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REVIEW ARTICLE

The Current Indication for Pacemaker in Patients with Cardioinhibitory Vasovagal Syncope

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Abstract: The most frequent cause of syncope is vasovagal reflex. It is associated with worse quality of life, depression, fatigue and physical injury. Recurrence of vasovagal syncope is an aggravating, reaching the rate of 69%. Initial step and pharmacological treatment may not work, especially in patients with recurrent syncope without prodrome. These patients can present cardioinhibitory response with asystole. Studies were designed to analyses the effectiveness of pacemaker for prevention of syncope. In this review, nonrandomized clinical trials, open-label randomized, double-blind randomized, placebo-controlled, and studies based on tilt test or Implantable Loop Recorder findings will be discussed.

1. INTRODUCTION: CLINICAL ASPECTS OF VASOVAGAL SYNCOPE

Syncope is a common symptom, characterized by short loss of consciousness, from 10 to 20 seconds, with spontaneous recovery, secondary to cerebral hypoperfusion. Considering a lifetime of 70 years, its cumulative incidence is 42%, with an annual number of episodes from 18.1 to 39.7 per 1000 patients in general population [1].

The most frequent cause is vasovagal syncope (21.2%), more common in young people, but with a bimodal distribution [1, 2]. There are precipitating factors for the occurrence of vasovagal syncope, as sitting or standing position, pain, venous puncture, emotional stress, heat, alcohol use, dehydration. Prolonged sitting or standing position can be extended only 2 to 3 minutes. In elderly, predisposing situations can be use of diuretics and vasodilators. Prodromal symptoms are diaphoresis, pallor, visual blurring, nausea, vomiting, abdominal pain, palpitations, dizziness, and are more common in young. There is no aura, sphincter release or mental confusion. If there are tonic-clonic contractions, they are of short duration (< 15 seconds). These movements can occur in approximately 10% of cases [3 - 6].

The pathophysiology of vasovagal syncope is still debatable. Since the 19th century, the role of the vagus nerve was associated with this reflex by August Waller and Foster [7]. The vasovagal term was used by William Gowers and Thomas Lewis [8]. Although the vasovagal syncope mechanism is assigned to the Bezold-Jarish reflex, there is no change in total peripheral vascular resistance in a proportion of patients [9]. The precipitating stimuli decrease venous return by the gravitational action with accumulation of about 800 mL in the lower extremities. This triggers the action of the mechanoreceptors (C fibers) located in the atria, ventricles (preferentially in the inferolateral wall of the left ventricle) and pulmonary artery, resulting in sympathetic influx, with vigorous cardiac contraction and inappropriate ventricular filling. Paradoxical bradycardia and hypotension occur because of sympathetic nervous system inhibition and subsequent parasympathetic hyperactivity [1, 6, 10]. However, the reduction in preload does not always play a dominant role. In the study by Fu *et al*. [9], 64% of patients had moderate fall in cardiac output coincident with

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vasodilatation; and 36% of patients experienced a drop in cardiac output, mainly due to the decrease in heart rate, without changes in total peripheral resistance in pre-syncope. There is also evidence of the persistence of muscle sympathetic nerve activity during vasovagal syncope, challenging the pathophysiology of loss of peripheral sympathetic activity [11].

The vasovagal syncope is not associated with mortality, but it is associated with worse quality of life, depression, fatigue and physical injury during unconsciousness [1, 2]. Recurrence is an aggravating, reaching the rate of 69% in those patients with more than 6 episodes in the preceding year [12]. Low risk is not no risk, because the mortality of patients with syncope admitted to the emergency was 10% in one year, regardless of its cause, and it must be taken into account that the vasovagal syncope is responsible for 66% of syncope in emergency room visits [1, 13].

The diagnosis of vasovagal syncope is clinical, but tilt test (TT) can be useful as class IIa recommendation. Implantable loop recorders (ILR) may be useful (Class IIa) for assessing older patients with recurrent and unexplained syncope and that are at low risk of a fatal outcome [6].

The initial approach of vasovagal syncope is non-pharmacological through nutrition guidelines, with fluid and salt intake (Class I). Precipitating factors should be identified. Drugs that result in hypotension should be withdrawn or replaced. Physical counterpressure maneuvers should be done in the prodromal period (Class IIa). Medications such as fludrocortisone and midodrine are Class IIb recommendations, as well as the beta-blocker metoprolol (for those over 40 years old) if failure of the initial steps [6]. Prospective, randomized, placebo-controlled with these drugs have not yet been published. On the other hand, the pathophysiology of vasovagal syncope has not been fully elucidated. Therefore, initial step and pharmacological treatment may not work, especially in patients without prodrome and recurrent syncope.

