Revista Portuguesa de
Cardiologia
Portuguese Journal of **Cardiology**

www.revportcardiol.org

Portuguese Society of
CARDIOLOGY

REVIEW ARTICLE

Diagnostic and therapeutic approach to cardioinhibitory reflex syncope: A complex and controversial issue[☆]

Bruno M.L. Rocha[a,*], Rita V. Gomes[a,b,1], Gonçalo J.L. Cunha[a,1], Beatriz M.V. Silva[a], Rita Pocinho[c], Rui Morais[a], Inês Araújo[a], Cândida Fonseca[a,d]

[a] *Unidade de Insuficiência Cardíaca, Serviço de Medicina III, Hospital de São Francisco Xavier, Centro Hospitalar Lisboa Ocidental, Lisboa, Portugal*
[b] *Serviço de Cardiologia, Hospital de Vila Franca de Xira, Vila Franca de Xira, Portugal*
[c] *Serviço de Medicina Interna 1.2, Hospital de São José, Centro Hospitalar Lisboa Central, Lisboa, Portugal*
[d] *NOVA Medical School, Faculdade de Ciências Médicas, Universidade Nova de Lisboa, Lisboa, Portugal*

Abstract Syncope is defined as a transient loss of consciousness due to global cerebral hypoperfusion and is one of the leading causes of emergency department admission. The initial approach should focus on excluding non-syncopal causes for loss of consciousness and risk stratification for a cardiac cause, in order to ensure an appropriate etiological investigation and therapeutic approach. Vasovagal syncope (VVS), the most common type of syncope, should be assumed once other causes are excluded. Pathophysiologically, the vasovagal reflex is the result of a paradoxical autonomic response, leading to hypotension and/or bradycardia. VVS has not been shown to affect mortality, but morbidity may be considerable in those with recurrent syncopal episodes. The management of VVS includes both non-pharmacological and pharmacological measures that act on various levels of the reflex arc that triggers the syncopal episode. However, most are of uncertain benefit given the scarcity of high-quality supporting evidence. Pacemaker therapy may be considered in recurrent refractory cardioinhibitory reflex syncope, for which it is currently considered a robust intervention, as noted in the European guidelines. Non-randomized and unblinded studies have shown a potential benefit of pacing in recurrent VVS, but double-blinded randomized controlled trials have not consistently demonstrated positive results. We performed a comprehensive review of the current literature and recent advances in cardiac pacing and pacing algorithms in VVS, and discuss the diagnostic and therapeutic approach to the complex patient with recurrent VVS and reduced quality of life
© 2019 Sociedade Portuguesa de Cardiologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

 * Corresponding author.
 E-mail address: bruno.rocha@campus.ul.pt (B.M.L. Rocha).
[1] Authors with equal contribution in carrying out the work.

Abordagem diagnóstica e terapêutica da syncope reflexa cardio-inibitória

Resumo   A síncope define-se como uma perda transitória do conhecimento devido a hipoperfusão cerebral global e representa uma das principais causas de vinda ao Serviço de Urgência. Na abordagem inicial do doente neste contexto é fundamental estratificar o risco para síncope de causa cardíaca, promovendo um adequado estudo etiológico e orientação terapêutica. A etiologia mais comum é o reflexo vasovagal, o qual parece resultar de uma resposta autonómica paradoxal com consequente hipotensão e/ou bradicardia. Ainda que a síncope vasovagal seja uma condição sem impacto na mortalidade, esta frequentemente afeta uma população jovem e causa uma morbilidade significativa, sobretudo quando associada a uma elevada taxa de recorrência. Na abordagem terapêutica da síncope incluem-se estratégias não-farmacológicas comportamentais e terapêuticas farmacológicas que atuam nos vários níveis do arco reflexo desencadeante do episódio sincopal. Contudo, ambas são suportadas apenas por evidência de robustez limitada. Nos casos em que estas intervenções se mostram insuficientes, o uso de *pacemaker* definitivo tem sido proposto como estratégia terapêutica, agora com maior força de robustez nas atuais Recomendações europeias. Os estudos iniciais não-aleatorizados e sem ocultação demonstravam um potencial benefício de tal intervenção, com redução da recorrência de episódios sincopais. Contudo, os estudos aleatorizados e de dupla ocultação têm resultados díspares. Tendo por base as diferenças destes estudos, os autores efetuaram uma revisão abrangente da literatura acerca da evidência do *pacing* cardíaco e respetivos algoritmos e quais os fatores a considerar na decisão diagnóstica e terapêutica individualizada, no doente com síncope vasovagal recorrente.

Introduction

Syncope is defined as a transient loss of consciousness due to global cerebral hypoperfusion characterized by short duration and spontaneous recovery.[1,2] It is one of the leading causes of emergency department admission, accounting for 1-3% of all cases, followed by hospitalization for etiological investigation in around 40% of these cases.[3,4] The vasovagal or neurocardiogenic reflex is the most common cause of syncope[5] and vasovagal syncope (VVS) can lead to considerable morbidity, even though it has not been shown to affect mortality.[6]

Reflex syncope is an important issue due to its high prevalence, incidence and associated morbidity, together with significant gaps in knowledge concerning the appropriate therapeutic approach. This review discusses the following issues: the pathophysiological mechanisms behind reflex syncope, particularly cardioinhibitory and vasodepressor responses; the definition of loss of consciousness and differential diagnosis of syncope; differential diagnosis of atrioventricular (AV) block of extrinsic and intrinsic cause; and a brief review of therapeutic approaches, particularly the potential role of pacemaker therapy.

Pathophysiology

The mechanism underlying reflex syncope is a paradoxical autonomic reflex that leads to hypotension (vasodepression) and/or bradycardia (cardioinhibition) (Figure 1). It begins with a specific stimulus that triggers the afferent pathway and culminates in an efferent response that leads to an increase in parasympathetic tone and/or in inhibition of sympathetic tone. In some circumstances, such as as carotid sinus hypersensitivity, the initial stimulus can be identified, while in others it is unknown.

