Usefulness of Head-Up Tilt Table Test and Pacemaker in Vasovagal Syncope

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Introduction

Syncope is defined as a sudden and transient loss of consciousness with spontaneous recovery (1, 2). A failure of the systemic circulation to keep arterial blood pressure high enough to perfuse the brain adequately causes global cerebral hypoperfusion (Figure 1). Neurally mediated syncope or reflex syncope is the most common type of syncope and includes vasovagal syncope (VVS), situational syncope, and carotid sinus syndrome (2). Although VVS is the most common form of neurally mediated syncopal syndromes, all types involve an inappropriate reflex with afferent, central, and efferent pathways (3). As a neuronal efferent response to several triggers like unpleasant thoughts or smells, eating a heavy meal, stretching, coughing, pain, or simply standing still, the cardioinhibitory and/or vasodepressor pathways can lower systemic blood pressure and cause cerebral hypoperfusion in reflex syncope (Figure 2).

Figure 1 Differential diagnosis of transient loss of conscious

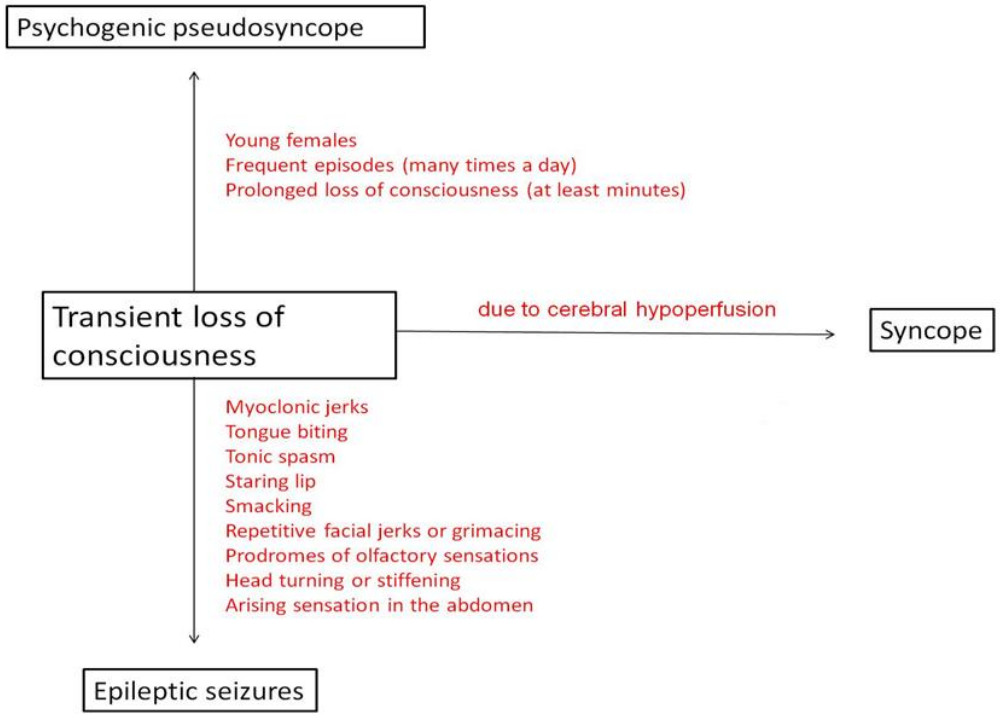
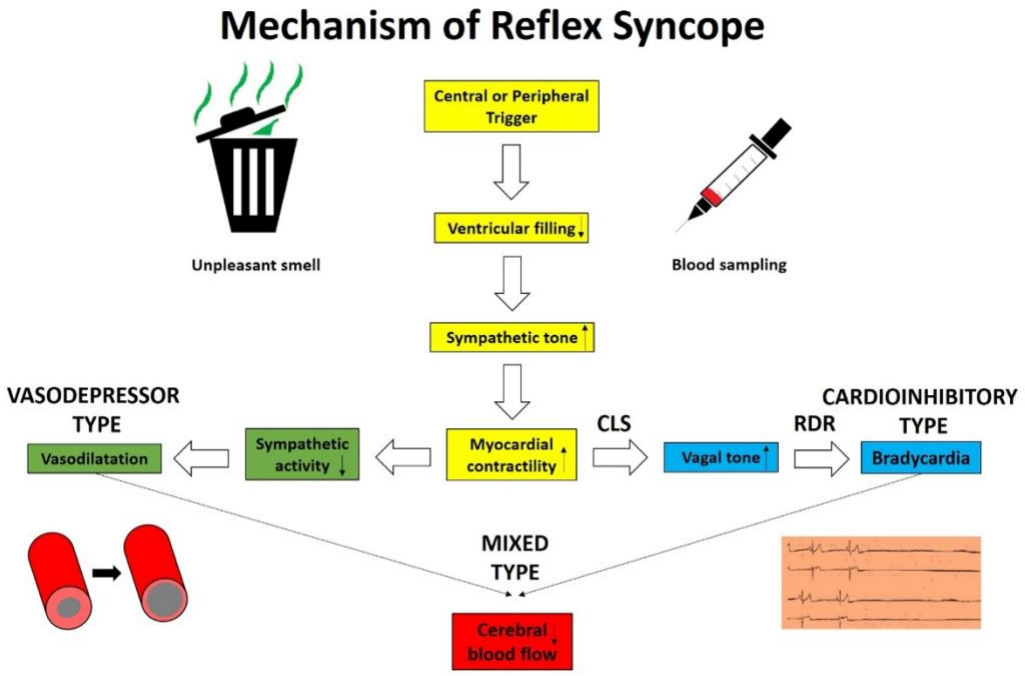


