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Task Force Report

Guidelines on management (diagnosis and treatment) of syncope*

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Preamble

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 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?

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*This document has been reviewed by members of the Committee for Practice Guidelines (formerly Committee for Scientific and Clinical Initiatives) and by the members of the Board of the European Society of Cardiology (see Appendix 1), who approved the document on 8 March 2001. The full text of this document is available on the website of the European Society of Cardiology in the section 'Scientific Information', Guidelines.

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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 panel met in August 1999 and developed a comprehensive outline of the issues that needed to be addressed in the document. Subgroups of the panel were formed and each was assigned the task of reviewing the literature on a specific topic 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 collection. The panel reconvened in January 2000, 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 is 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 of the document and their comments were incorporated. If changes in recommendations were suggested, these were brought to vote in a second meeting in August 2000. The executive committee met in February 2001 to consider the comments of external reviewers, and to make amendments. Finally, the document was discussed with the Presidents of the National Societies in March 2001.

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 to aid diagnosis from history and physical examination, and clear-cut guidelines on how to choose tests, how to evaluate test abnormalities and how to use the results to establish 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 for evaluating the aetiology of syncope is that it is not possible to measure test sensitivity because there is no 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. However, this is only rarely possible, for instance, if an arrhythmia occurred concurrently with syncope. These instances are uncommon, however, and most of the time decisions have to be made based on a 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 test which were diagnostic.

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 pre-defined 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 randomized-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 headed '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 'koptein' meaning 'to cut' or more appropriately in this case 'to 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[1–3]. 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. lightheadedness, 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 short-lasting severe cerebral hypoxia in adolescents induced by an 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%; the syncope duration averaged 12 s (range 5–22)[2]. 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[3].

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 to 15% of resting cardiac output — minimum oxygen requirements necessary to sustain consciousness (approximately 3·0 to 3·5 ml O_2/100 g tissue/min) are easily achieved[4]. However, in older individuals, or those with underlying disease conditions, the safety factor for oxygen delivery may be more tenuous[5–7].

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[8]. In regard to cardiac output, the most important physiological determinant is venous filling. 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 resistance during standing is the cause of orthostatic hypotension and syncope in patients using vasoactive drugs and in patients with autonomic neuropathies[9]. 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 to 8 s has been shown to be sufficient to cause complete loss of consciousness[1]. Experience from tilt testing showed that a decrease in systolic blood pressure to 60 mmHg is associated with syncope[10]. Further, it has been estimated that as little as a 20% drop in cerebral oxygen delivery is sufficient to cause loss of consciousness[1]. In this regard, the integrity of a number of control mechanisms is crucial for maintaining adequate cerebral nutrient 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 pCO_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.

Transient failure of protective mechanisms, or the intervention of other factors (e.g. drugs, haemorrhage) which reduce systemic pressure below the autoregulatory range for an extended period of time, may induce a syncopal episode. Risk of failure is greatest in older or ill patients[5,6,11]. Ageing alone has been associated with diminution of cerebral blood flow[5,6]. 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[7].

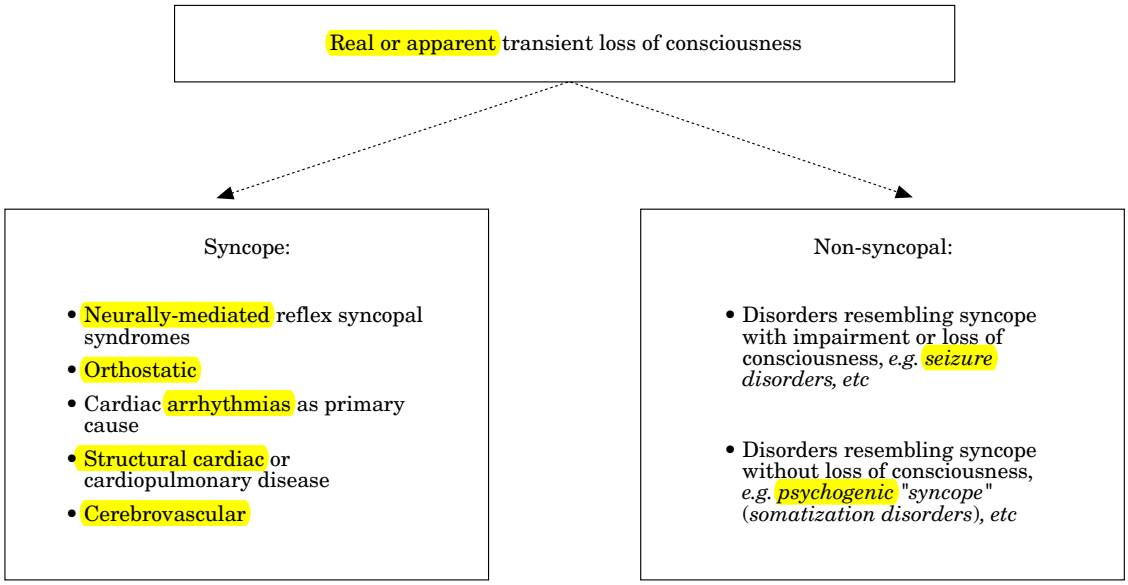

Figure 1 **Classification of transient loss of consciousness.**

Classification

Syncope must be differentiated from other 'non-syncopal' conditions associated with real or apparent transient loss of consciousness (Fig. 1). Table 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 syncopal syndrome' refers to a reflex that, when triggered, gives rise to vasodilatation and bradycardia, although the contribution of both to systemic hypotension and cerebral hypoperfusion may differ considerably.
- 'Orthostatic' syncope occurs when the autonomic nervous system is incapacitated resulting in a failure of vasoconstrictor mechanisms and thereby in orthostatic hypotension; 'Volume depletion' is another important cause of orthostatic hypotension and syncope.
- 'Cardiac arrhythmias' can cause a decrease in cardiac output, which usually occurs irrespective 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 resemble syncope in two different ways. In some, consciousness is impaired or lost as a result of metabolic disorders (including hypoxia, hyperventilation with hypocapnia, hypoglycaemia), epilepsy and intoxication. In several other disorders, consciousness is only apparently lost; this is the case with somatization disorders, cataplexy and drop attacks. Table 1.2 lists the most common conditions misdiagnosed as the cause of syncope. It should be noted that the conditions listed here do not result from sudden transient global cerebral hypoperfusion. A differentiation such as this is important because the clinician is usually confronted with patients whose sudden loss of consciousness may be due to causes not associated with decreased cerebral blood flow such as seizure and/or conversion reaction.

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, in part, be 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 enrolled, 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

Table 1.1 Causes of syncope

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

Orthostatic
- 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)
  –Drugs and alcohol
- 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

examinations were carried out over a 26-year period in 5209 free-living individuals, 2336 men and 2873 women) reported at least one syncopal event during the study period in approximately 3% of men and 3·5% of women[17]. The mean initial age of first syncope was 52 years (range 17 to 78 years) for men, and 50 years (range 13 to 87 years) for women. Further, prevalence of isolated syncope (defined as syncope in the absence of prior or concurrent neurological, coronary, or other cardiovascular disease stigmata) increased from 8 per 1000 person-exams in the 35–44-year-old age group, to approximately 40 per 1000 person-exams in the $\geq$75-year-old age group. These data, however, are in conflict with studies reported from selected populations such as among the elderly confined to long-term care institutions, where the annual incidence may be as high as 6% with a recurrence rate of 30%[18]. Several reports indicate that syncope is a common presenting problem in 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]
- 16% during a 10-year period in men aged 40–59[25]
- 19% during a 10-year period in women aged 40–49[25]
- 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 stratification: identification of factors predictive of adverse outcome

Mortality

Studies in the 1980s showed that 1-year mortality of patients with cardiac syncope was consistently higher

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

Disorders with impairment or loss of consciousness
- Metabolic disorders#, including hypoglycaemia, hypoxia, hyperventilation with hypocapnia
- Epilepsy
- Intoxication
- Vertebro-basilar transient ischaemic attack

Disorders resembling syncope without loss of consciousness
- Cataplexy
- Drop attacks
- Psychogenic 'syncope' (somatization disorders)*
- Transient ischaemic attacks (TIA) of carotid origin

#Disturbance of consciousness probably secondary to metabolic effects on cerebrovascular tone.
*May also include hysteria, conversion reaction.

