Journal of Arrhythmia 33 (2017) 545–552

Contents lists available at ScienceDirect

Journal of Arrhythmia

journal homepage: www.elsevier.com/locate/joa

Review

Reflex syncope: Diagnosis and treatment

Richard Sutton *

National Heart & Lung Institute, Imperial College, London, UK

ARTICLE INFO

Article history:
Received 9 February 2017
Accepted 27 March 2017
Available online 17 May 2017

Keywords:
Cardiac pacing
Catheter ablation
Diagnosis
Drugs
Management
Reflex syncope

ABSTRACT

For the diagnosis of reflex syncope, diligent history-building with the patient and a witness is required. In the Emergency Department (ED), the assessment of syncope is a challenge which may be addressed by an ED Observation Unit or by a referral to a Syncope Unit. Hospital admission is necessary for those with life-threatening cardiac conditions although risk stratification remains an unsolved problem. Other patients may be investigated with less urgency by carotid sinus massage (> 40 years), tilt testing, and electrocardiogram loop recorder insertion resulting in a clear cause for syncope. Management includes, in general terms, patient education, avoidance of circumstances in which syncope is likely, increase in fluid and salt consumption, and physical counter-pressure maneuvers. In older patients, those that will benefit from cardiac pacing are now well defined. In all patients, the benefit of drug therapy is often disappointing and there remains no ideal drug. A role for catheter ablation may emerge for the highly symptomatic reflex syncope patient.

Contents

1. Introduction

Much has been written on the diagnosis and treatment of reflex syncope. This review will attempt to offer emphasis on new aspects and approaches. Syncope is a common symptom that affects approximately 40% of humans during a lifetime [1]. Many episodes are unreported or are seen later by family physicians who, in the majority of cases, appropriately offer only reassurance [2]. More concerning episodes arrive in the Emergency Department (ED) accounting for about 1% of the workload [3]. In many countries attendance at the ED is followed by hospital admission as an inpatient for a costly attempt at diagnosis of the cause of syncope which often fails to yield the diagnosis sought [4]. In this unsatisfactory state of affairs, there is subsequent recurrence of syncope and mortality that is potentially avoidable [5].

* Correspondence address: Department of Cardiology, Hammersmith Hospital, Ducane Road, London W12 0NN, United Kingdom.
E-mail address: r.sutton@imperial.ac.uk

http://dx.doi.org/10.1016/j.joa.2017.03.007

The justification for the study of syncope is its common occurrence, frequent misdiagnosis, and mismanagement.

2. Methods

A PubMed search was conducted using the terms 'Syncope', 'Reflex Syncope', 'Diagnosis of Reflex Syncope', and 'Treatment of Reflex Syncope'. The selected articles from this search plus my own database act as the basis for this review.

3. Diagnosis of syncope

The diagnosis of syncope is clinical in the first instance which is demanding of the physician to address in a thorough, time-consuming, and detailed fashion. Without such an approach, there can be no clinically valuable result. This is not modern medicine, as is generally seen, but old-fashioned 'slow' medicine. As well as the details of all events experienced by the patient from beginning to end, a careful assessment of medication history including diet with special attention to fluid and salt consumption, activity, patient's background, and past medical history and family history are required [6]. Leading questions must be avoided, and when something does not fit into a preconceived pattern, it should not be ignored. When attacks are multiple, it may help to ask a family member or friend to record an attack on a cell phone. An appreciation of the circulatory physiology underlying the symptoms is essential to their full understanding. In the case of syncope, much anxiety is embodied in the patient and the family because of the drama of the event. It is necessary for the physician to understand this and to keep it in mind throughout the analysis of the symptom. An approach of this nature will gain the confidence of the patient, lead to more important details being revealed, and the enhancement of the doctor-patient relationship which is very essential during the possible tribulations of the treatment phase [6,7].

3.1. Transient loss of consciousness

Transient loss of consciousness (TLoC) will be reported by an observer or by the patient. It is necessary to determine the cause of the TLoC. There are three categories that are pertinent. First, concussion causes TLoC, but in such cases, trauma is usually evident before the TLoC, and the loss of conscious may be of a longer duration than that of a typical syncope which is 1–2 min. The second group of TLoC presentations is composed of syncope and epileptic seizures. An initial consideration is that syncope presenting in the ED is approximately 10 times more common than is epileptic seizure. The differential diagnosis between syncope and epilepsy has recently been reviewed by Sheldon [8]. Separation is of great importance as substantial numbers of patients have been shown to be attending epilepsy clinics where the diagnosis is reflex syncope [9]. Both reflex syncope and epilepsy carry risk to the patient in the short- and long-term, emphasizing the importance of correct diagnosis. The third category is syncope mimics which are mainly psychogenic pseudosyncope (PPS). These two latter categories will receive more attention and in doing so, a definition of syncope is helpful. This definition is now accepted in Europe [3] and in North America [10].

3.2. Syncope definition

Syncope is a syndrome in which loss of consciousness is of relatively sudden onset, temporary (usually < 1–2 min), self-terminating, and of usually rapid recovery. It is due to inadequate cerebral perfusion most often caused by a fall in systemic arterial pressure.

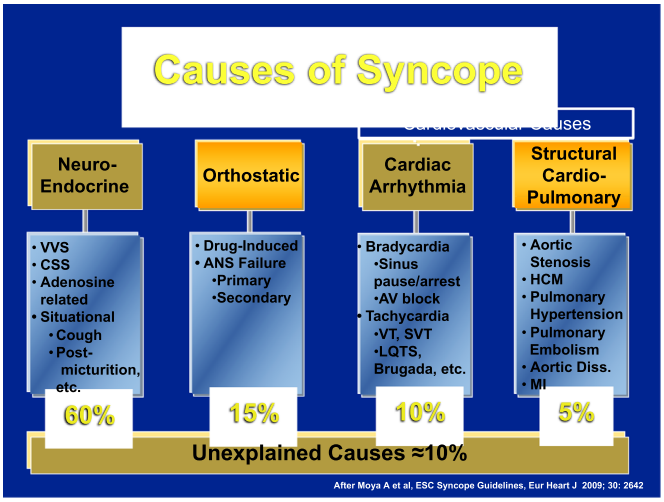

Fig. 1. Causes of syncope. Adapted from Moya et al. [3]. Abbreviations: ANS, autonomic nervous system; AV, atrioventricular; CSS, carotid sinus syndrome; Diss., dissection; HCM, hypertrophic cardiomyopathy; LQTS, long QT syndrome; MI, myocardial infarction; SVT, supraventricular tachycardia; VT, ventricular tachycardia; VVS, vasovagal syncope.

