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EDITORIAL

Management and therapy of vasovagal syncope: A review

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Abstract

Vasovagal syncope is a common cause of recurrent syncope. Clinically, these episodes may present as an isolated event with an identifiable trigger, or manifest as a cluster of recurrent episodes warranting intensive evaluation. The mechanism of vasovagal syncope is incompletely understood. Diagnostic tools such as implantable loop recorders may facilitate the identification of patients with arrhythmia mimicking benign vasovagal syncope. This review focuses on the management of vasovagal syncope and discusses the non-pharmacological and pharmacological treatment options, especially the use of midodrine and selective serotonin reuptake inhibitors. The role of cardiac pacing may be meaningful for a subgroup of patients who manifest severe bradycardia or asystole but this still remains controversial.

Key words: Vasovagal syncope; Midodrine; Adrenergic β-antagonists; Serotonin uptake inhibitors

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INTRODUCTION

Syncope is a common clinical problem challenging both cardiologists and general practitioners with an annual incidence of 1.3 to 2.7 events per thousand population[1]. The aim of this review is to present a review on the management and treatment of vasovagal syncope. It covers new aspects presented in current guidelines for the diagnosis and management[2], and new data for risk stratification[3].

The main aim of the evaluation is to distinguish patients with a benign cause like vasovagal syncope from patients with life-threatening conditions like arrhythmias, severe cardiovascular diseases or neurological causes to minimize the risk of sudden cardiac death. There is still a high unexplained syncope rate in all settings, so new strategies for evaluation and diagnosis are crucial.

DEFINITIONS: SYNCOPE, PRESYNCOPE, REFLEX SYNCOPE, VASOVAGAL SYNCOPE

Syncope is defined as a transient and self-terminating loss of consciousness (LOC) with rapid onset, short duration combined with spontaneous, prompt and complete recovery. Syncope is characterized by global cerebral hypoperfusion[2]. It is essential to discriminate syncope from other disorders with transient LOC, e.g. seizure, hypoglycemia, catalepsy or aborted sudden cardiac death. In most cases a detailed medical history and information about the trigger situation allows identification of cause. To avoid confusion, syncope should not be used as a synonym for transient loss of consciousness. The term 'pre-syncope' or 'near-syncope' is used to describe a state that resembles the prodrome of syncope but which is not followed by LOC[2]. It is important to underline that doubts remain

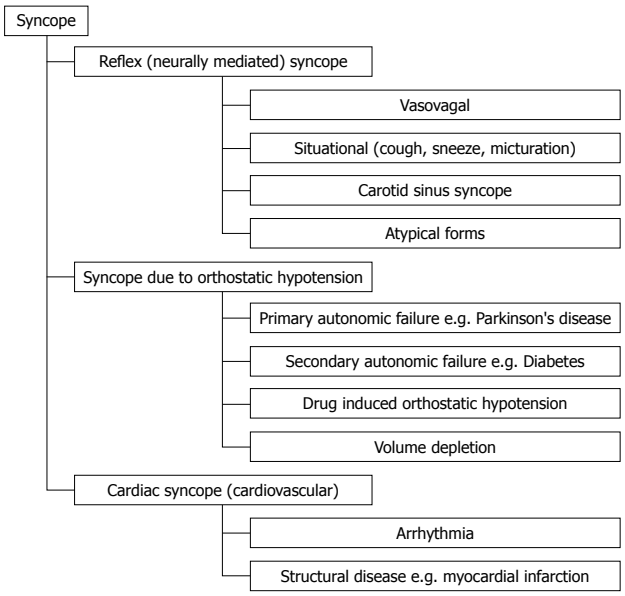

Figure 1 Classification of syncope.

as to whether the pathophysiological mechanisms of presyncope are the same as in syncope. Figure 1 displays a pathophysiological classification defined in the new guidelines: the first mechanism is a reflex causing bradycardia induced by typical triggers. The second is induced by inadequate venous return, due to volume depletion or venous pooling. The third is due to cardiovascular causes, such as arrhythmia and structural diseases[2].