Reflex syncope is often associated with orthostatic stress.[7] Orthostatism reduces venous return and hence cardiac output, blood pressure (BP), and end-diastolic volume. The reflex arc that maintains normal cerebral perfusion and prevents hypotension or syncope with orthostatic changes consists of three components. In response to lowered BP, baroreceptors in the carotid sinus, aortic arch and left ventricle send afferent stimuli to the vasomotor center in the medulla oblongata. Integration of this response results in efferent stimuli that increase sympathetic tone and circulating catecholamines and reduce parasympathetic tone, leading to vasoconstriction and positive chronotropic and inotropic effects. Triggers of the paradoxical response in patients with VVS appear to be reduced left ventricular end-diastolic volume and increased catecholamine secretion. Vigorous contraction of a relatively empty left ventricle, triggered by catecholaminergic action, stimulates mechanoreceptors in the ventricle (unmyelinated C-fibers found in all four cardiac chambers). This sends afferent impulses to the dorsal nucleus of the vagus nerve in the medulla, giving rise to an efferent impulse that paradoxically reduces sympathetic tone and/or increases parasympathetic tone, with vasodepressor (hypotension) and/or cardioinhibitory (bradycardia) effects, respectively (the Bezold–Jarisch reflex).[8] Hypotension and bradycardia, resulting in cerebral hypoperfusion, lead to loss of
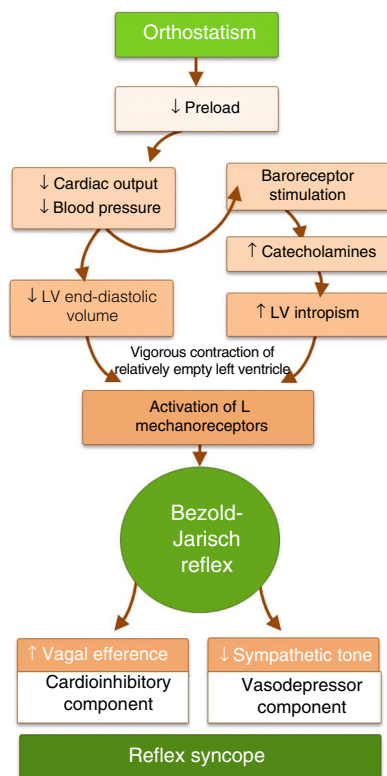
Figure 1 Pathophysiology of the Bezold–Jarisch reflex as a mechanism of reflex syncope. LV: left ventricular.

consciousness. Since both the sinoatrial and AV nodes are heavily innervated with autonomic nerves, bradycardia in the Bezold-Jarisch reflex may be due to increased vagal stimulation, decreasing the automaticity of the sinoatrial node and reducing conduction in the AV node, leading to AV block (Figure 2 and Table 1). As both vagal hyperactivity (extrinsic) and conduction system disease (intrinsic) can cause AV block and syncope, these must be distinguished due to their different therapeutic and prognostic implications.

Reflex syncope can result from a purely vasodepressor effect or, less frequently, a solely cardioinhibitory response,[9] depending on whether the efferent response inhibits sympathetic tone or increases parasympathetic tone, respectively. In the VASIS trial,[10] the cardioinhibitory response was divided into two types, 2A (defined as heart rate [HR] rising initially then falling to a ventricular rate <40 bpm for >10 s or asystole occurring for >3 s, with BP rising initially then falling before HR falls), and 2B (defined as the same behavior but with BP only falling to hypotensive levels <80 mm Hg systolic BP at or after the onset of rapid and severe HR fall). A mixed response, in which hypotension usually precedes bradycardia, appears to be the most common form.

Identifying the signals that trigger these efferent responses has proved to be a challenge, and research in humans has been limited.[7,11] Largely on the basis of animal studies, there appears to be more than one underlying mechanism. Small case-control studies on patients with a positive tilt test and simultaneous echocardiographic monitoring have shown reduced left ventricular volume during the test, supporting the concept of the 'empty ventricle'.[12,13] On

the other hand, similar studies have found no evidence of hypercontractility or increased left ventricular systolic pressure at the beginning of tilt testing,[14] which suggests that mechanical stimulation of the left ventricle is not necessarily a component of the reflex arc in all forms of VVS.[14] Interruption of ventricular C-fiber afferents in animals was shown to prevent hypotension and bradycardia in response to acute hemorrhage. However, a similar experimental study in dogs did not reproduce this result.[11] Furthermore, there are reports of heart transplantation patients who subsequently suffered VVS even though there was no evidence of significant reinnervation of the transplanted heart, which means that in these patients autonomic stimulation could not have been a cause of syncope.[15,16] Although most of these studies have been in animals and there is very little evidence from human studies, ventricular afferents do not appear to be absolutely necessary for the development of VVS; there may be other cardiovascular structures that cause VVS if stimulated as a result of hypovolemia, although there is as yet no experimental evidence for this theory.[17]

Although the Bezold–Jarisch reflex can explain hypotension and bradycardia in some cases, there must be other mechanisms that are responsible for recurrent VVS in other patients. Studies of alterations in neurotransmitters such as endogenous opioids, nitric oxide,[11] adenosine[18] or serotonin[19] suggest that they may inhibit sympathetic responses. Central or peripheral baroreceptor reflex abnormalities have been proposed as another possible pathophysiological mechanism.[17]

With regard to hemodynamic responses, in their review article, Jardine et al.[20] proposed that there is a sequence of hemodynamic changes, the 'four phases of syncope', that are common to all patients with VVS. In phase 1, termed early stabilization, a fall in venous return results in reduced systolic volume and cardiac output despite an increase in HR; mean arterial pressure is maintained by an increase in systemic vascular resistance. Phase 2, circulatory instability, occurs when there is an additional increase in lower body negative pressure (LBNP), exacerbating the effects seen in phase 1. In phase 3, terminal hypotension, as LBNP is increased, HR and cardiac output fall, BP variability virtually disappears and a classic VVS episode occurs. Phase 4 (recovery) occurs rapidly after cessation of LBNP.[20]

Differential diagnosis of vasovagal syncope

For patients with loss of consciousness in an urgent setting, VVS should be a diagnosis of exclusion after appropriate etiological investigation has ruled out other causes. Figure 3 presents a proposed simplified algorithm for the differential diagnosis of a patient with loss of consciousness admitted to the emergency department. The algorithm stresses the importance of prompt exclusion of common conditions that must be differentiated from the syncopal episode itself.[21] It also focuses on risk stratification for cardiogenic syncope, which is a simple way to identify the best approach to investigation and treatment of these patients. Although a definitive diagnosis is difficult to obtain in an urgent setting, such stratification is essential to enable low-risk patients to be appropriately and safely investigated as outpatients and
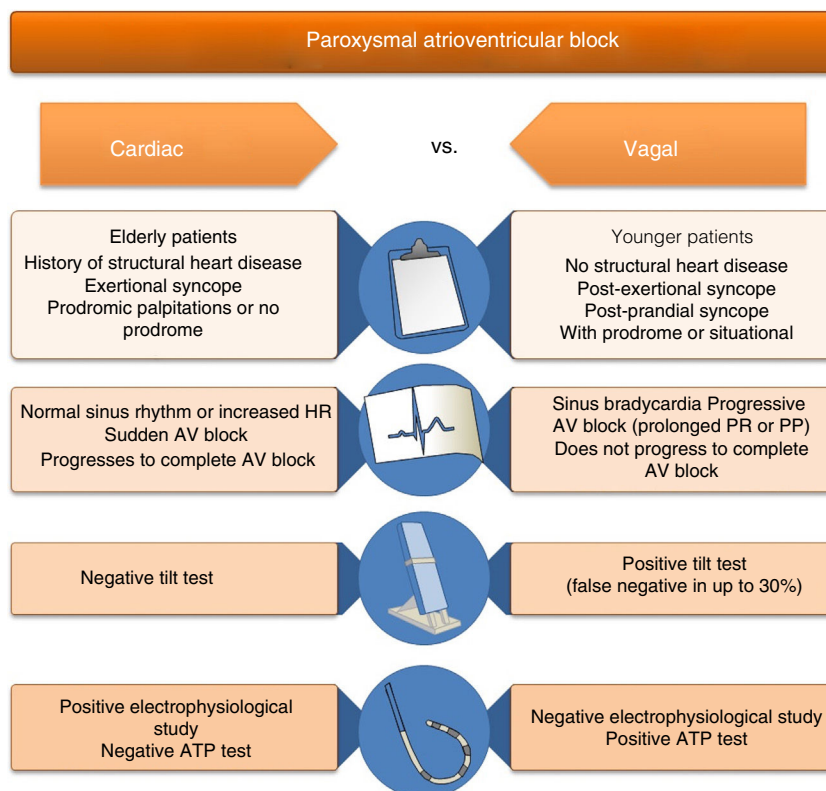
Figure 2 Differential diagnosis of causes of syncope associated with atrioventricular block. ATP: adenosine triphosphate; AV: atrioventricular; HR: heart rate.

