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Why is the Tilt Table Test Still Useful to Define who Should or Should Not Get A Pacemaker with Vasovagal Syncope?

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Abstract

The the tilt table test (TTT) has been used identify appropriate candidates for pacing in the majority of randomized trials. However, in recent years, it has been claimed—based largely on International Study on Syncope of Uncertain Etiology (ISSUE) studies—that the TTT demonstrates only a weak correlation with the mechanism documented by implantable loop recorder (ILR) at the time of syncope and thus confounds the correct diagnosis. Thus, cardiac pacing was supported in patients with recurrent vasovagal syncope (VVS) in whom clinically relevant asystole had been documented by ILR. In the present Editorial, we tried to discuss potential role of TTT in diagnostic workflow of VVS based on current data.

Introduction

Vasovagal syncope (VVS) is a clinical condition related to brady cardia (cardioinhibitory response) and/or hypotension (vasodepressor response), likely mediated by parasympathetic activation and sympathetic inhibition. Although clinical presentation is usually associated with a situational, isolated and/or self-limited event, in some cases, VVS might be recurrent, unpredictable and debilitating. There is still no specific medical therapy has been proven widely effective. For a long time, evidence of severe cardioinhibition on the tilt table test (TTT) in association with VVS has been used to offer permanent pacing to combat bradycardia/asystole [1]. However, its value has been debated. The temporal causative association of bradycardia with syncope by using TTT may help identify which patient could benefit from pacing but the timing and type of pacing in lieu of blood pressure changes may be critical. This brief review discusses randomized pacing trials in VVS and what we have learned about selection of patients for pacing benefit.

Trials of Pacing in Vasovagal Syncope

The first randomized controlled trial compared pacing with medication or no treatment (VPS I) was published in 1999 and were followed by 2 others (VASIS and SYDIT) including patients with documented evidence of severe cardioinhibition by TTT [2-4]. Although those studies demonstrated very encouraging results, following 2 trials (VPS II and SYNPACE) compared pacing "off" and "on" showed no pacing benefit [5,6]. As an important point, a rate-drop response pacemaker was implanted in all those studies. Although there is a trend in favour of active pacing in prolonging the time to first recurrence, especially for those patients who had had an asystolic response during TTT, a high percentage of patients with recurrent tilt-induced VVS continued to have syncopal relapses despite active cardiac pacing in SYNPACE trial [6]. Inefficacy of active pacing in preventing syncopal recurrence and placebo effect of inactive pacing were considered the main causes of negative results of pacemaker implantation by authors. However, in these two double-blind trials, patient selection failed to include documented evidence of severe cardioinhibition (Table 1).

In recent years, it has been claimed—based largely on International Study on Syncope of Uncertain Etiology (ISSUE) studies—that the TTT demonstrates only aweak correlation with the mechanism documented by implantable loop recorder (ILR) at the time of syncope and thus confounds thecorrect diagnosis [7-9]. Thus, cardiac pacing was supported in patients with recurrent vasovagal syncope (VVS) in whom clinically relevant asystole had been documented by ILR [10].Furthermore, some groups have argued that TTT for the workup of syncope should be abolished because the TTT fails to establish an explicit cause of syncope [11].

The double-blinded, randomized ISSUE-3 trial showed that dual-chamber rate-drop response cardiac pacing was effective in reducing the recurrence of syncope in patients ≥40 years with severe asystolic VVS documented by ILR, with the risk of syncope recurrence reduced from 57 % to 25 % (P=0.039) [8].To investigate the role of TTT response in predicting syncopal recurrence in the ISSUE-3 population, patients

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Table 1: Summary of Randomized Trials Evaluating the Utility of Pacing in Vasovagal Syncope*

