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STATE OF THE ART REVIEW

Twenty-five years of research on syncope

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Abstract

Over the last 25 years, the *Europace* journal has greatly contributed to dissemination of research and knowledge in the field of syncope. More than 400 manuscripts have been published in the journal. They undoubtedly improved our understanding of syncope. This symptom is now clearly differentiated from other forms of transient loss of consciousness. The critical role of vasodepression and/or cardioinhibition as final mechanisms of reflex syncope is emphasized. Current diagnostic approach sharply separates between cardiac and autonomic pathways. Physiologic insights have been translated, through rigorously designed clinical trials, into non-pharmacological or pharmacological interventions and interventional therapies. The following manuscript is intended to give the reader the current state of the art of knowledge of syncope by highlighting landmark contributions of the *Europace* journal.

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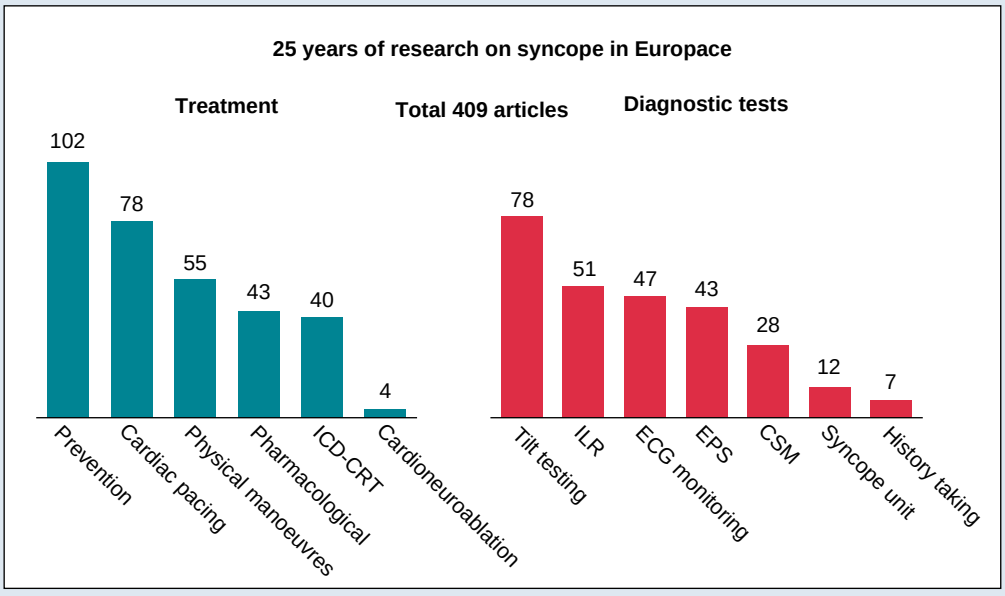
Graphical Abstract



Keywords Unexplained syncope • Syncope mechanism • Syncope diagnosis • Syncope treatment • Syncope Europace

What's new?

- More than 400 manuscripts on syncope have been published in *Europace* journal since its foundation.
- Syncope is now clearly differentiated from other forms of transient loss of consciousness.
- The critical role of vasodepression and/or cardioinhibition is well emphasized.
- Cardiac and autonomic diagnostic pathways are sharply separated.
- Non-pharmacological or pharmacological interventions and interventional therapies are still being developed.

Introduction

Since its creation by founding editor Prof. Richard Sutton, a pioneer and unanimously recognized expert in the area of syncope, the *Europace* journal has greatly contributed to dissemination of research and knowledge in this field. More than 400 manuscripts have been published in the journal, balanced between pathophysiology, diagnosis, and therapy (*Figure 1*). This significant scientific output has become possible as a result of sharing new research ideas and thought exchange among leading research groups in Europe and beyond. It has led to a completely new understanding of syncope and its management.

The following manuscript, coming from syncope experts whose contributions have substantially impacted the field, is intended to give the reader the current state of the knowledge about syncope by highlighting landmark contributions of the journal.

Epidemiology and mechanisms

In the end of the 1990s, at the time the *Europace* journal was founded, 'syncope' was often defined as any form of temporary loss of consciousness, promoting confusion with transient ischaemic attacks, hypoglycaemia, and epileptic seizures. The first syncope guidelines, published in *Europace* in 2001, separated the broad group of 'transient loss of consciousness (TLOC)' from the narrower entity of syncope defined as a fall in systemic blood pressure (BP) leading to global cerebral hypoperfusion.[1,2] As systemic BP depends on cardiac output, the product of heart rate (HR), stroke volume, and total peripheral resistance, a fall in any of these can cause syncope.[3] Low HR may result from reflex bradycardia or bradyarrhythmia, whereas low stroke volume can be due to reduced venous return, e.g. volume depletion, venous pooling, and tachyarrhythmia or structural heart diseases.[3] Finally, low peripheral resistance may result from impaired sympathetic control of vasoconstriction, causing, e.g. orthostatic hypotension while standing.[4] In parallel to a more accurate definition of syncope proposed in 2001, in vasovagal reflex, the early hypotensive phase was already gaining interest as something distinct from the later bradycardic phase, and a new 'dysautonomic' type of vasovagal reflex was proposed in the revised VASIS classification.[5]

Epidemiology

Syncope is extremely common, affecting approximately one-third to one-half of the general population during their lifetime, the majority due to vasovagal syncope (VVS).[3] Between 1% and 3% of all emergency department visits are due to syncope.[6] The prognosis of VVS is benign, but injuries occur in more than 30% of cases, with major injuries reported in ~14% of patients, particularly at old age and with recurrent syncope.[7,8] Moreover, VVS often causes psychological distress, impaired quality of life, and activity restriction, aspects deserving every clinician's attention.[9,10]

Predisposition to vasovagal syncope

Over the last decades, research on the pathophysiology of VVS has led to significant advances. It was hypothesized that VVS was due to a hypotensive susceptibility,[11] later supported by a comparison with unaffected cohorts: VVS was associated with lower systolic, higher diastolic BP, and higher HR[12,13] (*Figure 2*). These features suggest reduced venous return and lower stroke volume as possible reflex triggers. In individuals with hypotensive susceptibility, syncope may occur if triggering