The reflex syncope includes different types of syncope which all show a typical trigger circumstance and an induction of cardiovascular reflexes. Activation of these sympathetic and parasympathetic reflex loops instigates either hypotension (vasodepressor type) or bradycardia (cardioinhibitory type) or both (mixed type)[4]. The term neurocardiogenic syncope should not be used any longer.

Current guidelines subclassify reflex syncope into vasovagal, situational, carotid sinus syncope, and atypical reflex syncopes[2]. 'Vasovagal' syncope, also known as the 'common faint', is mediated by emotion or by orthostatic stress. It is usually preceded by prodromal symptoms of autonomic activation (sweating, pallor, nausea)[2].

EPIDEMIOLOGY

Epidemiological studies indicate that up to 40% of the general population has experienced at least one episode of syncope in their lifetime[5-9]. Savage *et al*[1] reported an incidence of 1.3 per 1000 person-years for at least one syncopal episode and 1.0 per 1000 person-years in subjects with criteria for isolated syncope (likely vasovagal syncope). Soteriades *et al*[7] reported an overall incidence of a first report of syncope in 6.2 per 1000 person-years. Recently a large database with reasons for encounters of general practitioners in the Netherlands revealed that 2 to 9 per 1000 encounters are due to blackouts or fainting[10].

A reflex syncope is the most frequent cause of syncope in any setting and age group[2] representing 21% of all syncopes in the general population[7], 35%-48% of syncopes presenting to the emergency department[11] and 56%-78% of syncopes in a specialized syncope unit[11,12]. The vasovagal syncope is by far the most common reflex syncope in young patients. Clinical studies reveal a peak incidence between 10 and 30 years of age[5,13]. The epidemiology of syncope is different in relation to age. In younger patients a neurally-mediated mechanism is the most common cause, while in older patients cardiovascular causes are more prevalent. The actual incidence and prevalence of vasovagal syncope in the elderly has not yet been established, but vasovagal syncope is now being diagnosed with increasing frequency in this age group, suggesting a bimodal age distribution of vasovagal syncope[14]. In the elderly, cardiac causes, orthostatic and postprandial hypotension, and the effects of medications are common, whereas typical vasovagal syncope is less frequent[10]. In the older patients the diagnostic work-up is more complex, the prognosis may not necessarily follow the benign course commonly observed in younger patients and therapy often remains uncertain. In this paper the management and treatment of vasovagal syncope focuses on patients with vasovagal syncope.

ETIOLOGY AND PATHOPHYSIOLOGY

The pathophysiology of the hypotension/bradycardia reflex responsible for vasovagal syncope is not completely understood. Central as well as peripheral mechanisms have been implicated in its pathogenesis; however their relative contribution is not fully elucidated. The different clinical presentation of vasovagal syncope, the variable outcome and the syncope tilt-induced with different drugs such as isoproterenol, nitroglycerin, or clomipramine, acting at very different levels of the reflex pathway, suggest that complex pathophysiological mechanisms may cause a vasovagal reaction.

The pathophysiology of vasovagal syncope is characterized by a reflex activation triggering a rapid decrease in heartbeat and a reduction of vascular tone[15]. The concept of depressor reflexes originating in the heart was first described by von Bezold in 1867 and was later revised by Jarisch in 1937. The change to an upright position causes venous pooling: up to 800 mL of blood flows down to the legs. By activation of the autonomous system contractility and heartbeat increases to maintain sufficient circulating heart volume[16]. In the first moments of a vasovagal syncope an empty heart is seen in echocardiographic investigations because of an acute loss of preload ('empty heart' syndrome)[17].