Trial	PM	Age for inclusion/ mean age	Case number	TTT	ILR	Type	Results	Limitation
VPS I[1]	**RDR**	>18 / 43	27 in PM 27 in CT	**HR <60 bpm or HR <70 bpm (≤2 mcg/min isoproterenol) HR <80 bpm (>2 mcg/min isoproterenol)**	**(-)**	**NB PM vs CT**	**Presyncope was similar 84% relative risk reduction in syncope**	**Placebo effect Early termination Baseline difference between groups**
VASIS[2]	RDR	>40 or <40 in refractory syncope/ 64 in PM 56 in CT	19 in PM 23 in CT	VASIS type 2A or type 2B	(-)	NB PM vs CT	Syncope 5% in PM 61% in CT	Placebo effect Mean age was higher in PM group 64 vs 56
SYDIT[3]	RDR	> 35 / 58	46 in PM 47 in CT	HR <60 bpm	(-)	NB PM vs atenolol	Syncope 4.3% in PM 25.5% in MT	Mean age was higher in PM group 61 vs 55 Study was stopped early
VPS II[4]	RDR	>19/ 50	52 in ODO 48 in DDD	HRXBP <6000/min X mmHg	(-)	DB Pacing on vs off	Syncope 40% in ODO 31% in DDD (no difference)	Each center used its own HUT protocol
SYNCPACE[5]	RDR	>18/ 52	16 in pace on 13 in pace off	(+) TTT response	(-)	DB Pacing on vs off		Study was stopped early due to VPS II
ISSUE 2[6]	RDR	>30/ 66	47 in pacing 50 in CT	88% TTT response was not an inclusion criterion	(+)	NB PM vs CT	Syncope 5% in pacing 41% in CT	Old age Typical presentation for VVS was seen in 41% No prodrome in 50%
ISSUE 3[7]	RDR	≥40/ 63	38 in pace on 39 in pace off	87% TTT response was not an inclusion criterion	(+)	DB	Syncope 57% in pacing off 25% in pacing on (P=0.039)	Typical presentation for VVS in only 47% of cases Uncertain presentation in 53%
ISSUE 3 sub-analysis[8]	RDR	≥40/ 62	76 in TTT (4) 60 in TTT (-)		(+)	DB	Syncope 31% in TTT (+) 4% in TTT (-)	Typical presentation for VVS in only 52% of cases Atypical ILR response in 28%
INVASY[12]	CLS	>18/ 58	2:1 DDD-CLS (17 patients) to DDI ratio (9 patients)	Type 2A or 2B	(-)	SB DDD vs DDI	Syncope 0% in DDD 44% in DDI (no difference)	Study was stopped early Variable follow up time
Russo V[13]	CLS	>40/ 53	50 patients Crossover	Type 2B	(-)	SB CLS on vs off	Syncope 2% during CLS on 16% during CLS on	Carryover effect
SPAIN[11]	CLS	≥40/ 56	DDD → DDI (21 patients) vs DDI → DDD (25 patients)	A HR <40 bpm for at least 10s or >3 s pause	(-)	DB	Syncope 8.7% in DDD 46% in DDI (37% absolute risk reduction)	A >50% reduction in syncope frequency was selected as the primary efficacy outcome

BP, blood pressure; CLS, closed loop stimulation; CT, conventional treatment; DB, double-blind; HR, heart rate; ILR, implantable loop recorder; INVASY, Inotropy Controlled Pacing in Vasovagal Syncope; ISSUE, Third International Study on Syncope of Uncertain Etiology; MT, medical treatment; NB, non-blinded; PM, pacemaker; RDR, rate drop response; SB, single-blind; SPAIN, Closed Loop Stimulation for Neuromediated Syncope; SYNPACE, the vasovagal Syncope and Pacing Trial; SYDIT, SyncopeDiagnosisandTreatment; TTT, tilt table test; VASIS, vasovagal syncope international study; VPS, the North American Vasovagal Pacemaker Study; VVS, vasovagal syncope.
*SyncopeUnit Project (SUP) trialsareexcluded in theanalysisbecausethepatientswithcarotidsinussyncopewerealsoincluded in thesestudies.

with asystole documented by ILR who received a pacemaker were divided into 2 groups: TTT was positivein 26 and negative in 26[9]. Although authors defined that patients with TTT (+) and TTT (-) had similar characteristics, patients were older at the time of first syncope in the TTT (-) group (48 vs 42). This older age in TTT (-) group is inconsistent with the classical presentation of VVS in which the first syncope episode typically occurs before the age of 40 years[4]. Furthermore, typical vasovagal presentation was also lower in TTT (-) group (42% vs 58%). Syncope recurred in 8 TTT (+) and in 1 TTT (-) patients (P=0.004). At multivariable analysis, TTT (+) and total number of events were the only independent predictor of syncope recurrence.