2. CARDIOINHIBITORY VASOVAGAL SYNCOPE

As modified VASIS classification [14], vasovagal syncope presents the following response patterns to tilt testing:

i. Type 1 mixed: there is drop in blood pressure (BP) and heart rate (HR). BP falls before HR falls. The ventricular rate does not fall to less than 40 beats per minute.
ii. Type 2A, cardioinhibition without asystole: there is a drop in HR, with ventricular rate less than 40 beats per minute for more than 10 seconds.
iii. Type 2B, cardioinhibition with asystole: there is asystole longer than 3 seconds duration. BP decrease occurs simultaneously or before HR fall.
iv. Type 3 vasodepressor: there is decrease in BP below 80 mmHg, but HR does not fall more than 10%, from its peak, at the time of syncope.

Cardioinhibitory response with asystole is rare. It occurs from 1.2 to 6.6% during the positive tilt test or up 17% in patients referred for suspected syncope [15 - 17]. The maximum recorded asystole time was 90 seconds [15]. It is most common in younger [18]. Although reproducibility by TT is low (36%), this cardioinhibitory response predicts a high probability of a spontaneous syncope by asystole. However, the vasodepressor response or mixed response or even negative response does not exclude the presence of asystole during spontaneous syncope [1, 19].

The classifications Type 1A, 1B and 2 type of electrocardiographic recordings obtained by ILR refer to the reflex response with falling heart rate or sinus arrest [20]. In type 1 classification there is asystole for at least 3 seconds. In type 1A, there is a progressive sinus bradycardia or initial sinus tachycardia followed by progressive sinus bradycardia until to sinus arrest. In type 1B, there is progressive sinus bradycardia followed by atrioventricular block and concomitant decrease in HR. Atrioventricular block may occur suddenly. In type 2, HR decreases more than 30% (type 2A) or HR drops below 40 bpm for more than 10 seconds (type 2B).

There are similar proportions of these different electrocardiographic patterns during syncope cardioinhibitory triggered by the TT and documented record by ILR during spontaneous vasovagal syncope [21]. Sinus arrest occurred in 23.3% during TT and 30.2% by ILR. Atrioventricular block associated with sinus bradycardia or sinus arrest occurred in 5.2% and 8.5%, respectively. Moreover, atrioventricular block alone occurred in 15% by ILR and it did not occur during syncope triggered by TT.

When compared with patients without asystole, patients with asystole during TT had more severe symptoms like seizures and physical injury [22]. Despite the benign course of vasovagal syncope, without mortality, there is recurrence

of syncope in these patients with cardioinhibitory response from 9% to 62.5% during follow up 24 to 77 months [15, 17, 18, 23, 24]. An interesting observation is that heart rhythm during the episode of recurrence is identical to the first spontaneous syncope [25].

3. NONRANDOMIZED CLINICAL STUDIES OF INTERVENTIONS

Early studies of permanent pacemaker in patients with vasovagal were developed from the 1990s. The studies included between 12 and 37 patients with vasovagal syncope and demonstrated a reduction in the number of episodes of syncope and improved quality of life [26 - 28]. There was more benefit for patients with asystole at least 4 seconds detected by TT [26]. However, not all patients showed cardioinhibitory response with asystole and these studies were retrospective and nonrandomized.

4. CLINICAL STUDIES BASED ON TILT TEST FINDINGS

To prevent the inclusion of patients with vasodepressor response, studies were developed based on response to TT. These studies were randomized and open-label or double-blind.

4.1. Randomized Open Studies

There were three nonblinded controlled studies based on the results of TT. The first study to evaluate pacemaker (PM) therapy for recurrent vasovagal syncope was Vasovagal Pacemaker Study (VPS) [29]. Eligible patients had presented at least 6 syncopal episodes and relative bradycardia during TT. This bradycardia was defined as a decrease in HR below 60 beats per minute (bpm) without isoproterenol or below 70 bpm, if administered isoproterenol at a dose of up to 2 mcg/min, or below 80 bpm, if a dose used was more than 2 mcg/min. A total of 54 patients were enrolled and were randomized by telephone to receive a permanent PM with rate-drop response function or not. Twenty-seven patients were included in each group, with a mean age, number of women and medications (such as beta-blockers) similar between groups. After implantation of dual chamber PM, recurrent syncope occurred in 70% of non-pacemaker patients and in 22% of patients with pacemakers, with 85.4% risk reduction of syncope. A total population of 284 patients was planned, but the study was terminated prematurely because of the pilot study results.