Figure 2 Mechanism of reflex syncope and different algorithms associated with pacing



CLS, closed loop stimulation pacing system; RDR, rate drop response pacing system

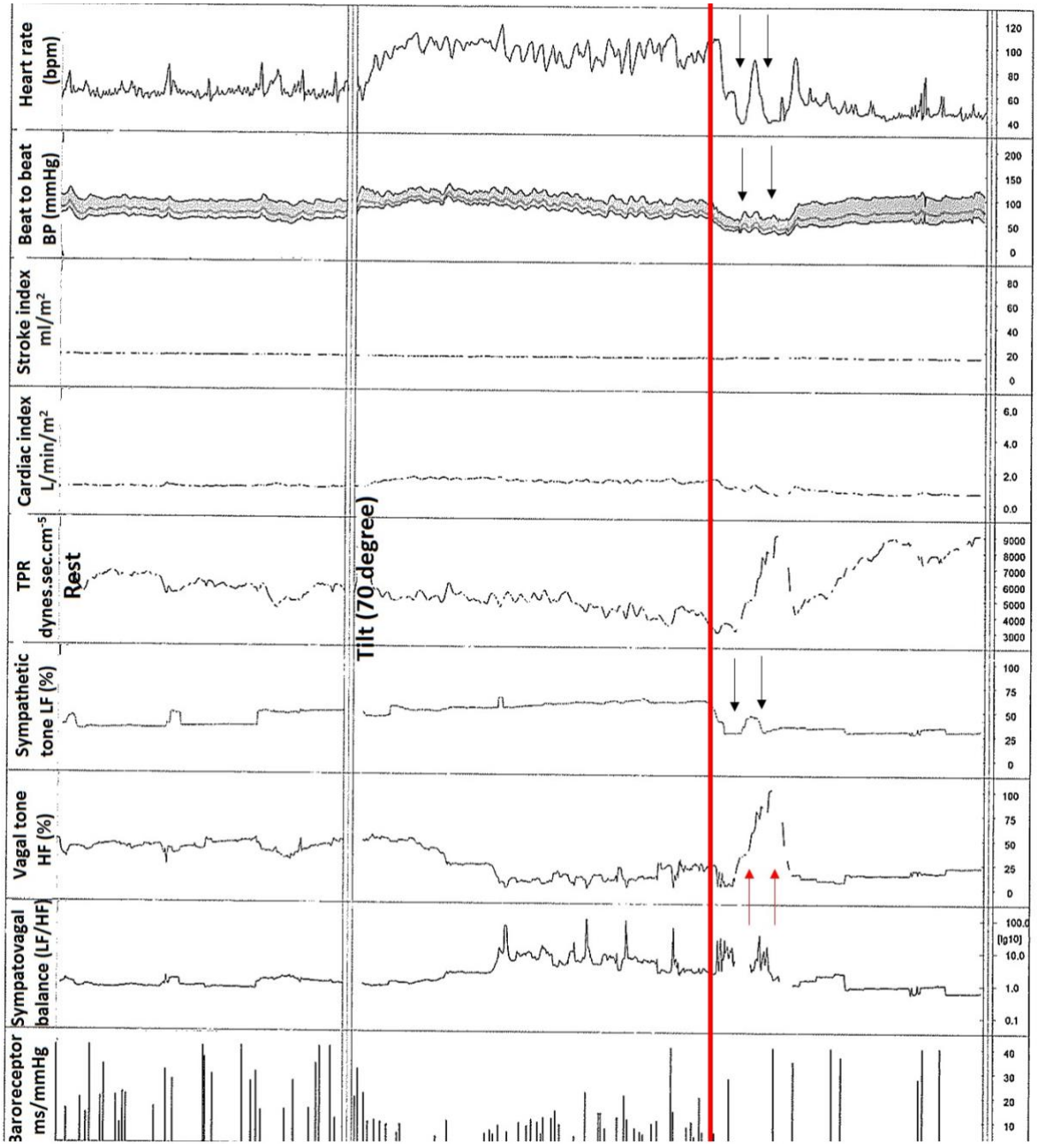
Although clinical presentation is usually related to a self-limited event, frequent episodes or events without prodrome might be debilitating (4). In existence of a dominant cardioinhibitory response on head-up tilt test (HUTT), the cornerstone of management is non-pharmacological treatment, including education, lifestyle modification, and physical counter-pressure maneuvers (5). No medical therapy has proven effective in randomized clinical trials in this group (6). Cardiac pacing may be necessary for patients with severe forms, such as those with very frequent syncope affecting quality of life; recurrent syncope without prodromal

