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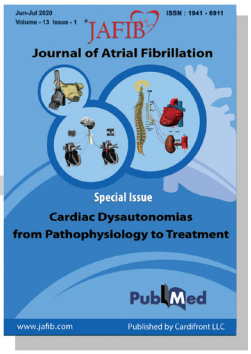

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Pacing Therapies for Vasovagal Syncope

Krishna Akella[1], *Brian Olshansky*[2], *Dhanunjaya Lakkireddy*[1], *Rakesh Gopinathannair*[1]

[1]Kansas City Heart Rhythm Institute (KCHRI), Overland Park, KS, USA
[2]University of Iowa Hospitals and Clinics, Iowa City, IA

Abstract

Vasovagal Syncope (VVS) is mediated by a cardiac autonomic reflex with resultant bradycardia and hypotension, precipitating syncope. While benign and mostly well controlled, recurrent VVS can be debilitating and warrants intervention. Non-pharmacological management of VVS have had variable success. In patients with recurrent cardioinhibitory VVS, permanent pacing can be effective. The utility of pacing to preempt the syncopal depends on the prominent temporal role of bradycardia during the vasovagal reflex. Current guidelines recommend pacing as a therapy to consider in older patients with recurrent VVS. Although younger patients can benefit, one should be cautious given the long-term risk of complications. Available data appears to favor a dual chamber pacemaker with closed loop stimulation algorithm to prevent recurrent cardioinhibitory VVS. Several aspects, including mechanistic understanding of VVS and appropriate patient selection, remain unclear, and require further study.

Introduction

Blood pressure and heart rate modulation by the autonomic system is tightly regulated. Vasovagal syncope (VVS), the most common cause of syncope, results from a neurocardiogenic reflex, representing an imbalance of the autonomic control, leading to bradycardia (cardioinhibitory response) and/or hypotension (vasodepressor response), preceding syncope. It also results in a variety of signs and symptoms ranging from prodromal nausea, diaphoresis and pallor to fatigue, headache, nausea and vomiting during the recovery period [1-4]. The clinical spectrum of VVS is complex, ranging from rare episodes with a clear trigger to recurrent episodes that can be debilitating [5]. Syncope associated with conditions such as hypertrophic cardiomyopathy, aortic stenosis, inferior myocardial infarction, gastrointestinal bleeding, and pulmonary embolism, is in many cases, mediated by the vasovagal reflex [6,7].

The exact mechanistic underpinnings of VVS remain unclear [1]. Afferent signals are carried through the vagus nerve to the nucleus of tractus solitarius with subsequent sudden efferent parasympathetic response resulting in bradycardia (due to sinus bradycardia, sinus arrest, or AV block) whereas a sudden loss of muscle sympathetic activity results in vasodilatation and hypotension [8-11]. Although parasympathetic augmentation and sympathetic attenuation are known to be associated, the temporal nature of this relationship can vary between patients, as well as between repeated events in the same patient [12,13].

While VVS is generally considered not life threatening, recurrence can be particularly problematic and lifestyle limiting. The integration of preventative measures, such as hydration, trigger avoidance, compression stockings, counter-pressure maneuvers, is anecdotally helpful and advocated but lacks clear evidence [14,15]. The purpose of this review is to explore the evidence regarding secondary prevention via pacing in recurrent neurocardiogenic syncope.