Another study was a multicenter (18 European centers) and included 42 patients with at least 3 episodes of syncope in the last two years and cardioinhibitory response (type 2A or 2B) to TT [30]. Eighty-six percent (86%) of patients had asystole that lasted more than 3 s. Patients were randomized to implantation of dual-chamber PM with rate hysteresis or no specific therapy. During the mean follow-up of 3.7 years, only one patient (5%) in the arm PM had syncope recurrence compared with 14 patients (61%) in non-pacemaker arm.

Syncope Diagnosis and Treatment Study (SYDIT) showed a significant effect in favor of permanent PM compared with medical treatment (atenolol 100 mg once a day) after a median follow up of 390 days [31]. This study included 93 patients from 14 centers, with more than 35 years old, and ≥ 3 episodes of syncope in two years, and with relative bradycardia by TT (<60 bpm). Patients were randomized to receive atenolol or PM with rate-drop response function. Patients with PM showed a significant reduction in the recurrence of syncopal episodes (4.3% *versus* 25.5%) compared to patients without PM and treatment with beta-blocker. With these results, the study was stopped.

4.2. Double-blind Randomized Trials

Double-blind randomized studies have been designed to avoid the placebo effect associated with PM implantation procedure, an important limitation of open studies (Table **1**).

Table 1. Double-blind randomized studies based on tilt test findings.

Trial	Inclusion criteria	Inactive pacemaker group				Active pacemaker group				Analysis
		N	Female (%)	Mean age (years)	Recurrence of syncope	N	Female (%)	Mean age	Recurrence of syncope	
VPS II	≥ 6 syncopal episodes or ≥ 3 episodes in 2 years and HR x BP < 6000 bpm x mmHg	52	48.1	47.8	42%	48	72.9	50.8	33%	Relative risk reduction 30%, p=0.14
SYNPACE	≥ 6 syncopal episodes in all life and with asystole or mixed response	13	54	54	38%	16	69	52	50%	p=0.58

N: number of patients.

Second Vasovagal Pacemaker Study (VPS II) included 100 patients older than 19 years with typical vasovagal syncope recurrence in 15 centers. Inclusion criteria were the presence of at least 6 episodes of syncope in all of life or at least 3 episodes in the last two years. Furthermore, patients should have presented positive tilt test with a HR x BP product <6000 bpm x mmHg [32]. Patients were randomized to receive dual-chamber pacemaker (DDD) with rate-drop response function or have just sensing without pacing (ODO). The cumulative risk of syncope at 6 months was 40% for the ODO group and 31% for the DDD group. Thus, authors concluded that pacemaker did not reduce the risk of recurrent syncope in patients with vasovagal syncope.

In the study SYNPACE were enrolled patients with over 18 years of age, recurrent syncope and positive TT with asystole or mixed response, with at least 6 episodes of syncope during the patient's life, or at least one recurrence within 12 months after positive TT [33]. Patients underwent implantation of dual chamber pacemaker and were randomized to double-blind fashion to pacemaker group in active mode (DDD) with response-drop rate, or the inactive pacemaker group (OOO). There was a trend in favor of active pacemaker regarding time longer to first recurrence, especially for those patients who had asystole response during TT. However, a high percentage of patients present with syncope recurrence despite the active pacing and this percentage was similar to that seen in patients with inactive pacing. The study was terminated early because of the publication VPS II study results and assessment of the results of the first formal interim analysis with a median of 715 days.

Another prospective, randomized, controlled, multi-center (INVASY) assessed whether the dual-chamber pacemaker implantation with closed loop stimulation would reduce the recurrence of syncope in at least 50% compared with the placebo group, with similar pacing programmed in DDI mode with frequency of 40 bpm [34]. However, this study was single blind and it included 57 patients over 18 years old with more than 5 episodes of syncope and/or two episodes in the last year, with 2 A or 2 B response to TT. During the follow-up period (range 12 to 36 months), none of the 41 patients in the closed loop stimulation arm experienced syncope. In the control arm, four of nine patients (44%) had two syncopal spells before the end of the first year. At the end of the first year the nine patients randomized to the DDI mode were reprogrammed to the closed loop stimulation mode and no syncope occurred after reprogramming. Despite the effectiveness of pacing prevent cardioinhibitory syncope, a possible placebo effect of PM implantation was demonstrated in 22% of patients.