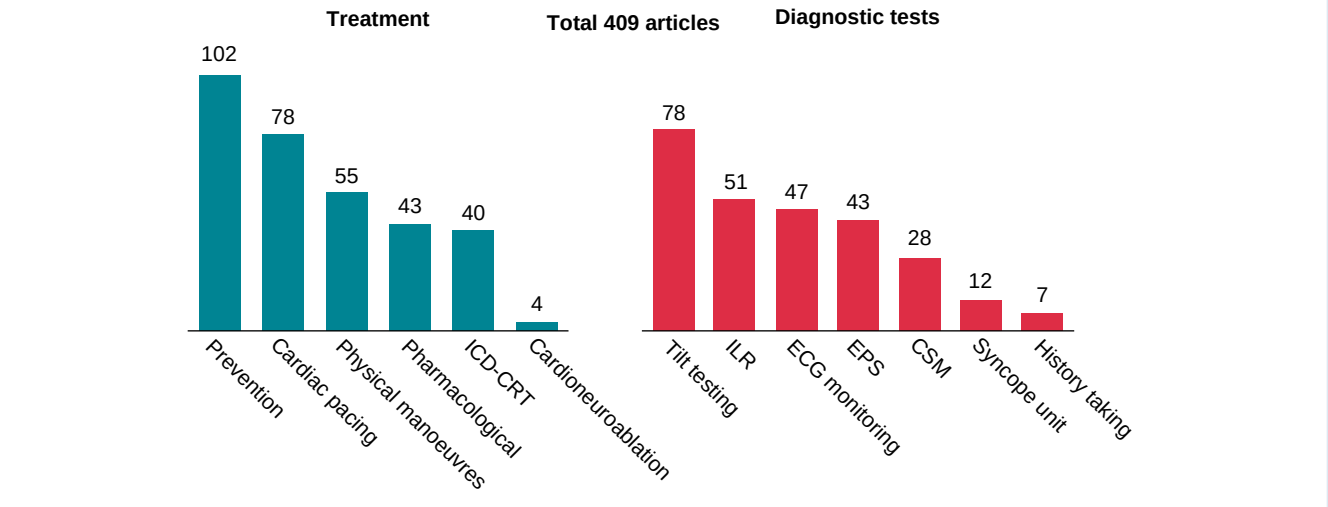


Figure 1 Graphical representation of the manuscripts related to syncope published in *Europace* from its foundation. ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy; ILR, implantable loop recorder; ECG, electrocardiogram; EPS, electrophysiological study; CSM, carotid sinus massage.

conditions (e.g. prolonged standing) overcome the capacity of compensatory mechanisms.[14] The reasons for the haemodynamic features of VVS patients remain currently unclear, although lower circulating blood volume, a tendency to increased venous pooling, and abnormal neuroendocrine activation have been hypothesized[12] (*Figure 2*). Reflex syncope patients also show higher anxiety levels as compared with individuals with no previous loss of consciousness,[15] suggesting that anxiety might be a component of the reflex-related phenotype. Finally, as for genetic basis of reflex syncope, a positive family history can be identified in a significant proportion of patients,[16,17] and recent genetic association study has suggested that syncope patients may share some genetic susceptibility to lower BP and altered autonomic control of circulation.[18]

A significant contribution to advances in pathophysiological knowledge was derived from tilt-induced syncope, a clinically useful model for spontaneous orthostatic VVS. Tilt-positive patients had lower systolic BP, diastolic BP, and HR compared with tilt-negative patients, independent of age and gender[19] (*Figure 2*). These results imply a reduced capacity to compensate for lower BP. Previous research consistently showed greater orthostatic tolerance in older than in younger individuals, due to higher systolic BP offering greater BP reserve.[20] Positivity rate of passive tilt test is known to decrease with advancing age,[21] confirming that older patients may require stronger stimuli to lower BP (e.g. nitroglycerine) to induce the cascade that results in syncope. Regarding another form of reflex syncope, due to carotid sinus hypersensitivity (CSH), data suggest that it might result from an age-related autonomic dysregulation leading to blunted sympathetic response.[22] However, CSH has been reported in a substantial proportion of patients with no history of syncope and falls, and its definition as a disease state is still controversial. As CSH, other reflex syncope subtypes, and orthostatic hypotension frequently coexist in older patients, complex underlying mechanisms should be considered in this group.[23]

Underlying haemodynamic phenomena

The main haemodynamic mechanisms of reflex syncope include cardioinhibition and vasodepression.[3] Cardioinhibition typically predominates in younger individuals, while vasodepression is stronger at old age[21,24] (*Figure 2*). Cardioinhibition is due to marked activation of the vagal nerve, while vasodepression is largely due to a transient inhibition of the sympathetic system. It has long been believed that the shift from sympathetic to parasympathetic predominance originates from cardiac mechanoreceptors activated by decreased preload and increased force of myocardial wall motion.[25] Decreased preload hypothesis has gained more attention in last decades. Vasodepression was traditionally attributed to diminished peripheral resistance due to reduced sympathetic arteriolar vasoconstriction, but later studies described a different scenario, in which a marked reduction in stroke volume, due to venous pooling, caused the initial BP fall, while peripheral resistance tended to increase during the prodromal phase of syncope.[26] More recent evidence provided further support to the central role of venous pooling and reduced stroke volume (*Figure 2*). In 163 patients with tilt-induced syncope,[27] early BP decrease was due to low stroke volume, with incomplete compensatory HR increase. A decrease of peripheral resistance provided a minor contribution, with a much smaller and very late effect on BP. The second major pathophysiological event was cardioinhibition, which appeared as the final determinant of BP fall, playing as large a role as low stroke volume, although later, i.e. around 1 min before syncope.[27]

Why and how cardioinhibition starts remains currently unknown. As atropine and cardioneuroablation seem to abort the cardioinhibitory part of the reflex, it is likely due to cholinergic stimulation of muscarinic M2 receptors in the sinus and atrioventricular nodes.[28] But what makes the heart turn from tachy- to bradycardia? It has been documented that pronounced increase in circulating epinephrine and vasopressin, most likely a compensatory mechanism against hypotension, heralds the imminent vasovagal reflex during tilt-testing[29,30] (*Figure 2*). This hypothesis has been supported by progressive decrease in cerebral tissue oxygenation, independent of mean arterial pressure, observed in patients with spontaneous vasovagal reflex during passive tilt test[31] (*Figure 2*). All of this could be hypothetically sensed by centrally situated receptors and trigger the vasovagal response. In addition, some authors hypothesized that transient arterial baroreceptors dysfunction might also occur, impairing the normal compensatory response to hypotension and contributing to syncope.[32]

Finally, a special group of patients without structural heart disease and cardiac arrhythmia, who suffer cardioinhibitory syncope, typically