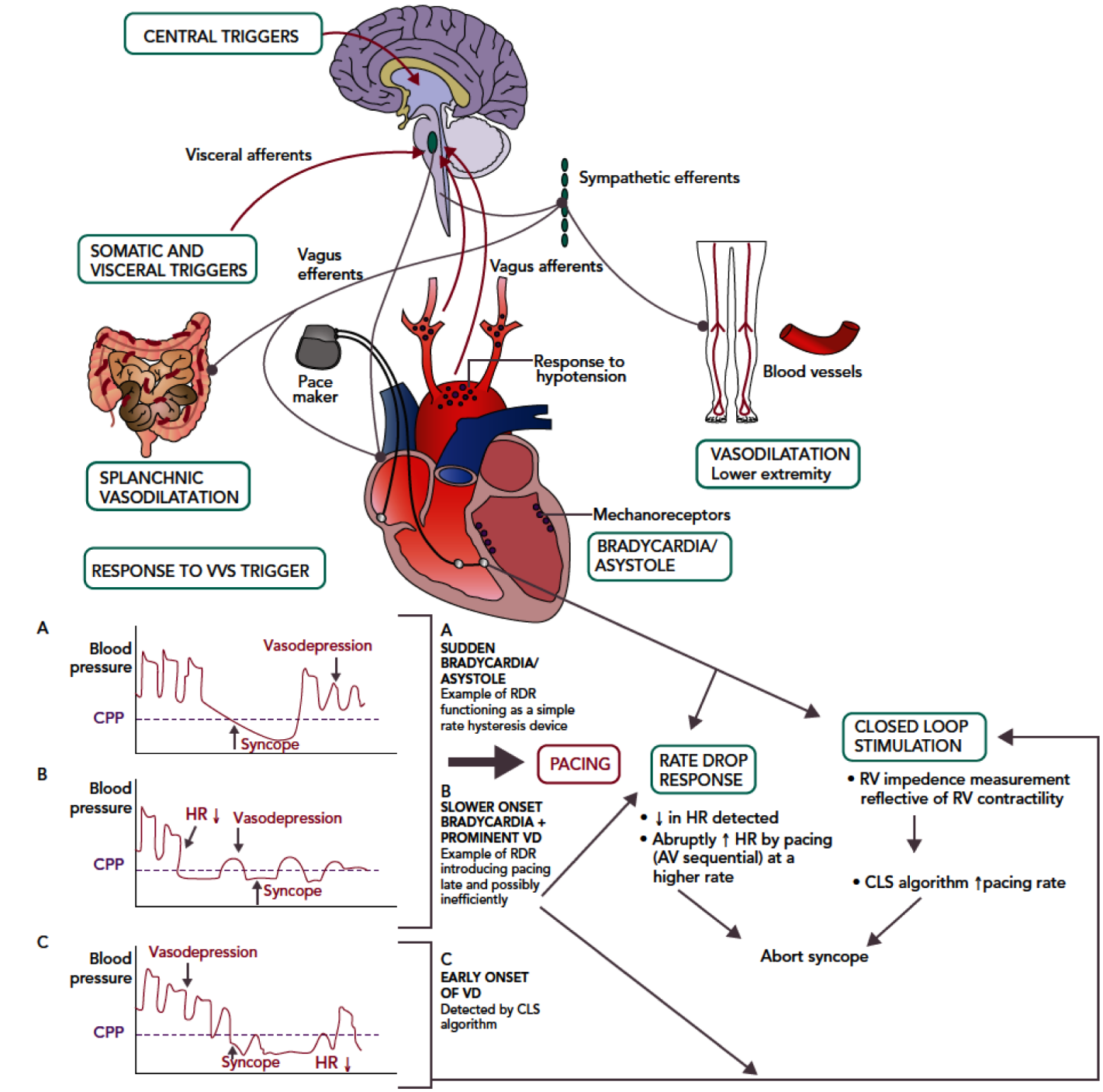
Pacing Therapies in Neurocardiogenic Syncope

Although pacing is unlikely to impact vasodilation and hypotension, early intervention with pacing may be able to attenuate the severity of vagal response and to maintain effective cardiac output to facilitate sufficient cerebral blood flow to the reticular activating system to prevent the faint [16,17]. Given the concomitant hypotension, AV sequential pacing at a relatively faster rate has been thought to be desirable [18]; however, this has been challenged recently by data showing comparable efficacy between dual chamber pacing versus single chamber leadless pacing[19]. Even the presence of asystole on a tilt table test may not play a significant role in longer term outcomes [20]. However, those patients who continue to have recurrent asystolic VVS may require a pacemaker for secondary prevention.