Table 1 Differential diagnosis of atrioventricular block due to extrinsic and intrinsic causes, based on clinical history, physical examination and diagnostic exams.

AV block of intrinsic cause (alarm signs suggesting cardiac etiology)	AV block of extrinsic cause (no alarm signs, suggesting reflex etiology)
Clinical history	
First syncopal episode at older age	• Recurrent syncopal episodes in younger women
Known structural heart disease	• No known structural heart disease
Family history of sudden cardiac death	• No family history of sudden death
Syncope without prodrome (or short prodrome with palpitations)	• Marked prodrome
Exertional syncope	• Post-exertional syncope
Syncope while sitting or lying	• Syncope following orthostatic stress
ECG	
• PP interval unchanged or reduced during bradycardia or asystole	• PP interval prolonged during bradycardia or asystole
• Rapid onset of bradycardia or asystole	• Progressive prolongation of PP interval before bradycardia or asystole
• Abnormal resting ECG (LBBB, RBBB with LAFB, short or long QT interval, Mobitz II or higher AV block, Brugada pattern, Ha?ssaguerre syndrome, AF, delta wave, epsilon wave)	• Normal resting ECG

AF: atrial fibrillation; AV atrioventricular: ECG: electrocardiogram; LAFB: left anterior fascicular block; LBBB: complete left bundle branch block; RBBB: complete right bundle branch block.
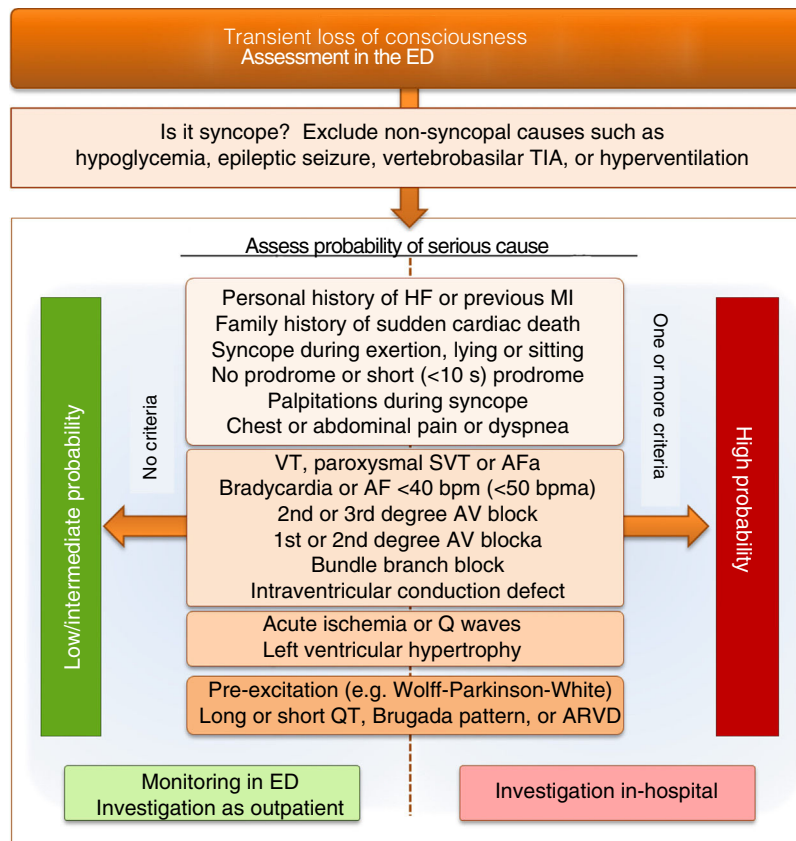
Figure 3 Differential diagnosis of loss of consciousness and syncope on admission to the emergency department, focusing on risk stratification for cardiogenic syncope. AF: atrial fibrillation; ARVD: arrhythmogenic right ventricular dysplasia; AV: atrioventricular; ED: emergency department; HF: heart failure; MI: myocardial infarction; SVT: supraventricular tachycardia; TIA: transient ischemic attack; VT: ventricular tachycardia. [a]only to be considered if history suggests arrhythmic syncope.

for high-risk patients to receive prompt monitoring, investigation and treatment in an in-hospital setting.[1,2]

In most high-risk patients with criteria for hospitalization, syncope is suspected to be of cardiogenic cause, either structural or arrhythmic. In the latter case, the implantable loop event recorder has become an indispensable diagnostic tool, especially when the cause of syncope is unknown. Published studies[22–25] have shown that implantable event recorders are more likely to diagnose the cause of syncope than Holter ECG monitoring, external event recorders, tilt testing or electrophysiological study. Although implantable event recorders are the preferred monitoring method in an outpatient setting, the European Society of Cardiology (ESC) guidelines[22] state that Holter monitoring or an external event recorder may be used in patients whose symptoms occur less than weekly or monthly, respectively.