symptoms, which exposes the patient to a risk of trauma; and syncope occurring during a high-risk activity (1, 2). However, the role of cardiac pacing for the prevention of syncope recurrences remains controversial due to difficulties in excluding potential role of the vasodepressor component during the episode. Furthermore, due to the lack of sufficient evidence from studies, cardiac pacing cannot be recommended for patients aged <40 years of age. The aim of the present article is to review usefulness of HUTT and pacemaker in patients with VVS.

Responses to head-up tilt test

Theoretically, HUTT enables the reproduction of VVS in a laboratory setting with a specificity of 92-94% (2). According to blood pressure and heart rate reaction, there are 3 types of response to HUTT (7): (1) type 1 (mixed): Heart rate falls at the time of syncope, but the ventricular rate does not fall to less than 40 beats.min^{-1} , or falls to less than 40 beats.min^{-1} for less than 10 s with or without asystole for less than 3 s. Blood pressure falls before the heart rate falls (Figure 3); (2) type 2A (cardioinhibition without asystole): Heart rate falls to a ventricular rate less than 40 beats.min^{-1} for more than 10 s, but asystole for more than 3 s does not occur. Blood pressure falls before the heart rate falls; (3) type 2B, (cardioinhibition with asystole): Asystole occurs for more than 3 s, heart rate fall coincides with or precedes blood pressure fall; (4) type 3 (vasodepressor): Heart rate does not fall more than 10%, from its peak, at the time of syncope. Syncope reproduction with the hypotension and/or bradycardia/asystole demonstrates positive response and should be accepted as diagnostic. If hemodynamic changes occur in the absence of symptom reproduction (or vice versa) the test should be interpreted as false positive.

Figure 3 Hemodynamical results of the case with mixed type response during tilt testing



Top trace shows the heart rate curve; bottom trace shows continuous blood pressure curves. Blood pressure stabilizes shortly after the assumption of the upright position with no changes for the duration of the preparatory phase; the heart rate immediately rises, then stabilizes. The vertical red line indicates the time of onset of the vasovagal reaction, which is characterized, at first, by a decrease in blood pressure with a steep fall in heart rate and syncope occurs. The total duration of the vasovagal reaction is about 4 min. Black arrows demonstrate decrease on heart rate, blood pressure and sympathetic tone during the vasovagal reaction. Red arrows show vagal overactivity during the vasovagal reaction.

Protocols for head-up tilt table test

Since the first published work (8), several methodologies and protocols have been used and suggested by different groups. Original passive protocols had low diagnostic sensitivity and long duration, which made them unsuitable for the clinical practice; so pharmacological challenges with different agents have been introduced (9-23). There is still no "gold standard" method to perfectly identify true positives and false negatives for the diagnosis.
Such a gold standard is required to accurately evaluate test sensitivity and diagnostic performance.