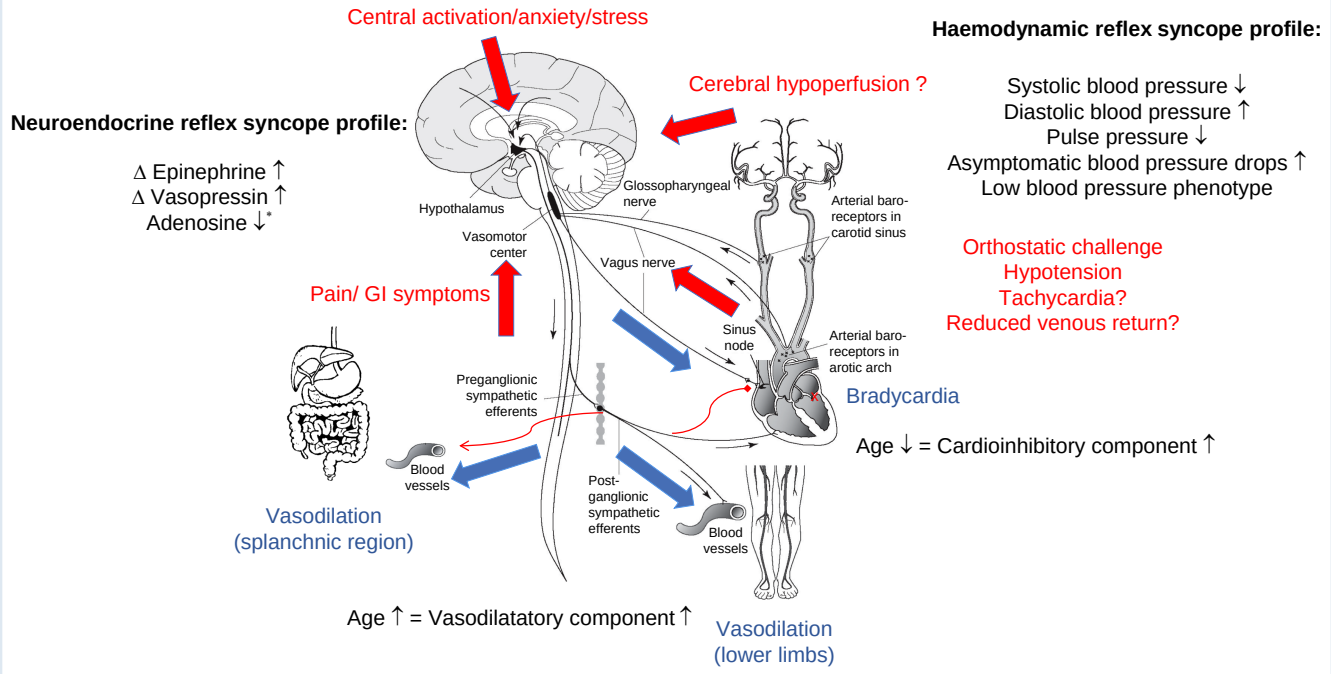


Figure 2 Main reflex syncope triggers and mechanisms.# Reflex syncope may be triggered by orthostatic challenge and hypotension, central stimuli such as emotional stress or blood sight, gastrointestinal symptoms (nausea), or pain. The efferent arm of vasovagal reflex is composed of vasodepressive component, usually preceding the cardioinhibitory component mediated by vagal activation and leading to profound bradycardia or asystole. Recent studies have identified a steep increase in epinephrine and vasopressin during tilt testing as both compensatory responses to haemodynamic instability and hypothetical reflex triggers. Moreover, a specific haemodynamic profile of VVS patients has been identified and is characterized by lower systolic and higher diastolic BP, lower pulse pressure, and presence of asymptomatic BP drops on 24- h ambulatory BP monitoring.

sudden-onset complete AV block, without prodromes may display a purinergic profile, which is opposite to VVS: low adenosine plasma level, low expression of A2A adenosine receptors, or presence of dysfunctional genetic variant. This group has been defined as adenosine-sensitive syncope.[33]

The last 25 years of VVS research showed that genetic, haemodynamic, autonomic, neuroendocrine, and psychological factors all contribute to VVS, but we still do not how, let alone why, the sight of blood can cause the heart and brain to come to a temporary standstill.

Diagnostic workup for syncope aetiology: summary of 25 years of experience

The *Europace* journal has contributed to our understanding of the diagnostic workup of syncope through the publication of over 200 articles over the past 25 years. The majority relates to tilt testing and prolonged electrocardiogram (ECG) monitoring (external and implantable), whereas other tests such as ambulatory BP monitoring (ABPM), home BP monitoring, and wearable BP monitors are either absent or underrepresented.

The initial evaluation consists of history taking and physical examination which includes active standing test and standard 12-lead ECG.[3,34,35] The diagnostic yield of the initial evaluation depends on the clinical setting in which the patient is being evaluated and its indications. In general, 50–90% of aetiological diagnoses can be made during the initial evaluation only in which history taking of all the events is the predominant factor.[35,36]

The diagnostic workup of syncope following the initial evaluation includes 'cardiac' and the 'autonomic' pathways, which can be selected based on the pre-test probability (*Figure 3*).[37]

Cardiac pathway

Sudden death and life-threatening conditions caused by the same mechanism that led to syncope are rare and typically, the case when cardiac arrhythmia is the underlying cause. An additional, indirect risk of death in syncope patients stems from underlying diseases, such as structural cardiac diseases.[38,39] In patients with a high risk of structural or arrhythmic heart disease, cardiac tests should be performed as the first step. Twenty-four h Holter monitoring is rarely useful, because, in most patients, symptoms do not recur during monitoring time, and the true yield of Holter monitoring in syncope may be as low as 1–2%.[3,40,41] Electrophysiological study (EPS) should be limited to patients with previous myocardial infarction, in patients with bifascicular bundle branch block (BBB), in patients with suspected sick sinus syndrome, and for risk stratification in patients with genetic arrhythmia syndrome.[3,42–47] Exercise testing is indicated in patients who experience syncope during or shortly after exertion.[3] Finally, in patients with syncope, the same indications for coronary angiography should be considered as in patients without syncope.[3,48]

Autonomic pathway

The autonomic pathway includes diagnostic tests to identify predominant haemodynamic mechanism of reflex syncope; diagnosis of hypotensive or bradycardic phenotype,[37–51] ABPM, home BP monitoring, wearable BP monitors, carotid sinus massage, tilt testing (HUTT), and external prolonged ECG monitoring are the most useful tests for