Therapeutic approach to the patient with reflex syncope

Initial non-pharmacological therapy

The first step in the approach to patients with VVS is to educate them, beginning by explaining the benign nature of the condition and instructing them on how to avoid triggering factors such as prolonged standing, dehydration and

extremes of temperature.[1,2] Isometric physical counterpressure maneuvers such as handgrip, leg crossing or squatting significantly increase BP and, especially in patients with long prodromes who can recognize the symptoms of presyncope early, can delay or even prevent loss of consciousness.[26–28] A multicenter clinical trial showed that such measures, when performed immediately after the onset of the prodrome, reduced the relative risk (RR) of recurrence by 39%. However, 35% of randomized subjects did not use the maneuvers, because of either absence of any warning or too short duration of prodromal symptoms.[29] Furthermore, such maneuvers may not be effective in older patients with reduced muscular strength. Although the above randomized trial is the only one to study the benefit of physical counterpressure maneuvers, their harmlessness and low cost make them a valid option to be considered in the initial approach to VVS,[30] with class of recommendation IIa for younger patients in the guidelines.[22]

Measures that increase venous return, such as volume expansion by drinking up to 3 l of fluids a day and ingesting 10 g/day of salt, and wearing elastic graded compression stockings, can be used if not contraindicated, although evidence for their efficacy is limited.[1,2,28]

Another option is orthostatic training, of which there are two main forms: tilt training with repeated monitored sessions on a tilt table, and daily standing against a wall at home

for prolonged periods.[30] In a non-randomized trial including 47 adolescents, tilt training followed by standing at home reduced recurrence of syncope at 18-month follow-up.[31] However, since this method requires a high degree of motivation, long-term adherence and thus efficacy are often poor.[32] Doubts concerning its effectiveness also persist due to its failure to reduce syncope recurrence in other studies.[33–35] Overall, the currently available evidence is insufficiently robust to recommend orthostatic training as a matter of routine.

Cardioneuroablation consists of the radiofrequency ablation of ganglionated plexuses on the endocardial surface. Non-randomized studies with small study populations have suggested benefits in reducing recurrence of syncopal episodes,[36,37] which was confirmed in a recent literature review.[38] However, there is currently little evidence on the efficacy of this technique.[36,37]

Psychotherapeutic measures may be a helpful component of treatment in patients with recurrent VVS, who frequently suffer from anxiety and negative psychosocial effects. Such measures may have a synergistic effect on the response to other therapies.[39]

Finally, a thorough review of the patient's usual medication is essential. Reducing the dosage or discontinuing drugs that can potentially induce syncope, such as vasodilators and diuretics, is an important measure for preventing or reducing the likelihood of future syncopal events.[22]

Pharmacological therapy

Pharmacological therapy may be considered in patients with recurrent syncope that has a significant impact on their quality of life and is associated with a high risk of trauma, as well as those whose activities (such as driving, flying, or competitive athletics[21]) involve high risks to themselves or to others, when the condition has proved refractory to the non-pharmacological measures described above. Various drugs, acting at different points of the reflex arc, have been investigated for the treatment of VVS.[28]

Beta-blockers

Beta-blockers act on the afferent limb of the reflex arc involved in VVS. Their efficacy has been tested in various randomized clinical trials, mostly on metoprolol, pindolol and atenolol.[40–44] The largest randomized controlled double-blinded trial (POST[43]) showed that metoprolol was not effective in preventing syncope recurrence at one-year follow-up. However, a subsequent meta-analysis that included the POST trial concluded that beta-blocker therapy can be beneficial in patients aged ≥42 years of age but not in those aged <42 years.[30] Several small studies have assessed different beta-blockers, analyzing different outcomes such as tilt test results or syncope recurrence, with conflicting results.[40,41,45–47] In the absence of robust evidence in favor of beta-blockers, and given the negative results of two randomized double-blinded trials[34,36] together with the known adverse side-effects of these drugs, they are contraindicated for prevention of VVS in patients of all ages in the current guidelines (class III recommendation).[22] The randomized, triple-blinded POST 5 trail (ClinicalTrials.gov

identifier NCT02123056) aims to determine if treatment with metoprolol in patients ≥40 years old will better suppress syncope recurrences than placebo. Its results are awaited.

Midodrine

Vasopressor agents counteract the vasodepressive effect that in VVS arises as a result of reduced sympathetic tone. Midodrine, an alpha-adrenergic agonist, is frequently used in this context. In a meta-analysis including 115 patients in four studies, syncope recurrence was lower and quality of life was better during midodrine treatment than with non-pharmacological therapy or placebo.[48] A subsequent meta-analysis that included 593 patients suggested that midodrine improves clinical outcomes in patients with recurrent VVS, although the evidence was of low or moderate quality.[49]

Results are awaited from the POST 4 trial (ClinicalTrials.gov identifier NCT01456481), a randomized clinical trial designed to assess the efficacy of midodrine compared to placebo in preventing syncope recurrence. Currently available evidence indicates that midodrine may be considered for patients with VVS requiring pharmacological therapy.[1,2] Its main disadvantages are its short half-life, requiring three doses a day, and side-effects that include urinary retention and supine hypertension, which particularly limit its utility in older patients.[39]

Fludrocortisone

Fludrocortisone, a mineralocorticoid, causes fluid retention and a slight increase in BP. The multicenter randomized controlled POST 2 trial in 210 patients compared the efficacy of fludrocortisone in reducing recurrent VVS with placebo over a one-year treatment period.[50] The benefit demonstrated was only a statistical tendency in favor of fludrocortisone, but when the analysis was restricted to outcomes after two weeks of dose stabilization, there was a significant reduction in syncopal episodes in the treatment arm. It should be noted that the median age of the patients enrolled was 30 years and that those with hypertension were excluded. Fludrocortisone should thus be reserved for patients with repeated episodes of VVS and without contraindications to its use, particularly hypertension. Besides supine hypertension and weight gain, the main adverse effects are nausea and hypokalemia.[30]

Serotonin uptake inhibitors

Serotonin uptake inhibitors such as paroxetine, sertraline and fluoxetine may be of benefit for the treatment of VVS in patients who do not respond to or do not tolerate other drugs.[19,45,51] In a recent randomized placebo-controlled trial of 106 patients with recurrent VVS, scoring positive on the Anxiety Sensitivity Index and not diagnosed with psychiatric disease, the number of patients with recurrent syncope or presyncope during a one-year follow-up was lower in the fluoxetine group.[45] However, the benefit of this drug class is still uncertain and its use is not recommended due to the scarcity of available evidence.[30]

Ivabradine

In a non-randomized, non-controlled trial published in 2014 including 25 patients with postural orthostatic tachycardia syndrome, ivabradine demonstrated some benefit in reducing episodes of VVS.[52] However, evidence of its benefit in these patients is lacking and further research should be undertaken.

Use of pacemakers to treat cardioinhibitory reflex syncope

According to the most recent ESC guidelines, implantation of a permanent pacemaker (PPM) should be considered in patients aged >40 years with cardioinhibitory reflex syncope with symptomatic asystolic pause(s) >3 s or asymptomatic pause(s) >6 s or with cardioinhibitory carotid sinus syndrome with recurrent frequent unpredictable syncope (class IIa recommendation).[22] The class of recommendation was upgraded based on a review of previously available evidence and recent studies.

It should be borne in mind that the main studies on VVS have different inclusion and exclusion criteria, age of patients included, definition of the cardioinhibitory response, population characteristics and results. The following sections focus on detailed comparisons between randomized trials (Table 2).