(ranging between 18–33%) than patients with non-cardiac cause (0–12%) or unexplained syncope (6%)[19,20,26–28]. One-year incidence of sudden death was 24% in patients with a cardiac cause compared with 3–4% in the other two groups[27,28]. 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[27,28]. However, a more recent study directly compared the outcomes of patients with syncope with matched control subjects without syncope[29]. 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 with similar degrees of heart disease[29]. This study showed that the 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[30].

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 recognized as having an average survival without valve replacement of 2 years[31]. 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[32]. In arrhythmogenic right ventricular dysplasia, patients with syncope or symptomatic ventricular tachycardia have a similarly poor prognosis[33]. 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[34]. 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 can be identified which have an excellent prognosis. Certain of these include:

- *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[35]. 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 syndromes*. 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%[36]. Most of these patients had normal hearts. None of these studies report patients who died suddenly.
- *Orthostatic hypotension*. The mortality rates of patients with orthostatic hypotension depend on the causes of this disorder. Many of the causes (e.g. volume depletion, drug-induced) are transient problems that respond to treatment and do not have long-term consequences. Disorders of the autonomic system have health consequences and may potentially increase mortality depending on the severity of the disease. In the elderly patients with orthostatic hypotension, the prognosis is largely determined by co-morbid illnesses.
- *Syncope of unknown cause*. An approximately 5% first year mortality in patients with unexplained syncope has been a relatively consistent observation in the literature[19,20,27,28,37]. Although the mortality is largely due to underlying co-morbidity, such patients continue to be at risk for physical injury, and may encounter employment and life-style 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[28,38]. Predictors of recurrence of syncope include having had recurrent syncope at the time of presentation (four or more episodes in one study[38]) or a psychiatric diagnosis[38–40]. In one study[41], more than five lifetime episodes gave a 50% chance of recurrence in the following year. In another study[39], 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[42].

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[35]. 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[35]. 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

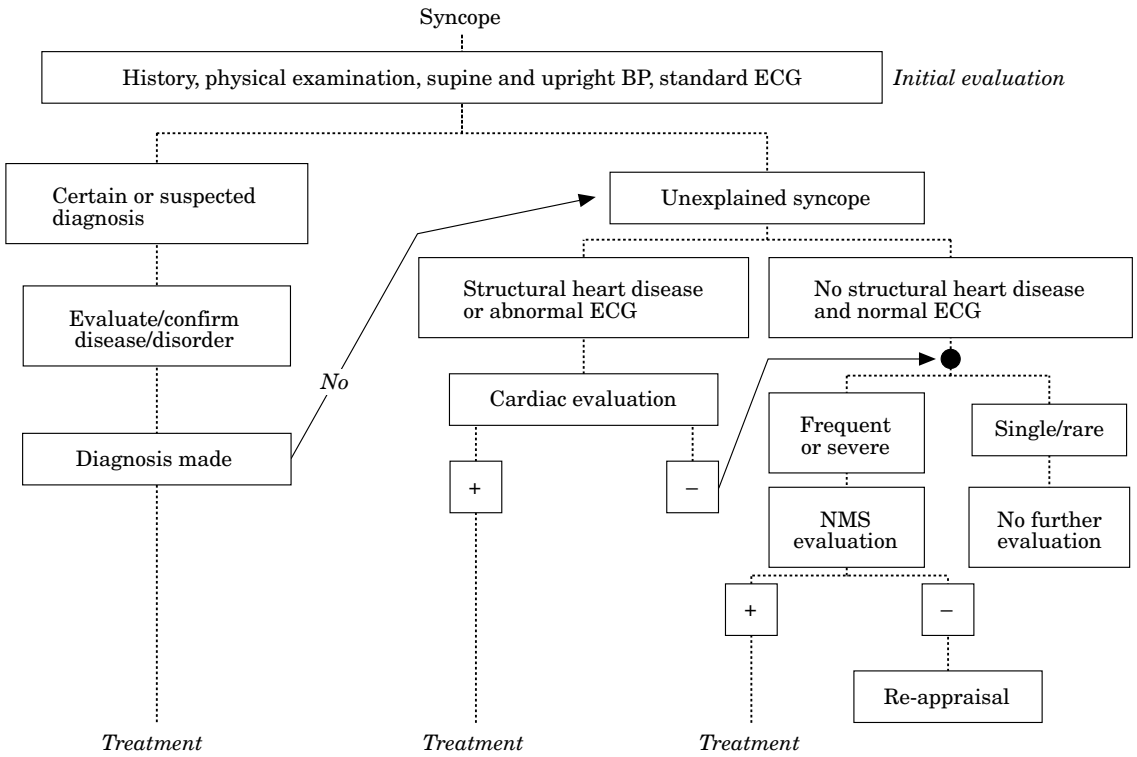

Figure 2 **The figure shows the flow diagram proposed by the Task Force on Syncope of an approach to the evaluation of syncope. BP=blood pressure; ECG=electrocardiogram; NMS=neurally mediated syncope.**

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 is no data on the risk of injury to others. Recurrent syncope is associated with fractures and soft-tissue injury in 12% of patients[38].

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 as rheumatoid arthritis, low back pain, and psychiatric disorders[43]. 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[41].

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. A study in 1982 showed that patients often underwent multiple diagnostic tests despite which a cause of syncope was established in only 13 of 121 patients[44]. 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 19 3164 syncope hospital discharges in 1993 in the U.S.A.[45]. The cost per discharge was calculated as $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.

Part 2. Diagnosis

Strategy of evaluation

Figure 2 shows a flow diagram of an approach to the evaluation of syncope.

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. Other than this, 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 is generally the first diagnostic challenge and influences the subsequent diagnostic strategy (see classification in Part 1 and Table 1). 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[46], heart disease was an independent predictor of a cardiac cause of syncope, with a sensitivity of 95% and a specificity of 45%; by contrast, the absence of heart disease ruled out a cardiac cause of syncope in 97% of the patients. Finally, accurate history-taking may be diagnostic per se 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 an accompanying symptom at the presentation of 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. These issues are not addressed in this report.

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

Certain or suspected 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 entitled Initial evaluation. Under such circumstances, no further evaluation of the disease or disorder may be needed and treatment, if any, can be planned. More commonly, the initial evaluation leads to a suspected diagnosis, which needs to be confirmed by directed testing (see Initial evaluation). 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 most important issue in these patients is the presence of structural heart disease or an abnormal ECG. These findings are associated with a higher risk of arrhythmias and a higher mortality at 1 year. In these patients, cardiac evaluation consisting of echocardiography, stress testing and tests for arrhythmia detection such as prolonged electrocardiographic and loop monitoring or electrophysiological study are recommended. If cardiac evaluation does not show evidence of arrhythmia as a cause of syncope, evaluation for neurally mediated syndromes is recommended in those with recurrent or severe syncope.

In patients without structural heart disease and a normal ECG, 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. The majority of patients with single or rare episodes in this category probably have neurally mediated syncope. Since treatment is generally not recommended in this group of patients, close follow-up without evaluation is recommended. Additional consideration in patients without structural heart disease and a normal ECG is bradyarrhythmia or psychiatric illness. Loop monitoring is needed in patients with recurrent unexplained syncope whose symptoms are suggestive of arrhythmic syncope. ATP testing may be indicated at the end of the diagnostic work-up. Psychiatric assessment is recommended in patients with frequent recurrent syncope who have multiple other somatic complaints and whose initial evaluation raises concern in terms of stress, anxiety and other possible psychiatric disorders.

Reappraisal

Once the evaluation, as outlined, is completed and no cause of syncope is determined, reappraisal of the work-up is needed since subtle findings or new historical information may change the entire differential diagnosis. Reappraisal may consist of obtaining details of history and reexamining patients as well as a 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 specialty services may be needed.