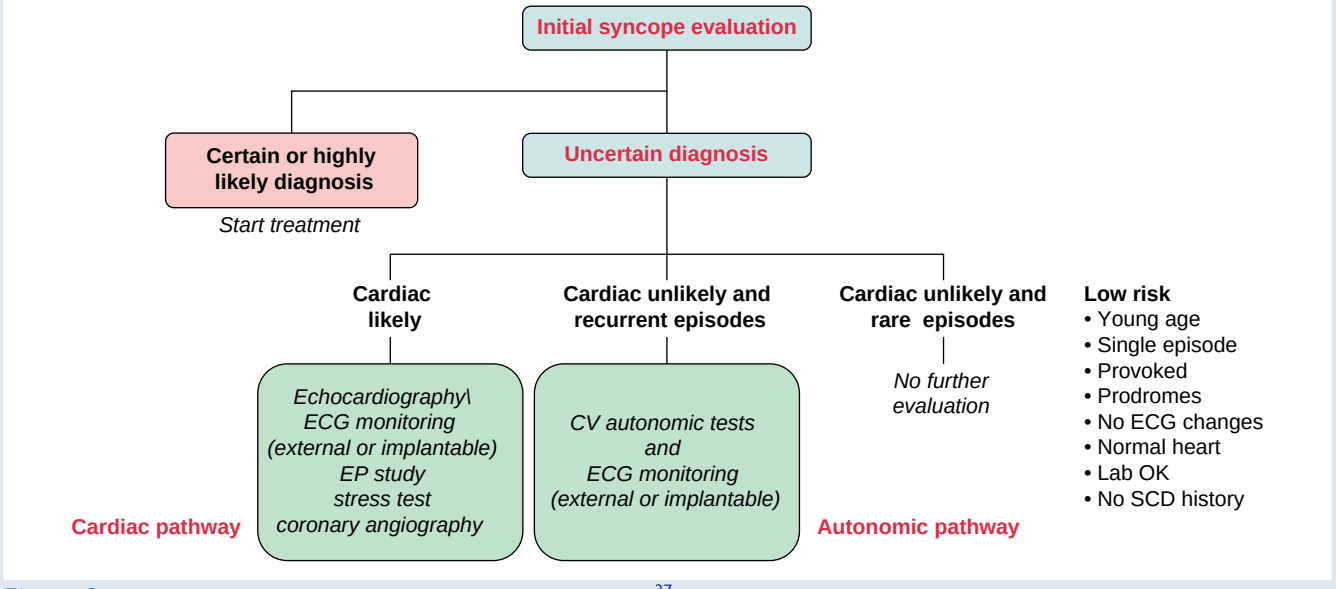


Figure 3 Diagnostic workup of syncope. Reproduced with permission.[37] ECG, electrocardiogram; EP study, electrophysiological study; CV, cardiovascular; SCD, sudden cardiac death.

this. In addition to these tests, basic autonomic function tests, e.g. Valsalva manoeuvre, deep breathing test, and other autonomic function tests, will identify underlying autonomic dysfunction. Moreover, videorecording of spontaneous episodes or during a provocative HUTT is a useful tool for the diagnosis of syncope or identification of other causes of TLOC such as psychogenic spells/pseudosyncope or epileptic seizures.[3,52]

Prolonged ECG monitoring by an implantable loop recorder (ILR) represents an 'ultima ratio' in the case of syncope that remains unexplained at the end of both cardiac and autonomic pathways ('when in doubt, use ILR').[3,37,51]

The diagnostic yield of syncope workup depends on several factors, mainly clinical settings, characteristics of the population, physician's skill, and availability of all necessary diagnostic instruments. The diagnostic workup as described above and in the guidelines has been validated in several studies, most of them performed in syncope units.[53] To summarize, in selected patients referred to syncope unit, a diagnosis of cardiac aetiology is made, on average, in 6–13%, reflex syncope in 56–73% %, orthostatic hypotension in 1–10%, and psychogenic pseudo syncope in 1–2%. Syncope aetiology remains uncertain or unexplained in 18–20% of cases.[37,51] Syncope units have been shown to be able to reduce underdiagnosis and misdiagnosis of syncope, to reduce hospitalization and costs.[54,55] Nevertheless, the diffusion of syncope unit is still limited to few centres.[56] The European Heart Rhythm Association considers that syncope units should be widely available in Europe and has proposed some models that permit each hospital to develop their own model to suit its particular environment.[55]

Non-cardiac syncope: distinguishing between hypotensive and bradycardic phenotypes

Traditionally, reflex syncope and orthostatic hypotension are classified by their aetiology and clinical presentation. Because of recent advances in technology, our ability to make a diagnosis based on the documentation of spontaneous events has increased. This resulted in a new classification of non-cardiac syncope based on the underlying mechanism, hypotension, bradycardia, or a combination of both.[37,49,50] Each clinical form can cause syncope by different mechanisms. Diagnostic tests should document the causal correlation between underlying mechanism and the syncope event. The efficacy of therapy is largely determined by the mechanism of syncope rather than its aetiology or clinical presentation. The dominant mechanism of syncope should be carefully assessed and assigned to hypotensive or to bradycardic phenotype, the choice of therapy (counteracting hypotension, bradycardia, or both) depending on the given phenotype. A typical dominant hypotensive phenotype is that of syncope due to classical orthostatic hypotension, and a typical dominant bradycardic phenotype is that of syncope due to low adenosine paroxysmal idiopathic AV block.[57] In many other cases, the final mechanism is often a combination of hypotension and bradycardia, albeit of variable magnitude, and therapy should often be aimed to counteract both mechanisms. For example, in patients with delayed orthostatic hypotension, when syncope occurs, a vagally reflex bradycardia is often present, triggered by orthostatic hypotension itself, making the distinction between reflex and orthostatic hypotension somehow arbitrary. Conversely, some patients with ECG documentation of a long asystolic pause at the time of a spontaneous syncope have syncopal recurrence despite cardiac pacing. In such cases, syncope is often due to an associated vasodepressor reflex which can be unmasked by tilt testing.[11,58] Finally, a compensatory sinus tachycardia may be present during the pre-syncopal phase of reflex syncope and in postural orthostatic tachycardia syndrome. The most useful tests for the mechanism of non-cardiac syncope are listed in the *Table 1*.

- *24 h ambulatory BP monitoring (ABPM)*

Office BP is frequently influenced by confounders such as white coat effect, which is especially common in older individuals[59] and is often the cause of over-medication, causing syncope. Therefore, out-of-office BP measurement techniques such as 24 h ABPM should be applied in patients with suspected hypotensive phenotype. Ambulatory BP monitoring may help the identification of persistent constitutional or drug-related hypotension, particularly in patients with a white coat

Table 1 Most useful tests for identifying the mechanism of non-cardiac syncope

Initial syncope evaluation: history, physical examination including active standing test, and standard electrocardiogram	
Hypotensive phenotype	***Bradycardic phenotype***
24 h ambulatory BP monitoring (ABPM)	Carotid sinus massage
Home BP and wearable BP monitoring	Tilt table test
Tilt table test	Prolonged ECG monitoring (implantable loop recorder)

BP, blood pressure; ECG, electrocardiogram.

effect.[60] Mean 24 h systolic BP <105 mmHg in men and <97 mmHg in women identifies patients affected by constitutional hypotension.[61] In a recent study,[13] mean 24 h systolic BP ≤110 mmHg predicted a diagnosis of reflex syncope with a sensitivity of 60% and a specificity of 70%. Moreover, ABPM might also reveal hypotensive episodes in patients with mean BP values within the normal range. Recent data from a large multicentre comparison between syncope patients and matched controls indicate that one or more episodes of daytime systolic BP <90 mmHg on ABPM permit a diagnosis of hypotensive susceptibility in reflex syncope with 91% specificity and 32% sensitivity (OR 4.6, $P < 0.001$), while two or more daytime SBP drops <100 mmHg achieved 84% specificity and 40% sensitivity (OR 3.5, $P < 0.001$).[14] Ambulatory BP monitoring is also of value in determining nocturnal BP behaviours such as supine hypertension indicating baroreflex dysfunction and nocturnal dipping.