Non-blinded randomized trials

The potential of permanent pacing to reduce syncope recurrence was initially assessed in trials in which the evidence was weakened by flaws in study design. Of these, the non-blinded randomized VPS I, VASIS and SYDIT trials will be discussed below.

VPS I (n=54) was the first randomized trial to investigate the role of permanent pacing in VVS with syncope or presyncope reproducible on tilt testing and demonstration of relative bradycardia. In this trial, there was a significant reduction in risk of syncope in patients who received a PPM with a rate-drop response (RDR) algorithm compared to placebo (22% vs. 70%; relative risk reduction [RRR] 0.85; 95% confidence interval [CI] 0.60-0.95; 2p=0.000022) at one year.[53]

The VASIS trial of 42 patients with cardioinhibitory VVS showed a statistically significant reduction in syncope recurrence in the DDI pacemaker arm compared to placebo (5% vs. 61%; RR 0.04; 95% CI 0.005-0.3; p=0.0006) in a mean follow-up of 3.76±2.2 years. Syncope recurrence was recorded in 61% of patients who did not receive a PPM, with a mean of 1.76±0.9 episodes per patient (0.44 episodes per year). Not only was recurrence rare in the PPM arm, but no syncopal episodes were associated with traumatic injury.[10]

The multicenter prospective SYDIT trial included patients aged >35 years with recurrent VVS (≥3 episodes in the previous two years) and a positive tilt test for syncope in association with relative bradycardia (HR<60 bpm). Participants were randomized to receive a DDD PPM with RDR function (n=46) or atenolol 100 mg/day (n=47) and followed for a mean of 520±266 days. In 56.0% of patients tilt-induced syncope was observed only after pharmacological provocation and a pure cardioinhibitory response to tilt testing (with asystole >3 s) was present in only 60.2%. Although this study did not have a placebo arm, and notwithstanding the limitations inherent to the study design, syncope recurrence was reduced with permanent pacing compared to medical treatment (4.3% vs. 25.5%, odds ratio [OR] 0.133; 95% CI: 0.028-0.632; p=0.004). The authors concluded that, in this population with a mean age >50 years and a high prevalence of cardioinhibitory syncopal episodes, DDR pacing was superior to pharmacological beta-blockade in reducing syncope recurrence.[54]

Blinded randomized trials

The non-blinded randomized trials described above indicated that permanent pacing could benefit selected patients. However, their study design has significant limitations and is subject to bias. Researchers accordingly proceeded with blinded randomized trials, with mixed results: some favored the use of pacing (ISSUE-3, Russo et al., SPAIN), while others showed no benefit (SYNPACE, VPS II).

The ISSUE-3 trial, in 77 patients aged ≥40 years who had experienced prolonged asystole (>3−6 s) and who received a DDD pacemaker, showed a statistically significant reduction in recurrence of cardioinhibitory VVS in the PPM ON group compared to the PPM OFF group (25% vs. 57%; RR 0.57; 95% CI 0.40-0.74; p=0.04) in a two-year follow-up. Although the trial demonstrated the efficacy of permanent pacing in this population, it should be noted that syncopal recurrence was 25% in the PPM ON group, which is higher than in the non-blinded studies described above. The authors attribute this to the likelihood of a vasodepressive component contributing to the mechanism of some syncopal episodes.[55]

The study by Russo et al. included 50 patients with cardioinhibitory VVS (asystole >3 s) who received a DDR pacemaker with closed-loop stimulation (CLS) and were randomized to CLS OFF or ON. Patients in the ON group had fewer syncopal episodes (2 vs. 15; p=0.007) over a 36-month follow-up.[56]

In the SPAIN trial (n=46), a crossover study with either DDD pacing with CLS or sham DDI pacing, there was a significantly greater number of patients with ≥50% reduction in the number of syncopal episodes in the former group (72% vs. 28%; p=0.017). Over the course of the study, syncopal events were less frequent in the DDD-CLS group than in the sham group (8.7% vs. 45.7%; hazard ratio 6.7; 95% CI 2.3–19.8) in a mean follow-up of 22.2±5.1 months. Following crossover in the second year, syncope recurred in 29% of those who had previously received DDD-CLS, while all the patients who crossed over from sham to treatment had a ≥50% reduction in the number of syncopal episodes (p=0.0003). These findings increased the weight of evidence in favor of this intervention.[57]

By contrast, in the VPS II trial (n=100), no reduction in cumulative risk of syncope was seen in patients who received DDD pacing with RDR compared to the PPM OFF group (31% vs. 40%; RRR 0.30; 95% CI -0.33-0.63; p=0.14) in a six-month follow-up.[58] Similarly, the SYNPACE study (n=29) failed to show statistically significant differences in outcomes between the group receiving DDD pacing with RDR and the PPM OFF group, including in subgroup analysis (cardioinhibitory and mixed response), after a median

Table 2 Summary of evidence from trials investigating permanent pacing compared to placebo for treatment of vasovagal syncope that randomized more than 20 patients.

Trial	VPS I (Connolly et al.[53])	VASIS-PM (Sutton et al.[10])	VPS II (Connolly et al.[58])	SYNPACE (Raviele et al.[59])	ISSUE-3 (Brignole et al.[55])	Russo et al.[56]	SPAIN (Baron-Esquivias et al.[57])
Center(s)	Multicenter	Multicenter	Multicenter	Multicenter	Multicenter	Multicenter	Multicenter
Study design	Randomized	Randomized	Randomized	Randomized	Randomized, 12-month crossover	Randomized, 18-month crossover	Randomized
Blinded	No	No	Double	Double	Double	Single	Double
No. of patients	54	42	100	29	77	50	46
PPM arm vs. placebo arm	27 vs. 27	19 vs. 23	48 vs. 52	16 vs. 13	38 vs. 39	NI	21 vs. 25
Placebo arm	No intervention	No intervention	PPM OFF	PPM OFF	PPM OFF	PPM OFF	Sham PPM
Mean follow-up	NI	3.76±2.2 years	6 months	715 (302–785) days	24 months	36 months	22.2±5.1 months
Inclusion criteria							
Type of syncope	Vasovagal	Vasovagal	Vasovagal	Vasovagal	Vasovagal	Vasovagal	Vasovagal
No. of syncopal episodes	≥6	≥3 in the last 2 years	≥3 in the last 2 years	≥6	≥3 in the last 2 years	≥2	≥5
Last syncopal episode	–	<6 months	–	<6 months	–	–	≥2 in the last year
Time between first and last episode	–	>6 months	–	–	≥1 month	–	–
Criteria of cardioinhibition with reproduction of syncope	HR<60 bpm if no isoproterenol used, or <70 bpm if ≤2 μg/min or <80 bpm if >2 μg/min of isoproterenol	HR<40 bpm for >10 s or asystole >3 s with BP fall	HR × BP product <6000	HR<60 bpm for >10 s or asystole ≥3 s	Asystole >3 s with syncope or >6 s with presyncope or asymptomatic	Asystole >3 s with BP fall	HR<40 bpm for >10 s or asystole >3 s with BP fall
Detection of cardioinhibition	TT	TT	TT	TT	ILR	TT	TT