On the contrary, double-blinded, randomized SPAIN trial supported the clinical utility of TTT in VVS population [12]. Patients were aged ≥40 with TTT confirmed cardioinhibitory response: bradycardia <40 bpm during >10 s or asystole >3 s, as per the Vasovagal Syncope International Study classification were included in the study. Mean age was 56.30 ± 10.63 years and significantly younger than ISSUE population. Only 8.7% of 46 patients who received dual-chamber pacing with closed loop stimulation suffered syncopal events, compared to 46% randomized to the sham DDI mode with an relative risk reduction of 89% and an absolute risk reduction of 37% ($p < 0.0001$). High clinical efficacy of closed loop stimulation system was compatible with previous single-blind randomized controlled trials [13,14].

How should We Interpret Disparateresults of Pacing Studies?

Considering older age, atypical presentation with no or subtle prodrome, and lack of recognizable triggers of cases in ISSUE 3, we can speculate that positive effect of pacing in TTT (-) cases might be

associated with non-reflex nature of syncope, and may have had sinus node dysfunction. TTTdemonstrated true reflex syncope cases, but pacing support with rate-drop response pacemaker, even at faster rates, may be too little and too late to counteract reflex arc and prevent the event. Thus, beside patient's characteristic and sinus node dysfunction, pacing method (closed loop stimulation vs. rate-drop response) might be another plausible explanation for the different results between SPAIN and ISSUE 3. Furthermore, SPAIN trial did not select patients on relative absence of prodrome or predominant vasodepressor response in contrast to ISSUE-3.

In a recently published study, by using TTT, Dijk et al [15] revealed that cardioinhibition is observed in 91% of patients at a median time of 58 seconds before syncope episode. Furthermore, at the onset of cardioinhibition, median heart rate was at 98 bpm higher than baseline. Cardioinhibition thus initially only represented a reduction of the corrective heart rate increase. At the time of syncope, stroke volume had a strong negative effect on blood pressure, total peripheral resistance a lesser negative effect, while heart rate had increased (all $p<0.001$). Thus, by detecting local impedance in the right ventricle which may relate to contractility, closed loop stimulation may evaluate autonomic function and improve the timing for onset of pacing. Also, the effect of cardiac pacingin asystolicTTT (+) patients who did not achieve the end point ofan ILR event documentation was not studied in the ISSUE III trial. Theoretically, these patients couldhave a better outcome with a pacemaker.

Although ISSUE trials suggest that among patients with ILR documented asystole during VVS, pacing efficacy was primarily of value in those individuals without evident vasodepressor susceptibility, it is not possible to quantify how much vasodepression and cardioinhibition contribute to cerebral hypoperfusion with ILR. By using TTT with continuous electroencephalographic monitoring, temporal relationships of vasodepression and cardioinhibitionmight be determined [15]. If asystole starts after the onset of syncope or within 3 s of syncope, it cannot be the main cause of syncope. Thus,we can avoid pacing without benefit by defining the timing of syncope.However, one plausible confounder contributing to the less than predictable nature of clinical response to pacemaker is the relative contribution of vasodepression and cardioinhibition at different times in a given patient may be variable.

Guidelines

Although many of the treatment recommendations were grossly similar between the European and U.S. guidelines, there were key differences noted in recommendations for patients with syncope [10, 16]. Both guidelines recommend pacemaker implantation for patients with recurrent reflex syncope older than age 40 years and evidence of symptomatic pauses for at least 3 s, or asymptomatic pauses for at least 6 s [10,16]. However, spontaneous asystole in patients with reflex syncope received a slightly different class of recommendation in the U.S. guidelines (Class IIb) when compared with the European guidelines (Class IIa) [10,16].