Recommendations

Indications

Class I:

- *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,*

Table 2.1 Important historical features

Questions about circumstances just prior to 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 attack
- Nausea, vomiting, abdominal discomfort, feeling of cold, sweating, aura, pain in neck or shoulders, blurred vision

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

Questions about 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

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.*

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[3,26,46–48].

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 history, all the items listed in the 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 to pursue 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 cases 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 direct testing (Table 2.3).

Recommendations

Diagnosis

Class I:

The results of the initial evaluation (history, physical examination, orthostatic blood pressure measurements

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

Symptom or finding	Possible cause
• After sudden unexpected unpleasant sight,sound, or smell	Vasovagal
• Prolonged standing or crowded, warm places	Vasovagal or autonomic failure
• Nausea, vomiting associated with syncope	Vasovagal
• Within 1 h of a meal	Post-prandial (autonomic failure)
• After exertion	Vasovagal or autonomic failure
• Syncope with throat or facial pain	Neuralgia (glossopharyngeal or trigeminal neuralgia)
• With head rotation, pressure on carotid sinus (as in tumours, shaving, tight collars)	Spontaneous carotid sinus syncope
• Within seconds to minutes upon active standing	Orthostatic hypotension
• Temporal relationship with start of medication or changes of dosage	Drug induced
• During exertion, or supine	Cardiac syncope
• Preceded by palpitation	Tachyarrhythmia
• Family history of sudden death	Long QT syndrome, Brugada syndrome, Right ventricular dysplasia, Hypertrophic cardiomyopathy
• Associated with vertigo, dysarthria, diplopia	Brainstem transient ischaemic attack (TIA)
• With arm exercise	Subclavian steal
• Differences in blood pressure or pulse in the two arms	Subclavian steal or aortic dissection
• Confusion after attack for more than 5 min	Seizure
• Tonic-clonic movements, automatism, tongue biting, blue face, epileptic aura	Seizure
• Frequent attack with somatic complaints, no organic heart disease	Psychiatric illness

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^{-1}) or sinoatrial block
- Pre-excited QRS complexes
- Prolonged QT interval
- Right bundle branch block pattern with ST-elevation in leads V_1-V_3 (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

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 pre-syncope. Orthostatic blood pressure measurements are recommended after 5 min of lying supine. Measurements are then continued after 1 or 3 min of standing and further continued, 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 $\geq$20 mmHg or a decrease of systolic blood pressure to <90 mmHg is defined as orthostatic hypotension regardless of whether or not symptoms occur*[49].
- *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**.
- *Arrhythmia-related syncope is diagnosed by ECG when there is*:

**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*

–Sinus bradycardia <40 beats . min^{-1} 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

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[50–52]. 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[51]. 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[53–66]. 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
Class I:
- *Echocardiography is recommended in patients with syncope when cardiac disease is suspected.*

Diagnosis
Class I:
- *Echocardiographic findings may be useful to stratify the risk by assessing the cardiac substrate.*
- *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 a 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 mmHg 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 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 1 or 2 min 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) the massage is usually repeated after intravenous administration of atropine (1 mg or 0·02 mg . kg^{-1}). 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, the 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 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[32,76], 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 intra-patient 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.

Whatever method is used, increasing importance has been given to the execution of the massage in the upright position, usually using a tilt table[78,79,85]. 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. Under-estimated in the past, a vasodepressor component of the reflex is present in most patients with an asystolic response[85]. 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 than in dominant cardioinhibitory forms[71,81].

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[86]. In one study[86], seven neurological complications were reported among 1600 patients (5000 massages) with an incidence of 0·45%. In another study[87], 11 neurological complications were reported in 4000 patients (16 000 massages) with an incidence of 0·28%. These complication rates apply to 5 s of carotid sinus massage supine/upright.

Even if these complications are rare, carotid massage should be avoided in patients with previous transient ischaemic attacks or stroke within the past 3 months (except when carotid Doppler studies excluded significant stenosis) or in patients with carotid bruits[86]. 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, usually no resuscitative measures are 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 done by analysing the recurrence rates of syncope in patients treated by pacing in several non-randomized studies[88–91]. 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[92]. 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 the pacemaker group vs 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[93].

Recommendations

Indications and methodology

Class I:

- *Carotid sinus massage is recommended in patients over age 40 years with syncope of unknown aetiology after the initial evaluation. In case of risk of stroke due to carotid artery disease, massage should be avoided.*
- *Electrocardiographic monitoring and continuous blood pressure measurements during carotid massage is mandatory. Duration of massage of a minimum of 5 and a maximum of 10 s is recommended. Carotid massage should be performed with the patient both supine and erect.*

Diagnosis
Class I:
- *The procedure is considered positive if symptoms are reproduced during or immediately after the massage in the presence of asystole longer than 3 s and/or a fall in systolic blood pressure of 50 mmHg 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[9]. 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: the heart cannot pump blood that it does not receive[9]. 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[9]. 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[9]. Failure of such 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[94–97].

Tilt test protocols

In 1986 Kenny *et al.*[98] observed an abnormal response to tilt test in 10 out 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.*[99] 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.*[100] and Waxman *et al.*[101] used intravenous isoproterenol during tilt testing. In the study of Almquist *et al.*[100], after 10 min of passive tilt test without drugs, patients were returned to the supine position and an isoproterenol infusion at initial doses of $1\ \mu g\ .\ min^{-1}$ was administered. When patients achieved a stable increase in heart rate they were tilted again. This manoeuvre was repeated at increasing doses up to $5\ \mu g\ .\ min^{-1}$. With this protocol nine of 11 patients with syncope of unknown origin and negative electrophysiological study showed hypotension and/or bradycardia, whereas such responses were found in only two of 18 control subjects. In 1992, Kapoor *et al.*[102] using an isoproterenol tilt test at 80°, in which isoproterenol was administered in progressive doses from 1 to $5\ \mu g\ .\ min^{-1}$, 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.*[103] and Natale *et al.*[104] proposed a 'shortened' low-dose isoproterenol tilt test, in which, after 15–20 min of baseline tilt at 60–70°, incremental doses of isoproterenol designed to increase average heart rate by about 20–25% over baseline (usually $\leq 3\ \mu g\ .\ min^{-1}$)

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.*[105] 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.*[106] 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.*[107] and Raviele *et al.*[108] have compared the isoproterenol 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 vs 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 163 patients from three other 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.

Other drugs used as provocative agents during tilt testing include isosorbide dinitrate[114,115], edrophonium[116,117], clomipramine[118] 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[119]. 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[120,121]. With the protocols that do not use venous cannulation, time in the supine position before tilting can be reduced to 5 min. Continuous beat-to-beat finger arterial blood pressure should be monitored non-invasively[122]. Invasive measurements of arterial blood pressure can affect the specificity of the test, especially in the elderly[120] and in children[121]. 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 foot-board 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.

Recommended 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 to 70°.*
- *Passive phase of a minimum of 20 min and a maximum of 45 min.*
- *Use of ether intravenous isoproterenol/isoprenaline or sublingual nitroglycerin for drug provocation if passive phase has been negative. Drug challenge phase duration of 15–20 min.*
- *For isoproterenol, an incremental infusion rate from 1 up to 3 µg . min^{-1} 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.*

Class II:

Divergence of opinion exists in the case of induction of pre-syncope.

Responses to the tilt test

In 1992, Sutton *et al.*[123], using the details of haemodynamic responses to tilt testing, proposed a classification of the positive responses, which has been recently modified[124]. This classification is shown in the Table 2.4.

Table 2.4 Classification of positive responses to tilt testing

- Type 1 Mixed. Heart rate falls at the time of syncope but the ventricular rate does not fall to less than 40 beats . min^{-1} or falls to less than 40 beats . min^{-1} 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^{-1} 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. 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^{-1}).

Since the decision to terminate tilting influences the type of response[125], for a correct classification of responses tilting should be interrupted at the precise occurrence of loss of consciousness with simultaneous loss of postural tone[124]. Premature interruption underestimates and delayed interruption over-estimates 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[105,106,124,126] have analysed 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 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 an 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 an inability to adapt promptly to some external influences ('hyposensitive' autonomic function). Different subtypes have been described with slight differences between them. The patients affected are mostly 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 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 head-up tilt test in treatment selection for vasovagal syncope

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[127–131]. The overall reproducibility of an initial negative response (85% to 94%) is higher than the reproducibility of an initial positive response (31% to 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[132–134]. Moreover, acute studies were not predictive of the long-term outcome of pacing therapy[135]. These data show that the use of tilt testing for assessing the effectiveness of different treatments has important limitations (level A).