Table 2 (*Continued*)

Trial	VPS I (Connolly et al.[53])	VASIS-PM (Sutton et al.[10])	VPS II (Connolly et al.[58])	SYNPACE (Raviele et al.[59])	ISSUE-3 (Brignole et al.[55])	Russo et al.[56]	SPAIN (Baron-Esquivias et al.[57])
Intervention	PPM vs. placebo	PPM vs. placebo	PPM ON vs. PPM OFF	PPM ON vs. PPM OFF	PPM ON vs. PPM OFF	PPM ON vs. PPM OFF	PPM vs. sham DDI
PPM programming	DDI-RDR	DDI-RDR	DDD-RDR	DDD-RDR	DDD-RDR	DDD-CLS	DDD-CLS
Other	–	Age >40 years or <40 years if refractory to drug therapy	Age >19 years	Age >18 years and ≥1 syncope within 12 months of positive TT	Age >40 years, refractory to therapy	Age >40 years, SR	Age >40 years with normal ECG
Exclusion criteria							
Pure vasopressor syncope	Excluded	Excluded	Included[b]	Excluded	Excluded	Excluded	Excluded
Other key criteria	Severe chronic disease, CSH, significant valve disease	MI <6 months, HF (NYHA III-IV), severe chronic disease	Abnormal ECG, severe chronic disease	MI <6 months, HF (NYHA III-IV), severe chronic disease, CSH	HSC, new-onset HF, LVEF≤40%, MI	Hypertension, diabetes, HF, anemia, CAD	CSH
Population characteristics (PPM arm)							
Mean age, years	46±18[a]	64±11[a]	50±18	52±19	63±14	53±5	57±13
Male	30%	58%	27%[a]	31%	53%	66%	48%
Mean previous syncopal episodes	14 (8–35)	5 (3–12)	15 (8–50)	14 (9–30)	7 (4–12)	7±3	12 (9–20)
Presyncope	NI	63%	71%	3 (0–10)	50%	NI	NI
Asystole >3 s	0%	86%	0%	52%	100%	100%	76%
History of trauma	NI	42%	13%	25% (major)	5% (major) 39% (minor)	8%	NI
Outcomes							
Recurrence of syncope (PPM vs. placebo)	22% vs. 70%[a]	5% vs. 61%[a]	31% vs. 40%	50% vs. 38%	25% vs. 57%[a]	2 vs. 15[a]	8.7% vs. 45.7%[a]

BP: blood pressure; CAD: coronary artery disease; CLS: closed-loop stimulation; CSH: carotid sinus hypersensitivity; ECG: electrocardiogram; HF: heart failure; HR: heart rate; ILR: implantable loop recorder; LVEF: left ventricular ejection fraction; MI: myocardial infarction; NI: no information; NYHA: New York Heart Association functional class; PPM: permanent pacemaker; RDR: rate-drop response; SR: sinus rhythm; TT: tilt test.

[a] p<0.05 compared to placebo.
[b] Based on the criteria for cardioinhibition and vasodepression from the VASIS trial.[10]

715-day follow-up. A cardioinhibitory response was defined as syncope reproducible on tilt testing associated with asystole ≥3 s or HR<60 bpm. Tilt testing was only positive after administration of nitroglycerin in 69% of patients. An asystolic response was present in 52% of patients and a mixed response in 48%.[59]

The results of these studies have been the subject of considerable debate. Possible reasons put forward for the apparent disparities include differences between studies in inclusion criteria, study design and PPM programming in the intervention arm, as well as a genuine absence of benefit of permanent pacing in VVS. Importantly, the positive studies tended to include older patients, which raises questions concerning the effect of age on the different pathophysiological mechanisms underlying VVS. Furthermore, in the SYNPACE trial, the criteria for mixed-response syncope were relatively broad, covering patients with HR<60 bpm (as opposed to the usual <40 bpm) for >10 s, and these patients represented 48% of the study population.[59] These criteria may have led to the inclusion of patients with syncope of predominantly vasodepressive pathophysiology. Similarly, the VPS II trial included patients with predominantly vasodepressive syncope, since the mean lowest HR recorded was 53 bpm and only 19% of patients had HR<40 bpm, in contrast to the inclusion criteria of the positive studies, which were more restrictive concerning a cardioinhibitory response.

The diagnostic value of tilt testing for accurate diagnosis of a cardioinhibitory response as a cause of syncope has been questioned.[60] However, current evidence indicates that a cardioinhibitory response during tilt testing predicts asystolic syncope with high probability, and on this basis, the latest ESC guidelines recommend tilt testing as essential in the diagnostic algorithm for asystole, guiding the decision to use pacemaker therapy, particularly in patients aged >40 years with recurrent cardioinhibitory syncope.[22]

According to a meta-analysis assessing whether pacing reduces risk of reflex syncope, the evidence for its use in this condition is limited.[61] Although its analysis of unblinded trials points to lower incidence of syncope with pacing, the only two double-blinded randomized trials included (SYNPACE and ISSUE-3) failed to show a statistically significant effect. The authors suggest that this discrepancy may be the result of bias in the unblinded trials.[61] Even so, it would be interesting to update this systematic review to include the recently published SPAIN trial, which satisfied all the requirements for inclusion criteria discussed by the authors, and could alter the conclusions of their analysis.

In summary, bearing in mind that reflex syncope does not affect mortality and is frequently found in younger individuals, as well as the risks involved in placement of a PPM and the conflicting evidence on its efficacy, pacing should be reserved for patients who are most likely to benefit from the intervention. The decision process should include assessment of recurrence, the underlying pathophysiological mechanism, and the impact of the condition on the patient's quality of life, as well as response to therapeutic measures such as physical counterpressure maneuvers. Pacemaker therapy should thus be considered for carefully selected patients aged >40 years
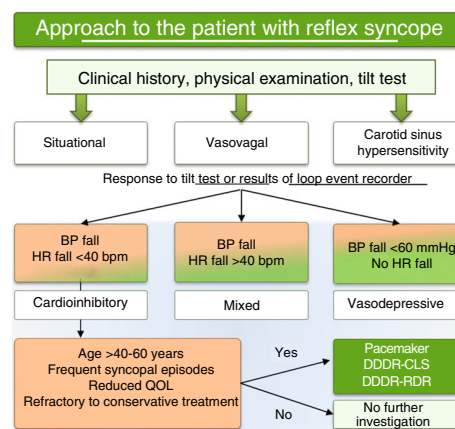

Figure 4 Treatment decision algorithm to select potential candidates for permanent pacing. BP: blood pressure; CLS: closed-loop stimulation; HR: heart rate; QOL: quality of life; RDR: rate-drop response.

with frequent recurrence and documented cardioinhibitory response.