- *Home BP monitoring and wearable BP monitors*

Home BP monitoring and wearable BP monitors may represent a useful tool in patients who complain of dizziness, orthostatic intolerance, or other symptoms of suspected hypotensive origin, with the purpose to measure BP at time of symptoms and throughout the day.[62] Symptoms more frequently occur while standing, during or immediately after meals, after taking medications, or after physical activity. Home BP monitoring and wearable BP monitors facilitate a better understanding of BP variations and vulnerable time periods and or symptoms.

- *Tilt table test*

Tilt table test is the most comprehensive test for reflex syncope. Indeed, it allows for investigation of both hypotensive and bradycardic phenotypes and other dysautonomia syndromes, i.e. delayed orthostatic hypotension and postural orthostatic tachycardia syndrome.[63] In a meta-analysis of 55 studies including 4361 patients undergoing HUTT for suspected reflex syncope, the average overall positivity rate was 37% with passive tilt protocol, 60% for isoproterenol protocol, and 66% for nitroglycerine protocol.[64] The 'Italian protocol' is probably the most widely used nitroglycerine protocol. It consists of a supine pre-tilt phase of 5 min when there is no venous cannulation, tilt angle between 60° and 70°, and passive phase of 20 min duration followed by 0.3 mg sublingual nitroglycerine administered with the patient in upright position if syncope had not occurred during the passive phase.[65] Continuous ECG and beat-to-beat BP monitoring is optimal for recording haemodynamic information. The test should be continued until complete loss of consciousness occurs or the protocol is completed in order to detect full vagal effect in the case of unexplained syncope.[66] In the case of a certain/highly likely diagnosis, HUTT can be of value for biofeedback. Recently, the *Fast* Italian protocol, consisting of 10 min passive and 10 min nitroglycerine phase, has been compared with the traditional protocol in a randomized trial in 544 patients. A positive response was observed in 57.8% and 62.4% of patients, respectively.[67] The prevalence of cardioinhibitory, mixed, and vasodepressor responses was similar with the two protocols. Therefore, the fast protocol can be used instead of the traditional protocol in clinical practice, allowing time saving and of costs of the test.

- *Carotid sinus massage*

The carotid sinus massage technique has evolved substantially over the years. Compared with the technique used before the 1980s, the current methodology also includes massage in the upright position. This way it is better to evaluate the vasodepressor component. Usually, carotid sinus massage is performed with the aid of a tilt table, under continuous ECG and non-invasive beat-to-beat BP monitoring. The current definition of carotid sinus syncope requires the reproduction of (pre) syncope, recognized by the patient itself, in addition to the documentation of abnormal cardioinhibitory and/or vasodepressor reflex, in agreement with the so-called method of symptoms.[3,38] In the absence of symptom reproduction, CSH has been reported in 35% of asymptomatic old subjects. Such poor specificity makes its role as syncope cause uncertain.[68]

- *Prolonged ECG monitoring*

In a meta-analysis[3] of 5 randomized controlled trials,[69–73] 660 patients with unexplained syncope were randomized to a conventional strategy or to prolonged monitoring with an ILR. The results showed that initial implantation of an ILR in the workup provided a 3.7 [95% confidence interval (CI) 2.7–5.0] increased relative probability of a diagnosis compared with the conventional strategy. Implantable loop recorder was more cost-effective than a conventional strategy.

In a meta-analysis from 4 studies involving 1046 patients aged >40 years undergoing ILR implantation for severe, recurrent, likely reflex syncope, 383 (36.6%) had an ECG documentation of a diagnostic event during mean follow-up after ILR implantation of 13 ± 10 months.[58] Among these, 201 (52%) had an asystolic event (mean duration 12.8 ± 11.0 s) duration compatible with a reflex mechanism. The asystolic event was sinus arrest in 52%, AV block in 20%, and sinus arrest plus AV block in 11% and remained undefined in 16% of cases. A predominant CI reflex syncope (bradycardic phenotype) is diagnosed in case of documentation of a syncopal asystolic pause >3 s or of an asymptomatic asystolic pause >6 s. The finding of a rapid decrease in HR concomitant with a syncopal event may suggest a mixed mechanism including both hypotension and bradycardia as causes of reflex syncope. The absence of a decrease in HR or its increase suggests a predominant hypotensive mechanism.[3,74] Sudden-onset AV block (and ventricular pause/s) with constant P-P cycle, in the absence of BBB or structural heart disease, suggests an extrinsic mechanism like 'low adenosine' idiopathic AV block.[57] Conversely, sudden-onset AV block (and ventricular pause/s), triggered by atrial or ventricular premature beats, in patients with BBB or structural heart disease suggests an intrinsic conduction disturbance.[75]

Recent guidelines acknowledge consideration of the ILR to out rule malignant arrhythmia as a cause of syncope in certain inherited arrhythmia patients at low risk of sudden cardiac death.[76]

Despite the above evidence, and recommendation of guidelines (1,48),[3,77] ILRs seem to be underused in clinical practice in Europe in patients with unexplained syncope and the use of this device in clinical practice.[78]

The diagnostic criteria of hypotensive phenotype are shown in *Table 2*, and the diagnostic criteria of bradycardic phenotype are shown in *Table 3*. It must be stated clearly that the diagnosis of the mechanism is only presumptive and, therefore, may be imperfect. Furthermore, when multiple tests are performed in the same patient, sometimes the response to a test is different from that of another test. It is important to complete all hypotensive or bradycardia tests, particularly in older patients, given that more than one diagnosis may be present and deciphering which abnormality is the attributable cause of symptoms is not always possible. An incomplete assessment may increase the

Table 2 Hypotensive phenotype: diagnostic criteria

Diagnosis	Definition	Test	Blood pressure cut-offs
Constitutional hypotension	Persistently low BP in the absence of hypotensive medications	– Office BP – 24 h ABPM and home BP monitoring	SBP < 110 mmHg (males) or < 100 mmHg (females) *Males* 24 h SBP <105 mmHg Daytime SBP <115 mmHg Nighttime SBP <97 mmHg *Females* 24 h SBP <98 mmHg Daytime SBP <105 mmHg Nighttime SBP <92 mmHg
Drug-related persistent hypotension	SBP values persistently below the recommended target in patients receiving hypotensive medications	– Office BP – 24 h ABPM and home BP monitoring	Age <65: SBP <120 mmHg Age ≥65: SBP < 130 mmHg 24 h SBP <110 mmHg
Hypotensive episodes	Orthostatic hypotension	Office BP	SBP fall ≥20 mmHg and/or DBP fall ≥10 mmHg or standing SBP <90 mmHg within 3 min of standing
	Post-prandial hypotension	24 h ABPM	SBP fall >20 mmHg within 75 min of eating meals, compared with the mean of the last three BP measurements before the meal
	Hypotensive drops	24 h ABPM HBPM/wearable BP monitors	≥1 episodes of daytime SBP <90 mmHg ≥ 2 episodes of daytime SBP <100 mmHg Correlation between low BP and symptoms
Hypotensive reflex syncope	1) Induction of syncope during TT	Tilt table test	Typical haemodynamic pattern of mixed or vasodepressor vasovagal syncope with hypotension and bradycardia but without asystolic pauses >3 s
	2) Reproduction of (pre)syncope during carotid sinus massage (method of symptoms)	Carotid sinus massage	Reproduction of spontaneous (pre)syncope, recognized by the patient itself, with fall in SBP >50 mmHg or below 85 mmHg and absence of asystolic pause/s > 3 s

