabolic disturbances are relatively infrequent causes of true loss of consciousness. More often these conditions may be responsible for confusional states or behavioural disturbances, lasting much longer than syncope. Nevertheless, making a clearcut distinction between such symptoms and syncope may not be possible by history alone.

Hyperventilation resulting in hypocapnia and transient alkalosis may be the most important clinical condition associated with impaired consciousness in this category, but it is in fact not known whether or not consciousness can be lost through hyperventilation. Cerebral vasoconstriction caused by the hypocapnia and alkalosis, with consequent diminished cerebral perfusion has been commonly accepted as the cause of the faint [5]. On the other hand, hyperventilation alone does not seem capable of inducing faints in supine subjects. Consequently, whether or not hyperventilation is actually the cause of the faint, the frequent clinical association with panic attacks warrants its being considered in the differential diagnosis of true syncope. Patients with recurrent faints associated with panic attacks warrant psychiatric consultation (see Part 2).

Sleep-disordered breathing, which includes obstructive sleep apnoea as its most extreme variant, is characterized by intermittent episodes of partial or complete obstruction of the upper airway during sleep that disrupts normal ventilation and sleep architecture and is typically associated with snoring and daytime sleepiness. Repetitive episodes of airway occlusion with hypoxia, hypercapnia, and the dramatic changes in intrathoracic pressures result in diverse autonomic, humoral, neuroendocrine, and haemodynamic responses. An apnoeic episode associated with hypoxia induces a substantial increase in vagal tone which can result in bradycardia. Differentiating sleep apnoea from true syncope occurring during sleep — which may be due to arrhythmia or vasovagal reflex — is sometimes difficult [349—350].

Part 4. Special issues in evaluating patients with syncope

Need for hospitalization

The admission decision can be considered with two different objectives: for diagnosis or for therapy. In patients with syncope in whom the aetiology remains unknown after the initial baseline evaluation a risk stratification can be used for hospitalization decision. In patients in whom the aetiology of syncope has been diagnosed after the initial clinical evaluation, the hospitalization decision depends on the prognosis of the underlying aetiology and/or the treatment that these patients need.

There are several prognostic markers that must be considered in patients with syncope which have been discussed in the previous sections. The presence of underlying structural heart disease and abnormalities of the baseline ECG are important marker for cardiac syncope. An important, but less frequent, prognostic marker is the family history of sudden death. Rarely, have malignant ventricular arrhythmias a genetic basis. In some of these cases, baseline ECG can be, permanently or transiently, normal. These entities have already been discussed. A summary of recommendations is shown in Table 4.1.

When is it safe not to hospitalize?
Patients with isolated or rare syncopal episodes, in whom there is no evidence of structural heart disease and who have a normal baseline ECG, have a high probability of having a neurally-mediated syncope and a low risk of cardiac syncope. These patients have a good prognosis in terms of survival irrespective of the results of head up tilt test. The evaluation of these patients generally can be completed entirely on an ambulatory basis. Patients with neurally-mediated syncope, in the absence of structural heart disease and normal ECG, have a good prognosis in terms of survival, and generally do not need specific treatment apart from counselling and general measures already defined. If treatment is needed because of recurrences it can be initiated on an ambulatory basis. If syncope evaluation is to be completed outside hospital, cautionary advice regarding driving, occupations, and/or avocation restrictions should be provided at such time.

Table 4.1 When to hospitalize a patient with syncope

For diagnosis
- Suspected or known significant heart disease
- Those ECG abnormalities suspected of arrhythmic syncope listed in Table 2.3
- Syncope occurring during exercise
- Syncope causing severe injury
- Family history of sudden death
- Other categories that occasionally may need to be admitted:
  - patients without heart disease but with sudden onset of palpitations shortly before syncope, syncope in the supine position and patients with frequent recurrent episodes
  - patients with minimal or mild heart disease when there is high suspicion of cardiac syncope

For treatment
- Cardiac arrhythmias as cause of syncope (see Recommendations for initial evaluation, Part 2)
- Syncope due to cardiac ischaemia (see Recommendations for initial evaluation, Part 2)
- Syncope secondary to the structural cardiac or cardiopulmonary diseases (listed in Table 1.1)
- Cardioinhibitory neurally-mediated syncope when pacemaker implantation is planned

Syncope in the elderly

Background

In the Framingham study [17], the incidence of syncope was 11 per 1000 person-years for both men and women at the age of 70—79 and 17 per 1000 person-years for men and 19 per 1000 person-years for women at the age $\geq$ 80. The incidence of syncope in an elderly instituzionalized population is 6% per year, with a 10% prevalence and 30% 2 year recurrence rate [18]. These data are probably underestimates because of the exclusion of syncopal episodes which present as falls. Morbidity related to syncope is more common in older persons and ranges from loss of confidence, depressive illness and fear of falling to fractures and consequent institutionalization [351]. Age associated physiological changes in heart rate, blood pressure, cerebral blood flow, baroreflex sensitivity and intravascular volume regulation, combined with comorbid conditions and concurrent medications, account for the higher incidence of syncope in the elderly [6].

Causes

The commonest causes of syncope in older adults are orthostatic hypotension, carotid sinus hypersensitivity, neurally-mediated syncope and cardiac arrhythmias [352,353]. The prevalence of orthostatic hypotension varies from 6% in community dwelling elderly [354], to 33% in hospital inpatients [355]. Orthostatic hypotension is an attributable cause of syncope in up to 30% of older patients [352]. In symptomatic patients 25% have 'age-related' orthostatic hypotension, in the remainder orthostatic hypotension is predominantly due to culprit medications, primary autonomic failure, secondary autonomic failure (diabetes), Parkinson's disease and multisystem atrophy. Supine systolic hypertension is often present in older patients with orthostatic hypotension [356—358]. Hypertension not only blunts the capacity of cerebral autoregulation and increases the risk of cerebral ischaemia from sudden declines in blood pressure [359], but it also complicates treatment, given that most agents used for treatment of orthostatic hypotension will exacerbate supine hypertension [358,360].