DDD pacing with CLS detects alterations in the contraction dynamics of the right ventricle by measuring changes in intracardiac impedance. If such an alteration is detected in the initial stage, before a syncopal episode begins, the PPM is able to respond early and prevent the syncope from occurring. The benefits of this capability were first seen in small observational studies.[62,63] In the INVASY trial (n=50), a single-blind prospective study including patients with recurrent syncope and positive tilt test with cardioinhibition and refractory to conventional measures randomized to DDD pacing with CLS or DDI, no syncope occurred in patients programmed to CLS.[64] The study by Russo et al.[56] and the SPAIN trial[57] described above provided further evidence in favor of this programming algorithm.

Treatment decision algorithm

Current evidence does not support the routine use of pacing in patients with VVS, but does indicate a role for pacing with RDR or CLS capability in subgroups with frequent recurrence of cardioinhibitory syncope, especially those aged >40-50 years and refractory to other treatment. We accordingly present a treatment decision algorithm for the use of permanent pacing based on current evidence, designed to reduce overuse in patients unlikely to benefit and to avoid underuse in patients for whom the intervention is potentially beneficial (Figure 4). The proposed algorithm is in line with the latest ESC guidelines for the diagnosis and management of syncope,[22] which put forward the novel idea that treatment of reflex syncope is better guided by the form of presentation (bradycardia and/or hypotension) than by its etiology. This is in line with the evidence that pacing is only beneficial in certain clinical entities, particularly cardiogenic syncope due to significant bradycardia, cardioinhibitory carotid sinus syndrome, and cardioinhibitory VVS. Based on this reasoning and the results of the ISSUE-3 and SPAIN trials, pacing is a class IIa recommendation in the current ESC guidelines

for patients aged >40 years with recurrent cardioinhibitory syncope.[22]

Conclusion

The therapeutic approach to VVS remains a challenge, particularly in patients whose quality of life is affected by recurrent syncopal episodes and who fail to respond to pharmacological and non-pharmacological measures. Permanent pacing is an option in appropriately selected patients, i.e. those in whom reflex syncope is predominantly cardioinhibitory and who suffer from frequent recurrent syncopal episodes with a significant effect on their quality of life (including a history of major trauma), when other therapeutic options have been exhausted.

Funding

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Moya A, Sutton R, Ammirati F, et al. Guidelines for the diagnosis and management of syncope (version 2009). Eur Heart J. 2009;30(21):2631–71.
2. Shen WK, Sheldon RS, Benditt DG, et al. 2017 ACC/AHA/HRS guideline for the evaluation and management of patients with syncope: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Heart Rhythm. 2017;14(8):e155–217.
3. Toarta C, Mukarram M, Arcot K, et al. Syncope prognosis based on emergency department diagnosis: a prospective cohort study. Acad Emerg Med. 2017. SN: 1069-6563.
4. Sousa P, Marques N, Faria R, et al. Syncope unit: experience of a center using diagnostic flowcharts for syncope of uncertain etiology after initial assessment. Rev Port Cardiol. 2013;32(7-8):581–91.
5. da Silva RM. Syncope: epidemiology, etiology, and prognosis. Front Physiol. 2014;5:471.
6. Soteriades ES, Evans JC, Larson MG, et al. Incidence and prognosis of syncope. N Engl J Med. 2002;347(12):878–85.
7. Alboni P, Alboni M. Typical vasovagal syncope as a defense mechanism for the heart by contrasting sympathetic overactivity. Clin Auton Res. 2017;27(4):253–61.
8. Campagna JA, Carter C. Clinical relevance of the Bezold–Jarisch reflex. Anesthesiology. 2003;98(5):1250–60.
9. Barón-Esquivias G, Pedrote A, Cayuela A, et al. Long-term outcome of patients with asystole induced by head-up tilt test. Eur Heart J. 2002;23(6):483–9.
10. 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(3):294–9.
11. Rea RF, Thames MD. Neural control mechanisms and vasovagal syncope. J Cardiovasc Electrophysiol. 1993;4(5):587–95.
12. Nwosu EA, Rahko PS, Hanson P, et al. Hemodynamic and volumetric response of the normal left ventricle to upright tilt testing. Am Heart J. 1994;128(1):106–13.
13. Yamanouchi Y, Jaalouk S, Shehadeh AA, et al. Changes in left ventricular volume during head-up tilt in patients with vasovagal syncope: an echocardiographic study. Am Heart J. 1996;131(1):73–80.
14. Liu JE, Hahn RT, Stein KM, et al. Left ventricular geometry and function preceding neurally mediated syncope. Circulation. 2000;101(7):777–83.
15. Montebugnoli L, Montanari G. Vasovagal syncope in heart transplant patients during dental surgery. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1999;87(6):666–9.
16. Scherrer U, Vissing S, Morgan BJ, et al. Vasovagal syncope after infusion of a vasodilator in a heart-transplant recipient. N Engl J Med. 1990;322(9):602–4.
17. Mosqueda-Garcia R, Furlan R, Tank J, et al. The elusive pathophysiology of neurally mediated syncope. Circulation. 2000;102(23):2898–906.
18. Shen WK, Hammill SC, Munger TM, et al. Adenosine: potential modulator for vasovagal syncope. J Am Coll Cardiol. 1996;28(1):146–54.
19. Di Girolamo E, Di Iorio C, Sabatini P, et al. Effects of paroxetine hydrochloride, a selective serotonin reuptake inhibitor, on refractory vasovagal syncope: a randomized, double-blind, placebo-controlled study. J Am Coll Cardiol. 1999;33(5):1227–30.
20. Jardine DL, Wieling W, Brignole M, et al. Pathophysiology of the vasovagal response. Heart Rhythm. 2018;15(6):921–9.
21. Brignole M. Diagnosis and treatment of syncope. Heart. 2007;93(1):130–6.
22. Brignole M, Moya A, de Lange FJ, et al. ESC Scientific Document Group. 2018 ESC Guidelines for the diagnosis and management of syncope. Eur Heart J. 2018:1–69.
23. Krahn AD, Klein GJ, Yee R, et al. Randomized assessment of syncope trial: conventional diagnostic testing versus a prolonged monitoring strategy. Circulation. 2001;104(1):46–51.
24. Farwell DJ, Freemantle N, Sulke N. The clinical impact of implantable loop recorders in patients with syncope. Eur Heart J. 2006;27(3):351–6.
25. Podoleanu C, DaCosta A, Defaye P, et al. Early use of an implantable loop recorder in syncope evaluation: a randomized study in the context of the French healthcare system (FRESH study). Arch Cardiovasc Dis. 2014;107(10):546–52.
26. Brignole M, Croci F, Menozzi C, et al. Isometric arm counterpressure maneuvers to abort impending vasovagal syncope. J Am Coll Cardiol. 2002;40(11):2053–9.
27. Krediet CT, van Dijk N, Linzer M, et al. Management of vasovagal syncope: controlling or aborting faints by leg crossing and muscle tensing. Circulation. 2002;106(13):1684–9.
28. Sutton R. Reflex syncope: diagnosis and treatment. J Arrhythm. 2017;33(6):545–52.
29. van Dijk N, Quartieri F, Blanc JJ, et al. Effectiveness of physical counterpressure maneuvers in preventing vasovagal syncope: the Physical Counterpressure Manoeuvres Trial (PC-Trial). J Am Coll Cardiol. 2006;48(8):1652–7.
30. Lee AK, Krahn AD. Evaluation of syncope: focus on diagnosis and treatment of neurally mediated syncope. Expert Rev Cardiovasc Ther. 2016;14(6):725–36.
31. Di Girolamo E, Di Iorio C, Leonzio L, et al. Usefulness of a tilt training program for the prevention of refractory