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ABPM, ambulatory blood pressure monitoring; BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure; TT, tilt testing.

risk of selecting an inappropriate treatment, exposing patients to the risk of recurrence and injuries. Algorithms for the diagnosis of hypotensive phenotype[4] and bradycardic phenotype[79] have been proposed.

A possible diagnostic pathway for a comprehensive workup is shown in *Figure 4*.

Syncope, bifascicular bundle branch block, and cardiac pacing

The presence of bifascicular BBB is a marker of impaired infra-Hisian conduction and is associated with progression to intermittent complete AV block. The diagnostic and therapeutic strategy for patients with syncope, BBB, and preserved left ventricular ejection fraction is a matter of debate, since many patients do not progress and syncope may be due to other aetiologies that do not respond to pacemakers.

An HV interval ≥ 70 ms or the induction of infra-Hisian block during atrial pacing, either at baseline or after drug challenge, identifies a subgroup of patients at higher risk of developing AV block. The positive predictive value of the EPS is unknown, but a significant reduction of syncope has been observed after pacemaker implantation in patients with positive EPS.[42] A recent meta-analysis showed that the EPS has negative predictive value of only 70% if ILRs are used to detect eventual AV block, an insufficiently accurate test characteristic.[80] This pleads for completing the workup in case of negative EPS.

An alternative and pragmatic attitude, the empirical implantation of pacemakers, has been evaluated. Two randomized studies addressed whether to simply implant a pacemaker in patients with syncope and bifascicular block. In one, all patients were implanted with a pacemaker and randomized to mode ON vs. OFF,[81] while in the other, patients were randomized to pacemaker vs. ILR.[82] The primary outcome in both studies was a composite outcome of different clinical events, but when syncopal recurrences were analysed in secondary analyses, there was no benefit from pacing. In both studies, there was a significant rate of complications related to pacemakers.

Putting together these pieces of evidence, it seems reasonable to perform an EPS and, when negative, to keep ECG monitoring the patients through an ILR, as recommended.[3] In frail and older patients with syncope, especially in the scenario of recurrent and traumatic events, an empirical pacemaker seems reasonable. In parallel, when EPS/ILR are negative, CV autonomic tests might be considered for alternative syncope aetiology (e.g. VVS or orthostatic hypotension).[3]

Treatment of vasovagal syncope

Most clinical investigators searching for effective therapies for recurrent VVS have had strong cardiovascular physiologic curiosity, and most studies were driven by the cardiovascular physiology of VVS. This

Table 3 Bradycardic phenotype: diagnostic criteria

Diagnosis	Definition	Test	CI cut-offs
CI reflex syncope	1) Reproduction of spontaneous symptoms during CSM (method of symptoms)	Supine and standing 10 s CSM	Reproduction of spontaneous (pre)syncope, recognized by the patient itself, with fall in SBP >50 mmHg and asystolic pause/s > 3 s[a]
	2) Reproduction of spontaneous syncope during tilt table test	Tilt table test	Typical ECG pattern of vasovagal syncope during hypotension and asystolic pause >3 s)
	3) Asystolic pauses of likely reflex origin during prolonged ECG monitoring	Prolonged ECG monitoring (wearable and ILR)	Typical ECG pattern of asystolic (>3 s) vasovagal syncope or documentation of asymptomatic asystolic pause >6 s of likely reflex origin
Idiopathic AV block (low adenosine syncope)	Symptomatic paroxysmal AV block	Prolonged ECG monitoring (wearable and ILR)	Typical ECG pattern of idiopathic AV block

Reproduced with permission.[37]
CI, cardioinhibitory; CSM, carotid sinus massage; SBP, systolic blood pressure; ILR, implantable loop recorder.
[a]Recognition of (pre)syncope sometime is made by staff. This occurs in older patients who are unaware of loss of consciousness during real-time episodes but lose consciousness during CSM with diagnostic hypotension or bradycardia.