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[136] the presence of such prolonged asystole during a positive response cannot be considered a complication, since this is an end-point of the test. A rapid return to the 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; brief resuscitation manoeuvres are seldom needed. Case reports have documented life-threatening ventricular arrhythmias with isoproterenol in the presence of ischaemic heart disease[137] or sick sinus syndrome[138]. No complications have been published with the use of nitroglycerin. Minor side effects are common and include palpitations with isoproterenol and headache with nitroglycerin. Atrial fibrillation can be induced during or after a positive tilt test and is usually self-limited[139].

Recommendations

Indications

Class I:

Tilt testing is indicated for diagnostic purposes:

- *In cases of unexplained single syncopal episodes 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 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 pre-syncope or dizziness.*

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.*

Diagnosis

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:

- *The clinical meaning of abnormal responses other than induction of syncope is unclear.*

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.

Holter monitoring in syncope.

Most ECG monitoring in syncope is undertaken with external 24 h cassette tape-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.

A recurrence of presenting symptoms may not occur 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[140] of the results of eight studies of ambulatory monitoring in syncope, only 4% of patients (range between 6 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[141–143]. 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 maximized leading to unnecessary therapy, e.g. pacemaker implantation in a patient with vasomotor syncope. Alternatively, there is potential for symptoms to be inappropriately minimized 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 ECG event monitoring 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[144], external retrospective loop recorders showed relatively higher diagnostic yield in syncope, 25% of enrolled 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.

Implantable ECG event monitoring in syncope

Recently an implantable ECG event monitor (Implantable Loop Recorder) has become available. This device 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. 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[145]. In a larger series[146], symptom–ECG correlation 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 pre-syncope–ECG correlation in 32%; pre-syncope 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).

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 current need for patient activation, though data suggest that this is usually possible after recovery of consciousness (now avoided by automatic versions); the high cost of the implantable device.

The implantable loop recorder carries a high up-front 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. This remains to be confirmed[145–147].

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 an aetiological treatment. There are several areas of interest: patients who have a diagnosis of neurally-mediated syncope when the understanding of the exact mechanism of spontaneous syncope may alter the therapeutic approach; patients with bundle branch block in whom a paroxysmal AV block is likely despite a complete negative electrophysiological evaluation; patients with severe left ventricular dysfunction and non-sustained ventricular tachyarrhythmias in whom a ventricular tachyarrhythmia is likely despite a completed negative electrophysiological study.

ECG monitoring in syncope — where in the work-up?

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. 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[148].

Recommendations

Indications

Class I:

- *Holter monitoring is indicated in patients with structural heart disease and frequent (or even infrequent) symptoms when there is a high pre-test probability of identifying an arrhythmia responsible for syncope.*

- *When the mechanism of syncope remains unclear after full evaluation, External or Implantable Loop Recorders are recommended when there is a high pre-test probability of identifying an arrhythmia responsible for syncope.*

Diagnosis

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 sinus rhythm.*
- *In the absence of such correlations additional testing is recommended with the possible exception of:*
  –ventricular pauses longer than 3 s when awake
  –periods of Mobitz II or third-degree atrioventricular block when awake
  –rapid paroxysmal ventricular tachycardia

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 a 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[149,150].

Invasive electrophysiological study

The diagnostic efficiency 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 a 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[148,151–153] have compared the findings of the electrophysiological study with the arrhythmia documented during a spontaneous syncopal episode by electrocardiographic monitoring. In the study by Fujimura *et al.*[151], the utility of the 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.*[148] showed that the presence of an 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[154,155]. 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.*[152] 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.*[153] 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.*[156] 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 ($P<0{\cdot}001$ for both comparisons). Thus, positive results at electrophysiological study occur predominantly in patients with evidence of organic heart disease (level B).

Suspected bradycardia. The pre-test probability of a transient symptomatic bradycardia is relatively high when there is an asymptomatic sinus bradycardia (<50 beats . min^{-1}) or sinoatrial block and syncope occurs 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 a 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 not yet useful clinically[157–159]. The major concern lies in limited sensitivity with all the 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[160], and recovery time assessment is therefore usually preferred. A prolonged sinus node recovery time reflects abnormal sinus node automaticity, sino-atrial conduction, or both[161] (Table 2.5). The sensitivity of SNRT >1500–1720 ms and/or CSNRT (SNRT corrected for heart rate) >525 ms is approximately 50 to 80%, while the specificity is >95%[158]. The value of including assessment after administration of atropine and propranolol for inhibition of autonomic tone is accepted for distinguishing between intrinsic and extrinsic sinus node dysfunction[158], but its diagnostic value is still debated. According to two studies[154,162] 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 ($0{\cdot}2\ mg\ .\ kg^{-1}$ body weight) and intravenous atropine sulphate ($0{\cdot}04\ mg\ .\ kg^{-1}$ body weight) according to the seminal work by Jose and Collison, defining the so called intrinsic heart rate[163]. Normal values for intrinsic heart rate can be determined by using a linear regression equation, which relates predicted intrinsic heart rate (IHRp) to age; $IHRp = 118{\cdot}1 - (0{\cdot}57 \times age)$[163]. 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[164,165], and later modified to 75% by Tonkin *et al.*[166]. From a diagnostic point of view it seems sufficient to use propranolol $0{\cdot}1\ mg\ .\ kg^{-1}$ body weight and atropine $0{\cdot}02\ mg\ .\ kg^{-1}$ body weight, since higher doses might cause adverse effects, at least in patients older than 60 years[154].

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[167]. Recently Menozzi *et al.*[168] addressed a related issue in a small prospective study, showing that the patients with a CSNRT of ≥800 ms had an 8 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[161,169] or 525 ms for CSNRT[167]. In one study[169], 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 the opinion of the panel that, in the 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[170], is still the most clinically useful, albeit being a simplification[171,172]. 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[173].

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[174]. The prognostic value of the HV interval was prospectively studied by Scheinman *et al.*[175]; 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 with 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 (Table 2.5). The development of intra- or infra His block at incremental atrial pacing[173,176–179] is highly predictive of impending AV block, but is rarely observed and has a low sensitivity. For example, in the study by Gronda *et al.*[180] on 131 patients, an HV prolongation of >10 ms was observed in 6% and second-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.*[181], 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 $1\ mg\ .\ kg^{-1}$[180–182], procainamide at a dosage of $10\ mg\ .\ kg^{-1}$[183], and disopyramide at a dosage of $2\ mg\ .\ kg^{-1}$[155]. Importantly,

not only should the occurrence of high-degree AV block during spontaneous rhythm be looked for, but also any intra- or infra-His block at incremental atrial pacing or after short sequences of ventricular pacing[155]. In five studies[173,180–183] 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 $\geq$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[173,180,181] 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.*[180] and 80% in that of Bergfeldt *et al.*[173] (level B). On the other hand, in patients with negative electrophysiological studies, Link *et al.*[184] observed development of AV block in 18% (after 30 months) and Gaggioli *et al.*[185] in 19% (at 62 months). 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[175,176,182].

Importantly, a high incidence of total deaths and sudden death was observed in patients with bundle branch block. In pooled data from nine studies for a total of 1761 patients the total mortality was 28% at 40 months and 32% of deaths were sudden[173–175,179,182,185–187]. However, neither syncope nor a prolonged HV interval was associated with a higher risk of death[174,186], and pacemaker therapy did not decrease this risk[175]. 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[179,182,187,188]). In one study[187], sustained monomorphic ventricular tachycardia 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[187].