Key Words

Syncope, Neurocardiogenic, Vasovagal, Pacemaker, Closed Loop Stimulation, Rate Drop Response

Corresponding Author
Rakesh Gopinathannair, MD, FAHA, FACC, FHRS
Cardiac EP Lab Director, Kansas City Heart Rhythm Institute
Professor of Medicine, University of Missouri-Columbia, 5100 W 11th street, Ste 200
Overland Park, KS 66211.



There is generally considered to be a close relationship between systolic blood pressure and CPP with a critical level of 60-70 mmHg. CPP = cerebral perfusion pressure; CLS = closed loop stimulation; HR = heart rate; VD = vasodepression; RV = right ventricle; RDR = rate drop response.

Figure 1: **Pathophysiological Mechanisms in VVS Leading to Bradycardia and Hypotension, Role of Pacing and Currently Used Pacing Algorithms. Reproduced with Permission from [1]**

Evidence for Permanent Pacing for Vasovagal Syncope

Table 1 shows a summary of the studies evaluating the utility of cardiac pacing in VVS. [1] Early studies evaluating pacing therapies in VVS showed promise, showing reduction in syncopal episodes [21-23]. In a study of VVS patients who had bradycardia and/or asystole along with hypotension during tilt table testing, blood pressure was noted to decline much earlier (42±29 seconds) than heart rate. With temporary AV sequential pacing, the majority of patients continued to have a blood pressure drop with symptoms but to a lesser degree than without pacing [24]. This particular finding was important as it allowed more time for patients to adopt a safer position or do counterpressure maneuvers to prevent syncope and associated injury. Moreover, it also suggested that pacing at a faster rate than the base rate would be needed to mitigate the risk of syncope. This resulted in

development of the rate-drop response (RDR) algorithm whereby a sudden drop in heart rate during VVS would lead to AV sequential pacing at a rate much faster than the base rate for a period of time. Initial data was promising [25,26].

The North American Vasovagal Pacemaker Study (VPS I), which randomized patients with ≥ 3 syncopal episodes and a positive tilt table test (hypotension and bradycardia) to dual chamber pacing (lower rate of 60 beats/min with RDR) versus no pacemaker, showed recurrent syncope in 70 % with no pacemaker versus only 22 % in the pacemaker group, an impressive 85 % decrease (CI [59.7–94.7 %]; p=0.00002). However, a placebo response to pacing could not be ruled out as this study was not blinded [17]. The VASIS (Vasovagal Syncope International Study), a multicenter randomized study, compared DDI pacing with rate hysteresis to standard therapy in patients with ≥ 3 syncopal episodes over the preceding 2 years and manifest cardioinhibitory response on tilt-table testing. This study showed that only one patient (5 %) in the pacing group had syncope when compared to 61 % in the standard therapy group (p=0.0006) [27]. The Syncope Diagnosis and Treatment (SYDIT), a multicenter, randomized study of dual-chamber pacing with RDR versus atenolol in patients ≥35 years who had ≥ 3 syncopal episodes over the preceding 2 years and positive tilt-table test showing relative bradycardia, showed a 4.3 % syncope recurrence rate over a median follow-up of 390 days in the pacemaker group versus 25.5 % after median follow-up of 135 days in the atenolol group (OR 0.133; 95 % CI [0.028–0.632], p=0.004). A potential placebo response to pacing continued to be a concern with SYDIT as well [28].

The VPS II (North American Vasovagal Pacemaker Study II) evaluated the role of a placebo response to pacing. In this multicenter, double-blinded randomized trial, 100 VVS patients received a dual chamber pacemaker [16]. Patients were then randomized to 'active' pacing (DDD pacing with RDR) or to pacemaker off (ODO group). Of the 52 patients randomized to ODO, 22 (42%) had recurrent syncope within 6 months compared with 16 (33%) of 48 patients in the DDD group. There was a 30% relative risk reduction in time to syncope with DDD pacing (95% CI, -33% to 63%; 1-sided P =.14) but was not statistically significant. This suggested a potential contributory placebo effect of pacing; however, the study may have been underpowered to show a difference [16] Moreover, follow-up was only 6 months and careful evaluation of cardioinihibition as the primary entry criterion for enrollment was not done. These data were further supported by the SYNPACE (The vasovagal Syncope and Pacing Trial), a multicenter randomized, double-blinded, placebo-controlled study of syncope positive tilt-table test patients who underwent pacemaker placement [29]. SYNPACE also did not require documentation of severe bradycardia as an inclusion criterion.