Mechanoreceptors located in the wall of the left ventricle, the aorta and the pulmonary trunk were activated. Sensory receptors with non-myelinated vagal afferent pathways (found mainly in the left ventricle but also in the bladder, lungs or esophagus), detect and control cardiac filling to preserve a sufficient vascular tone. Stimulation of these inhibitory cardiac receptors by stretch forces, chemical substances or drugs heightens parasympathetic

activity and inhibits sympathetic activity[18]. Vagal c-type nerve fibers connect the heart with the brainstem. Within the brainstem vagal neurons are stimulated and the activity of cells of the sympathetic nervous system is depressed.

Activation of this reflex mechanism provokes bradycardia, vasodilatation and hypotension. Furthermore, non-cardiac, humoral effects are part of the efferent leg of this reflex loop: e.g. renin, catecholamine and glucocorticoid secretion is augmented[19]. Conversely, a decrease in the activity of these inhibitory sensory receptors stimulates an increase in sympathetic activity, vascular resistance, plasma renin activity and vasopressin. The main trigger for this reflex loops is a reduction in venous return during upright position. Factors which augment this reflex response include extravascular factors such as a warm environment or psychological stress[20].

The different types of vasovagal syncope are explained by different degrees of activation or depression of the autonomous nervous system: a more intensive activation of the parasympathetic nervous system provokes bradycardia, the main symptom of cardioinhibitory vasovagal syncope. The primarily acute loss of sympathetic stimulation is the reason for the drop of blood pressure, the main symptom of the vasodepressive type. Nevertheless in most cases a combined mechanism is seen. Recent data in patients with vasovagal syncope undergoing tilt testing potentiated by intravenous clomipramine, suggested that the neurally-mediated syncope can not only be provoked by increased sympathetic nerve tone, but can also be initiated by some central nervous system triggers of the serotoninergic system[21]. In addition, in older subjects the mechanisms of tilt-induced syncope seems to be different than in younger subjects, justifying at least partially the different clinical pattern of neurally-mediated reflex syncope.

CLINICAL PRESENTATION

Although most patients display typical conditions and signs of a vasovagal syncope such as symptom onset during standing, light-headedness and full recovery after a few minutes, up to 30% have an atypical presentation. In some cases syncope occurs without any prodromal symptoms[22]. The loss of consciousness is usually brief and fatigue is rarely seen. In the case of longer lasting cerebral hypoperfusion seizure-like movements are observed, imitating an epileptic seizure.

Symptoms before fainting are caused by reduced cerebral perfusion. The patients complain of fatigue, weakness, dizziness, wetness of the skin, a dimming of vision, and sometimes tinnitus and complete loss of vision. Some patients suffer trauma, though severe traumatic injuries are rare.

DIAGNOSTICS

Basic diagnostics

Many sophisticated tools, provocation tests and diagnostic methods have been introduced to diagnose vasovagal syncope though none are definitive. An exhaustive in-depth history and detailed examination are essential for diagnosis[23,24]. The identification of life-threatening conditions in which syncope is only the indicator of an underlying cardiovascular disease is paramount.

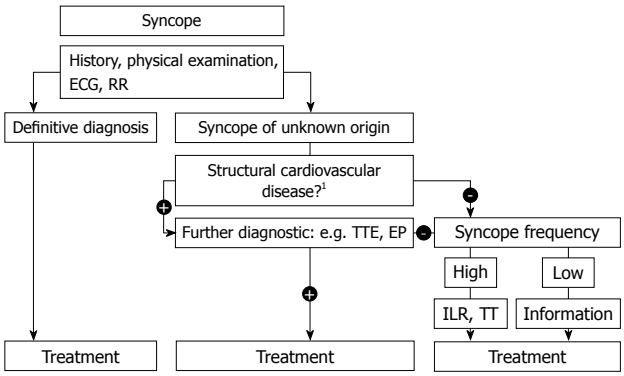

Figure 2 Diagnostic pathway in syncope. [1]Structural heart disease (e.g. valvular, myocardial infarction) or vascular diseases (e.g. pulmonary embolism, aortic disease). ECG: Electrocardiography; RR: Non-invasive blood-pressure; TTE: Transthoracic echocardiography; EP: Electrophysiologic study; ILR: Implantable loop recorder; TT: Head-up tilt table test.