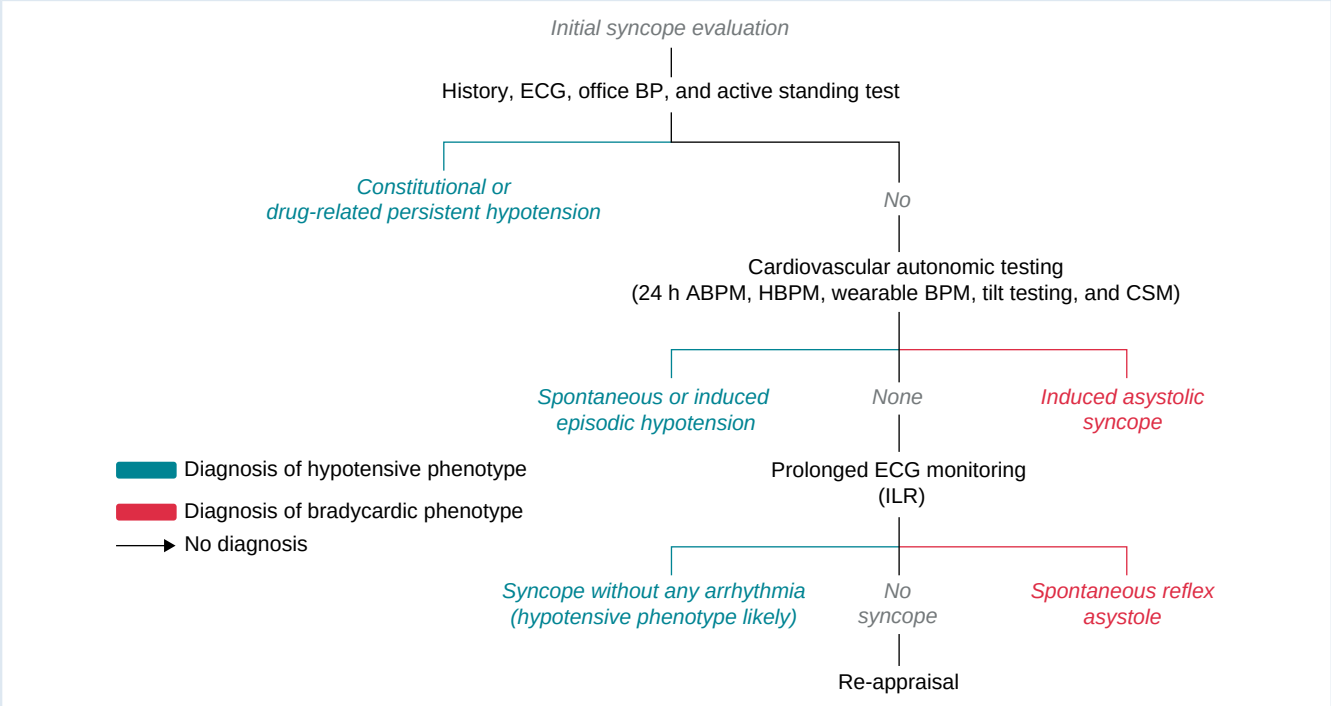

Figure 4 Diagnostic flow chart for the identification of hypotensive and bradycardic phenotypes. Reproduced with permission.[37] BP, blood pressure; ABPM, ambulatory blood pressure monitoring; HBPM, home blood pressure monitoring; CSM, carotid sinus massage; ILR, implantable loop recorder.

interaction between evolving physiologic concepts and the need to provide treatment has provided decades of fascination, and *Europace* has played an important role.

Non-pharmacologic treatment

Education and lifestyle modifications have not been evaluated in randomized studies, but there is a consensus for implementing them as first-line therapy in all cases. They comprise reassurance regarding the benign nature of the disease, education regarding awareness and possible avoidance of triggers, and early recognition of prodromal symptoms in order to lie down quickly. If possible, triggers should be addressed directly, such as cough suppression in cough syncope, dehydration, and agents that lower BP should be avoided or reduced. A large observational study[83] evaluated a standardized education protocol in VVS patients.

In a pre–post comparison conducted in 316 patients, education significantly reduced traumatic injuries and syncope recurrences.

The cascade of events culminating in orthostatic VVS usually begins with venous pooling, most likely in the splanchnic venous circulation. It is still unknown whether emotional VVS and carotid sinus syndrome have the same cascade as orthostatic VVS. Most strategies focus on maintaining blood volume to prevent or just extend presyncope and thereby prevent its progression to syncope.

Increased fluid and salt intake may improve orthostatic tolerance,[84] although hydration alone does not seem to prevent symptoms.[85] In the absence of contraindications, patients should be encouraged to increase their hydration with close monitoring of BP in patients at risk of hypertension. Reducing anti-hypertensive polypharmacy may help. In a small cohort of elderly hypertensive patients with confirmed VVS, withdrawing or reducing hypotensive therapy significantly reduced presyncope and syncope.[86]

Physical counterpressure manoeuvres (PCM) can abort VVS in patients with prodromes to act on time. The first randomized open-label controlled trial showed a 36% relative risk reduction in recurrence with PCM.[87] In a meta-analysis of 688 patients enrolled in 11 trials out of which 2 were randomized, Dockx et al.[88] concluded that PCM might be effective for prevention of VVS, but with a low level of evidence. None were blinded or adequately controlled. Physical counterpressure manoeuvres may be less effective in older patients and patients with minimal prodromes so the action of PCM comes too late.[89] The most effective manoeuvre and the most appropriate age remain to be determined.

Tilt training and stand training[90] may not be effective. Long-term compliance and effectiveness are poor.[91–94]

Overall the evidence for non-pharmacologic treatment is modest, but increases in dietary salt and fluid, deprescribing hypotensive polypharmacy, and teaching counterpressure manoeuvres are often recommended.

Beta-blockers

The rationale for beta-adrenergic blockers preventing the vasovagal reflex arose from animal studies in which catecholamines potentiated the low pressure ventricular baroreceptor, triggered by relative volume loss. The report that isoproterenol greatly potentiated tilt testing demonstrated the role of beta-agonists in triggering the vasovagal cascade in humans. This was followed by six randomized controlled trials of β-adrenergic blockers.[95] On the whole, they were negative.[96] Beta-blockers have a limited role, if any, in the prevention of VVS (class III recommendation).[3,97]

Fludrocortisone

The mineralocorticoid fludrocortisone should cause fluid retention and maintain cardiac preload. In the Prevention of Syncope Trial II (POST2),[98] a randomized, placebo-controlled, double-blind trial, fludrocortisone significantly reduced the likelihood of syncope after 2 weeks of dose stabilization and at a dose of 0.2 mg daily. Fludrocortisone 0.2 mg daily is a reasonable first-line medical therapy, but should be avoided in patients with hypertension, heart failure, or fluid overload.

Midodrine

Midodrine is a prodrug whose active metabolite is a peripherally acting alpha-agonist. This should reduce venous pooling and peripheral vasodilation, with the intent of maintaining preload and BP. The Prevention of Syncope Trial IV,[99] a randomized, placebo-controlled, double-blind trial of midodrine, reported a significantly reduced relative risk of 0.69, $P = 0.035$. After dose adjustment in the first 2 weeks, the hazard ratio for syncope recurrence in the midodrine arm fell to 0.51, $P = 0.012$. In a meta-analysis, midodrine had a relative risk of 0.71, $P = 0.02$.[100] Therefore, midodrine 2.5–10 mg three times daily is a reasonable first-line medical therapy, but should be avoided in patients with hypertension, heart failure, fluid overload, or liver disease. Recent observations on asymptomatic BP falls during daytime among syncope patients may cast some light on the selection of responders to antihypotensive therapy.[13,14]

Norepinephrine transporter inhibition

Synaptic norepinephrine is either cleared by diffusion or reuptake through active transport into terminals by the presynaptic norepinephrine transporter (NET).[101] This decreases intrasynaptic norepinephrine and sympathetic nervous system tone. Three NET inhibitors—atomoxetine,[102,103] reboxetine,[103–105] and sibutramine[105]—reduce the likelihood of VVS induction during tilt testing, and the empiric use of atomoxetine[106] and sibutramine[107] was associated with a reduction in VVS. There are no high-level data supporting the use of these drugs.

Serotonin reuptake inhibition

These drugs block presynaptic reuptake of serotonin, leading to complex, time-dependent changes in synaptic signalling and neuroplasticity. Selective serotonin reuptake inhibitors (SSRIs) based on old, small studies with inconsistent results[108–110] did not reach sufficient evidence to be considered among recommendation of the European Society of Cardiology (ESC) guidelines.[3]

Table 4 gives a summary of the most useful treatment options in reflex syncope.