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). 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[189]. 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[190] and the lack of a standard protocol[191] (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 spontaneous monomorphic ventricular tachycardia. Applying the opposite perspective, the induction of monomorphic ventricular tachycardia is thought to be a specific event that should guide therapy. For example, in the ESVEM trial[192], syncope, associated with induced ventricular tachyarrhythmias at electrophysiological testing, indicated a 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[187]. Polymorphic ventricular tachycardia and ventricular fibrillation, on the other hand, have previously been considered non-specific findings, a concept that probably needs modification depending on the clinical setting. One example is patients with the Brugada syndrome in whom the induction of polymorphic ventricular arrhythmias seems to be the most consistent finding[193,194]. Another patient category, in which programmed electrical stimulation with induction of ventricular fibrillation is of unsettled value, is survivors of cardiac arrest with significant coronary artery disease undergoing coronary bypass surgery[195,196]. Programmed ventricular stimulation has a low predictive value in patients with non-ischaemic dilated cardiomyopathy[30] and one study[197] 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.

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. Seven studies[197–203] have evaluated the utility of ICDs in highly selected patients with syncope. Link *et al.*[198] 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.*[199], 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. Three studies concerned patients affected by coronary artery disease[200–202]. In the study by Mittal *et al.*[200], which evaluated 67 consecutive patients with coronary artery disease, mostly with a prior myocardial infarction and a depressed ejection fraction (mean 37 ± 13%), a 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 syncope 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.*[201], 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 two 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.*[202] 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. Two studies concerned patients affected by non-ischaemic dilated cardiopathy[197,203]. Knight *et al.*[197], 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 two groups (50% vs 42%) and the relapses of syncope or pre-syncope 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. Finally, improved survival with an ICD in respect of conventional therapy has been observed in the study of Fonarow *et al.*[203] 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.

In conclusion, 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 who might not represent the patients encountered in clinical practice.

Recommendations

Indications

Class I:

- *An invasive electrophysiological procedure is indicated when the initial evaluation suggests an arrhythmic cause of syncope (in patients with abnormal electrocardiography and/or structural heart disease or syncope associated with palpitations or family history of sudden death).*

Class II:

- *Diagnostic reasons: to evaluate the exact nature of an arrhythmia which has already been identified as the cause of the syncope.*
- *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.*

Class III:

- *In patients with normal electrocardiograms and no heart disease and no palpitations an electrophysiological study is not usually undertaken.*

Diagnosis

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.*

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^{-1} higher than sinus rate) and two higher pacing rates*.
- 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^{-1} i.v.), procainamide (10 mg . kg^{-1} i.v.), or disopyramide (2 mg . kg^{-1} 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^{-1} and 140 or 150 beats . min^{-1}), with up to two extrastimuli**.
- Assessment of supraventricular arrhythmia inducibility by any atrial stimulation protocol.

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

- *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 ≥100 ms, 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
  –previous myocardial infarction and induction of sustained monomorphic ventricular tachycardia
  –arrhythmogenic right ventricular dysplasia and induction of ventricular tachyarrhythmias
  –induction of rapid supraventricular arrhythmia which reproduces hypotensive or spontaneous symptoms

Class II:

Divergence of opinion exists on the diagnostic value of electrophysiological study in case of:
  –HV interval of >70 ms but <100 ms
  –induction of polymorphic ventricular tachycardia or ventricular fibrillation in patients with ischaemic or dilated cardiomyopathy
  –in Brugada syndrome

ATP test

Intravenous injection of adenosine triphosphate (ATP) has recently been proposed as a tool in the investigation of patients with unexplained syncope[204,205]. In predisposed patients with unexplained syncope, the stimulation of purinergic receptors, with a powerful dromotropic effect on the atrioventricular node[206], 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[206].

Protocol of the ATP test

The protocol proposed by Flammang *et al.*[204] 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[205].

Interpretation of the result of the test is exclusively based on the duration of the cardiac 'pause'. A value of >6 s[205] 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[205,207].

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[204,205]. Moreover, in a small group of patients with syncope electrocardiographically documented to be caused by transient pause, Brignole *et al.*[205] found that the 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. The logical inference is that ATP testing can identify patients with syncope due to transient atrioventricular block even when the electrophysiological findings and other conventional tests are unremarkable. However, this remains an interesting hypothesis to be confirmed by prospective studies. Whether a positive response to the ATP test also identifies an adenosine-mediated mechanism of the paroxysmal atrioventricular block or simply reveals a non-specific susceptibility of the atrioventricular node to different triggers (for example vagal hyperactivity or intermittent atrioventricular node conduction disorders) that could not otherwise be recognized, is unknown.

Pre-post comparisons were done by analysing the recurrence rates of syncope in patients treated by pacing[204] or by theophylline, an adenosine-receptor antagonist[205]. These studies showed fewer recurrences at follow-up.

Relationship between ATP and tilt testing

Both ATP and tilt testing were performed in patients with unexplained syncope in two studies[208,209]. 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 tests, 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.

Other authors[210,211] 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. The diagnostic and predictive value of the test remains to be confirmed by prospective studies. In the absence of sufficient hard data, the test may be indicated at the end of the diagnostic work-up (Class II).

Ventricular signal-averaged electrocardiogram

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 signal averaging techniques if the area of slow conduction is activated late during ventricular depolarization[212].

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[213–216]. Therefore, the signal-averaged electrocardiogram 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 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)[217,218] or cardiac involvement in systemic disorders (amyloidosis, systemic sclerosis, muscular dystrophy)[219–221]. 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[222].

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[223].

Recommendations

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

Exercise testing

Exercise testing should be performed in patients who have experienced episodes of syncope during or shortly after exertion. Exercise testing should be symptom-limited and 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[224–236]. These two

situations should be considered separately. 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[226,229]. Reflex syncope occurring during exercise is caused by marked hypotension without bradycardia[226,229]. By contrast, post-exertional syncope is almost invariably due to autonomic failure[236] or to a neurally-mediated mechanism[225,227,228] and is characterized by hypotension which can be associated with marked bradycardia or asystole; it typically occurs in subjects without heart disease (level B). Tilt testing has been used to diagnose neurally-mediated syncope, which may manifest as post-exertional syncope[230]. A failure of reflex vasoconstriction during exercise in splanchnic capacitance vessels and in forearm resistance vessels has been shown in patients with vasovagal syncope[233].

Tachycardia-related (phase 3) exercise-induced second- and third-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[237–239] (level B).

Exercise testing is not particularly cost-effective when used in a general population with syncope. Its diagnostic yield was less then 1% in a population study[28]. However, when its use is limited to selected patients with exertional syncope, it may represent an important diagnostic test.

Recommendations

Indications

Class I:

Patients who experience an episode of syncope during or shortly after exertion.

Class III:

Use of exercise testing is not recommended in patients who do not experience syncope during exercise.

Diagnosis

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- or third-degree AV block develop during exercise even without syncope.*

Cardiac catheterization and angiography

Cardiac catheterization may consist of ventriculography to assess cardiac chamber morphology, coronary arteriography to visualize 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 a decrease in myocardial contractility; ischaemia-induced cardiac arrhythmias, asystole or complete heart block[240]; and ischaemia-induced vasovagal reaction[241]. It may also reveal coronary artery spasm as a cause of syncope[242,243]. In such cases, the ergonovine test during coronary angiography may be indicated[244].

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 discussed separately.

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 often occur, and can be assessed easily through history-taking. There are three groups of autonomic failure[245,246].

- 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[246]. 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[247–249] 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[245] 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 cases 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 internal 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 clogged, 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. 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.
- It is doubtful whether or not transient ischaemic attacks (TIAs) can cause true loss of consciousness. Only TIAs in the vertebrobasilar circulation may theoretically do so, but other signs, such as paralysis, 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[250] and during an attack[251]. 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 groups 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[252]. Aura patterns are usually repetitive over time in patients, who will therefore learn to recognize 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')[253], 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) are massive synchronous jerks of the arms and/or legs[3,253]. 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.
- There are many neurological reasons to cause a 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[254]. 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'[255] describing women (very rarely men) who suddenly drop on their knees without any apparent reason, 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. There are no associated signs or symptoms or signs of any kind. The disorder can exist unaltered for many years. If used in

Table 2.6 When to suspect seizure at initial evaluation? The value of history for distinguishing seizure from syncope. Adapted from Hoefnagels et al.[3]

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)*
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)
- Lightheadedness before the event
- 'Pins and needle' before the event
- Incontinence after the event
- Injury after the event
- Headache after the event
- Sleepy after the event

*Nausea and abdominal discomfort may be present also in partial complex seizure.

this strict sense, the term has a specific meaning. If it is used in the wide sense, it obscures rather than elucidates a variety of diverse disorders, and hampers understanding.