Most experts recommend a standard 12-lead electrocardiography (ECG) as a routine investigation to rule out heart rhythm disturbances[22]. In any patient with a history of cardiac disease and/or an abnormal examination, e.g. heart murmurs, echocardiography and/or stress-ECG is justified (Figure 2).

Special tests in suspected vasovagal syncope

Tilt table test: In patients with unexplained syncope and ambiguous history for a vasovagal syncope, a tilt table test may help to support a diagnosis[2]. Fundamental to tilt testing is the ability to replicate the patient's symptoms, during which critical observations of heart rate and blood pressure are documented[25]. A head-up tilt table test is a widely employed method in the diagnosis of syncopal disorders. Many investigations reported its usefulness in detecting neurally-mediated syncope[26]. Different tilt table protocols are introduced with variations in the initial stabilization phase, duration of tilting (20 to 45 min) and application of pharmacological agents[27,28]. Currently the most used protocols are the intravenous isoproterenol test, and the protocol using sublingual nitroglycerin[29,30]. Some protocols use adenosine[31], clomipramine[32] or alcohol[33] to provoke syncope. We use a method commonly known as the Westminster protocol, which was first introduced by Fitzpatrick *et al*[34]. After maintaining a supine position of 10 min the patient is tilted to a head-up angle of 60°. If symptoms are not proved within a few minutes sublingual nitroglycerin is administered as additional provocation. Using the same protocol, Raviele *et al*[35] observed a positive test response in 51% of patients with unexplained syncope; the test resulted in a specificity of 94%. In a recent analysis of pooled data published by Brignole, a positive head-up tilt table test was found in 62%-69% of patients with unexplained syncope, with a sensitivity of

94%[36]. Due to a lack of a gold standard, sensitivity and specificity of the tilt table test for patients with vasovagal syncope is not exactly known. Furthermore, the tilt table test presents several disadvantages. First, the test is time-consuming and requires experienced medical staff and appropriate technical equipment such that small clinics and general practitioners cannot perform this investigation. Second, the reproducibility of a positive head-up tilt table test varies enormously. Foglia-Manzillo *et al*[37] could reproduce a first positive head-up tilt table test in 77% of 34 patients, whereas Ruiz *et al*[38] found a reproducibility rate for the positive and negative head-up tilt table test of 54.5% and 84.3%, respectively. Third, several studies have shown that the mechanism of syncope during a tilt table test is not equivalent to that of a spontaneous syncope. For this reason, the tilt table test is not a useful method to determine therapeutic strategies for patients with vasovagal syncope.

The implantable loop recorder: The main goal of the evaluation of patients with syncope is to rule out cardiac arrhythmia as a marker of a high risk for cardiac death[15]. Continuous monitoring increases the likelihood of arrhythmia detection, with modern implantable loop recorders (ILRs) capable of continuous recording for up to 18 months. The ILR is implanted subcutaneously in the left hemithorax with automatic and patient-activated ECG-documentation modes available on most devices. Many studies have shown its value in detection of infrequent arrhythmias[39-41]. Current guidelines suggest ILR implantation for unexplained syncopes. In patients with vasovagal syncopes a significant cardioinhibitory reaction is seen in 25% and a mild decrease of the heart rate in 50% of all falls. Even documented asystole does not necessarily indicate that an anti-bradycardic therapy would result in symptoms relief, if the setting is typical for vasovagal syncope. Particularly in young patients, the question "when to implant" and "whom to implant" a pacemaker is often far from clear even with current trial evidence. We believe that a conservative pacing policy in younger patients without any evidence for structural heart disease or conduction disease is justifiable. In contrast every patient with a history of structural heart disease, unexplained syncope or high risk for cardiac arrhythmia may benefit from an ILR or a pacemaker.