3.3. Causes of syncope

The causes of syncope are many and these are laid out in Fig. 1.

Physicians attending patients with syncope are required to know these causes and consider them. The Figure has been modified from that in the European Society of Cardiology (ESC) Guidelines to include adenosine-related syncope, but since this is not considered to be a reflex syncope, it is not covered in this article. Reflex syncope includes vasovagal syncope (VVS), situational syncope, and carotid sinus syndrome (CSS).

Having first determined from the patient's history and a witness account that the episode was TLoC and subsequently determined that it was syncope, with further probing by history taking, better termed history-building, the cause of syncope can be determined in up to 90% of cases. The history from a witness is as important as the history from the patient because the patient can tell us nothing about the period of loss of consciousness. A witness may not necessarily attend the hospital with the patient but may often be reached by cell phone. This must be part of the history-building. History-building is an old technique of bringing the patient into a face-to-face discussion of what happened with interest, empathy, and enthusiasm shown by the physician in contrast to today's norm of a physician, invisible to the patient behind a computer, bawling out questions with great rapidity, and barely listening to the answers. The slow and empathetic approach not only builds the history but also builds the doctor-patient relationship [7,11]. The two aims of history-building are (1) to identify the specific cause and mechanism of the event in order to apply effective treatment, and (2) to assess the prognostic risk including death, severe adverse events, and syncope recurrence.

For syncope, interrogation must begin with how the day started, for example, was the patient tired on arising from bed? The role of triggers must be probed. Details of the prodrome must be collected. The unconscious period will be reported by the witness and the patient will explain how the recovery and the remainder of the day were. This is the required level of detail for each and every attack [6,7,11].

Syncope has a bimodal distribution through life with peaks in teenage years and when old, rising progressively beyond 40 years

Table 1
Predisposing factors for syncope. Adapted from Sutton et al. [6].

Volume depletion (blood loss, dehydration, diarrhea/vomiting, sweating);
High ambient temperature;
Confined spaces;
Crowding;
Emotional circumstances;
Pain;
Menstrual period;
Hypocapnia;
Hypoxia;
Fever;
Rapid weight loss;
Alcohol intake (usually small quantities);
Insufficient food, Starvation, Anorexia nervosa;
Sleep deprivation, Tiredness;
Prolonged bed rest;
Prolonged weightlessness;
Boredom;
After strenuous exercise;
During exposure to high G-forces;
Medication such as beta-blockers, vasodilators, and diuretics

Table 2
Triggers for syncope. Adapted from Sutton et al. [6].

Typical reflex syncope
Prolonged standing;
Pain/invasive procedures;
Emotion: sight of blood, injury to oneself or to others, stress;
Post-exercise;
Situational syncope
Gastro-intestinal (GI): swallowing, colic, defecation, GI tract instrumentation
Urogenital (UG): micturition, vaginal examination, prostate examination/massage, UG tract instrumentation;
Eyeball pressure;
Respiratory: Cough, sneeze, laugh, wind-instrument paying, singing, weight-lifting, mess trick, stretching

[1]. Young people will more often have a typical trigger, a prodrome, no family history of sudden death, and a normal examination and ECG [6,7,11]. Older people may have known heart disease, an abnormal examination and/or ECG, and less often a trigger and a prodrome. Amnesia for the event increases with age [12]. This is important because the older patient may present with an unexplained fall.

Tables 1 and 2 show a list of predisposing factors and triggers which will prompt appropriate questions. The list is inevitably incomplete because of the diversity of possible presentations but offer areas of exploration with every patient.

The clinical history is the first part of the ESC Guideline recommendation for the initial evaluation [3]. After the history, a routine physical examination should be performed, paying special attention to the presence of left ventricular hypertrophy, cardiac murmurs, and neurological deficits. These do not require high-level acumen in the physical examination. Blood pressure recordings are required while lying, standing, and standing after 3 min to detect abnormalities or notably orthostatic hypotension. Abnormalities on the 12-lead ECG such as left ventricular hypertrophy and old or fresh myocardial infarction can usually be readily seen. More subtle abnormalities such as prolonged QT interval and Brugada syndrome pattern may require cardiological help. Today, almost all ECG machines have an electronic reporting system. These are very accurate in terms of duration of ECG intervals and highly dependable at separating normality from abnormality. Thus, they can be very helpful to non-cardiologists at an early stage of assessment, for example, in the ED. They should not be expected to make diagnoses such as Brugada syndrome.

Table 3
Indications for hospital admissions. Adapted from the European Society of Cardiology Guidelines 2009 [3].

FOR DIAGNOSIS
Suspected or known important heart disease
ECG suggesting arrhythmic syncope
Syncope during exercise
Syncope causing severe injury
Family history of sudden unexpected death at <40 years
Syncope when supine
FOR TREATMENT
Life-threatening arrhythmia
Syncope related to structural cardiopulmonary disease
CIED implantation required
OTHER REASONS
Sudden palpitation before syncope
High suspicion of cardiac syncope
Recurrent episodes
Lack of available home-care

Abbreviations: CIED, cardiac implantable electronic device; ECG, electrocardiogram.

When the initial assessment is completed by an experienced physician but not a syncope expert, approximately 60% of patients may have their cause of syncope identified [13]. The age of the patient is influential in this context as 68% of young patients are correctly labelled, in contrast only 54% of older patients are diagnosed [13]. The history may be assisted by use of a questionnaire although this is more appropriate in an outpatient setting than in the ED. This could be termed Phase 1 of the history-building process. In the ED, a computer driven program [14] may be a way of facilitating Phase 2 in tandem with the emergency physician's assessment of the patient. This step will allow patients to be divided into those with a known benign cause who can be discharged with a follow-up appointment in a syncope clinic or with a syncope specialist. If the cause of syncope is determined to be potentially dangerous, the patient will require hospital admission for observation or treatment (ideally 20% of all). The remaining patients without a clinical diagnosis at this stage (intermediate group) require risk stratification to decide on management [15]. This is a controversial area as no fool-proof system currently exists. The Canadian Cardiovascular Society's attempt at this is generally considered the best yet available [16].