Psychiatric evaluation

Syncope-like symptoms may be due to anxiety, hysteria, panic attacks and major depression. Despite the presence of psychiatric disorders, a careful search for other causes of syncope is needed since the attribution of psychiatric disorder to syncope is often difficult. However, when other causes are excluded or are considered unlikely, treatment of psychiatric disorders should be initiated and patients followed closely. Patients with syncope associated with psychiatric illnesses are young, with a low prevalence of heart disease but with frequent recurrent syncope. Patients with conversion reactions (hysteria) may faint in the presence of a witness and may not have injury.

Syncope may be mimicked by somatization disorder. 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[256]. 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[257] 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)[258,259]. Two referral studies[258,259] showed a significant correlation between hyperventilation manoeuvres (resulting in near-syncope or syncope) and psychiatric causes of syncope.

Electroencephalography

In the early 1980s, electroencephalography (EEG) was one of the cornerstones of the work-up for patients with syncope[260]. The possible contribution of the EEG is to disclose epileptiform abnormalities; there are no specific EEG findings for any loss of consciousness other than epilepsy. Accordingly, several studies[27,44,260–263] 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 a priori the most likely cause for a transient loss of consciousness; it is beneficial in patients with a relatively high likelihood of epilepsy, such as a history of seizures.

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[19,27,44,244,261] 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. 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 syncope (somatization disorder) or if the patient has a known psychiatric disorder.*

Class III:

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

Diagnostic yield and prevalence of causes of syncope

Data from seven population based studies[19,20,26,28,48,261,265] 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 department is low, ranging between 1% and 11% (mean 7%)[19,26,28,265]. 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, a hyperadrenergic state and the serum glucose value is <40 mg . dl^{-1}. 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[19,26,28,261,265], performed in the 1980s, the cause of syncope could not be determined in 34% of cases (range 13%–41%) and in one recent study[46] the cause of syncope could not be determined in 17% of cases.

The prevalence of the causes of syncope has been evaluated in six population-based studies of a total of 1499 unselected patients[19,26,28,48,261,265]. 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 a recent study[46] on 342 patients referred to a syncope unit in which carotid sinus massage and tilt testing were used extensively, the percentage neurally-mediated was 58%, while 18% had cardiac causes. That 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 in their discovery when the history alone is not diagnostic.

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 about the aetiology of the symptoms (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 given co-morbidities in the patient being evaluated).

Neurally-mediated reflex syncopal syndromes

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

In general, the 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.

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 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 a review of their medical history, patients should be informed of the likelihood of syncope recurrence. Initial advice should also include a 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[266,267]. 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[268]. 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 such as 'sport' drinks, salt tablets) or moderate exercise training[269–272] appear to be among the safest initial approaches (level B). Additionally, 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[273,274] (level B).

Many drugs have been used in the treatment of vasovagal syncope (beta-blockers, disopyramide, scopolamine, clonidine, theophylline, fludrocortisone, ephedrine, etilephrine, midodrine, clonidine, serotonin reuptake inhibitors, etc). In general, while the results have been satisfactory in uncontrolled trials or short-term controlled trials[275–288] with few exceptions[132,289], several long-term placebo-controlled prospective trials have been unable to show a benefit of the active drug over placebo[133,134,290–294] with one exception[295].

In vasovagal syncope beta-blockers, owing to their negative inotropic effect, have been supposed to lessen the degree of mechanoreceptor activation associated with an 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[275,277–281] or in one short-term controlled study[276], but have failed to be effective in five long-term follow-up controlled studies[290–294] and in one short-term controlled study[288]. 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 etilephrine. Etilephrine was studied as a segment of the randomized placebo-controlled VASIS trial[134]. Etilephrine proved to be ineffective and that arm of the study was abandoned (level B). Recently, Ward *et al.*[282] have performed a controlled prospective study on the short-term effect of midodrine in severely symptomatic old patients affected by vasovagal 'hypotensive' syncope and the authors have shown a beneficial effect of the drug compared to no therapy; however the study was not placebo controlled.

Paroxetine has been shown to be effective in one placebo-controlled trial[295] which included a very large number of highly symptomatic patients in one institution. 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[296–300]. As a result, there is a strong consensus of opinion that cardiac pacing should play only a minor role in the treatment of patients with vasovagal faints. Nevertheless, unlike most other treatment avenues in this condition, pacing has been the subject of a number of both small single/multiple-centre studies[296–302], as well as two major multicentre randomized controlled trials[135,303] demonstrating effectiveness in highly select patient populations. In this regard, the strongest supportive evidence is provided in the published report of the North American vasovagal pacemaker study[301], and the recently reported European VASIS trial[135]. In both studies, the focus was treatment of individuals who appeared to demonstrate predominantly cardioinhibitory faints. In the case of the North American trial, syncope recurrence rate was substantially less in the pacemaker group than in control patients. The results showed an actuarial 1 year rate of recurrent syncope of 18% for pacemaker patients and 60% for controls. The results of the pacing arm of the VASIS trial[135] were similar to those of the North American Study but with much longer follow-up in less severely affected (and thus perhaps more typical) patients: 5% of patients in the pacemaker arm experienced recurrence of syncope compared with 61% in the no-pacemaker arm during a mean follow-up of 3·7 years ($P=0{\cdot}0006$). However, the studies have weaknesses[304], and further follow-up studies addressing many of these limitations (particularly the potential placebo effect of a pacemaker implant) 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).

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% to 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[71,81,91,93,305–309]. For the most part, dual-chamber cardiac pacing is preferred (level B)[306–308], 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[310,311]. 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[312]. 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, defecating, 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 lifestyle 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 [defecation 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 defecation syncope, avoidance of excessive fluid intake (especially alcohol) just prior to bed-time 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 on deciding to implant a pacemaker implant. However, further study is needed to determine whether this is the case.

Recommendations

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

Patients who have syncope in a 'high risk' setting (e.g. commercial vehicle driver, machine operator, pilot, commercial painter, competitive athlete) merit specific consideration for treatment. There is no information available regarding the efficacy of treatment in this type of patient, and whether it differs from other patients with neurally-mediated faints.

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

Class I:

- *Explanation of the risk, and reassurance about the prognosis in vasovagal syncope.*
- *Avoidance of trigger evens as much as possible and reducing the 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.*
- *Cardiac pacing in patients with cardioinhibitory vasovagal syncope with a frequency >5 attacks per year or severe physical injury or accident and age >40.*
- *Tilt training in patients with vasovagal syncope.*

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[313]. The classification and 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 the 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[314]. 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 so that it is once again within the auto regulatory zone can make a substantial functional difference[315]. 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 the daytime, straining during micturition and defecation, 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:

1. Chronic expansion of intravascular volume by encouraging a higher than normal salt intake and fluid intake of 2–2·5 litres per day[313,315]. Additional options include use of fludrocortisone in low dose (0·1 to 0·2 mg per day), and raising the head of the bed on blocks to permit gravitational exposure during sleep[315–318]. By way of a cautionary note, it is desirable to avoid supine/nocturnal hypertension as much as possible (level B).

2. Reduce vascular volume into which gravitation-induced pooling occurs by use of abdominal binders and/or waist height support stockings or garments[313,319].
3. Make use of portable chairs[320].
4. Small frequent meals with reduced carbohydrate content[313].
5. Introduce physical counter manoeuvres such as leg crossing and squatting[321,322].
6. Judicious exercise of leg and abdominal muscles, especially swimming[313].

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[313]. The use of salt retaining steroids (i.e. principally fludrocortisone) is usually considered first[313,315,316]. 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 its rapidly expanding and generally positive experience (level B)[319–326]. 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 post-prandial hypotension and erythropoietin in those with anaemia[313]. 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 treatment value.

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[327].