The ISSUE 3 (Third International Study on Syncope of Uncertain Etiology) trial was a randomized, placebo-controlled, double-blinded study that included patients ≥40 years of age, with ≥3 syncopal episodes in the previous 2 years, who had documented syncope with an implantable loop recorder (ILR) showing ≥3 seconds of asystole in a symptomatic episode or ≥6 seconds of asystole in an asymptomatic episode [30]. Patients were randomly assigned to DDD pacing with RDR or sensing only. The syncope recurrence rate at 2 years was 57% (95% CI, 40-74) with pacemaker OFF and 25% (95% CI, 13-45) with pacemaker ON (p=0.039), with a relative risk reduction of 57% with pacing. However, one of the main concerns about ISSUE-3 was that the average age of patients was 63 years and only 44% had a typical VVS presentation. This suggested other reasons, such as sinus node dysfunction, for the bradycardia noted on ILR and consequent benefit from pacing. This was further supported by follow-up data showing that those who had asystole during tilt-table testing had less benefit from pacing [31].

Closed Loop Stimulation for Cardioinhibitory Vasovagal Syncope

One of the main issues with RDR was that pacing support may be too late to counteract the vasovagal reflex, especially reflex vasodilatation [17]. Closed loop stimulation (CLS) is a Biotronik proprietary algorithm which uses intracardiac impedance measurement during cardiac systole as an indirect measurement of right ventricular contractility. An algorithm then adjusts pacing rate based on measured impedance, to preempt VVS early in the process [13,32,33]. An initial observational study evaluated pacing in patients with ≥2 syncopal episodes over the preceding 6 months and documented asystole (>10 seconds) or severe bradycardia (≤30 beats/min) by ILR tilt testing. Compared to rate hysteresis or RDR, those who received dual chamber pacemakers with the CLS algorithm had less recurrence (59% vs 83%) and burden (25% vs 84%, p=0.002) of syncope [32].

The INVASY (Inotropy Controlled Pacing in Vasovagal Syncope) study randomized patients with recurrent VVS and a positive tilt-table test with cardioinhibitory response to DDD-CLS vs DDI pacing. Of 50 patients, 9 were randomized to DDI and 41 to DDD-CLS. Of the 9 in the DDI arm, 7 had recurrent syncope whereas none among the 41 DDD-CLS patients had recurrent syncope [34].

In a prospective, randomized, single-blinded, multicenter study of patients with cardioinhibitory VVS (mean age 62±14 years), DDD-CLS, compared to DDD pacing, significantly reduced syncope induced by tilt testing (30 % vs. 77 %; p<0.001). Importantly, DDD-CLS pacing also reduced the blood pressure drop during tilt testing thereby significantly delaying the onset of syncope [35]. Another prospective, randomized, single blind, crossover study compared patients with DDD-CLS 'on' vs. 'off". Over 36 months, the number of syncopal episodes with DDD-CLS 'on' was significantly lower than those in whom CLS was turned 'off' (2 vs 15 syncopal episodes; p=0.007) [36].

The SPAIN (Closed Loop Stimulation for Neuromediated Syncope) trial was a randomized, double-blinded, crossover study that enrolled patients ≥ 40 years of age with high burden of syncope (≥5 episodes or ≥2 episodes in the preceding 12 months) and a cardioinhibitory response to tilt testing (bradycardia <40 BPM for 10 seconds or asystole >3 seconds). Patients were randomized to DDD-CLS versus sham DDI pacing (30 pulse/minute subthreshold) and crossed over at 12 months or when three syncopal episodes occurred within 1 month. The results showed that 72 % (95 % CI [47–90 %]) in the DDD-CLS arm had a ≥50 % reduction in syncopal episodes vs. 28 % (95 % CI [9.7–53.5 %]) in the sham DDI mode (p=0.017). Overall, 4 patients in the CLS group vs. 21 patients in the DDI