For patients presenting to the ED without a firm diagnosis emanating from the initial evaluation, two approaches have been advocated. The first is temporary admission to an observation unit in or close to the ED where patients can be monitored and assessed for up to 24 h [17]. The second is early referral to a Syncope Unit which has full capability for investigation and diagnosis [18]. The former is efficient and expensive. Although first published in 2004 [17], data obtained from the ED observation unit has not been widely accepted and only recently offered additional favorable data [19]. The second, the syncope clinic, has had more acceptance and is not very expensive, but even in Europe where acceptance is currently the greatest, such units are by no means ubiquitous.

Table 3 provides guidance on which patients require hospital admission with the remainder being managed more conservatively [3]. If the diagnosis remains elusive, the ideal approach is for a syncope specialist to see the patient, with a rate of diagnosis of 90% [13]. This is Phase 3, but it is unrealistic to think that a syncope specialist is available in every ED 24 h per day as there are too few of them. When an attempt at diagnosis is made, the rate of diagnoses improves [20].

A syncope specialist is someone who has a broader knowledge beyond that of syncope. Considering that the patient may present with TLoC, the specialist must possess extensive experience with TLoC patients by continuous learning from clinical practice,

reflection and self-criticism, reading to maintain a deep knowledge in the specialty, listening to other experts, and consistently exhibiting superior performance in the management of patients with TLoC [6,7,11]. A trainee can learn to be a syncope specialist by learning from patients; gaining clinical experience; reading papers by experts; seeking a mentor, even by email; watching syncope specialists in action, when possible; leaning from Neurologists, Internists, Pediatricians, and Geriatricians as they see different patients and each has a different approach; and learning from ED specialists as their approach is completely different [6,7,11].

3.4. Diagnosis of syncope by investigations

When the diagnosis is impossible by means of the ESC-recommended initial evaluation [3], investigations must be entertained. These are mostly directed toward the intermediate-risk group. It is assumed that high-risk patients have been excluded. In the intermediate-risk group, the first consideration is carotid sinus massage in patients over the age of 40 years. It is advised that this is carried out in the tilt laboratory in both supine and upright positions with 10 s of massage on the right carotid artery in the neck followed by the left artery in both positions. It is further recommended to use the 'method of symptoms' as introduced originally by Brignole's group [21]. If the massage is positive, with reproduction of symptoms, in a patient presenting with syncope, a diagnosis of CSS is made. A positive finding with asystole of >3 s (cardioinhibition) and reproduction of syncope should be followed by treatment with dual chamber pacing. A positive finding with hypotension (vasodepression) and reproduction of syncope should be followed by a different treatment [22].

The second consideration is a tilt test as this is an inexpensive and helpful test. When reflex syncope is suspected, the tilt test is likely to confirm the diagnosis. However, this test has additional benefits as follows: (1) The patient will experience usual symptoms during the attack and be able to confirm that these are similar to what has previously happened. Thus, this will be a learning experience for the patient taking place in a clinical environment rather than the real world. (2) The patient will understand that the diagnosis of the previous episode(s) is clear to the treating team and confidence will be built. (3) Other conditions will, if pertinent, be revealed such as orthostatic hypotension, postural orthostatic tachycardia, and PPS. (4) The presence of tilt positivity with reproduction of symptoms in older patients points to a less favorable result of pacing therapy. In this area, tilt testing is a risk of recurrence stratification tool (please refer to Section 4.1) [22].

The third step is insertion of an ECG loop recorder (ILR) subcutaneously. These devices are battery powered and last 3 years providing very high quality ECG monitoring. Further, they can be accessed through the same wireless systems as are used for pacemaker and defibrillator follow-up. Thus, they offer very close follow-up and permit rapid action should a further syncope be recorded which demands intervention, such as pacing [3]. The tendency, driven by serial ESC reports [3,23,24] is to bring the ILR forward to an earlier point in the management of the intermediate-risk group. The above discussion also deliberately describes the SUP-2 (syncope unit project) recommendations of how to manage an older patient with likely reflex syncope [25,26]. This Italian syncope unit group of 10 centers has combined to formulate a policy as enumerated above and put it into practice. The results will be discussed later.

Other investigations are seldom needed. Exercise testing may be valuable if symptoms occur in relation to exercise (3). Echocardiography is indicated when there is any clinical suggestion of a cardiac abnormality. Coronary angiography is indicated on usual grounds. Electrophysiological studies (EPS) have little role in patients yet undiagnosed. However, they may prove useful in confirmation of an arrhythmia recorded by an ILR or other means. In bradyarrhythmias, documentation of sinoatrial disease and demonstration of His-Purkinje disease are the two areas of greatest potential. For ventricular tachycardia, an implantable cardioverter defibrillator may be indicated without the need for an EPS [3]. Both EPS and tilt are affected by their inability to offer a definitive diagnosis in many cases where they appear to be required. Tilt has been condemned as inaccurate by the United Kingdom body, National Institute of Clinical Excellence, but they failed to comprehend what tilt positivity really is, as argued by Brignole and Sutton [22]: a demonstration of a vasodepressor or hypotensive tendency.

Managing younger patients with reflex syncope in terms of diagnosis will not include carotid sinus massage but will likely adopt the second and third steps as described above. There is a considerable weight of evidence supporting the use of ILRs for precise diagnosis in both young and old patients [27–31]. The diagnostic yield is around 35% in the first year and may rise as high as 80% in 4 years [32]. In contrast, it is necessary to state clearly that there are many tests still frequently used across the world which have almost no value in diagnosis at all. These include electroencephalogram, brain scanning by computed tomography or magnetic resonance, carotid ultrasound, Holter monitoring, exercise testing except when symptoms are related to exercise, and coronary angiography [3].