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[328–333] (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 the risk of developing atrial fibrillation and systemic embolism (Class I, level A)[331,332]. 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[329–332] (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 to 61%[334,335]) occurs due to the often long delay before these pacemakers begin to 'fire'. In addition these subsidiary pacemaker sites typically have relatively slow rates (25 to 40 beats . min^{-1}); 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 isoproterenol) 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)[336–338]. 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 an 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 the 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 the heart rate is not particularly high[14,339]. 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 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).

In regard to implantable devices for symptomatic ventricular tacharrhythmias, several prospective treatment trials provide evidence favouring ICD efficacy in terms of mortality risk compared to 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[197–203]; their results are discussed in Part 2, under Electrophysiological test. There are some situations, which are consistent with those reports, in which ICD therapy has been suggested to be useful in interrupting syncopal ventricular tachyarrhythmias and perhaps in increasing survival (Table 3.2).

Table 3.1 Drugs that can prolong the QT interval and cause torsades de pointes (modified from[340])

Antiarrhythmic agent	Psychoactive Agents *Continued*
Class I	Pericycline*
Ajmaline*	Pimozide
Disopyramide*	Prochlorperazine*
Quinidine*	Sertindole*
Procainamide*	Sultopride*
Propafenone*	Thioridazine*
Class III	Timiperone
Amiodarone*	Trifluoperazine*
Azimilide*	Zimeldine
Dofetilide*	Antimicrobial
Ibutilide*	Amantadine*
N-acetylprocainamide (NAPA)*	Clarythromycin*
Sematilide*	Chloroquine*
Sotalol*	Cotrimoxazole*
Vasodilators/Antianginal Agents	Erythromycin*
Bepridil*	Fluconazole
Lipoflazine*	Grepafloxacin*
Prenylamine*	Halofantrine*
Psychoactive Agents	Ketoconazole*
Amitryptiline*	Pentamidine*
Clomipramine	Quinine*
Cloral hydrate*	Spiramycine*
Chlorpromazine*	Sparfloxacine
Citalopram*	Non-sedating antihistamines
Desipramine*	Astemizole*
Doxepin*	Diphenhydramine*
Droperidol*	Ebastine
Fluphenazine	Hydroxyzine
Haloperidol*	Terfenadine*
Imipramine*	Others
Lithium*	Cisapride*
Maprotiline	Probucol*
Mesoridazine	Terodiline*
Nortryptiline	Vasopressin

*Torsades de pointes reported.
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.

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:
  –previous myocardial infarction and 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)
  –unexplained syncope in patients with 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)

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[341].

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[342], device re-programming to eliminate the problem is usually feasible although replacement is occasionally needed (e.g. replacing 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 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[343]. 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[60]. 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 pulmonic 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 to ameliorate the underlying problem adequately. 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[344] or acquired basis[345], 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 of 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 disturbances are responsible for confusional states or irregular

behaviour. 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. It is not known whether or not consciousness can be lost through hyperventilation. The basis for the loss of consciousness is not certain. Cerebral vasoconstriction caused by the hypocapnia and alkalosis, with consequent diminished cerebral perfusion, has been commonly accepted as the cause of the faint[346]. 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 anxiety episodes and/or 'panic' attacks warrants its being considered in the differential diagnosis of true syncope. The patient with recurrent faints associated with hyperventilation may have an important psychiatric component to their condition, which would warrant psychiatric consultation (see Part 2).

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 3, Part 2
- 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 supine position and patients with frequent recurrent episodes;
  — patients with minimal or mild heart disease when there is high suspicion for 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 Part 1, Table 1)
- Stroke or focal neurologic disorders
- Cardioinhibitory neurally-mediated syncope when a pacemaker implantation is planned

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, the baseline ECG can be permanently or transiently, normal. These entities have already been discussed. A summary of recommendations is shown in the 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.

Syncope in the older adult

Background

The incidence of syncope in older adults is at least 6% per year, with a 10% prevalence and a 30% 2-year recurrence rate[18]. These data are probably underestimates because of the exclusion of syncopal episodes which present as falls. Age-associated physiological changes in heart rate, blood pressure,[347–354], cerebral blood flow[345], baroreflex sensitivity[346] and intravascular volume regulation[355–358], combined with co-morbid conditions[5,11] and concurrent medications, account for the high incidence of syncope in the elderly.

Once serious underlying structural heart disease and arrhythmias have been excluded, the elderly experience loss of confidence[359], and fear the impact on their ability to live alone as well as fracture risk[350–361]. The latter is particularly important given the enormous health care and cost burden of fractures in old age[362].

The commonest causes of syncope in older adults are orthostatic hypotension, carotid sinus hyper-

sensitivity, neurally-mediated syncope and cardiac arrhythmias[363–365]. The prevalence of orthostatic hypotension in older adults varies from 6% in community dwelling elderly[366], to 33% in elderly hospital inpatients[367]. Orthostatic hypotension is an attributable cause of syncope in 20% to 30% of older patients[363,364]. In symptomatic patients up to 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 multisystemic atrophy. Supine systolic hypertension is often present in older patients with orthostatic hypotension[368–372]. Hypotension may increase the risk of cerebral ischaemia from sudden declines in blood pressure[373,374], but it also complicates treatment, given that most agents used for treatment of orthostatic hypotension will exacerbate supine hypotension[371,375].

Carotid sinus hypersensitivity is an age-related diagnosis, rare before age 40; the prevalence increases with advancing years and with cardiovascular, cerebrovascular and neurodegenerative co-morbidity[76,77,83,376]. Cardioinhibitory carotid sinus syndrome has been considered in recent reports to be an attributable cause of symptoms in up to 20%; further study is ongoing to better assess the true frequency, but it is fair to point out that it is probably more common than previously thought. Carotid sinus syndrome of predominantly vasodepressor form is probably equally prevalent, but its potential role in causing syncope in this population is much less certain[363,364,377–379].

Up to 15% of syncope is neurally mediated[363,364]. In over half, episodes are related to prescription of cardiovascular medications[363–365]. The pattern of blood pressure and heart rate responses during testing is similar to that described in younger patients (see Part 2) although patterns reflecting autonomic failure are more common in drug-related episodes[124].

Up to 20% of syncope in older patients is due to cardiac arrhythmias[363–365] (see Part 2).

Diagnostic evaluation

Aspects of history taking in older adults may vary in emphasis and clinical details from younger adults[380]. This is explained in some by amnesia for loss of consciousness[377]. Gait and balance instability and slow protective reflexes are present in 20% to 50% of community dwelling elderly[381–383]. 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%[363,377,381,380–385]. Up to one-third of events will present as falls[361,363].

Cognitive impairment is present in 5% of 65-year-olds and 20% of 80-year-olds. Cognitive status will influence the accuracy of recall of events. The history should include details of social circumstances, injurious events, impact of events on confidence and the ability to carry out activities of daily living independently.

The time when events occur can be also be helpful for diagnosis. Events due to orthostatic hypotension usually occur in the morning[372]. The history should include any association with meals (post-prandial)[372,386], ingestion of medications, nocturnal micturition[378], 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 co-morbid 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.

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[387] is a 20 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, 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%[363,364]. 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].

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[388].

Twenty-four hour ambulatory blood pressure recordings may be helpful if culprit medication or post-prandial hypotension is suspected as a cause of symptoms[372]. The methodology is a limiting factor, however, and obtaining these recordings may interfere with the autonomic changes that the physician is trying to record. In older patients, orthostatic hypotension diurnal patterns of blood pressure are the mirror image of normal blood pressure behaviour i.e. highest at night and lowest in the mornings and possibly after meals. Knowledge of diurnal blood pressure behaviour can guide treatments and modification of culprit medications.

Over one-third will have more than one possible attributable cause[83,363,364]. If symptoms continue or more than one diagnosis is suspected, further evaluation is necessary. There is no evidence to support the use of head-up tilt studies as part of the initial evaluation, although this is common practice in many facilities. Otherwise, the same criteria for evaluation of younger adults apply.

Evaluation of the frail elderly

Age per se is not a contraindication to assessment and intervention. However, in frailer patients, rigour 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[373,374]. If patients have difficulty standing unaided, the head-up tilt can be used to assess orthostatic blood pressure changes[49].