neurocardiogenic syncope in adolescents: a controlled study. Circulation. 1999;100(17):1798–801.

32. Ector H, Reybrouck T, Heidbüchel H, et al. Tilt training: a new treatment for recurrent neurocardiogenic syncope and severe orthostatic intolerance. Pacing Clin Electrophysiol. 1998;21 1 Pt 2:193–6.

33. Foglia-Manzillo G, Giada F, Gaggioli G, et al. Efficacy of tilt training in the treatment of neurally mediated syncope. A randomized study. Europace. 2004;6(3):199–204.

34. On YK, Park J, Huh J, et al. Is home orthostatic self-training effective in preventing neurally mediated syncope? Pacing Clin Electrophysiol. 2007;30(5):638–43.

35. Tan MP, Newton JL, Chadwick TJ, et al. Home orthostatic training in vasovagal syncope modifies autonomic tone: results of a randomized, placebo-controlled pilot study. Europace. 2010;12(2):240–6.

36. Pachon JC, Pachon EI, Cunha Pachon MZ, et al. Catheter ablation of severe neurally meditated reflex (neurocardiogenic or vasovagal) syncope: cardioneuroablation long-term results. Europace. 2011;13(9):1231–42.

37. 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;5(2):279–86.

38. Aksu T, Güler TE, Bozyel S, et al. Cardioneuroablation in the treatment of neurally mediated reflex syncope: a review of the current literature. Turk Kardiyol Dern Ars. 2017;45(1):33–41.

39. Raj SR, Coffin ST. Medical therapy and physical maneuvers in the treatment of the vasovagal syncope and orthostatic hypotension. Prog Cardiovasc Dis. 2013;55(4):425–33.

40. 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(6):1250–3.

41. 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(2):554–9.

42. 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(3):499–504.

43. 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(9):1164–70.

44. 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(3):339–42.

45. Theodorakis GN, Leftheriotis D, Livanis EG, et al. Fluoxetine vs. propranolol in the treatment of vasovagal syncope: a prospective, randomized, placebo-controlled study. Europace. 2006;8(3):193–8.

46. Cohen MB, Snow JS, Grasso V, et al. Efficacy of pindolol for treatment of vasovagal syncope. Am Heart J. 1995;130(4):786–90.

47. Iskos D, Dutton J, Scheinman MM, et al. Usefulness of pindolol in neurocardiogenic syncope. Am J Cardiol. 1998;82(9):1121–4. A9.

48. Liao Y, Li X, Zhang Y, et al. Alpha-Adrenoceptor agonists for the treatment of vasovagal syncope: a meta-analysis of worldwide published data. Acta Paediatr. 2009;98(7):1194–200.

49. Izcovich A, González Malla C, Manzotti M, et al. Midodrine for orthostatic hypotension and recurrent reflex syncope: a systematic review. Neurology. 2014;83(13):1170–7.

50. Sheldon R, Raj SR, Rose MS, et al. Fludrocortisone for the prevention of vasovagal syncope: a randomized, placebo-controlled trial. J Am Coll Cardiol. 2016;68(1):1–9.

51. Grubb BP, Samoil D, Kosinski D, et al. Use of sertraline hydrochloride in the treatment of refractory neurocardiogenic syncope in children and adolescents. J Am Coll Cardiol. 1994;24(2):490–4.

52. Sutton R, Salukhe TV, Franzen-McManus AC, et al. Ivabradine in treatment of sinus tachycardia mediated vasovagal syncope. Europace. 2014;16(2):284–8.

53. 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(1):16–20.

54. 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(1):52–7.

55. 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 Uncertain Etiology (ISSUE-3): a randomized trial. Circulation. 2012;125(21):2566–71.

56. Russo V, Rago A, Papa AA, et al. The effect of dual-chamber closed-loop stimulation on syncope recurrence in healthy patients with tilt-induced vasovagal cardioinhibitory syncope: a prospective, randomised, single-blind, crossover study. Heart. 2013;99(21):1609–13.

57. Baron-Esquivias G, Morillo CA, Moya-Mitjans A, et al. Dual-chamber pacing with closed loop stimulation in recurrent reflex vasovagal syncope: the SPAIN study. J Am Coll Cardiol. 2017;70(14):1720–8.

58. Connolly SJ, Sheldon R, Thorpe KE, et al. 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(17):2224–9.

59. Raviele A, Giada F, Menozzi C, et al. A randomized, double-blind, placebo-controlled study of permanent cardiac pacing for the treatment of recurrent tilt-induced vasovagal syncope. The vasovagal syncope and pacing trial (SYNPACE). Eur Heart J. 2004;25(19):1741–8.

60. Brignole M, Donateo P, Tomaino M, et al. 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 Arrhythm Electrophysiol. 2014;7(1):10–6.

61. Varosy PD, Chen LY, Miller AL, et al. Pacing as a treatment for reflex-mediated (vasovagal, situational, or carotid sinus hypersensitivity) syncope: a systematic review for the 2017 ACC/AHA/HRS guideline for the evaluation and management of patients with syncope: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Heart Rhythm. 2017;14(8):e255–69.

62. Kanjwal K, Karabin B, Kanjwal Y, et al. Preliminary observations on the use of closed-loop cardiac pacing in patients with refractory neurocardiogenic syncope. J Interv Card Electrophysiol. 2010;27(1):69–73.

63. Bortnik M, Occhetta E, Dell'Era G, et al. Long-term follow-up of DDDR closed-loop cardiac pacing for the prevention of recurrent vasovagal syncope. J Cardiovasc Med (Hagerstown). 2012;13(4):242–5.

64. Occhetta E, Bortnik M, Audoglio R, et al. INVASY Study Investigators. Closed loop stimulation in prevention of vasovagal syncope. Inotropy Controlled Pacing in Vasovagal Syncope (INVASY): a multicentre randomized, single blind, controlled study. Europace. 2004;6(6):538–47.