Table 1: Summary of Studies Evaluating the Utility of Pacing in Vasovagal Syncope. Reproduced with Permission from [1]

Author	Study Design	Inclusion Criteria	Pacing mode	Number of patients	Follow up	Outcome
Fitzpatrick et al.[21]	Cross-sectional; external pacemaker placed, and tilt-table test performed	Positive tilt-table test and significant bradycardia (<60 bpm)	External DVI pacing with rate hysteresis	10 (6 male, mean age 60.2)		Syncope aborted by pacing in 5/6 undergoing tilt-table test
Petersen et al.[22]	Prospective; dual chamber PPM in 35 patients and VVI PPM in 2 patients	Patients with PPM for VVS. Median of 6 syncopal episodes, median frequency 2/year) with cardioinhibitory response with tilt-table test (<60 bpm)	84% DDI with rate hysteresis	37 (21 male, mean age 62.5)	5 0 . 2 months	62% syncope-free 27% symptom free
Sutton et al. 2000 (VASIS study) [27]	Multicenter, randomized; DDI PPM at 80 bpm with hysteresis of 45 bpm vs. no PPM	>3 syncope episodes over prior 2 years and a positive 2A/2B cardioinhibitory (VASIS classification) response (median previous episodes were 6) (asystolic response to tilt-test in 86%).	DDI with rate hysteresis	42 (24 male, mean age 60)	Minimum 1 year and maximum 6.7 years	1 (5%) in PPM arm had syncope vs. 14 (61%) in no-pacemaker arm (P=0.0006)
Connolly et al. 1999 (VPS Study)[17]	Randomized; DDD PPM with RDR vs. no PPM	>6 lifetime episodes of syncope, positive tilt-table test, and relative bradycardia (<60 bpm if no isoproterenol, <70 bpm if up to 2 mcg/min isoproterenol used or <80 bpm if > 2 mcg/min isoproterenol).	DDD with RDR	54 (16 male, mean age 43)	21 months	RRR 85.4%, 95% CI 59.7% to 94.7%; 2p=0.000022
Ammirati et al. 2001 (SYDIT)[44]	Multicenter, randomized, controlled trial; DDD RDR PPM vs. beta-blocker	>35 years old, ≥3 syncopal episodes in preceding 2 years and positive tilt-table test occurring with relative bradycardia	DDD with RDR	93 (38 male, mean age 58.1±14.3)	30 months	Syncope recurrence in 2 (4.3%) after median of 390 days vs. recurrence in 12 (25.5%) with medical treatment after median 135 days; OR 0.133; 95% CI, 0.028 to 0.632; P=0.004)
Connolly et al. 2003 (VPS II Study)[45]	Multicenter, randomized, double-blinded DDD vs ODO	>19 years old, typical history of recurrent syncope with ≥6 total episodes of syncope or ≥3 episodes in 2 years before enrollment	DDD with RDR vs. ODO	100 (40 male, mean age 49.3)	6 months	42% had recurrent syncope vs. 33% in DDD group. The RRR in time to syncope with DDD was 30% (95% CI, -33-63%; 1-sided P=0.14)
Raviele et al. 2004 (SYNPACE Study)[46]	Randomized, double-blind, placebo-controlled; DDD with RDR comparison of PPM ON vs. OFF.	Severe recurrent tilt-induced vasovagal syncope (median 12 syncopal episodes in lifetime)	DDD with RDR	29 (10 male, mean age 53±16)	715 days	8 patients (50%) in the PPM-ON group had recurrence of syncope vs.5 patients (38%) in the PPM-OFF group (p=ns). Median time to first syncope longer in PPM-ON vs. PPM-OFF group, although not significant (97 vs. 20 days; p=0.38)
Brignole et al. 2012 (ISSUE-3)[30]	Double-blind, randomized, placebo-controlled, multicenter; DDD with RDR On vs. OFF	≥40 years old, with ≥3 syncopal episodes in the previous 2 years	DDD with RDR	77 (36 male, mean 63 years)	24 months or first syncope	Syncope recurred in 27 - 19 in PPM-OFF group and 8 PPM-ON. 2-year estimated syncope recurrence rate was 57% (95% CI: 40-74) with PPM OFF and 25% (95% CI: 13-45) with PPM ON (P=0.039). The observed 32% absolute and 57% relative reduction in syncope in PPM On group.
Brignole et al. 2015 (SUP-2)[47]	Prospective, multicenter, observational study; carotid sinus massage, Tilt-table testing followed by ILR implantation. Those with asystolic response received dual chamber PPM.	≥40 years with recurrent unpredictable reflex syncope	DDD with RDR vs sensing only	253 (128 male, mean 70 ±12)	1 3 ± 7 months	Decrease of total syncopal episodes from 200 episodes before PPM to 11. Total syncope recurrence was 9% (95% CI: 6-12) at 1 year and 15% (95% CI: 10-20) at 2 years.
Brignole et al. 2016 (SUP-2) 64	Prospective, multicenter, observational study; carotid sinus massage, Tilt-table testing followed by ILR implantation. Those with asystolic response received dual chamber PPM	≥40 years with recurrent unpredictable reflex syncope	DDD with RDR in 101/137 vs sensing only	137 (82 male, mean 73 ±11) received a pacemaker vs 142 who did not	2 6 ± 1 1 months	Decrease in total number of syncopal episodes from 206 to 16 in year after pacemaker and 39 episodes of syncope in total follow-up
Kanjwal et al. 2010 [32]	Prospective non-randomized; CLS pacing	≥ 2 syncopal episodes in preceding 6 months, refractory to medical therapy, evidence of asystole (>10 s) or severe bradycardia (<30 bpm) on ILR or during tilt-table test.	DDD with RDR vs. CLS	35 (6 male, mean age 41±11)	9 ± 3 months	Recurrence (59% vs. 83%) reduction in syncope burden and pacemaker success (84% vs. 25%, P=0.002) in the CLS group.
Occhetta et al. 2004 (INVASY study)[48]	Prospective, randomized; DDD-CLS and DDI pacing	Severe recurrent syncope with positive tilt-table test	DDD-CLS vs. DDI	55 (27 male, mean age 59±18)	1 year	7/9 patients in DDI group had recurrence of syncope. When reprogrammed to CLS they had no syncope. Of 41 programmed to CLS none had recurrence in 19± 4 months
Bortnik et al. 2012[49]	Prospective, long-term evaluation of patient before and after PPM implantation with CLS pacing	Positive type 2A or 2B (VASIS classification) cardioinhibitory response to tilt-table testing. Age >18 years. Proven refractoriness to conventional drug therapy and tilt training	CLS	35 (mean age 59±15) (no data about gender)	3 years (6 1 ± 3 5 months)	29/35 (83%) were asymptomatic. 5 patients experienced syncope recurrence after CLS (1-7, with a total of 15 episodes). In each case syncopal spells were less than before implantation.