Passive Protocols

The Westminster protocol is the mostly applied to passive protocols and includes tilting to 60° for 45 minutes without intravenous cannulation or administration of vasoactive substances (10). Authors described a sensitivity of 75% and a specificity of 93%. The main concern about the technique was the long duration of tilting. Stein et al (13) evaluated the effect of the duration of passive tilt testing on the utility of HUTT for diagnosing VVS. They analyzed 11 published studies for the following parameters: (1) 60 to 80 degrees upright tilt, (2) footboard support, and (3) 15- to 60-minute duration and performed HUTT in 213 patients for 30 to 60 minutes. They demonstrated that diagnostic accuracy varied from 60% to 84%, and was not greatly influenced by duration of the test after 30 minutes.

Provocative tests

Passive tilt testing has been replaced by provocative tests to shorten the tilting time and to increase sensitivity and specificity. The addition of isoproterenol to HUTT increased the test sensitivity up to 87%, but decreased its specificity to s between 55% and 100% (mean 76%) which prompted the use of other provocative agents such as epinephrine and edrophonium (24-28). The protocol has been replaced by usage of nitroglycerin derivatives and was called "the Italian protocol" since it was first tried by Italian researchers (18). Although nitroglycerin infusion was tried in the original report, sublingual or oral administration of

nitroglycerin was tested in the following studies to simplify and to speed up the test (18, 29). This protocol yielded a sensitivity of 62% and a specificity of 92% (30). In 2008, an update of the Newcastle protocol was published (31). The technique was summarized as 20/15 Italian protocol including a passive non-medicated phase of tilting to 70° for 20 minutes, and if positivity/discontinuation criteria not achieved, administration of 400 μg sublingual nitroglycerine, with tilting continued for further 15 minutes. Where psychogenic or hyperventilation syncope is suspected, 40-minute passive tilt should be the sole HUT. In our current approach, we use the Newcastle protocol during HUTT because of simplified, more rapid and practical aspects of the protocol (32, 33).

However, it should be kept in mind that although HUTT demonstrates a high level of diagnostic specificity, its sensitivity, in contrast, is still far from ideal. While a positive cardioinhibitory response to HUTT may predict, with a high probability, an asystolic spontaneous syncope, a negative response or even a positive vasodepressor or mixed response may not exclude the presence of asystole during spontaneous syncope. Therefore, HUTT should be offered to patients believed to have a high pretest likelihood of VVS to reveal dominant part of reflex arc in occurrence of clinical picture as an (admittedly imperfect) estimate of sensitivity.

Head-up tilt table test and clinical outcomes with pacing

The first randomized trial of pacing in VVS was published in 1999 (34). Although this study comparing pacing with medication or no treatment showed very promising results, the next 2 trials, in which implanted pacemaker was programmed “off” in controls, showed no benefit with pacing (34-38). Although HUTT was used to select candidates for pacing in all of these studies, patient selection failed to include documented evidence of severe cardioinhibition in the pacing off trials. In VPS II trial, inclusion criterion was a positive HUTT result with a heart rate × blood pressure product of less than 6000/min × mm Hg (37). The ratio of patients

demonstrating lowest heart rate of <40 beats/min was lower than 25%. Furthermore, syncope occurred in 70% of cases during HUT. In SYNPACE trial, only 29 patients were included in the study (about 1.8% of the source population) (38). Of the 29 patients enrolled, 16 were randomized to pacemaker ON (asystolic group, 8; mixed group, 8), and 13 to pacemaker OFF (asystolic group, 7; mixed group, 6) (38). Mixed response was defined as development of bradycardia <60 beats per minute for at least 10 beats, but without asystole.