Situational syncope is a subdivision of reflex syncope. Reflexes are involved, but each type of situational syncope has its own profile. These have recently been classified [6]. Some are very inclusive in this category placing such syncope as that which occurs after exercise, during blood donation, and during eating. This is not valuable in my view. The common situational syncopes are while coughing, at medical instrumentation, and during or after urination. These truly involve triggers and are very dynamic, natural autonomic events. There is usually a considerable overlap with vasovagal syncope. Each situational syncope must be investigated as usual by history-building in order draw a correct picture of the type of reflex involved. For example, cough syncope almost always involves vasodepression with little cardioinhibitory component [33]. Micturition syncope more often involves some cardioinhibition.

3.5. Cardiac disease and coincidence with reflex syncope

The common occurrence of VVS makes it extremely likely that patients with heart disease, both structural and arrhythmic may also suffer VVS raising an important challenge to the physician. Here is an area where it might be hoped that tilt testing will be a valuable discriminatory test. Unfortunately, this is not the case as tilt testing is revealing a hypotensive or vasodepressor tendency that is intrinsic and may or may not reveal the etiology of the patient's presenting episode [17]. Understanding this brings benefit in terms of risk stratification of recurrence during subsequent therapy but no benefits in terms of diagnosis of syncope cause in heart disease.

3.6. Psychogenic pseudosyncope

This condition is classified as a syncope mimic. PPS has been known for a long time and was probably the so-called swoon of 19th century novels. In medical terms, it was suspected but infrequently diagnosed until the advent of physiological monitoring during a maneuver likely to precipitate syncope in potentially susceptible subjects such as tilt testing. The condition was found in a few tilted patients with heart rate and arterial pressure

monitoring and clearly identified because there was no fall in heart rate and no fall in blood pressure at the time of apparent syncope [34,35]. Later, much more detailed studies including continuous electroencephalographic monitoring, showing little change in contrast to the typical and dramatic pattern of VVS, allowed a full description of the syndrome [36]. Collapses due to VVS and PPS have occurred during the same tilt test, raising a possibility that some of the events of the syncope are subconsciously learnt by the patient. In PPS, the patient appears to lose consciousness but has no color change and closed eyes. There is a modest tachycardia preceding and coinciding with the event [36]. The clinical presentation is typically with a great number of syncope episodes, some of which may present as rather active syncope, for example, an almost active fall [30]. The combination of a detailed history and a tilt test showing no blood pressure fall, a slight tachycardia, and a normal electroencephalogram makes the diagnosis of PPS.

Regarding the causes of syncope, in approximately 10% or more of patients, there is no diagnosis. Eventually, the diagnosis is likely to reveal itself and be benign in nature.

4. Management

The term management is more accurate than treatment which implies that there is effective treatment for reflex syncope. Currently, there are some methods of management, but regrettably, no widely agreed specific treatments. This, however, should not be surprising because in reflex syncope, we are trying to treat an intrinsic tendency that probably exists in all humans, manifesting itself in a mere 40% of the population [1]; this tendency that may evolve over decades to become what we normally call a disease [37,38]. Many treatments have been attempted aiming at different points in the assumed reflex arc, but there has been little success.

Management must begin with patient education (Table 4). It is important that the patient understands what an attack is and the difficulties that exist in managing the condition. The message that attacks are not mortal is essential information for the patient and family. In cases where there is warning, there are some effective ways of management. The first is to be aware of the potential for an attack, keeping in mind previous circumstances and feelings. Evasive action is then possible. For example, leaving the room, sitting down, and drinking cold water can all be helpful, but such measures are often taken too late to have any benefit. The second is use of counter-pressure maneuvers. These involve a form of isometric exercise which includes linking fingers and attempting to pull them apart without letting go, crossing the legs and squeezing them together, buttock tensing, and squatting. All these measures can be useful, but they must be employed as soon as warning signs are present. The literature supports these maneuvers [39,40] but they are likely to be ineffective in older people with less muscle power and bulk as was shown in an ISSUE-3 substudy (International study of syncope of unknown etiology) [41].

Table 4
Available therapy for reflex syncope.

Therapy	Proof of efficacy	Which patients?
Explanation	None	All
Counter-Pres.	Good	Warning required
Fluid increase	Little	All
Salt increase	Little	All except HBP
Beta-blockers	None	None
Adrenergic	Some	Frequent syncope not responding to GM
SSRIs	None	None
Fluid-retaining	Some	Frequent syncope not responding to GM
Ivabradine	None	Tachycardia pre-syncope
Tilt-training	Little	Any patient willing
Cardiac pacing	Some	Older patients with documented brady/asyst
Catheter ablation	Little	Very severely affected

Abbreviations/definitions: Adrenergic, midodrine and droxidopa; Any patient willing, any patient who is motivated to comply with the therapeutic protocol; Brady/asyst, intense bradycardia or asystole; Counter-pres. Counter pressure maneuvers; Fluid-retaining, fludrocortisone; GM, general measures (upper 4 in this Table); HBP, hypertension; SSRIs, selective serotonin reuptake inhibitors.

General useful advice may have some benefit such as drinking more water and increasing salt consumption. The aim is to increase blood volume. Three liters of water per day and at least 6 g of salt are the usual recommendations. There is little scientific evidence to support this. Caffeine is a diuretic and works, to an extent, to oppose the fluid and salt recommendations. Thus, it seems reasonable to reduce caffeine consumption but, again, there is no scientific evidence in its favor.

Beyond these measures, drugs are the other option, but they should be considered with reluctance. With drugs, treatment must be taken continuously because of the unpredictable nature of the attacks. Very frequent VVS occurs on six occasions per year [42], therefore, in such cases medication is taken on 359 days when it was not needed. Medications have side-effects which, if prominent, could easily outweigh any available benefit. Moreover, an important percentage of patients is female and of child bearing age, so drugs must have no teratogenic effects. Drugs considered in the past have been beta-blockers on which there have been numerous randomized controlled trials [43–47], but all except one showed no benefit. The trial showing a positive result in favor of the selected beta-blocker [43] was flawed as the trial lasted only 1 month, and repeat tilt testing was the main end-point. The ESC has strongly recommended [3] against repeat tilt testing to demonstrate the effect of therapy prompted by a study of midodrine by Moya and colleagues [48] and the VASIS trial of dual-chamber pacing versus no treatment in VVS [49], as in both trials, the protocol-determined repeat tilt testing gave misleading results.