Vasovagal syncope and pacemakers

After early trials emphasized the need for rigorously designed and conducted, placebo-controlled trial investigators focused on patient selection and sensing modalities. The ISSUE 3 study[111] was a randomized study of patients older than 40 years with recurrent asystolic syncope and non-syncopal asystole of >6 s documented by ILR. The pacemaker was implanted in all patients, who were then double-blindedly randomized to DDD pacing vs. sensing only. There was a significant reduction in syncope recurrences in patients with active pacemakers.[112] The findings became more difficult to interpret when a subsequent analysis reported that pacing was less effective in patients with a positive tilt test.[79,113,114] In a meta-analysis,[58] the estimated 3-year recurrence rate of syncope was 2% in tilt-negative patients and 33% in tilt-positive patients; a positive tilt test response was the only significant predictor of syncope recurrence. Therefore, specific treatment for hypotensive susceptibility should be provided in these patients, in addition to cardiac pacing.[3]

More recently, prolonged ambulatory ECGs during clinical syncope[58,74,77,115,116] showed that asystole during tilt tests predicted asystole to a high extent during clinical syncope. Two randomized controlled studies included patients older than 40 years with recurrent syncope and tilt-induced asystole. They were randomized to pacemakers with between either DDD-CLS pacing or ODO sensing. Both studies reported significant benefit of CLS pacing.[117,118] There is a theoretical concern that patients were included with asystole starting so late that syncope had already happened due to vasodepression.

Pacing may prevent syncope in reflex syncope when cardioinhibition has a much stronger effect on BP than vasodepression throughout the episode and when pacing succeeds in blocking cardioinhibition early enough to prevent it causing syncope.

The current European recommendations[3,119] are to implant pacemakers in patients older than 40 years, with severe, recurrent, and unpredictable syncope who do not respond to initial treatment and who have a cardioinhibitory response to carotid sinus massage or tilt testing, or in those documented asystole during spontaneous syncope. These

Table 4 Summary of the most useful therapeutic options in reflex syncope

Intervention	Rationale	Target population	ESC recommendation
Explanation. That is, of mechanisms, good prognosis, and all therapeutic steps including hydration and counter manoeuvres, plus feedback of efficacy of counter manoeuvres	Explanation may produce a placebo effect and reduce fear of syncope, itself helping to reduce attack frequency	Everyone with reflex syncope	I
Stopping vasodepressor drugs	Avoiding hypotension	Syncope patients treated with hypotensive drugs	IIa
Permanent pacing with CLS pacemaker	Bradycardia/asystole prevention	Very symptomatic asystolic reflex syncope > 40 years	IIa
Midodrine	Alpha-agonist causing peripheral vasoconstriction and blood pressure rise	Low blood pressure phenotype Hypotensive (vasodepressor) reflex syncope	IIb
Fludrocortisone	Intravascular volume expansion	Low blood pressure phenotype Hypotensive (vasodepressor) reflex syncope	IIb
Tilt training	Restoring proper reflexes	Young highly motivated	IIb
Fluid and salt intake	Intravascular volume expansion; maintains preload	All patients except contraindications (hypertension and heart failure)	None
Fluoxetine	Selective serotonin reuptake inhibitor—increase pre- and post-synaptic serotonin concentration in CNS and prevents Bezold–Jarish reflex	Vasovagal syncope, especially if clinically anxious	None
Atomexetine and reboxetine	Inhibition of norepinephrine reuptake transporter. Prevents or reduces terminal bradycardia	Vasovagal syncope	None
Theophylline	Non-selective adenosine receptor—prevention of AVB	Functional AVB low adenosine phenotype	None
Cardioneuroablation	Bradycardia/asystole prevention	Very symptomatic asystolic reflex syncope	None

AVB, atrioventricular block; CNS, central nervous system; CLS, close-loop stimulation; ESC, European Society of Cardiology.

are indicated in a very selective but highly symptomatic group of patients.

Cardioneuroablation

This technique attempts to denervate vagal inputs to the sinus node and AV node in order to prevent cardioinhibitory VVS. The parasympathetic postganglionic neurons are in ganglionated plexi (GP) in epicardial fat and have extensions to myocardial and endocardial tissue. These areas became the target for radio-frequency cardioneuroablation.[120] Subsequent case reports and uncontrolled studies reported in Europace[121–127] culminated in a randomized, unblinded study that reported high efficacy after a 2-year follow-up.[128]

Currently, cardioneuroablation is mainly proposed in asystolic reflex syncope, especially in young people in whom non-invasive treatments have failed and permanent pacing is unwanted. The method is experimental and is not yet recommended in the guidelines. There are many unknowns, including how to select patients, which atria to target, how to identify the GP and ascertain vagal denervation, which ablation settings to use, and whether re-innervation occurs.[28] Patients should be selected if they are highly symptomatic and have frequently recurrent and drug-resistant syncope consistently due to asystole, and this has not usually been the case. Most studies have reported modestly symptomatic patients.

The long-term safety of cardioneuroablation is not known. The most common complication is inappropriate sinus tachycardia, which occurs in 6–20% of patients, at times requiring further treatment. The long-term effects of ablating parasympathetic cardiac control by GP are unknown.[129] In summary, cardioneuroablation is an interesting potential therapy for highly symptomatic patients with asystolic reflex syncope. Many of the seminal publications have appeared in *Europace*.

Mind and heart

Attention is now turning to the mind–body axis, with focus on central modulation, specific neurotransmission axes, peripheral ganglia, and the final events preceding syncope.

Emotional and psychological factors play important roles in VVS. Many patients have a lifelong predilection to syncope, and syncopal spells can occur in discrete clusters that last weeks to years, interspersed with long quiescent periods. Many patients develop a vasovagal reflex in medical settings or at the site of blood. The vasovagal reflex can begin at night while patients are asleep.

Psychological factors are very likely to modulate syncope frequency, i.e. worsening but also improving. Most patients in the control arms of all randomized and observational clinical studies do not faint in the follow-up period, despite having fainted recurrently before randomization. Patients have improved quality of life while in a study, regardless of whether they receive placebo or active medication. In a randomized clinical trial of (ineffective) pacemakers vs. (ineffective) beta-blockers for VVS, the pacemaker patients did much better. In essence, this showed that an invasive placebo was more effective than a non-invasive placebo. Finally, two recent studies reported that yoga improves outcomes and quality of life.[130,131] Few of the specific poses could plausibly improve peripheral physiology to prevent syncope. In fact, one of the most important poses was the corpse pose.

Conclusion

The last 25 years of research have undoubtedly improved our understanding of syncope, allowing this very common symptom to be clearly differentiated from other forms of TLOC. The critical role of vasodepression and/or cardioinhibition as final mechanisms of reflex syncope is emphasized although the upstream causes remain unknown. Current diagnostic approach now sharply separates between cardiac and autonomic pathways. We also have come a long way, translating physiologic insights into both pharmacologic and interventional therapies. We have learned the critical importance of rigorously designed clinical trials and of optimizing non-medical treatments and the placebo effect. *Europace* has consistently published landmark studies in all these fields.

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Data availability

No new data were generated or analysed in support of this article.

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