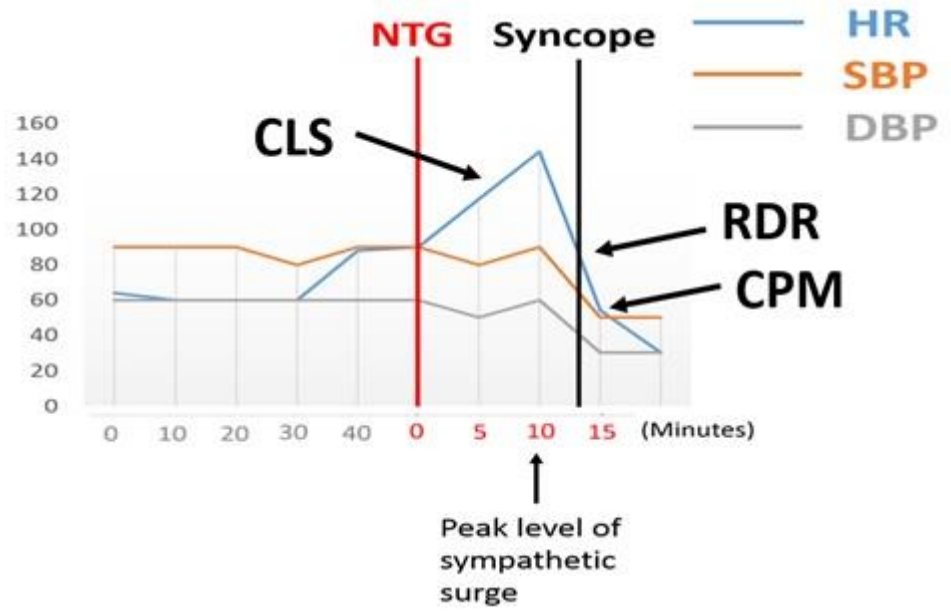
The multicenter, prospective, randomized, double-blind controlled trial, ISSUE-3 compared rate drop response dual-chamber pacing with sensing only mode in reflex syncope patients age ≥40 years (39). Although HUTT was not obligatory for inclusion, it was performed in 87% of patients. The pacemaker implantation criteria were documentation of syncope with ≥3 seconds of asystole or ≥6 seconds of asystole without syncope. Patients who met the criteria for pacemaker implantation were randomly assigned to dual-chamber pacing with rate drop response or to sensing only. The 2-year estimated syncope recurrence rate was 57% with pacemaker OFF and 25% with pacemaker ON. The risk of recurrence was reduced by 57% (95% CI: 4–81%). It should be noted that unlike the known epidemiological features of reflex syncope, the majority of patients were over 60 years old (mean age 63±12 years) and about 50% of cases had no prodromal symptoms. Furthermore, the first syncope occurred at a mean age of 45 years. These features may complicate the differential diagnosis of non-reflex causes of syncope such as sinus node dysfunction, which may present with asystole in implantable loop recorder (ILR).

In a subgroup analysis of the ISSUE-3 study, the role of HUTT in predicting recurrences was studied (40). HUTT was considered positive if syncope occurred in the presence of hypotension with or without bradycardia. As an important finding, existence of asystolic cardioinhibitory HUTT response predicted a similar asystolic form during ILR monitoring, with a positive predictive value of 86%. The corresponding values were 48% in patients with

non-asystolic HUTT (p=0.001 versus systolic HUTT) and 58% in patients with negative HUTT (p=0.001 versus systolic HUT). In multivariable analysis, a positive HUTT response and the total number of syncopal events were the only independent predictors of syncope recurrence following pacemaker implantation. Furthermore, the recurrence rate in patients with positive HUTT response was similar to that seen in 45 untreated controls. There was no significant difference according to the type of positive response, such as vasodepressor or cardioinhibitory. However, the number of patients with asystolic and non asystolic responses were only 14 and 12, respectively.

Recently, closed loop stimulation (CLS) pacing system has emerged as a new strategy which appears superior to conventional pacing for patients with refractory syncope. Conventional pacing systems can only detect changes in heart rate; thus they sense the occurrence of syncope only after the process is underway, and are less likely to fully prevent it (Figure 4). In the contrary, CLS pacing algorithm has a sensing strategy that detects an increase in myocardial contractility by measuring localized cardiac impedance utilizing a right ventricular lead in the early phases of VVS (41) (Figure 5). This triggers atrioventricular sequential pacing at rates high enough to substantially improve cardiac output and blood pressure.