Multiple risk factors are more common in the frail elderly and the boundaries between falls and syncope are poorly delineated. Patients have a median of five risk factors for syncope or falls[373,374]. 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[383,384], 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 attendance are deemed inappropriate it may be necessary to treat 'blind' using limited clinical data i.e. by altering possible culprit medication, prescribing antiarrhythmic agents and/or cardiac pacing. Thus, in the frail elderly, physicians should make clinical judgments, after a comprehensive examination about the benefits to the individual of a syncope evaluation.

Recommendations

Class I:

- *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[389]. As many as 15% 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[390]. Neurally-mediated (reflex) syncope is by far the most frequent (61–71%), followed by cerebrovascular and psychogenic syncope (11–19%) and cardiac syncope (6%)[389,391,392].

Differential diagnosis

Careful personal and family history and physical examination is most important in distinguishing the benign neurally-mediated syncopes from other causes. Most children with neurally-mediated syncope have a first-degree relative who faints, which may be used in differential diagnosis[393]. In young patients, syncope may, however, also be an initial manifestation of rare but life-threatening conditions like the long-QT syndrome[394], Kearns–Sayre syndrome (external ophthalmoplegia and progressive heart block), Brugada syndrome[194], atrial fibrillation in patients with the Wolff–Parkinson–White syndrome[395], catecholaminergic polymorphic ventricular tachycardia[396], right ventricular dysplasia[397], arrhythmias after repair of congenital heart disease[398], hypertrophic cardiomyopathy, anomalous coronary artery, pulmonary artery hypertension or myocarditis. A cardiac aetiology should be considered in the presence of congenital, structural or functional heart disease and whenever syncope occurs with exertion or does not fit into the typical picture of neurally-mediated mechanism. An appropriate and extensive diagnostic work-up should then be started.

Diagnostic work-up

In the case of a history typical of neurally-mediated syncope, the absence of abnormalities on physical examination and ECG are usually sufficient to make a diagnosis and stop investigations. Tilt testing can probably be deferred and performed after a second occurrence. Unfortunately, head-up tilt tests seem 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[17,399,400]. 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 teenagers than in adults; in one study[401] 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[402].

Diagnostic work-up for other than neurally-mediated syncopes is case specific. Twenty-four hour Holter monitoring or loop-recording event monitoring should be used in patients with a history of palpitations associated with syncope. Cardiology consultation including

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%

echocardiography should be obtained in cases of heart murmur. Electrophysiological study has a minor role in paediatric patients. Electroencephalography is indicated in patients with prolonged loss of consciousness, seizure activity and a postictal phase of lethargy and confusion.

Therapy

Successful treatment of neurally-mediated syncope in childhood includes behaviour modification[400], salt and increased fluids[400,402], and pharmacological agents. Behaviour modification alone may be, however, as effective as pharmacological therapy and should be tried first in the majority of cases[400]. Drinking enough salty or sweet liquid without caffeine, ruling out salt avoidance and performing 'anti-gravity manoeuvres' at the earliest recognition of pre-syncope[322,403] 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[399,402,404], alpha-fludrocortisone[399,402] and alpha-agonists[405] have been supposed be efficacious in the paediatric age group (level B). Even in the instance of cardioinhibitory syncope with an exaggerated asystolic response, a pacemaker should be avoided whenever possible; as an alternative, effective management with pharmacological therapy without the need for pacemaker implantation has been shown[406]. Breath-holding spells generally do not require specific therapy unless connected with longer asystole associated with potential cerebral injury[22,392].

Driving and syncope

General comments

First it should be emphasized 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 of 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[407]. The most common causes of road accidents, involving syncope at wheel, are listed in Table 4.2[408].

In 1995 the Board of the European Society of Cardiology set up a task force on driving and heart disease. In the report, driving and syncope, especially neurally mediated syncope is discussed[408]. In an 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 discussed briefly[409]. The following recommendations on driving and syncope are put forward and are based on the two reports mentioned above (Table 4.3). The level of evidence in these two reports is level C with a few exceptions.

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 1 comprises drivers of motorcycles, cars and other small vehicles with and without a trailer. Group 2 includes drivers of vehicles over 3·5 metric tonnes (3·500 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 judgment in addition to some individual technical measurements. 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.

Comment

This Task force has the benefit of further publications that are relevant. Repeat tilt testing to assess any therapy probably has no predictive value. There is no evidence that allowing 3 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.

Glossary of uncertain terms

The literature on syncope and associated conditions can be very confusing because of a lack of consistency. For some terms an originally clear meaning has become obscured over time, because the term was later used in a different context or with 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.

Convulsive syncope

Involuntary jerking movements of the limbs can occur in syncope from any cause, meaning that a distinction between syncope with and syncope without movements carries no information regarding the nature of the

Table 4.3 Recommendations for driving rules in patients suffering from syncope (adopted from a task force report of the European Society of Cardiology on driving and heart disease)

Diagnosis	Group 1 Disqualifying criteria	Group 2 Disqualifying criteria
Cardiac arrhythmias	Any disturbance of cardiac rhythm which is likely to cause syncope	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.*
Pacemaker implant Successful catheter ablation	Within one week	Any persistent symptoms. (Re-) licensing may be permitted after at least 6 weeks has elapsed, and provided that there is no disqualifying condition.
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	Permanent
Neurally-mediated reflex syncope		
Vasovagal syncope		
Single episodes, mild symptoms	No restrictions	Specialist evaluation including neurological review
Severe symptoms	Until symptoms controlled	Until symptoms controlled
Carotid sinus syndrome		
First episode, mild symptoms	No restrictions	No restrictions
Severe symptoms	Until symptoms controlled	Until symptoms controlled. (Re-) licensing after 3 months and possibly negative tilt-test; careful follow-up mandatory
Situational forms	No restriction	No restrictions
Syncope of uncertain cause	In case of severe syncope until cause identified especially in patients with heart disease or at least 3 months without symptoms before (re-) licensing	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.

*See Guidelines for Cardiac Exercise Testing, Eur Heart J 1993; 969–98.

syncope. Movements are obviously important in the distinction between epilepsy and syncope. Myoclonic jerks are very often interpreted as epileptic by physicians and eyewitnesses alike, but not all such movement is epilepsy. The description of such movements should be neutral, so as to prevent an immediate connotation with epilepsy. As 'convulsions' are often used by neurologists to indicate either the movements in an epileptic fit ('seizure') or sometimes the seizures themselves, this term is not neutral in this respect. 'Convulsive syncope' carries the risk of inadvertently associating the movements with epilepsy. Terms than can be used to describe movements irrespective of their nature are 'jerking movements' or 'myoclonic jerks'.

- *The panel advises not to use 'convulsive' syncope, because it carries the risk of increasing confusion between syncope and 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 an 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 suggest reserving 'dysautonomia' for use in the Riley–Day syndrome; 'dysautonomic' may be used to indicate 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.*

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 near to syncope, although they are only indirectly linked to the loss of consciousness.

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

Neurally-mediated syncope
This is a synonym for 'reflex syncope' that emphasizes the role of the nervous system. It is as widespread as 'reflex syncope', and has no immediate disadvantages except for being longer.

- *The panel recognizes 'neurally-mediated syncope' as a synonym for 'reflex syncope'. In the future, one term may be preferred over the other.*

Neurocardiogenic syncope
The term is in use as an alternative for 'reflex syncope', or sometimes 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. As an alternative to 'reflex syncope' the term is preferred for similar reasons, and because it indicates that a triggering event is involved. '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. Even in that sense, the wording is unfortunate, as 'cardiogenic reflex syncope' would have conveyed the intended content with more clarity.

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

Vasodepressor syncope
The term is in use as an alternative for 'vasovagal' syncope. As an alternative for 'vasovagal' the 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 advocates conserving 'vasodepressor syncope' strictly for a type of reflex syncope in which the vasodepressor reflex is documented to occur in the absence of reflex bradycardia.*

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 is unambiguous. 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 to restrict the use of 'orthostatic intolerance' to summarize a patient's complaints.*

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Appendix 1

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Appendix 2

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