The value and cost-effectiveness of ILR is well documented[42-44]. Implantation at an early stage in the investigation may reduce the costs of unnecessary investigations[45].

What treatment options do we have?

Once the diagnosis is clear the next questions that arise include, who needs therapy and what kind? Every patient benefits from information and education; some patients need medical therapy and only a few people need a pacemaker.

As there are many causes of syncope, a specific treatment cannot be administered without knowing the exact mechanism responsible for syncope. The main therapeutic innovations of the most recent years are isometric counterpressure maneuver, lower limb compression bandage and therapy guided by external and ILR in patients with recurrent suspected neurally-mediated syncope. Most drugs are considered ineffective. However, some drugs such as midodrine and paroxetine showed positive results in patients with recurrent vasovagal syncope. The cornerstone of therapy for young patients with vasovagal syncope remains education and reassurance, except in rare and isolated cases of patients with a high frequency of recurrent episodes despite nonpharmacological measures. In the elderly, specific treatment is often necessary. In these patients, determination of the hemodynamic mechanism of spontaneous syncope by means of an external or implantable cardiac monitor seems to be the most advisable option for optimal management. Limited data exist for the role of drugs in the treatment of vasovagal syncope in older patients.

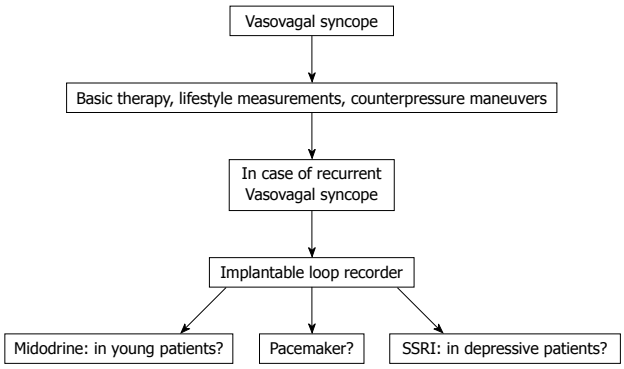

Figure 3 Treatment of vasovagal syncope. SSRI: Selective serotonin reuptake inhibitors.

The main goal of treatment is to reduce syncope recurrence and physical trauma. However, patients with a single syncope without any high-risk occupations (e.g. professional drivers, pilots) may not necessarily need specific therapy. Clear education and counseling about the nature of the benign condition and how to avoid triggers may be sufficient. Patients with a high risk of recurrence or injury can be identified by risk scores and may require tailored treatment (Figure 3). Known risk factors for recurrent vasovagal syncope are the number of preceding syncopal spells and female gender[3]. In contrast, the head-up tilt test response has no predictive value ($P = 0.881$)[3].

Non-medical therapy

An informative and instructive talk with the patient about the benign nature and prognosis is the first step in the treatment of patients with vasovagal syncope. Conditions triggering vasovagal reflexes should be avoided such as a hot environment, humid atmosphere, prolonged standing, and reduced water intake[2]. A reduction or cessation of vasoactive substances may be necessary[46]. Discontinuation of hypotensive drug treatment for concomitant conditions is an important first line measure for the prevention of syncope recurrences in many subjects, especially in older patients. Substitution of salt and intake of isotonic

drinks expands the circulating blood volume and may improve venous return[47].

Patients should be motivated to identify prodromals of syncope. Lying or sitting down when initial symptoms appear may avert or attenuate syncope or traumatic falls.

Furthermore counterpressure maneuvers such as hand-grip and leg crossing may inhibit vasovagal syncope by increasing the venous return[48]. Leg crossing combined with tensing of muscles at the onset of prodromal symptoms can delay or even prevent vasovagal syncope[48]. A more complex and time-consuming concept is that of tilt training: orthostatic training was found to significantly improve symptoms in adolescents with neurocardiogenic syncope[49]. Twice-a-day training sessions of 40 min tilt positioning at home by standing against a wall significantly reduced the incidence of recurrence[49]. However, the compliance in a tilt training program is rather low[50,51] and no long-term data are available.