Carotid sinus hypersensitivity rarely occurs before age 40; the prevalence increases with advancing years and with cardiovascular, cerebrovascular and neurodegenerative co-morbidity [76,77,83,361].Cardioinhibitory carotid sinus syndrome is an attributable cause of symptoms in up to 20% of elderly patients with syncope [352]; further studies will assess the true frequency, but it is fair to point out that it is likely to be more common than previously thought. Carotid sinus hypersensitivity of predominantly vasodepressor form is equally prevalent [361], but its potential role in causing syncope in this population is much less certain [362—364].

Up to 15% of syncope is vasovagal [352]. In over half, episodes are related to prescription of cardiovascular medications [352,364]. The pattern of blood pressure and heart rate responses during testing is similar to that described in younger patients (see Part 2) but the prevalence of patterns differs. Bradyarrhythmic responses (VASIS 2B) are less common and progressive hypotensive responses (VASIS 3) and chronotropic incompetence are more common [364] although patterns reflecting autonomic failure are more common in drug related episodes [126].

Up to 20% of syncope in older patients is due to cardiac arrhythmias [352] (see Part 2).

Diagnostic evaluation

History

Some additional components in history taking are of relevance in older patients. The time when events occur can be helpful for diagnosis. Events due to orthostatic hypotension usually occur in the mornings. The history should include

any association with meals (post prandial) [365], ingestion of medications, nocturnal micturition, etc. One third of over 65 year olds are taking three or more prescribed medications. Medications frequently cause or contribute to syncope. Details of the medication history should include duration of treatment and time-relationship of this to the onset of events. The history should include details of comorbid diagnoses, in particular associations with physical frailty and locomotor disability (for example arthritis, Parkinson's disease and cerebrovascular disease) and diagnoses which increase the likelihood of cardiovascular syncope, for example diabetes, anaemia, hypertension, ischaemic heart disease and heart failure. In the older patients the common prodromic warning symptoms suggestive of vasovagal syncope are less frequent than in the younger, so that neuroautonomic assessment (i.e., carotid sinus massage and tilt test) became more relevant for diagnosis [366].

Aspects of history taking may vary in emphasis and clinical details from younger adults.This is explained in some by amnesia for loss of consciousness [362]. Gait and balance instability and slow protective reflexes are present in 20—50% of community dwelling elderly [351,367]. In these circumstances moderate haemodynamic changes insufficient to cause syncope may result in falls. Therefore, it is important to pursue a witness account of episodes, although this is not available in up to 40—60% [352,365]. For these reasons, up to one quarter of events will present as falls [159,351,368].

Cognitive impairment is present in 5% of 65 year olds and 20% of 80 year olds. Cognitive status will influence the accuracy of recall for events [366,368]. Indeed, when taking the history, the cognitive status should be determined in addition to details of social circumstances, injurious events, impact of events on confidence and the ability to carry out activities of independent daily living.

Examination

Assessment of the neurological and locomotor systems, including observation of gait and standing balance (eyes open, eyes closed) are recommended. If cognitive impairment is suspected, this should be formally determined. The mini mental state examination [369] is a 30 item internationally validated tool, adequate for this purpose. Otherwise the clinical examination is as for younger adults.

Investigations

In cognitively normal older patients with syncope or unexplained falls the diagnostic work-up is the same as for younger adults with the exception of routine supine and upright carotid sinus massage at the first assessment of older patients, given the high prevalence of carotid sinus syndrome as a cause of syncope and unexplained falls in this age group [79].

At the first assessment, a detailed history, clinical examination, orthostatic blood pressure measurement and supine and upright carotid sinus massage will achieve a diagnosis in over 50% [340]. In up to a third of older patients a diagnostic cardioinhibitory response is only present when upright, reasons for this are unclear but may relate to technique or changes in reflex sensitivity with postural change [79]. For the evaluation of vasovagal syncope in the older patients the tilt table test is well tolerated and safe with sensitivity and positivity values similar to those observed in the younger patients [114].

Orthostatic hypotension is not always reproducible in older adults. This is particularly so for medication related or age related orthostatic hypotension. Repeated morning measurements are recommended [370] if this is suspected as the cause of syncope.

Twenty-four hour ambulatory blood pressure recordings may be helpful if culprit medication or post prandial hypotension is suspected as a cause of symptoms.

Over one third of older persons will have more than one possible attributable cause [352,364]. If symptoms continue or more than one diagnosis is suspected further evaluation is necessary.

Evaluation of the frail elderly

Age per se is not a contraindication to assessment and intervention. However, in frailer patients, the rigor of assessment will depend on compliance with tests and on prognosis.

Orthostatic blood pressure measurements, carotid sinus massage and head up tilt studies are well-tolerated tests, even in the frail elderly with cognitive impairment [370].If patients have difficulty standing unaided, head up tilt can be used to assess orthostatic blood pressure changes [57].

Multiple risk factors are more common in the frail elderly and the boundaries between falls and syncope are poorly delineated. In one recent study, symptomatic elderly patients with cognitive impairment had a median of five risk factors for syncope or falls [371]. Risk factor stratification, and the contribution of individual abnormalities to symptom reproduction are more complex. There is some evidence that modification of cardiovascular risk factors for falls/syncope reduces the incidence of subsequent events in community dwelling frail elderly, even those with dementia [371], but

no evidence of benefit for institutionalized elderly. Whether or not treatment of hypotension or arrhythmias decelerates cognitive decline in patients with dementia is not known, and is not recommended at present for this indication.