Palmisano et al. 2012[50]	Retrospective; CLS vs. RDR	≥2 syncopal episodes in the year prior to pacemaker implantation and positive 2A or 2B (VASIS classification) cardioinhibitory response to tilt-table test.	CLS vs. RDR	41 (44% male, mean 53±16)	4.4± 3 years	1 patient in the CLS group (4%) and 6 in the RDR group (38%) had syncope recurrences (P=0.016)
Palmisano et al. 2017[35]	Prospective, randomized, single-blind, multicenter; CLS vs. DDD during tilt-table testing	Recurrent unpredictable VVS with significant limitation of social and working life, refractory to drug therapy, and/or tilt training treated with PPM implantation according to current guidelines. A positive 2A or 2B (VASIS classification) cardioinhibitory response to tilt-table testing performed before PPM implantation. Exclusion of other causes. Age > 18 years old.	CLS vs. DDD	30 (18 male, age 62.2±13.5)		CLS significantly reduced syncope induced by tilt-table test (30% vs 76.7%; P<0.001)
Russo et al. 2013[36]	Prospective, randomized, single-blind, crossover study; CLS ON or OFF	>40 years old, sinus rhythm, recurrent unpredictable syncope, no medication that could affect circulatory control, type 2B (VASIS classification) cardioinhibitory VVS, refractory to conventional drug therapy and/or tilt training	CLS	50 (33 male, mean age 53±5.1)	36 months	The number of syncopal episodes during CLS ON was significantly lower than the CLS OFF group (2 vs. 15; P=0.007)
Baron-Esquivas et al. 2017 (SPAIN Study) [37]	Randomized, double blind, controlled study, multicenter; DDD-CLS for 12 months following by sham DDI for 12 months or sham DDI mode for 12 months followed by DDD-CLS for 12 months	≥40 years, ≥5 episodes of syncope or ≥2 in the last year, cardioinhibitory tilt-table test response	CLS vs. DDI. 12 months cross-over	46 (22 male, mean age 56±11)	24 months	72% (95% CI, 47-0%) ≥50% reduction of syncopal episodes with DDD-CLS vs. 28% (95% CI: 9.7-53.5%) during DDI (HR: 6.7; 95% CI: 2.3-19.8)