Midodrine, an alpha-adrenergic drug, has some mildly encouraging trial data [50–52], but no trial was sufficiently powered. It is a drug frequently selected today. It has many clinical disadvantages which include its short half-life requiring administration at least 3 times daily, its complete lack of teratogenic data, and its tendency to cause urinary retention in older male subjects. Its problems of lack of availability and United States Food and Drug administration approval have largely been overcome. Fludrocortisone seems to be a logical therapy to increase blood volume. No trial has been convincing until the Prevention of syncope trial (POST-2). This trial was sufficiently large but gave only weakly positive results [53]. Nevertheless, it is also a drug frequently selected to treat patients today.

Ivabradine has some adherents, but, as yet, no trial has been undertaken. If a trial of this drug were to be mounted, it would have to address only those patients in whom a tachycardia can be demonstrated before VVS by tilt or on ILR. Ivabradine can attenuate this and in so doing might be preventative of syncope [54].

Other drugs have been tried and have failed. These include etilefrine and droxidopa, alpha adrenergic agonists, and selective serotonin reuptake inhibitors for which one small trial showed some benefit not supported by other work. All, except droxidopa, for which little data yet exists, are summarized in the 2009 ESC Guidelines [3].

Tilt training is among other techniques that have been reported and attempts to re-educate the autonomic nervous system by prolonged periods of standing [55]. The results available do not yet support its wide acceptance [3]. Another technique is intracardiac catheter ablation of ganglionic plexi on the epicardial surface of the heart [56–58]. A limited number of very symptomatic patients

have had their symptoms well controlled, but to date, there is no randomized controlled trial.

4.1. Treatment of vasovagal syncope by pacing

From the inception of tilt testing to diagnose VVS [59], attention has been focused on the possibility that pacing could provide control and relief because of the dramatic and severe associated symptoms of asystole in VVS. An early series report was encouraging [60], prompting randomized controlled trials. The first two to be published were the Vasovagal pacemaker study-1 (VPS-1) [61] and Vasovagal Syncope International study (VASIS) [49]. These trials of small sample size seemed promising, but their protocols were flawed because pacemaker therapy was compared with no therapy or atenolol [62], and the favorable results were quickly explained by a placebo effect on the operated patients. Further trials were warranted, and in VPS-2 [63] together with the syncope and pacemaker trial (SYNPACE) [64], pacemakers were implanted in all patients of whom approximately half in each trial were randomized to being switched to a sensing-only mode. Neither trial showed any benefit for active pacing.

The next phase in the study of the possible benefit of pacing was to turn attention to patient selection. This was done initially in the International study of syncope of unknown etiology (ISSUE-2) [29] by implantation of ILRs in all patients. Those whose spontaneous attacks were bradycardiac could be paced in this registry. Approximately half of those patients received pacing, and their outcomes were much better than those of patients who were not paced. These results prompted the ISSUE-3 trial [65] where a clear and significant benefit in terms of syncope recurrence was demonstrated for those paced in comparison with the other half of the group whose devices were in sensing-only mode. Recurrence of syncope in 2 years was 24% with pacing and 57% without pacing ($p < 0.039$). This was the first pacemaker trial to show unequivocal benefit for pacing in older reflex syncope (not CSS) patients.

A striking finding [66], when follow-up was extended and registry patients refusing randomization were included, was that a positive pre-implant tilt test indicated a high likelihood of syncope recurrence not significantly different from no pacing. On the other hand, a negative pre-implant tilt implied excellent symptom control with 5% recurrence in 21 months. The implications of this result were interpreted by Sutton and Brignole [22]. The subsequent study Syncope Unit Project-2 (SUP-2) [25,26] has strongly supported the initial conclusions, although the results of pacing those with a positive tilt pre-implant seem better than those in the ISSUE-3 trial [65].

Thus, it can now be stated that, in older patients with non-CSS reflex syncope with documented bradycardia in spontaneous attacks by ILR, a tilt test should be performed prior to implant to risk stratify the likelihood of syncope recurrence. Further, many of these patients are taking hypotensive medications that probably exacerbate their tendency to syncope recurrence implying that these drugs may have to be withdrawn or reduced in dosage. More studies are required in this area.

It must be emphasized that, while pacing is a valuable therapy, it is indicated for a very small percentage of those presenting recurrent syncope. Second, the results will be less effective for some patients. Third, the mode of assessing the need for and the delivery of pacing is still controversial. Most implanted devices rely on the onset of bradycardia to trigger pacing. It is well known that bradycardia follows hypotension in almost all VVS cases [67]. Therefore, this method leaves much to be desired and there may be better options; one method that is currently available detects reducing right ventricular volume (reflecting diminishing venous return) and increase in ventricular contractility (reflecting rise in circulating epinephrine) and is currently being evaluated in a randomized controlled trial (BIOPACE-Biotronik).

4.2. Treatment of carotid sinus syndrome

For patients with documented cardioinhibitory CSS, the treatment of choice is dual-chamber pacing [3,68]. Good results can be expected in terms of syncope recurrence. As CSS is not considered to be mortal, symptom control is the aim. However, it must now be recommended that prior to implantation the patient undergoes a tilt test. If positive, more syncope recurrence must be expected than if the test is negative [17,69,70]. The SUP-2 studies [25,26] give the most up-to-date and useful information about what can be expected in practice.

There was a hope in the early years of this millennium that carotid sinus hypersensitivity (CSH) (patients with positive carotid sinus massage but having no symptoms and no definite syncope) presenting with unexplained falls could be treated with pacing. It was anticipated that CSH was a precursor of CSS, but this has not yet been established. Unfortunately, after the first encouraging trial [71] subsequent trials with more patients and more sophisticated protocols were unable to confirm the early results [72,73]. Research in this area has now switched to inserting an ILR in patients with unexplained falls. In a pilot study, a high incidence of arrhythmias was found, many of which are likely to have been of reflex origin [74].