A meta-analysis of nine randomized trials (2 double blind, 7 open label or single blind) was published [35]. In unblinded studies and in studies comparing algorithms, permanent PM reduced the risk of recurrent syncope (an 84% reduction in the studies where the control group did not receive a PM). However, no effect was observed in double-blind studies (non-significant 17% reduction in syncope). The authors concluded that these trials overestimate the treatment effect of pacemakers due to a lack of doctors and patients masking. The ineffectiveness of the pacemaker can be attributed to its inability to prevent the vasodepressor component present in most episodes of vasovagal syncope and usually preceding the cardioinhibitory response and bradycardia. In addition, early termination of a trial may overestimate the treatment effect [36].

5. CLINICAL STUDIES BASED ON IMPLANTABLE LOOP RECORDER FINDINGS

For the reasons previously exposed and the conflicting results, studies were developed based on findings by ILR. The tilt-table test has a sensitivity rate of 78-92% for patients with vasovagal syncope and high pretest probability [6]. However, BP may decrease before fall of HR in cardioinhibitory response and, therefore, 2B response to TT could not be identified. ILR is an effective tool to establish a cause for unexplained syncope and has a diagnostic accuracy between 35% and 80% over its lifetime [6, 37, 38]. Thus, ISSUE 2 and ISSUE 3 were developed to analyze the benefit of PM in patients with syncope due to asystole diagnosed by ILR (Table **2**).

Table 2. Clinical studies based on Implantable Loop Recorder findings.

| Trial | Inclusion criteria | No therapy or pacemaker OFF arm | | | | Pacemaker ON arm | | | | Analysis |
		N	Female (%)	Mean age (years)	Recurrence of syncope	N	Female (%)	Mean age	Recurrence of syncope	
ISSUE 2	≥ 3 episodes in 2 years	50	50	64	41%	53	62	69	10%	Relative risk reduction 80%, p=0.002
ISSUE 3	≥ 3 episodes in 2 years	39	59	63	57%	38	47	63	25%	57% relative reduction, p=0.039

N: number of patients.

International Study on Syncope of Uncertain Etiology 2 (ISSUE 2) was a prospective, multicenter study, which included patients at least 30 years old and with three or more episodes of suspicious vasovagal syncope in last 2 years without significant electrocardiographic or cardiac abnormalities [39]. Patients with postural hypotension or carotid sinus hypersensitivity were excluded. Three hundred ninety-two patients underwent ILR implant. During the one year follow up, syncope recurrence rate was 33%. Among the 103 patients who were kept in follow-up, 53 were submitted to specific therapy for syncope as ILR results and 50 patients did not receive specific therapy. Thus, 47 patients with response type 1 and 2 (asystole of a median 11.5 s duration) by ILR underwent dual-chamber PM implantation. There was recurrence of syncope in 10% of the group with specific therapy (5% in those with PM) and in 41% of patients without specific therapy during follow-up of one year. The authors concluded that specific therapy based on ILR was safe and effective in patients with vasovagal syncope. However, this study was not double-blind.

Another study was ISSUE 3, double-blind, randomized, placebo-controlled performed in 29 centers [40]. A total of 511 patients aged ≥ 40 years, at least three syncopal episodes in the last 2 years, were included. Patients receive an ILR and 89 of them experienced asystole at least 3 s duration (with syncope) or at least 6 s (without syncope). Seventy-seven patients were randomized to dual-chamber pacing with rate drop response (38 patients) or only with response to sensing (39 patients). Syncope recurrence rate was 25% and 57% at 2 years, respectively, based on the intention-to-treat analysis. There were relative risk reduction of 57% and absolute reduction of 32%. The authors concluded that permanent PM dual-chamber is effective in reducing syncope recurrence in patients with at least 40 years of age with neurally mediated syncope with severe asystole.