If invasive diagnostic procedures and repeated hospital attendances are deemed inappropriate it may be necessary to treat 'blind' using limited clinical data i.e., by altering possible culprit medication, prescribing anti-arrhythmic agents and/or cardiac pacing. Thus, in the frail elderly, physicians should make clinical judgements after a comprehensive examination about the benefits to the individual of a syncope evaluation.

Recommendations

Class I

- Accurate history, where possible, with witness observation, and details of medications.
- Morning orthostatic blood pressure measurements and supine and upright carotid sinus massage are integral to the initial evaluation unless contraindicated.
- The evaluation of mobile, independent, cognitively normal older adults is as for younger individuals.
- In frailer older adults evaluation should be modified according to prognosis.

Syncope in paediatric patients

Background

The incidence of syncope coming to medical attention in childhood and adolescence was 126/100,000 population in the single available population based study [372]. As many as 15 percent of children may, however, experience at least one episode before the age of 18 [22]. Moreover, up to 5% of toddlers undergo a similar syndrome, called breath-holding spells [373]. Neurally-mediated (reflex) syncope is by far the most frequent (61—71%), followed by cerebrovascular and psychogenic syncope (11—19%) and cardiac syncope (6%) [260,372,374].

Differential diagnosis

Careful personal and family history and standard ECG is most important in distinguishing the benign neurally-mediated syncopes (also-called reflex anoxic seizure or breath holding spells in infants and children) from other causes. Most children with neurally-mediated syncope have a first degree relative who faints, which may be used in differential diagnosis [375]. In young patients, syncope may, however, also be an initial manifestation of rare but life-threatening conditions like the long QT syndrome [376], Kearns—Sayre syndrome (external ophthalmoplegia and progressive heart block), Brugada syndrome [203], atrial fibrillation in patients with the Wolff—Parkinson—White syndrome [377], catecholaminergic polymorphic ventricular tachycardia [378], right ventricular dysplasia [379], arrhythmias after repair of congenital heart disease [380], hypertrophic cardiomyopathy, anomalous coronary artery, pulmonary arterial hypertension or myocarditis. There are numerous 'warning bells' from the history that should indicate a potentially life-threatening cause [381,382]. These are:

- syncope in response to loud noise, fright, or extreme emotional stress
- syncope during exercise
- syncope while supine
- family history of sudden death in young person <30 years old.

An appropriate and extensive diagnostic work-up should then be started.

Diagnostic work-up

In the case of a history typical for neurally-mediated syncope, the absence of abnormalities on physical examination and ECG are usually sufficient to make a diagnosis and stop investigations. Tilt testing seems to have a high false-negative and false-positive rate and should be used with caution for primary identification of patients with neurally-mediated syncope [17,383,384]. A remarkably high incidence of near-fainting (40%) was reported during a head-up tilt test after placement of a simple intravenous line in healthy children and teenagers [17]. Tilt protocols commonly used in adults lack specificity in teenage patients. In order to obtain acceptable specificity tilt test duration should be shorter in teenage than in adults; in one study [385] specificity was $>$ 85% by performing the tilt test at 60° or 70° for no longer than 10 min. Regardless of the results of the tilt test, almost all patients with neurally-mediated syncope have improved or resolved symptoms with simple interventions during long-term follow-up [386].

Diagnostic work-up for other than neurally-mediated syncopes is case specific. Twenty-four hour Holter monitor or loop-recording event monitor should be used in patients with a history of palpitations associated with syncope. Cardiology consultation including echocardiography should be obtained in case of heart murmur. Electrophysiological study has a minor role in paediatric patients. Electroencephalography is indicated in patients

showing prolonged loss of consciousness, seizure activity and a postictal phase of lethargy and confusion.

Therapy

The mainstay of management of neurally-mediated syncope in childhood includes reassurance, education, behaviour modification [381,382], salt and increased fluids [384,386]. Drinking enough salty or sweet liquid without caffeine, ruling out salt avoidance and performing 'anti-gravity manoeuvres' at the earliest recognition of presyncope [328,387] is helpful in many patients (Level B). Pharmacological therapy should be reserved for patients with continued symptoms despite behaviour modification. In uncontrolled studies, beta-blockers [383,386,388], alpha-fludrocortisone [383,386] and alpha-agonists [389] have been supposed be efficacious in the paediatric age group (Level B). Even in the instance of cardioinhibitory syncope with an asystolic response (VASIS 2B), pacemakers should be avoided whenever possible; as an alternative, effective management with pharmacological therapy without need for pacemaker implantation has been shown [390].

Recommendations

Class I

- Syncope in childhood is common. The vast majority of episodes are benign and are due to neurally-mediated syncope. Only a minority are due to some potentially life-threatening causes.
- The diagnosis and differentiation of benign from more serious causes is made primarily by the history and standard ECG.
- The mainstay of management of neurally-mediated syncope in childhood includes reassurance, education, behaviour modification, salt and increased fluid. Even in the instance of cardioinhibitory syncope with an asystolic response, pacemakers should be avoided whenever possible.

Syncope management facilities

A proposed model of organization for the evaluation of the syncope patient in a community is as follows.

Background

Given that syncope is a common symptom, the following considerations are important when developing local strategies for the management of the patient with syncope.