Treatment of vasodepressor CSS is similar to that of dominantly vasodepressor VVS including fluids, increase in salt consumption if the patient is not hypertensive, and drugs such as midodrine but with great care in male patients or fludrocortisone. In hypertensive patients, the first step is to reduce hypotensive medication [75]. As for VVS, the result of treatment tends to leave much to be desired. Support hose and abdominal binding might be useful in an uncontrolled case.

4.3. Treatment of situational syncope

Treatment of situational syncope depends totally on the presenting pathophysiology of the syncope. For example, the vasodepression of cough syncope may be the target for therapy, but in ideal circumstances the cough itself should be addressed. In micturition syncope, considerations are, for male patients, to urinate in the sitting position together, if necessary, with physical counterpressure maneuvers. Situational syncope is rarely dominantly cardioinhibitory, implying that pacing is seldom required. The principles of treatment, however, are the same as in VVS.

4.4. General considerations

Syncope as a symptom causes much anxiety in the patient and family. This prompts consultation particularly if the symptom presents in a cluster as is quite common in VVS. The fact that the symptom tends to resolve spontaneously over time should not be surprising. Sheldon's group has recently studied the phenomenon of ‘reversion to the mean’ in the context of syncope [76]. This aspect must be taken into account when making major management decisions.

Conflict of interest

RS is a consultant to Medtronic Inc., a member of the speakers' bureau of St Jude Medical Inc. (Abbott Inc.), a stockholder in the following companies: Boston Scientific Inc., Edwards Lifesciences Inc., Shire PLC, AstraZeneca PLC, and Roche SA.

References

[1] Ganzeboom KS, Mairuhu G, Reitsma JB, et al. Lifetime cumulative incidence of syncope in the general population: a study of 549 Dutch subjects aged 35–60 years. J Cardiovasc Electrophysiol 2006;17:1172–6.

[2] Olde Nordkamp LRA, van Dijk N, Ganzeboom KS, et al. Syncope prevalence in the ED compared to general practice and population: a strong selection process. Am J Emerg Med 2009;27:271–9.

[3] Moya A, Sutton R, Ammirati F, et al. Guidelines for the diagnosis and treatment of syncope (version 2009). Eur Heart J 2009;30:2631–71.

[4] Bartoletti A, Fabiani P, Adriani P, et al. Hospital admission of patients referred to the Emergency Department for syncope. A single-hospital prospective study based on the application of the European Society of Cardiology guidelines on syncope. Eur Heart J 2006;27:83–8.

[5] Del Rosso A, Ungar A, Maggi R, et al. Clinical predictors of cardiac syncope at initial evaluation in patients referred urgently to a general hospital. Heart 2008;94:1620–6.

[6] Sutton R, van Dijk N, Wieling W. Clinical history in management of suspected syncope: a powerful diagnostic tool. Cardiol J 2014;21:651–7.

[7] Wieling W, van Dijk N, de Lange FJ, et al. History taking as a diagnostic test in patients with syncope: developing expertise in syncope. Eur Heart J 2015;36:277–80.

[8] Sheldon R. Syncope diagnostic scores. Prog Cardiovasc Dis 2013;55:390–5.

[9] Zaidi A, Clough P, Cooper P, et al. Misdiagnosis of epilepsy: many seizure-like attacks have a cardiovascular cause. J Am Coll Cardiol 2000;36:181–4.

[10] Shen WK, Sheldon RS, Benditt DG, et al. ACC/AHA/HRS Guideline for the evaluation and management of syncope. Circulation 2017. http://dx.doi.org/10.1161/CIR0000000000000000499.

[11] Wieling W, Thijs RD, Linzer M, et al. Great expectations: what patients with unexplained syncope desire. J Intern Med 2015. http://dx.doi.org/10.1111/joim12450.

[12] O'Dwyer C, Bennett K, Langan Y, et al. Amnesia for loss of consciousness is common in vasovagal syncope. Europace 2011;13:1040–5.

[13] van Dijk N, Boer KR, Colman N, et al. High diagnostic yield and accuracy of history, physical examination and ECG in patients with transient loss of consciousness in FAST: the fainting assessment study. J Cardiovasc Electrophysiol 2008;19:48–55.

[14] Daccarett M, Jetter TL, Wasmund SL, et al. Syncope in the emergency department: comparison of standardized admission criteria with clinical practice. Europace 2011;13:1632–8.

[15] Sutton R, Brignole M, Benditt DG. Key challenges in the current management of syncope. Nat Rev Cardiol 2012;9:590–8.

[16] Sheldon RS, Morillo CA, Krahn AD, et al. Standardized approaches to the investigation of syncope: Canadian Cardiovascular Society position paper. Can J Cardiol 2011;27:246–53.

[17] Shen WK, Decker WW, Smars PA, et al. Syncope evaluation in the emergency department study (SEEDS). A multidisciplinary approach to syncope management. Circulation 2004;110:3636–45.

[18] Kenny RA, Brignole M, Dan G-A, et al. Syncope Unit: rationale and requirement – the European Heart Rhythm Association position statement endorsed by the Heart Rhythm Society. Europace 2015;17:1325–40.

[19] Sun BC, McCreath H, Liang LJ, et al. Randomized clinical trial of an emergency department observation syncope protocol versus routine inpatient admission. Ann Emerg Med 2014;64:167–75.

[20] Grossman SA, Fischer C, Kancharla A, et al. Can benign etiologies predict benign outcomes in high risk syncope patients? J Emerg Med 2011;40:592–7.

[21] Puggioni E, Guiducci V, Brignole M, et al. Results and complications of the carotid sinus massage performed according to the "Method of Symptoms". Am J Cardiol 2002;89:599–601.

[22] Sutton R, Brignole M. Twenty-eight years of research permit reinterpretation of tilt-testing: hypotensive susceptibility rather than diagnosis. Eur Heart J 2014;35:2211–2.