group had syncope. The time to first syncope was substantially longer in the CLS group (29 months vs. 9 months in sham DDI; OR 11; p<0.0001). Following crossover, significant reductions in syncopal events were seen with DDD-CLS pacing in both groups with CLS resulting in a 37 % absolute risk reduction in the time to first syncope. The number needed to treat to prevent one syncopal episode was 2.7 [37].

In 2018, Rattanawong et al [38] reported a meta-analysis comparing conventional pacing to CLS-based pacing in patients with recurrent VVS. The study included a group of 6 studies (3 of which were randomized control trials) and demonstrated clear superiority for CLS-based pacing. Overall study population was 224 patients and no significant heterogeneity or publication bias was noted.

A systematic review of 5 studies (n=228) compared RDR to CLS-based pacing and showed that RDR-based pacing demonstrated no added benefit in comparison to no pacing for recurrent VVS, whereas CLS-based pacing had a significant reduction in syncopal burden [39]. A second metanalysis of 4 studies (n=275) addressed the role of pacing in a broader population of refractory VVS with a positive head-up tilt test. The results showed that, in comparison to sham or other pacing modality, CLS-based pacing was associated with reduction in syncope risk, even when a subgroup of randomized control trials was assessed [40].

Detecting changes in cardiac impedance early in the vasovagal reflex arc using the CLS algorithm might provide prompt heart rate support to prevent severe bradycardia or asystole and may help modulate hypotension enough to prevent syncope. The role of cardiac pacing as well as the commonly used pacing algorithms are shown in Figure 1.

Leadless Pacing in VVS

A recent multicenter, retrospective study compared patients who received leadless pacemaker with conventional algorithm or dual chamber transvenous pacemaker for drug-refractory cardioinhibitory VVS, diagnosed by cardiac monitoring and head-up tilt testing [19]. Of 72 patients (32±5.5 years; 90% female), 24 had leadless pacemakers and the rest had dual chamber transvenous pacemakers. Syncope frequency was 7.6±3.4/year. At 1-year follow-up, 91% (22/24) in the leadless group and 94% (43/48) in the dual chamber group were free of syncope (p=0.7). The incidence of device-related adverse events were similar between groups. This study thus provided initial evidence of the efficacy of single chamber leadless pacing in drug-refractory cardioinhibitory VVS.

Indications and Guidelines

Although most patients with VVS have a benign course, there is a subset of patients who may benefit from pacemaker implantation. This includes patients with severe and recurrent syncopal episodes and documented asystole despite conservative management (The ACC/AHA/HRS 2017 guidelines for recurrent neurocardiogenic syncope list dual chamber pacing as a class IIb indication for patients over the age of 40 which remains in alignment with the 2012 ACCF/AHA/HRS Focused Update on Device-Based Therapy, which also awarded a Class IIb recommendation for pacing in patients with significantly symptomatic neurocardiogenic syncope associated with bradycardia documented spontaneously or at the time of tilt-table testing [35]. However, the ESC 2018 guideline lists pacing as a Class IIa recommendation for patients over 40 years of age with spontaneous symptomatic pause > 3 seconds, asymptomatic pause > 6 seconds due to sinus arrest, atrioventricular block or a combination [11].