- The model of care delivery should be that which is most appropriate to existing practice and will maximize resources and local expertise while ensuring implementation of published practice guidelines.
- Models of care delivery will vary from a single 'one site, one stop' syncope facility to a wider based multi-faceted practice where several specialists are involved in syncope management. The management strategy should be agreed upon and practised by all practitioners involved in syncope management.
- The age range and symptom characteristics of patients appropriate for syncope investigation should be determined in advance. Some facilities investigate paediatric and adult patients while others limit practice to adult or paediatric cases.
- The referral sources should also be taken into consideration. Referral can be directly from family practitioners, from the accident and emergency department, from acute hospital in-patients, or from patients in institutional settings. The scope of referral source has implications for resources and skill mix.
- In a single dedicated facility the skill mix will depend on the speciality designated to take a lead in the development of the facility. There are existing models where cardiologists (commonly with an interest in cardiac pacing and electrophysiology), neurologists (commonly with an interest in autonomic disorders and/or epilepsy), general physicians and geriatricians (with an interest in age-related cardiology or falls) have lead syncope facilities. There is no evidence for superiority of any model.
- One factor which will influence the skill mix (i.e., the types of professionals/expertise required to staff the facility) is the extent to which screening of referrals occurs prior to presentation at the facility. If referrals hail directly from the community and/or from the accident and emergency department, a broader skill mix is required. Under these circumstances, other differential diagnoses such as epilepsy, neurodegenerative disorders, metabolic disorders and falls are more likely to be referred.
- Regular communication with all stakeholders (i.e., patients, referring physicians, staff in the accident and emergency department, neurology, general medicine, orthopaedic surgery, geriatric medicine, psychiatry and ear nose and throat departments, hospital/clinic management, nurses and other allied medical professionals) should ensure a consensus for and understanding of proposed management strategies. This includes the implications of and implementation of published guidelines.

Need for coordinating the syncope evaluation

Emerging data suggest that up to 20% of cardiovascular syncopes in older patients (over 70 years) presents as non-accidental falls. There is also evidence from the 'falls' literature that multifactorial intervention, which includes cardiovascular interventions (treatment of arrhythmias, orthostatic hypotension, carotid sinus hypersensitivity, and vasovagal susceptibility) significantly reduces subsequent events in fallers with recurrent episodes—even if these are accidental falls. This has enormous implications for the volume of patients seen. It requires access to, or incorporation of, assessments and interventions for other common co-morbid risk factors such as gait and balance instability, cerebrovascular disease, home hazard modifications etc. An example of the scope of this issue is illustrated in a study in the accident and emergency department from Newcastle. Forty-four per cent of accident and emergency attendees over 65 years attended because of a fall or syncopal event. Of these patients, 35% had accidental falls, 25% were patients who had cognitive impairment or dementia (therefore a clear distinction between falls/syncope was often not possible), 22% had a medical explanation for the event, and 18% had unexplained falls or syncope [47,159,371].

Present syncope management (diagnosis and treatment) situation

Syncope is a common symptom in the community and in emergency medicine. For example, in the UK, syncope and collapse (ICD code 10) are the sixth commonest reason for admission of adults aged over 65 years to acute medical hospital beds. Given that half of all emergency admissions are over 65 years, this constitutes a large volume of activity. The average length of stay for these admissions is 5—17 days—emphasizing the diversity of syncope management strategies and availability of existing investigations [400]. Hospital admission alone accounted for 74% of the cost of investigating syncope [47].

Currently, the strategies for assessment for syncope vary widely among physicians and among hospitals and clinics. More often than not, the evaluation and treatment of syncope is haphazard and unstratified. The result is a wide variation in the diagnostic tests applied, the proportion and types of attributable diagnoses and the proportion of syncope patients in whom the diagnosis remains unexplained [47,53,391—393]. For example, in a prospective registry [391] enroling patients referred to the emergency department from 28 general hospitals in Italy, carotid sinus massage was performed in from 0% to 58% and head up tilt tests in from 0% to 50% syncopal patients. Consequently, the final diagnosis for neurally-mediated syncope ranged from 10% to 79%. These disparate patterns of assessment can explain why pacing rates for carotid sinus syndrome vary, even within countries, from 1% to 25% of implants, depending on whether carotid sinus hypersensitivity is systematically assessed in the investigation profile. Some authors have evaluated the impact of the introduction of in-hospital protocols [53,393]. These studies showed that it is possible to improve diagnostic rates and the use of appropriate investigations. However, significant numbers of inappropriate investigations and hospital admissions still occurred. As a consequence, costs of investigations and costs per diagnosis increased rather than decrease.

If the status quo for the evaluation of syncope is unchanged, diagnostic and treatment effectiveness is unlikely to show substantial improvement. Furthermore, the implementation of the published syncope management guidelines will be diverse and incomplete. Thus, to maximize implementation of the guidelines it is mandatory that models of care for assessment and management of syncope are in place and that information about the models within each organization is adequately communicated to all parties involved with syncope patients.

It is the view of the European Society of Cardiology Syncope Task Force that a cohesive, structured care pathway — either delivered within a single syncope facility or as a more multi-faceted service — is the optimal for quality service delivery. Furthermore, considerable improvement in diagnostic yield and cost effectiveness (i.e., cost per reliable diagnosis) can be achieved by focusing skills and following well defined up-to-date diagnostic guidelines.

Some existing syncope management unit models

The service model adopted by the Newcastle group is a multidisciplinary approach to referrals with syncope or falls. All patients attend the same facility (with access to cardiovascular equipment, investigations and trained staff) but are investigated by a geriatrician or cardiovascular physician according to the dominant symptom cited in referral correspondence—falls or syncope. Recently, this group showed that activity at the acute hospital at which the day case syncope evaluation unit was based, experienced in 1 year 6116 fewer bed days for the diagnostic categories comprising syncope and collapse, compared with peer

teaching hospitals in the UK. This reduction translated into a significant saving in emergency hospital costs (4 million euros). The savings were attributed to a combination of factors—reduced re-admission rates, rapid access to day case facilities for accident and emergency staff and community physicians, and reduced event rates because of effective targeted treatment strategies for syncope and falls [47].