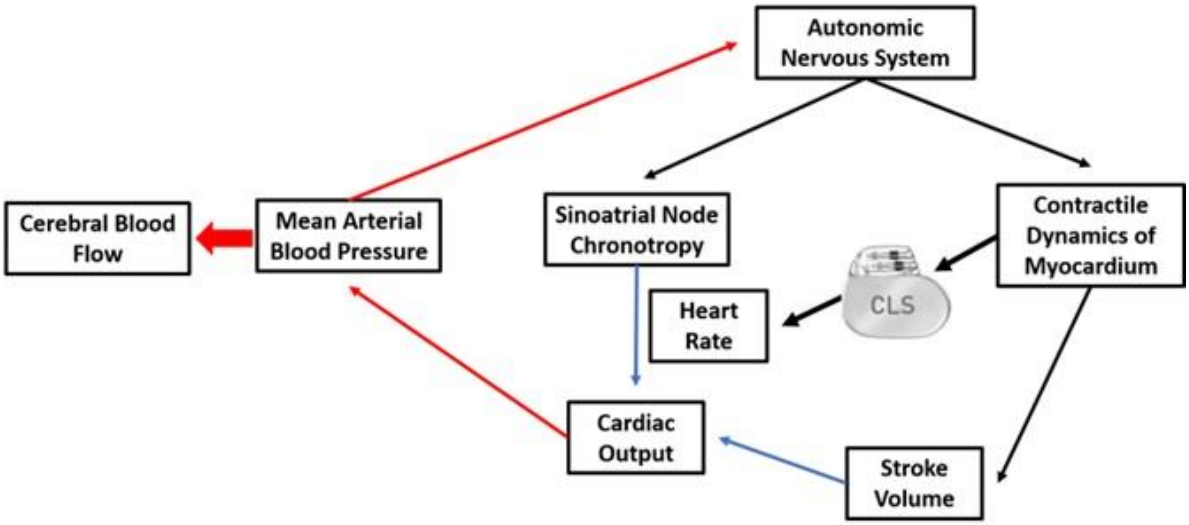
Figure 4 Typical hemodynamic responses in a patient with mixed type reflex syncope



Before occurrence of syncope a decrease on blood pressure is detected while heart rate increases. At the onset of cardioinhibition, heart rate is higher than baseline. Cardioinhibition thus initially only represents a reduction of the corrective heart rate increase, but is usually accompanied by an immediate acceleration of the ongoing blood pressure decrease. At syncope, a steep decrease on heart rate is seen with accompanying decrease on blood pressure.

CLS, closed loop stimulation pacing system; CPM, conventional pacemaker; DBP, diastolic blood pressure; HR, heart rate; NTG, nitroglycerine; RDR, rate drop response pacing system; SBP, systolic blood pressure

Figure 5 Close loop stimulation pacing algorithm



Close loop stimulation monitors myocardial contraction dynamics to regulate heart rate. Decreased right ventricular filling (such as in the early stages of syncope) leads to increase lead impedance that triggers close loop stimulation algorithm.

After publication of the first retrospective study in 2002, 2 prospective trials were published by the same group (42-44). Although cases with both cardioinhibitory and mixed HUT responses were included in the first 2 studies, randomized, controlled, single-blinded, multicenter INVASY study included patients with only cardioinhibitory VVS (44). In the early phase of the study, 26 patients were randomized into DDI mode (nine patients) and DDD-CLS mode (17 patients). None of the patients in the CLS arm experienced new syncope episode. Contrary, seven patients in the conventional pacing group (DDI mode) experienced at least one recurrence of syncope. In the second phase of the study, 24 new patients were enrolled in the CLS arm of the study with a total of 41 patients with DDD-CLS mode and nine patients with DDI mode. During a follow-up period of 19 ± 4 months, seven patients with the DDI mode experienced syncope compared to no patients with the DDD-CLS mode. These encouraging results were recently confirmed in randomized, double-blind, controlled SPAIN study (45). Patients age ≥40 years, with high burden syncope (≥5 episodes, ≥2

episodes in the past year), and a cardioinhibitory HUTT (type2A or type 2B) were randomized to either dual-chamber pacing with closed loop stimulation for 12 months followed by sham DDI mode pacing at 30 pulses/min for 12 months (group A), or sham DDI mode for 12 months followed by DDD-CLS mode for 12 months (group B). The proportion of patients with ≥50% reduction in the number of syncopal episodes was 72% with DDD-CLS mode compared with 28% with sham DDI mode ($p = 0.017$). A total of 4 patients (8.7%) had events during DDD-CLS and 21 (45.7%) during sham DDI. DDD-CLS mode significantly reduced syncope burden and time to first recurrence by 7-fold. These findings were reproduced in the recently published BioSync study (46). This double-blinded randomized controlled trial of DDD-CLS (n=63) vs. sense only (n=64) included patients ≥40 years with ≥2 VVS episodes in the last year and HUTT(+) with an asystolic pause ≥3 s. DDD-CLS pacing decreased syncope recurrence from 53% to 16% ($P<0.001$).