[23] Brignole M, Alboni P, Benditt D, et al. Task force on syncope, European Society of Cardiology. Guidelines on management (diagnosis and treatment) of syncope. Eur Heart J 2001;22:1256–306.

[24] Brignole M, Alboni P, Benditt DG, et al. Guidelines on management [diagnosis and treatment] of syncope – update 2004. Eur Heart J 2004;28:2054–72.

[25] Brignole M, Ammirati F, Arabia F, et al. Assessment of a standardized algorithm for cardiac pacing in older patients affected by severe unpredictable reflex syncopes. Eur Heart J 2015;36:1529–35.

[26] Brignole M, Arabia F, Ammirati F, et al. Standardized algorithm for cardiac pacing in older patients affected by severe unpredictable reflex syncope: 3-year insights from the Syncope Unit Project 2 (SUP 2) study. Europace 2015. http://dx.doi.org/10.1093/europace/euv343.

[27] Krahn A, Klein GJ, Yee R, et al. Randomized assessment of syncope trial. Conventional diagnostic testing versus a prolonged monitoring strategy. Circulation 2001;104:46–51.

[28] Farwell D, Freemantle N, Sulke N. The clinical impact of implantable loop recorders in patients with syncope. Eur Heart J 2006;27:351–6.

[29] Brignole M, Sutton R, Menozzi C, et al. Early application of an implantable loop recorder allows effective specific therapy in patients with recurrent suspected neurally mediated syncope. Eur Heart J 2006;27:1085–92.

[30] Edvardsson N, Frykman V, van Mechelen R, et al. Use of an implantable loop recorder to increase the diagnostic yield in unexplained syncope: results from the PICTURE registry. Europace 2011;13:262–9.

[31] Sulke N, Sugihara C, Hong P, et al. The benefit of a remotely monitored implantable loop recorder as a first line investigation in unexplained syncope: the EaSyAS II trial. Europace 2016;18:912–8.

[32] Furukawa T, Maggi R, Bertolone, et al. Additional diagnostic value of very prolonged observation by implantable loop recorder in patients with unexplained syncope. J Cardiovasc Electrophysiol 2012;23:67–71.

[33] Mereu R, Taraborelli P, Sau A, et al. Diagnostic role of head-up tilt test in patients with cough syncope. Europace 2016;18:1273–9.

[34] Grubb BP, Wolfe GG, Samoil D, et al. Syncope and seizures of psychogenic origin: identification with head-up tilt table testing. Clin Cardiol 1992;15:839–42.

[35] Petersen ME, Williams TR, Sutton R. Psychogenic syncope diagnosed by prolonged head-up tilt testing. QJM 1995;88:209–13.

[36] Tannemaat M, van Niekerk J, Reijntjes R, et al. The semiology of tilt-induced psychogenic pseudosyncope. Neurology 2013. http://dx.doi.org/10.1212/WNL.0b013e3182a1aa88.

[37] Stewart J, Medow M, Sutton R, et al. Mechanisms of vasovagal syncope in the young: reduced systemic vascular resistance versus reduced cardiac output. J Am Heart Assos 2017;6:e004417. http://dx.doi.org/10.1161/JAHA.116.004417.

[38] Alboni P, Brignole M, Degli Uberti CE. Is vasovagal syncope a disease? Europace 2007;9:83–7.

[39] Brignole M, Croci F, Menozzi C, et al. Isometric arm counter-pressure maneuvers to abort impending vasovagal syncope. J Am Coll Cardiol 2002;40:2053–9.

[40] van Dijk N, Quartieri F, Blanc J-J, et al. Effectiveness of physical counter-pressure maneuvers in preventing vasovagal syncope: the Physical Counterpressure Manoeuvres Trial (PC-Trial). J Am Coll Cardiol 2006;48:1652–7.

[41] Tomaino M, Romeo C, Vitale E, et al. Physical counter-pressure manoeuvres in preventing syncopal recurrence in patients older than 40 years with recurrent neurally mediated syncope: a controlled study from the Third International Study on Syncope of Uncertain Etiology (ISSUE-3). Europace 2014;16:1515–20.

[42] Rose MS, Koshman ML, Spreng S, et al. The relationship between Sheldon R (2000) The relationship between health-related quality of life and frequency of spells in patients with syncope. Clin Epidemiol 2000;53:1209–16.

[43] Mahanonda N, Bhuripanyo K, Kangkagate C, et al. Randomized, double-blind, placebo-controlled trial of oral atenolol in patients with unexplained syncope and positive upright tilt table test results. Am Heart J 1995;130:1250–3.

[44] Madrid AH, Ortega J, Rebollo JG, et al. Lack of efficacy of atenolol for the prevention of neurally mediated syncope in a highly symptomatic population: a prospective, double- blind, randomized and placebo-controlled study. J Am Coll Cardiol 2001;37:554–9.

[45] Flevari P, Livanis EG, Theodorakis GN, et al. Vasovagal syncope: a prospective, randomized, crossover evaluation of the effect of propranolol, nadolol and placebo on syncope recurrence and patients' well-being. J Am Coll Cardiol 2002;40:499–504.

[46] Sheldon R, Connolly S, Rose S, et al. Prevention of Syncope Trial (POST): a randomized, placebo-controlled study of metoprolol in the prevention of vasovagal syncope. Circulation 2006;113:1164–70.

[47] Brignole M, Menozzi C, Gianfranchi L, et al. A controlled trial of acute and long-term medical therapy in tilt-induced neurally mediated syncope. Am J Cardiol 1992;70:339–42.

[48] Moya A, Permanyer-Miralda G, Sagrista-Sauleda J, et al. Limitations of head-up tilt test for evaluating the efficacy of therapeutic interventions in patients with vasovagal syncope: results of a controlled study of etilefrine versus placebo. J Am Coll Cardiol 1995;25:65–9.

[49] Sutton R, Brignole M, Menozzi C, et al. Dual-chamber pacing in the treatment of neurally mediated tilt-positive cardioinhibitory syncope: pacemaker versus no therapy: a multicenter randomized study. The Vasovagal Syncope International Study (VASIS) Investigators. Circulation 2000;102:294–9.