The service model adopted in some Italian hospitals [394] is a functional unit managed by cardiologists inside the department of cardiology, with dedicated medical and support personnel. The patients attending this Syncope Unit have preferential access to all the other facilities and investigations within the department including admission to cardiology wards or the intensive care unit if indicated. Where appropriate, patients are jointly managed with other specialists, i.e., neurologists. The patients are referred to the unit from the emergency department as well from in-patient or out-patient clinics but the personnel of the unit is not usually involved in the initial evaluation of the patient. This model substantially improved the overall management of syncope compared with peer hospitals without such a facility [394] and reduced the number of unnecessary investigations in addition to increasing the appropriateness of indications and the diagnostic yield of the tests; in 66% of the patients, less than two tests were necessary for diagnosis [145].

Professional skill mix for the syncope evaluation facility

It is probably not appropriate to be dogmatic regarding the training needs of personnel responsible for a dedicated syncope facility. These skills will depend on the pre-determined requirements of local professional bodies, the level of screening evaluation provided prior to referral, and the nature of the patient population typically encountered in a given setting. In general, experience and training in key components of cardiology, neurology, emergency and geriatric medicine are pertinent to the assessment and diagnosis of syncope, in addition to access to other specialities such as psychiatry, physiotherapy, occupational therapy, ear nose and throat specialities and clinical psychology.

Core medical and support personnel should be involved full time or most of the time in the management of the unit and should interact with all other stakeholders in the hospital and in the community.

Staff responsible for the clinical management of the facility should be conversant with the recent syncope guidelines. A structured approach to the management of syncope also expedites clinical audit, patient information systems, service developments, and continuous professional development.

Equipment

Core equipment for the syncope evaluation facility include: surface ECG recording, phasic blood pressure monitoring, tilt table testing equipment, external and internal (implantable) ECG loop recorder systems, 24 h ambulatory blood pressure monitoring, 24 h ambulatory ECG monitoring, and autonomic function testing. The facility should also have access to echocardiography, intracardiac electrophysiological studies, stress testing, cardiac imaging, computed tomography and magnetic resonance imaging head scans and electroencephalography.

Patients should have preferential access to hospitalization and to any eventual therapy for syncope, namely pacemaker and defibrillator implantation, catheter ablation of arrhythmias, etc.

Dedicated rooms for assessment and investigation are required.

Setting

The majority of syncope patients can be investigated as out-patients or day cases. Indications for hospital admission are defined in another section (see Part 4 'Need for hospitalization').

The role of a local integrated syncope service is to set standards for the following in keeping with the objectives of the Guidelines on Syncope of the European Society of Cardiology and other appropriate guideline publications:

- the diagnostic criteria for causes of syncope
- the preferred approach to the diagnostic work-up in subgroups of patients with syncope
- risk stratification of the patient with syncope
- treatments to prevent syncopal recurrences.

A major objective of the syncope facility is to reduce the number of hospitalizations by offering the patient a well defined, quick, alternative evaluation pathway. An example of a possible model of organization for the evaluation of the syncope patient in a community is shown in the Fig. 3.

When establishing a newly structured service, current experience suggests that careful audit of the syncope unit activity and performance will rapidly justify the initial resource allocation and requests for additional funding, further enhancing service development, and providing a legitimate magnet for increasing patient referrals.

Recommendations

- A cohesive, structured care pathway — either delivered within a single syncope facility or as a more multi-faceted service — is recommended for the global assessment of the patient with syncope.
- Experience and training in key components of cardiology, neurology, emergency and geriatric medicine are pertinent.
- Core equipment for the facility include: surface ECG recording, phasic blood pressure monitoring, tilt table testing equipment, external and internal (Implantable) ECG loop recorder systems, 24 h ambulatory blood pressure monitoring, 24 h ambulatory ECG and autonomic function testing.
- Preferential access to other tests or therapy for syncope should be guaranteed and standardized.
- The majority of syncope patients should be investigated as out-patients or day cases.

Driving and syncope

General comments

First it should be emphasised that all available evidence suggests that the medical condition of a driver, with the exception of the effect of alcohol is not an important factor in road accidents causing injury to other road users. Secondly most medical causes for road accidents occur in drivers who are already known to have pre-existing disease. Thirdly, sudden driver incapacity has been reported with an incidence approximating one per thousand of all traffic accidents only [395]. The most common causes of road accidents, involving loss of consciousness at wheel are listed in Table 4.2 [396]. In an anonymous survey [397], 3% of patients with syncope reported ever having had syncope while driving, but only 1% reported having had a car crash; only 9% of those who received driving abstinence recommendation stopped driving because of syncope. Among patients with life-threatening ventricular arrhythmias enroled in the AVID trial [398], symptoms suggestive of tachyarrhythmia recurred frequently while the patients were driving, but such symptoms were unlikely to lead to motor vehicle accidents (0.4 percent per patient-year); the probability of an accident was lower than the annual accident rate in the general population and was independent of the duration of abstinence from driving.

In 1995 the Board of the European Society of Cardiology formed a task force on driving and heart disease. In the report driving and syncope especially neurally mediated syncope is discussed [396]. In a AHA/NASPE medical/scientific statement dealing with personal and public safety issues related to arrhythmias that may affect consciousness, driving regulations and syncope are also briefly discussed [399]. The following recommendations on driving and syncope are put forward and are based on the two above mentioned reports (Table 4.3). The level of evidence in these two reports is Level C with a few exceptions.