Although each of the guidelines define reflex syncope encompassing VVS, carotid sinus syndrome (hypersensitivity), and situational syncope, the European guidelines also describe adenosine-sensitive syncope in which the patients often present without prodrome, have a structurally normal heart, normal ECG, and a negative response to TTT [10,16]. Thus, the European guidelines also provide Class IIb recommendations for pacing in patients older than age 40 years with tilt-induced asystolic response and frequent unpredictable recurrent syncope, and in patients with clinical features of adenosine-sensitive syncope, without direct parallel U.S. recommendations [10, 16]. The subtlest change in the European guidelines was related to TTT. Recommendation of TTT dropped from I B to IIa B–and the diagnostic criteria indication falled from I to IIa. In addition, its lack of ability to direct management is maintained [16]. Application of TTT was still considered useful for assessing vasodepressor component, differential diagnosis of epilepsy and psychogenic pseudosyncope.

The Existing Knowledge Gaps

Despite existence of randomized controlled trials outlined above, there is still several knowledge gaps. The exact mechanism of VVS and underlying hemodynamics need further studies.A well-performed TTT may clarify pathophysiology of VVS by demonstrating the temporal relationship among vasodepression, loss of consciousness, and cardioinhibition [17].

By using an algorithm to predict VVS during TTT based on the simultaneous analysis of heart rate and beat-to-beat systolic blood pressure, a sensitivity of 97.6% and a specificity of 88.2% might be achieved in VVS [18]. The data is scarce whetherpacing is useful for those under the age of 40 years with recurrent VVS associated with severe bradycardia and/or asystole or not. We need more data which patients with VVS over 40 years of age may more benefit from pacing. It should be investigated whether TTT combined with ILR monitoring may provide better insights to select the best candidates for pacing in VVS. Finally, the best pacing algorithm and how it is it best to programme the pacemaker for better success in VVS patients need further investigation.

Preliminary results of the double-blind, randomized, and placebo-controlled BIOSync trial (NCT02324920) was presented at the European Society of Cardiology Congress 2020 [19,20]. The trial conducted across 24 sites in Europe and Canada with a medium follow-up of 11.2 months. When comparing the CLS-paced group versus the control group, syncope recurrence rate and the combined rate of syncope and/or pre-syncopewere reduced by 77% and by 56% in a medium follow-up of 11.2 months.Although the use of TTT to select patients with severe recurrent VVS for cardiac pacing was controversial until this study, the positive results of this trial demonstrate that asystolic response to HUT is a valuable criterion for cardiac pacing.

As an emerging therapy, catheter ablation of cardiac of ganglionic plexi (cardioneuroablation) provided promising observational data in patients with cardioinhibitory type VVS and vagally mediated bradycardia [21-26]. In all cohorts related cardioneuroablation, VVS cases were included in the study according to TTT results. Furthermore, we recently demonstrated that TTT seems as a valuable diagnostic tool not only to select suitable candidates and but also toevaluate success of cardioneuroablation [24]. Fifty-one consecutive patientswith VVS were included in the study. After confirmation of >3 s asystoleon TTT, all

patients underwent cardioneuroablation. TTT was repeated 1 and 6 months after cardioneuroablation.The main outcome measures were recurrence of syncopeepisode and positive response on TTT. Repeated TTTs were negative in 44 (86.2%)patients. When patients with recurrent syncope were excluded, vasodepressor response was seen in three casesand cardioinhibitory response in one case, respectively. Cardioneuroablationcaused significant and durable shorteningof RR interval in all cases. This effect was significantly higher in patients without positive TTT responses.

Conclusions

TTT can be helpful to predict outcome of pacing with respect to syncope recurrence which can lead physicians away from implantation of an ineffective rate drop responsepacemakers in this scenario. It may also demonstrate the patients who benefit from dual-chamber closed loop stimulation pacing.

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