ISSUE 3 study sub-analysis also showed a reduction in syncope recurrence in patients undergoing PM implantation [41]. Sixty patients with vasovagal syncope asystole received cardiac pacing therapy and 86 (33 with asystole and 53 without asystole) were not treated. The two groups had similar clinical features. During follow-up of 21 months, 10 patients (17%) with PM and 40 patients (46%) without PM had recurrence of syncope. There was absolute reduction of 27% of syncope recurrence with cardiac pacing (*p*=0.01). The differential in the present study was the analysis of the treatment, which included, additionally, all patients non-randomized. The number of 5.1 ILRs was necessary to identify a patient with asystole which was finally subjected to PM implantation.

6. ISSUES STILL TO BE RESOLVED

The benefit of permanent PM implantation was evidenced in a selected population of patients with vasovagal syncope of middle age or older with recurrent episodes without prodrome and therefore with physical injury. Young patients were not included in well-designed studies. It is not known about the effectiveness of the pacing in these patients, since they have prodrome and more adhesion to non-pharmacological recommendations. The highly selected population from those studies and that benefited from PM implantation corresponds to 9% of patients with vasovagal syncope referred for evaluation [36, 40]. The effectiveness of pharmacological treatment is also not well established. The use of beta-blockers (especially metoprolol) in older patients of 42 years can be effective, but there are no prospective, randomized, placebo-controlled studies focused on this population [6, 42].

The tool for identification of asystole as rhythm during vasovagal syncope is another important issue. ILR enables identifying the rhythm of asystole during spontaneous syncope, guiding the diagnosis. Nevertheless, this diagnostic yield is a function of observation time. An event recorded by ILR showed an estimated probability of 31% at 1 year, 40% at 2 years and 47% in 3 years [43].

There is a growing skepticism about the diagnostic accuracy of TT for diagnosis of syncope. Moreover, there was insufficient evidence of efficacy of cardiac pacing in preventing episodes of syncope, even documented spontaneous asystole and positive TT [44].

On the other hand, there is evidence to support the use of tilt testing in the evaluation of vasodepressor response and postural hypotension [6, 45]. This hypotensive reflex probably occurred in a quarter of patients in the study ISSUE 3, which presented recurrence of syncope despite the active PM [44]. The tilting test has a sensitivity of 78-92% and a specificity of 87-92% [45]. In addition, asystole response observed during the tilting test is very specific to asystole during spontaneous syncope, and it has a positive predictive value of 75% -80% [46]. The tilt-down time also influences the response by TT. This longer time (47 *versus* 10 s) increased the prevalence of cardioinhibitory reflex and duration of loss of consciousness [47]. Beyond the discriminatory power of this test, TT is more cost-effective, when the initial investigation is done by TT as a strategy to indicate the MP implantation in patients with vasovagal syncope. The incremental cost-effectiveness ratios were £5960, £24620 and £19110 for TT alone, ILR alone and TT followed by ILR,

respectively, compared with no testing [48].

Use of a diagnostic algorithm was able to identify older patients (about half) with severe recurrent syncopes without prodromes, who have a reflex asystole, and can benefit from PM. The investigation was initiated by carotid sinus massage. If this massage was negative, the patient was submitted to TT. If TT was negative or the response was vasodepressor, the patient underwent the implantation of ILR [49].

There are also aspects related to PM to be considered. In most studies, PM used was a dual-chamber with rate-drop response function or rate hysteresis. The effectiveness of conventional rate hysteresis systems may be limited, since fall in BP may precede fall in HR in cardioinhibitory syncope. Therefore, PM with closed loop stimulation may be more effective than conventional PM with rate hysteresis systems in preventing vasovagal syncope recurrence [50]. The closed loop stimulation algorithm is a physiological system which detects changes in the dynamics of myocardial contraction by measurement of intracardiac impedance and it can act quickly in the initial phase of the vasovagal reflex.

Pacemaker implantation is not without risk, with complication rate of 12.4% in the short-term (2 months) and 9.2% in the long-term [51]. Complication rates of studies on pacemaker in syncope vasovagal ranged from 6.5% to 26% [29, 32, 40, 41]. The main complications were lead dislodgement, venous thrombosis, infection, haemothorax, pericardial tamponade.

CONCLUSION

Pacemaker implantation may be indicated for selected patients with cardioinhibitory form of vasovagal syncope, 40 years of age or older, with frequent episodes of syncope recurrence associated with physical trauma, limited prodromes and asystole (at least 3 seconds duration with clinical syncope or an asymptomatic pause of at least 6 seconds) documented by monitoring. The tilt test should be considered as an investigation strategy for the diagnosis of hypotensive response.

CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

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