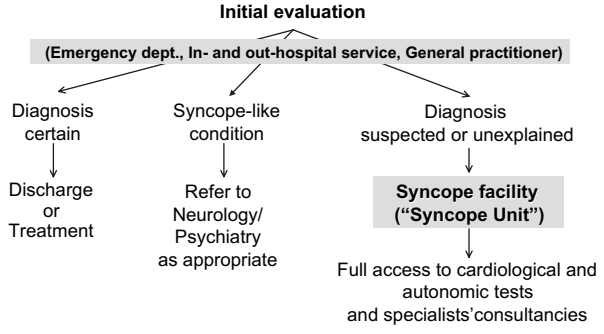

Figure 3 A proposed model of organization for the evaluation of the syncope patient in a community.

Recommendations

An ESC Task Force report on driving and heart disease was published in 1998 which is the present reference standard for Europe (Table 4.3). Two groups of drivers are defined. Group one comprises drivers of motorcycles, cars and other small vehicles with and without a trailer. Group two includes drivers of vehicles over 3.5 metric tonnes (3500 kilo) 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.

The guidelines listed in Table 4.3 aim at being practical and enforceable. The guidelines reflect a combination of clinical judgement in addition to some individual technical measurements. Each case needs to be considered on its merits and in relation to local regulations. In any case group 2 drivers with severe heart disease and syncope of any cause should not be allowed to drive on a professional basis.

For group 1 drivers the task force advises minimal restrictions and, thus, only temporarily should patients with heart disease and syncope in this group be advised not to drive.

Table 4.2 Causes of 2000 road accidents involving loss of consciousness at the wheel, based on reports by the police to driver vehicle licensing agency

Epilepsy	38%
Syncope	21%
Diabetes (on insulin)	18%
Heart condition	8%
Stroke	7%
Others	7%

Table 4.3 Suggested recommendations for driving rules in patients suffering from syncope (modified after Task Force Report of the European Society of Cardiology on Driving and Heart Disease [408])

Diagnosis	Group 1 (private drivers)		Group 2 (vocational drivers)	
	Disqualifying criteria according to 1998 ESC document	Modified disqualifying criteria according to 2004 Syncope Task Force	Disqualifying criteria according to 1998 ESC document	Modified disqualifying criteria according to 2004 Syncope Task Force
Cardiac arrhythmias				
Cardiac arrhythmias, medical treatment	Any disturbance of cardiac rhythm which is likely to cause syncope	Until successful treatment is established	Driving will not be permitted if the arrhythmia (i.e., non-sinus bradycardia, significant conduction defect, atrial flutter or fibrillation narrow or broad complex tachycardia) has caused or is likely to cause syncope. Once the arrhythmia has been controlled (re-) licensing may be permitted provided that left ventricular ejection fraction is >0.40, ambulatory electrocardiography excludes ventricular tachycardia, and exercise requirements can be met[a]	Until successful treatment is established
Pacemaker implant; successful catheter ablation	Within 1 week	No change	Any persistent symptoms. (Re-) licensing may be permitted after at least 6 weeks has elapsed, and provided that there is no disqualifying condition	For pacemaker, until appropriate function is established. For ablation, until long-term success is confirmed, usually 3 months
ICD implant	Within 6 months if no arrhythmia recurrence and no disabling symptoms at time of ICD discharge. For drivers receiving prophylactic ICD implant no restrictions are imposed	Low risk, controversial opinions, tendency to shorten the time of restriction	Permanent	No change

(continued on next page)

Table 4.3 (*continued*)

Diagnosis	Group 1 (private drivers)		Group 2 (vocational drivers)	
	Disqualifying criteria according to 1998 ESC document	Modified disqualifying criteria according to 2004 Syncope Task Force	Disqualifying criteria according to 1998 ESC document	Modified disqualifying criteria according to 2004 Syncope Task Force
Neurally-mediated syncope				
(a) Vasovagal:				
— Single/mild	No restrictions	No change	Specialist evaluation including neurological review	No restriction unless it occurred during high risk activity[a]
— Severe[a]	Until symptoms controlled	No change	Until symptoms controlled. (Re-) licensing after three months and possibly negative tilt-test; careful follow-up mandatory	Permanent restriction unless effective treatment has been established
(b) Carotid sinus:				
— Single/mild	No restrictions	No change	No restrictions	No restriction unless it occurred during high risk activity[a]
— Severe[a]	Until symptoms controlled	No change	Until symptoms controlled	Permanent restriction unless effective treatment has been established
(c) Situational:				
— Single/mild	No restriction	No restrictions	No restrictions	No restriction unless it occurred during high risk activity[a]
— Severe[a]	—	Until appropriate therapy is established	—	Permanent restriction unless effective treatment has been established
Syncope of uncertain cause				
— Single/mild	—	No restrictions unless it occurred during high risk activity[a]	—	Until diagnosis and appropriate therapy is established
— Severe[a]	In case of severe syncope until cause identified especially in patients with heart disease or at least 3 months without symptoms before (re-) licensing	Until diagnosis and appropriate therapy is established	Requires specialist evaluation including a neurological review if appropriate. Following unexplained syncope, provocation testing and investigation for arrhythmia must be implemented, especially also in patients with heart disease. If the results are satisfactory (re-) licensing may be permitted after 3 months. Careful follow-up is mandatory	Until diagnosis and appropriate therapy is established

[a] Neurally-mediated syncope is defined as severe if it is very frequent, or occurring during the prosecution of a 'high risk' activity, or recurrent or unpredictable in ''high risk'' patients (see Part 3, treatment).

Comment
This task force has the benefit of further publications that are relevant. Data suggest that the risk for car accident related to syncope is low. Repeat tilt testing to assess any therapy probably has no predictive value. There is no evidence that allowing three asymptomatic months to elapse provides any confirmation that attack will not recur. To date, the evidence in favour of drug therapy remains unconvincing. Neurological review in syncopal patients is of little value. Modified disqualifying criteria according to 2004 Syncope Task Force are also reported in Table 4.3.