Pharmacological therapy

A number of drugs have been tested in the treatment of vasovagal syncope. These have included β-blockers, disopyramide, scopolamine, theophylline, ephedrine, etilefrine, midodrine, clonidine, and serotonin reuptake inhibitors (SRI)[2]. Actually, no convincing data exist to support the use of one over another as a first line therapy. There is only limited data from placebo-controlled trials.

β-blockers: β-blockers have been the first choice for many years. Several small non-randomized, uncontrolled trials have shown a benefit, supporting the pathophysiological concept that β-blockers reduce sympathetic activity and avoid an "overshooting" vagal reaction[52]. However, there was no positive outcome in randomized, long-term, controlled trials for metoprolol[53], propanol, nadolol[54] or atenolol[55]. According the guidelines of the European Society of Cardiology, β-blockers should not be used to treat reflex syncope[2].

Midodrine: Midodrine, an alpha-agonist vasoconstrictor, affects smooth muscle cells both in arteries and veins without effecting heart rhythm or negative inotropy. There is no effect on the central nervous system. It is metabolized to the active drug desglymidodrine[56]. It has to be administered 3 times per day starting with 5 mg, because of a half-life of only 2-3 h. In 3 small randomized, placebo-controlled trials, midodrine had a beneficial effect on symptom frequency, symptoms during head-up tilt, and quality of life[57-59] (Table 1). Ward *et al*[57] evaluated 16 patients (mean age 56 years) in a 2 × 2 crossover trial: group 1 received placebo for the first 28 d (period 1) and midodrine for the second 28 d (period 2); while group 2 received midodrine for period 1 and placebo for period 2. Patients treated with midodrine showed more symptom-free days ($P < 0.0001$), a higher quality of life and fewer positive tilt testing results ($P = 0.01$).

However, these patients probably had overlap with some forms of orthostatic hypotension. In an acute double-blind placebo-controlled tilt study performed in 12 patients with a history of neurally-mediated syncope, Kaufmann *et al*[59] (Table 1) reported that a positive tilt result was observed in 67% of patients in the placebo group *vs* 17% of patients in the active medication group. The patients were randomized to receive a nonpressor dose of midodrine (5 mg) or placebo on day 1 and the opposite on day 3. One hour after drug or placebo administration, patients underwent 60-degree head-up tilt lasting 40 min (unless hypotension or bradycardia developed first). Positive results were also obtained in one small randomized trial of pediatric patients. These data suggest that midodrine is more effective in the treatment of orthostatic hypotension caused by autonomic dysfunction than in the neurally-mediated syncope. The available data are still insufficient to prove an efficacy of midodrine in vasovagal syncope. Midodrine may be indicated in patients with frequent vasovagal syncope refractory to lifestyle measures (recommendation Ⅱ B, level B)[2] (Figure 3).

Table 1 Midodrine: randomized placebo-controlled trials

Author, year	*n*	Follow-up period	Endpoint	*P*
Ward *et al*[57], 1998	16	1 mo	TT	0.01
Perez-Lugones *et al*[58], 2001	61	6 mo	Syncope recurrence	< 0.01
Kaufmann *et al*[59], 2002	12	1 wk	TT	< 0.02
Qingyou *et al*[60], 2006	26	42 mo	TT	< 0.05

TT: Head-up tilt table test.

Table 2 Selective serotonin reuptake inhibitors: randomized placebo-controlled trials

Author, year	*n*	Drug	Follow-up period	Endpoint	*P*
Theodorakis *et al*[63], 2006	96	Fluoxetine	6 mo	Time to vasovagal episode	< 0.05
				Well-being	0.01
				Syncope episodes	NS
Di Girolamo *et al*[62], 1999	68	Paroxetine	6 mo	TT	< 0.001
				Syncope recurrence	0.001

TT: Head-up tilt table test; NS: Not significant.