The effectiveness of HUTT in selecting suitable candidates for CLS pacing has been confirmed in a recent meta-analysis (47). Two single-blinded and one double-blinded randomized controlled trials, two prospective observational studies, and three retrospective observational studies were included in the analyses. Studies that used pacing algorithms other than CLS, studies with no clinical follow-up, and studies that included patients who had bradycardia/asystole on telemetry but did not have HUTT were excluded. Use of CLS pacing was associated with a significant reduced risk of syncope (3.5% vs 34.7%). Furthermore, the results were similar when limiting the analyses to randomized controlled trials.

Comparison of head-up tilt table test with implantable loop recorders

Loop recorders are introduced to reveal spontaneous episodes of arrhythmia by continuous rhythm monitoring. In reflex syncope, the main advantage of ILRs may more precisely define a cause-effect relationship between bradyarrhythmia and syncope and exclude cause of syncope related tachyarrhythmia (48-53). The most common indication for HUTT is to

confirm a diagnosis of VVS in patients in whom this diagnosis has been suspected but not confirmed by the initial evaluation. A positive HUTT is reassuring for patients that their symptoms have been witnessed and interpreted correctly by clinicians. HUTT educates patients to recognize evolving symptoms during spontaneous events and to permit initiation of preventive measures such as physical counterpressure maneuvers. HUTT might be also recommended to discriminate relative contributions of parasympathetic and sympathetic efferent arms in syncope episode (32, 33). In other words, while HUTT demonstrates both hypotension and bradycardia, ILR recordings during spontaneous episodes can only reveal asystole. HUTT is cost saving over ineffective expensive tests such as brain imaging, electroencephalography, and repetitive valueless Holter monitoring (1, 2). Relative advantages and disadvantages of both techniques are discussed in Table 1.

Table 1 Advantages and disadvantages of head-up tilt table test and implantable loop recorders

Modality	**Advantages**	**Disadvantages**
Head-up tilt table test	Non-invasive	The negative predictive value is poor
	Cheap	Prediction of symptom burden and clinical outcome is poor
	The positive predictive value is good	
	Can be used to distinguish reflex syncope from orthostatic hypotension, pseudosyncope, epilepsy, structural based sinus node dysfunction	Ideal protocol is unclear
	Positive test result can be used to predict inadequate response to the pacing	Reproducibility is moderate
	Can demonstrate vasodepressor component of syncope	

	It has been used as a major inclusion criteria not only in observational and randomized studies, but also in one randomized, double-blind clinical study	
Implantable loop recorder	Diagnostic value is higher in unexplained syncope	Invasive
	Predicts good response to pacing in patients aged older than 40 years of age	Expensive
	Can reveal arrhythmic cause of syncope	Cannot distinguish asystole due to structural based sinus node dysfunction from reflex syncope
	It has been used as a major inclusion criterion in double-blind randomized trials of permanent pacing	Cannot demonstrate vasodepressor component of syncope

Ongoing questions

Many questions remain concerning pacing for VVS First, how should the VVS patients be selected? The recent SPAIN (45) and BioSync (46) studies both used a positive HUTT with asystole as the inclusion criteria. Some have recently questioned the value of HUTT (54) due to its limited sensitivity and specificity, while others have argued that a high sensitivity and specificity could be achieved with the simultaneous analysis of heart rate and beat-to-beat systolic blood pressure (55). Second, the recent positive pacing in VVS studies have all involved DDD-CLS pacing. There has yet to be a clinical trial comparing DDD-CLS pacing to non-CLS DDD pacing. Such a trial could more clearly guide physicians on the optimal devices for our VVS patients. Third, all of the VVS pacing RCT published since 2010 have included only patients ≥40 years. This has largely been to avoid subjecting younger patients to a lifetime of pacemaker generator changes. It does, however, beg the question as to how best to manage younger patients with refractory, recurrent VVS (56).

Conclusions

Despite existence of some well-known limitations, HUTT is still an important tool in the diagnosis of VVS. The similarity between clinical and induced VVS during the test demonstrates its value. When provocative tests are applied, the results seem highly reproducible. Given considering the absence of any serious complications, low cost, and non-invasive nature, HUTT should be a part of our clinical practice in evaluation in VVS. While permanent pacing does appear to be beneficial for some patients, further studies are needed to clarify patient selection and types of pacemaker.

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