Glossary of terms

The literature on syncope and associated conditions can be very confusing because of a lack of consistency in use of terms rendering them uncertain. For some terms an originally clear meaning has become obscured over time, because the term was later used in a different context or in a different meaning. Other terms were introduced as neologisms to compete with older, often equally adequate terms. This glossary is provided in an attempt to clarify the nomenclature. The choice, which terms are approved and which are controversial, is to some extent arbitrary.

Breath holding spells

Breath holding spells concern attacks of transient loss of consciousness in infants. Two types are usually recognised: 'pallid' and 'cyanotic'. In all likelihood attacks of the pallid type are nothing other than vasovagal syncope, meaning that 'breath holding' has nothing to do with bringing on the attacks. A Valsalva manoeuvre has been implied in the pathophysiology of the more common cyanotic type, so 'breath holding' may be of importance in this type. Both types may well occur in the same child, implying that the pathophysiology may be very similar. In either case, it seems safe to state that both types concern syncope.

- *The panel stresses that 'breath holding spells' concern a form of syncope affecting infants and younger children. As the name is probably a misnomer, 'infantile vasovagal syncope' is to be preferred.*

Classical vasovagal syncope

The two parts of the word 'vasovagal' would be eminently suited to describe neurally-mediated syncope, as they stress both the vasodepressor sympathetic part of the efferent part of the reflex ('vaso…') as well as the cardioinhibitory part ('…vagal'). As such, the term might be used as a third synonym, but this is excessive, and in practice the term seems to be used preferentially for those forms of reflex syncope in which pain and/or anxiety act as the main trigger to evoke the reflex.

- *The panel advocates that the term 'vasovagal syncope' is reserved for description of neurally-mediated/reflex syncope in which pain, emotional distress, instrumentation or prolonged standing trigger syncope.*

Convulsive syncope

The pathogenesis of involuntary jerking movements of the limbs during syncope is unclear. There is no evidence that distinguishing between syncope with and syncope without movements helps refine the diagnosis or helps guide treatment. Myoclonic jerks are often interpreted as epileptic by physicians and eyewitnesses alike, but not all that moves is epilepsy. As distinguishing between epilepsy and syncope is extremely important, care must be taken to avoid confusion. 'Convulsions' are often used by neurologists to indicate either the movements in an epileptic fit ('seizure') or sometimes seizures themselves.

- *The panel advises use of 'convulsive syncope' only as a short form for 'syncope accompanied by myoclonic jerks and other involuntary movements'; the term does not imply epilepsy.*

Drop attacks

'Drop attacks' was originally used to indicate a very specific and benign syndrome, describing how middle-aged and elderly women suddenly fell to their knees without loss of consciousness. Later use included grouping all possible causes of falls with or without loss of consciousness under this heading. It is sometimes used as a synonym for Adams—Stokes attacks. Over time, the term has become so unclear that its use is now more likely to cause confusion than to increase understanding. If medical practitioners feel a need for a phrase to describe the problem of frequent falls, 'falling' is clear, simple, and does not carry any false sense of a medically meaningful content.

- *The panel feels that the use of 'drop attacks' should be restricted strictly to the original meaning.*

Dysautonomia/dysautonomic

When used as part of 'familial dysautonomia' (Riley—Day syndrome) the term has a specific and clear meaning. When used in a different context, the meaning is less clear. 'Dysautonomic' may then refer to abnormal functioning of the autonomic nervous system, or to a specific heart rate and blood pressure response pattern during tilt testing. If used in the first sense, it should be understood that the term does not discriminate between the types of abnormality in autonomic failure and in reflex syncope, which are of a fundamentally different nature (the first involves normal attempts at maintaining cardiac output that are ineffective due to damage to the autonomic nervous system, and the second implies a improper reflex by an otherwise normal autonomic nervous system). To use 'dysautonomic' as a term for a response pattern during tilt testing carries the risk of making it ever more vague.

- *The panel suggests that 'dysautonomia' is reserved for the Riley—Day syndrome; 'dysautonomic' may be used as a name indicating any type of dysfunction of the autonomic nervous system, but the panel prefers the use of terms that specify the nature of the dysfunction.*

Hyperventilation syncope

Hyperventilation reduces cerebral blood flow through vasoconstriction. Unconsciousness abolishes voluntary influence over respiration, thereby restoring autonomic control over respiration. The time course of events and the level of impairment of consciousness needed to normalize ventilation are imperfectly known. At present, it is not known whether or not consciousness can be lost through hyperventilation. Note that hyperventilation as such is not featured in the DSM-IV (psychiatric diagnostic classification system); the symptoms usually attributed to hyperventilation fall under the heading 'panic attacks'.

- *The panel stresses that it is not certain whether or not hyperventilation can cause loss of consciousness.*

Neurally-mediated syncope

This is a synonym for 'reflex syncope' that emphasises the role of the nervous system. The word 'reflex' in fact implies the same, but with less emphasis for some. The advantage of 'reflex syncope' is that is stresses the role of a trigger in eliciting syncope.

- *The panel recognizes 'neurally-mediated syncope' and 'reflex syncope' as synonyms.*

Neurocardiogenic syncope

The term is in use as an alternative for 'neurally-mediated/reflex syncope', or sometimes as an alternative for 'vasovagal' syncope. As an alternative to 'vasovagal' that term is preferable, as it is older and simpler. As an alternative for 'reflex syncope' that term is preferred for similar reasons. 'Neurocardiogenic' has the disadvantage of emphasizing the heart, and in so doing draws attention away from the fall in systemic vascular resistance, that, in the absence of a clear cause-effect relationship, is at least as important as bradycardia in reflex syncope. 'Neurocardiogenic' has also been used in a more specific sense, referring to a type of reflex syncope in which the trigger for syncope originated in the heart itself. But in that sense the wording is unfortunate, as 'cardiogenic reflex syncope' would convey the intended content with more clarity.