[50] Ward CR, Gray JC, Gilroy JJ, et al. Midodrine: a role in the management of neurocardiogenic syncope. Heart 1998;79:45–9.

[51] Perez-Lugones A, Schweikert R, Pavia S, et al. Usefulness of midodrine in patients with severely symptomatic neurocardiogenic syncope: a randomized control study. J Cardiovasc Electrophysiol 2001;12:935–8.

[52] Kaufmann H, Saadia D, Voustianiouk A. Midodrine in neurally mediated syncope: a double-blind, randomized, crossover study. Ann Neurol 2002;52:342–5.

[53] Sheldon R, Raj SR, Rose S, et al. The second prevention of syncope trial (POST 2): a randomized, placebo-controlled study of fludrocortisone in the prevention of vasovagal syncope. J Am Coll Cardiol 2016;68:1–9.

[54] Sutton R, Salukhe TV, Franzen-McManus A-C, et al. Ivabradine in the treatment of sinus tachycardia mediated vasovagal syncope. Europace 2014;16:284–8.

[55] Reybrouck T, Heidbuchel H, Van De Werf F, et al. Long-term follow-up results of tilt training therapy in patients with recurrent neurocardiogenic syncope. Pacing Clin Electrophysiol 2002;25:1441–6.

[56] Pachon JC, Pachon EI, Pachon JC, et al. "Cardioneuroablation" – new treatment for neurocardiogenic syncope, functional AV block and sinus dysfunction using catheter RF ablation. Europace 2005;7:1–13.

[57] Pachon JC, Pachon MEI, Pacon MZC, et al. Catheter ablation of severe neurally mediated reflex (neurocardiogenic or vasovagal) syncope: cardioneuroablation long-term results. Europace 2011;13:1231–42.

[58] Yao Y, Shi R, Wong T, et al. Endocardial autonomic denervation of the left atrium to treat vasovagal syncope: an early experience in humans. Circ Arrhythm Electrophysiol 2012. http://dx.doi.org/10.1161/CIRCEP.111.966465.

[59] Kenny RA, Ingram A, Bayliss J, et al. Head-up tilt: a useful test for investigating unexplained syncope. Lancet 1986;1:1352–5.

[60] Petersen MEV, Chamberlain-Webber R, Fitzpatrick AP, et al. Permanent pacing for cardio-inhibitory malignant vasovagal syndrome. Heart 1994;71:274–81.
[61] Connolly SJ, Sheldon R, Roberts RS, et al. The North American Vasovagal Pacemaker Study (VPS). A randomized trial of permanent cardiac pacing for the prevention of vasovagal syncope. J Am Coll Cardiol 1999;33:16–20.
[62] Ammirati F, Colivicchi F, Santini M. Syncope diagnosis and treatment study investigators. Permanent cardiac pacing versus medical treatment for the prevention of recurrent vasovagal syncope: a multicenter, randomized, controlled trial. Circulation 2001;104:52–7.
[63] Connolly SJ, Sheldon R, Thorpe KE, et al. VPS II Investigators. Pacemaker therapy for prevention of syncope in patients with recurrent severe vasovagal syncope: second vasovagal pacemaker study (VPS II): a randomized trial. JAMA 2003;289:2224–9.
[64] Raviele A, Giada F, Menozzi C, et al. The vasovagal syncope and pacing trial [SYNPACE]. A randomised, double-blind, placebo-controlled study of permanent cardiac pacing for the treatment of recurrent tilt-induced vasovagal syncope. Eur Heart J 2004;25:1741–8.
[65] Brignole M, Menozzi C, Moya A, et al. Pacemaker therapy in patients with neurally-mediated syncope and documented asystole. Third international study on syncope of unknown etiology (ISSUE-3): a randomized trial. Circulation 2012;125:2566–71.
[66] Brignole M, Donateo P, Tomaino M, et al. The benefit of pacemaker therapy in patients with presumed neurally-mediated syncope and documented asystole is greater when tilt test is negative. An analysis from the third international study on syncope of uncertain etiology (ISSUE 3). Circ AE 2014. http://dx.doi.org/10.1161/CIRCEP.113.001103.
[67] Wieling W, Jardine DL, de Langhe FJ, et al. Cardiac output and vasodilatation in the vasovagal response: an analysis of the classical papers. Heart Rhythm 2016;13:798–805.
[68] Epstein AE, Di Marco JP, Ellenbogen KA, et al. ACCF/AHA/HRS focused up-date incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities. J Am Coll Cardiol 2012;2013:e6–75.
[69] Gaggioli G, Brignole M, Menozzi C, et al. A positive response to head-up tilt testing predicts syncopal recurrence in carotid sinus syndrome patients with permanent pacemakers. Am J Cardiol 1995;76:720–2.
[70] Solari D, Maggi R, Oddone D, et al. Clinical context and outcome of carotid sinus syndrome diagnosed by means of the 'method of symptoms'. Europace 2014;16:928–34.
[71] Kenny RA, Richardson DA, Steen IN, et al. Carotid sinus syndrome: a modifiable risk factor for nonaccidental falls in older adults (SAFE PACE). J Am Coll Cardiol 2001;38:1491–6.
[72] Ryan DJ, Steen N, Seifer MC, et al. Carotid sinus syndrome, should we pace? A multicentre, randomized controlled trial (Safepace 2) Heart 2010;96:347–51.
[73] Parry SW, Steen N, Bexton RS, et al. Heart rhythm disorders and pacemakers: a randomized, double-blind, placebo controlled crossover trial. Heart 2009;95:405–9.
[74] Bhangu J, McMahon CG, Hall P, et al. Long term cardiac monitoring in older adults with unexplained falls and syncope. Heart 2016. http://dx.doi.org/10.1136/heartjnl-2015-308706.
[75] Solari D, Tesi F, Unterhuber M, et al. Stop vasodepressor drugs in reflex syncope (STOP-VD). A randomized controlled trial. Heart 2017;103:449–55.
[76] Pournazari P, Sahota I, Sheldon R. High remission rates in vasovagal syncope: systematic review and meta-analysis of observational and randomized studies. JACC Clin Electrophysiol 2016. http://dx.doi.org/10.1016/j.jacep2016.10.012.