As another difference, the European guideline also provides Class IIb recommendations for pacing in patients older than age 40 years with tilt-induced asystolic response and frequent unpredictable

Table 2: Optimal programming of closed loop stimulation (CLS) for vasovagal syncope patients. Adapted from Kanjwal K, Grubb BP. Journal of Innovations in Cardiac Rhythm Management 2011;2:395-9. [33]

1.	Resting Rate Control should be turned "off" to allow CLS algorithm to vary rate response from base rate to the maximum programmed CLS rate based on cardiac impedance measurement variations, enabling earlier intervention
2.	Set pacing mode to "DDD-CLS", with lower rate of 60-65 beats/min, upper tracking rate of 160 beats/min, and maximum CLS rate (maximum sensor rate) between 130-140 beats/min
3.	CLS response (aggressiveness of the CLS algorithm) should be set to "high" or "very high".

recurrent syncope, and in patients with clinical features of adenosine-sensitive syncope, without direct parallel U.S. recommendations. These recommendations, especially the age cutoff of 40 years, reflect trial entry criteria. There is no specific reason that a pacemaker will not be effective for debilitating cardioinhibitory VVS in a <40-year-old patient.

Based on the results of the SUP 2 and SPAIN trials (these data were not available at the time the U.S. guidelines were ready for publication), the European guideline offers a specific recommendation against the implantation in patients with an absent cardioinhibitory reflex, derived from the assumption that pacing would not be effective in the absence of bradycardia [37, 47].

Management Considerations and Knowledge Gaps

The temporal sequence of bradycardia and hypotension during a vasovagal reflex can be variable between patients as well as between episodes in the same patient [1]. A gold standard assessment for patient selection is lacking. Asystolic syncope during tilt testing can improve with conservative management and may not always signify the need for pacing [20]. Asytolic pauses on the ILR associated with syncope may not always represent cardioinhibitory VVS. Furthermore, hypotension, and its temporal relationship to asystole and syncope cannot be appreciated. In older patients, pauses noted on event monitoring or ILR could represent sinus node dysfunction and not VVS [1].

To make matters more complicated, there are individuals known to have idiopathic atrioventricular block during syncope detected by ECG monitoring, yet have an unremarkable workup [41]. These patients appear to benefit from pacing. In patients younger than 40 years with recurrent asystolic VVS , a careful risk-benefit analysis should be undertaken with a high threshold for pacing therapies keeping in mind the risks of pacing, including lifestyle limitations, multiple generator changes as well as lead and device related complications. Furthermore, the natural history of VVS can include spontaneous resolution obviating the need for a lifetime of pacing. More studies are needed in this regard. In summary, permanent pacing should only be considered as a management option in recurrent refractory frequent asystolic VVS. Whether other pacing algorithms can have better success in VVS patients need further investigation. Catheter ablation of cardiac of ganglionic plexi (cardioneuroablation) is an emerging therapy for cardioinhibitory VVS and vagally mediated bradycardia, with promising observational data [42, 43].

Conclusions

Vasovagal syncope is a common problem that is mostly benign. While tilt table testing may provide information on vulnerable populations and show the temporal relationship of hypotension and asystole with regard to syncope, it does not always provide "real life" accurate and reproducible physiologic heart rate/blood pressure relationships. Most patients with VVS can be managed conservatively; however, those with frequent recurrent syncope remain a challenging group to treat. As medical therapy has been shown to be unsuccessful, pacing appears to be a viable option - the closed loop stimulation algorithm appears to be particularly promising in secondary prevention for patients with frequent and/or debilitating VVS recurrence. As more evidence regarding cardioneuroablation arises, this may be a viable alternative intervention.

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