- *The panel advocates conserving 'neurocardiogenic syncope' strictly for a putative type of reflex syncope in which the reflex trigger originates in the heart.*

Neurogenic syncope

This too is a synonym for 'reflex syncope', but there is no need for various alternatives.

- *The panel regards 'neurogenic syncope' as a superfluous alternative for 'reflex syncope'.*

Orthostatic intolerance

When used to describe only what the words imply, i.e., the occurrence of symptoms associated with the upright position, the meaning of the term isunambiguous. It may for instance be used to describe the symptoms in orthostatic hypotension or in the Postural Orthostatic Tachycardia Syndrome (POTS). The term is however not useful to indicate a specific type of syncope, because suitable other terms already exist, and because the phrase carries no specific meaning as to the pathophysiological mechanism involved.

- *The panel advocates restriction of the use of 'orthostatic intolerance' to summarize a patient's complaints.*

Pre-syncope

When cerebral blood flow stops or diminishes, patients may be aware that something is amiss before consciousness is lost altogether (near-syncope). They describe lightheadedness or dizziness. Sensations that are specific to diminished cortical functioning have been evoked experimentally, and consist among others of a loss of control over eye and other movements, blurring of vision, and constriction of the field of vision. These feelings may justifiably be called 'pre-syncope' or 'near-syncope'. Symptoms of another kind may also occur before syncope that are related to the mechanism causing syncope rather than to decreased cerebral blood flow itself. These may include pain in the head and shoulder region in autonomic failure, sweating and nausea in reflex syncope, and tingling in hyperventilation. Note that these sensations occur close in time to syncope, although they are only indirectly linked to the loss of consciousness.

- *The panel advises use of 'pre- syncope' as an imprecise descriptive term for all sensations directly preceding syncope whether or not they are followed by complete loss of consciousness.*

Psychogenic syncope

Patients may pretend to be unconscious when they are not. Although this state often lasts longer than syncope, and therefore may resemble coma more than syncope, it may also resemble syncope. This condition can be seen in the context of factitious disorders, malingering and conversion. In the past, 'psychogenic syncope' was used to describe it, but the addition of 'cerebral hypoperfusion' to the definition of syncope makes this impossible, as there would otherwise be a way to shut down the cerebral circulation through a mental process.

- *The panel recommends use of 'pseudo-syncope' or 'psychogenic pseudo-syncope' to describe patients pretending to be unconscious, and no longer use 'psychogenic syncope'.*

Reflex anoxic seizure

This term designates syncopal attacks in infants and children, and particularly those associated with convulsive movements. It has been used as a synonym for breath holding spells. The use of 'seizure' in 'reflex anoxic seizures' was never intended to imply epilepsy, but simply to describe an 'attack' without any pathophysiological connotation. However, for many physicians the word 'seizure' is strongly associated with epilepsy, and such attacks in children are often mistaken for epilepsy. The phrase 'reflex anoxic seizures' therefore carries the risk of obscuring the distinction between syncope and epilepsy, contrary to that needed.

- *The panel advises not to use 'reflex anoxic seizures', but to use 'infantile vasovagal syncope' instead.*

Seizures

For some, the word 'seizure' may be used for a variety of attacks, including epilepsy but also syncope, particularly if accompanied by myoclonic jerks (for instance, 'reflex anoxic seizures' refers to vasovagal syncope, a type of neurally-mediated syncope). For probably more people, the meaning of 'seizures' is restricted to epileptic attacks. When used in the first sense, there is a risk that syncope is mistaken for epilepsy because of differences in interpretation of the word.

- *The panel advocates use of 'seizures' is reserved exclusively for epileptic attacks.*

Transient loss of consciousness

The English language lacks a word to encompass the syndrome representing the group of disorders that may mimic syncope. Its four common features are loss of consciousness, that is transient in nature, self-limited, and not due to a trauma of the head and brain. These features are meant to exclude conditions with only impaired consciousness, exclude coma (implying a longer duration for 'coma'), and to exclude the vast majority of cases of concussion, in which trauma is usually evident. Note that unconsciousness by itself implies 'loss of postural control', i.e., falling, which does not therefore have to be included as a separate item in the definition. The phrase 'transient loss of consciousness' (TLOC) only includes two of these features, but lacking a term including all four it will have to suffice. Note that TLOC should be used when no probable cause can yet be identified. Other terms should only be used when a specific cause of TLOC, such as syncope or epilepsy, is at least

probable. The probability derives from other features than the four items mentioned here, such as a specific trigger or typical epileptic phenomena.

- *The panel advises that use of 'transient loss of consciousness' (TLOC) to designate, firstly, a group of disorders with four common presenting features, and secondly, for individual attacks or patients when no probable cause can be established.*

Vasodepressor syncope

The term is in use as an alternative for 'vasovagal' syncope. As an alternative for 'vasovagal ' that term is preferable, as it is older, simpler, and emphasizes both the sympathetic ('vaso…') and parasympathetic aspects ('…vagal') of the syncope. 'Vasodepressor' has the disadvantage of emphasizing the fall in systemic vascular resistance, that, in the absence of a clear cause-effect relationship, is at least as important as bradycardia in reflex syncope.

- *The panel advises that conserving 'vasodepressor syncope' is reserved strictly for a type of reflex syncope in which the vasodepressor reflex is documented to occur in absence of reflex bradycardia.*

Appendix A

ESC Task Force on Guidelines on Management (Diagnosis and Treatment) of Syncope

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