Serotonin reuptake inhibitors: In contrast to vasoconstrictors, SRI may reduce the central sympathetic nervous system activity[61]. Some open-label studies and one randomized, placebo-controlled trial demonstrated that SRI may reduce recurrent vasovagal syncope: during a follow-up of 25 mo, 17.6% of patients who randomly received paroxetine had syncope recurrence compared to 52.9% of the placebo group ($P < 0.001$)[62], although fluoxetine failed to show a significant reduction compared to propanolol[63] (Table 2). However Takata *et al*[64] reported that

Table 3 Pacemaker-therapy: randomized trials

Author, year	Trial	*n*	Design	Follow-up period (yr)	Endpoint	*P*
Conolly *et al*[65], 1999	VPS I	54	No placebo	1	Syncope recurrence	< 0.001
Sutton *et al*[66], 2000	VASIS	42	No placebo	3.7	Syncope recurrence	< 0.001
Ammirati *et al*[67], 2001	SYDIT	93	No placebo	1.5	Syncope recurrence	0.004
Conolly *et al*[68], 2003	VPS II	100	Placebo	0.5	Syncope recurrence	NS
Raviele *et al*[69], 2004	SYNPACE	29	Placebo	2 yr	Syncope recurrence	NS

NS: Not significant.

paroxetine does not prevent the vasovagal reaction associated with carotid sinus massage and/or lower body negative pressure in healthy volunteers. Until the result of the study is confirmed by other trials, use of this drug cannot be recommended.

Cardiac pacing

The role of cardiac pacing is controversial. Non-placebo-controlled trials (VPS I , VASIS, SYDIT) showed some benefit with dual-chamber pacing in reducing syncope recurrence[65-67] (Table 3). However, placebo-controlled trials in which all patients received a dual-chamber pacemaker and were randomly assigned to DDD or 0D0-Mode could not reproduce these results (VPS II , SYNPACE)[68,69] (Table 3). A recently published meta-analysis of all studies suggested a non-significant 17% reduction in syncope from the double-blinded studies, and an 84% reduction in the studies where the control group did not receive a pacemaker[70]. In conclusion, the results of small, initial trials have overrated the treatment effect of pacemakers due to a lack of blinding of physicians and patients. Blinded trials suggest that the apparent effect is due to a strong expectation response to pacing[70].

ILRs may identify patients with severe cardioinhibitory vasovagal syncope and hence a better detection rate may identify responders to pacing more accurately. This is supported by the observation that patients with syncope associated with abrupt bradycardia displayed a better response to cardiac pacing therapy than those with gradual onset bradycardia[71]. The syncope burden decreased from 2.7 per year to 0.45 per year ($P < 0.02$)[71]. A larger trial, the ISSUE 2 study, hypothesized that spontaneous asystole and not tilt test results should form the basis for patient selection for pacemaker therapy. This study followed 392 patients with presumed reflex syncope with an ILR. Patients with ILR-guided therapy, predominantly pacing for asystole, experienced a reduction in recurrence of syncope compared to non-ILR-guided therapy (10% *vs* 41%, $P < 0.002$). It is noteworthy that ISSUE 2 was not a randomized trial in contrast to the ongoing ISSUE 3 study which will give new insights into ILR-guided pacemaker therapy in vasovagal syncope[72].

Given a IIa/B classification by the European Society of Cardiology, pacemaker implantation may play a role in special circumstances. It should be considered in patients with frequent recurrent reflex syncope, e.g. when no prodromes occur, an age > 40 years and documented spontaneous bradycardia or asystole during monitoring[2].

CONCLUSION

The management of vasovagal syncope is evolving. The pathophysiology of vasovagal syncope is not fully understood. Non-pharmacological treatment options are a fundamental first step of all treatment pathways. Only limited data exist showing a modest benefit using midodrine or SRI for recurrent vasovagal syncope. An ILR is a useful tool to detect or exclude hazardous cardiac arrhythmia.

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