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## Tilt-table testing of patients with pacemaker and recurrent syncope

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### ABSTRACT

The diagnosis of recurrent syncope in patients with pacemakers (PM) is quite challenging and the etiology of syncope is often multifactorial. To portray the mechanism of syncope in PM patients, we report the results of head-up tilt table testing (HUT) in a series of patients with PM, originally implanted for reasons other than neurally mediated syncope, referred due to syncope or pre-syncope (aborted syncope, vertigo, suspected orthostatic hypotension).

Forty-one patients with PM undergoing a HUT in our syncope unit between January 1st, 2007 and December 31st 2011 were included. A standard HUT protocol with nitroglycerine provocation was used and the test results were classified according to current guidelines. Baseline data were retrieved from the medical records.

Overall, 54% of patients had a positive response to HUT. Vasodepressor or orthostatic hypotensive response were the most prevalent responses accounting for 72% of patients with a positive test. There were no differences between groups with positive or negative test result regarding age, gender, resting blood pressure and heart rate, daily fluid intake, pacing mode, pacing indication or pacing rhythm at rest.

HUT in patients with pacemakers has a high diagnostic yield. Although, the majority of patients had a vasodepressor or orthostatic hypotensive response, cardioinhibitory response leading to syncope was also seen.

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## Introduction

Reflex syncope, also known as neurally-mediated syncope or neurocardiogenic syncope is prevalent with a mixed reaction of vasodilatation and bradycardia (vasovagal syncope) being the most common response [1,2]. Even though the cause of reflex syncope is benign, recurring syncope can have profound impact on the quality of life comparable to chronic illnesses such as rheumatoid arthritis [1,3]. Diagnosing reflex syncope can be challenging and patients often undergo multiple diagnostic tests (i.e., echocardiography, Holter monitoring, CT scans etc). HUT is suggested for the evaluation of suspected reflex syncope both in patients with and without structural heart disease [4]. In trials focusing on pacemaker (PM) treatment for neurocardiogenic syncope, the recurrence rate for syncope in patients with PM varies quite considerably (0–78%) depending on mode of pacing and population investigated [5–11] illustrating that PM treatment does not exclude the presence of reflex syncope. However, little information is available concerning these patients with “break-through” episodes— especially concerning the type and mode of syncope.

The aim of our study was thus, to further illustrate the relation between recurrent syncope and pacemaker therapy and its mechanisms. We wanted to describe the outcome of head-up tilt table test (HUT) in patients with pacemakers implanted for a variety of conditions and referred with syncope or pre-syncope to our syncope unit.

## Methods

Forty-one patients with PM undergoing a HUT in our syncope unit between January 1st, 2007 and December 31st, 2011 were included. No patients were excluded due to technical issues or lack of data. A standard protocol was used with an initial 10 min of supine rest and then 20 min head-up tilt to 60° [1,12,13]. If only limited changes in heart rate (HR) or blood pressure (BP) had occurred, nitroglycerine 400 µg was administered sublingually and patients remained tilted for up to 15 min. After discontinuation of tilting patients were monitored for a minimum of 5 min in the supine position. HR and BP were continuously measured using standard 3-lead ECG and finger photoplethysmography (Finometer, Finapres Medical Systems B.V., The Netherlands) respectively. The accuracy of finger-BP was assured by continuously comparing to standard arm BP, not allowing for more than 25 mmHg divergence [13]. HR and BP together with temporal markers for tilt start, nitroglycerine dosing and tilt stop were recorded digitally by commercial software (Chart 5.59 with HRV module, AD Instruments Inc, Colorado Springs, CO, USA). Tilting was discontinued if syncope or severe symptoms occurred coinciding with significant HR or BP changes or with completion of the protocol in the absence of symptoms. The test was supervised by an experienced nurse with a physician immediately available if needed. Tests were classified according to the current guidelines [1,13,14]. In order for a test to be designated positive, HR and/or BP changes had to occur simultaneously with symptoms, which the patient could associate with earlier

experienced syncope/pre-syncope episodes [1,13]. Patients were divided in two groups according to tilt table outcome, one group with any type of positive HUT and the other group with negative (normal) HUT. Data were retrieved from the department's digitized medical records. All patients had normal functioning PM, with normal checks and pacemaker readout before and after tilt table testing. The distribution of PM types were as follows –18 with DDD-R pacemakers (one of which was an ICD), 10 with ICD-VVI-R pacemakers, 9 with VVI-R pacemakers, 3 with AAI-R pacemakers and one with VDD pacemaker. Indications for PM implantations were as seen in Fig. 1, and no patients had PM implanted specifically due to neurocardiogenic syncope.

## Statistics

Descriptive statistics are presented as mean and SD, categorical data are presented in percentage. In tables with comparisons mean and SEM are used. Patients were allocated into two groups according to tilt table test outcome (positive/negative). A student t-test was used to test for difference between the groups for numerical data and tested with  $\chi^2$ -test for categorical data. In case of less than 5 expected values in any column, Fisher's exact test was computed. A two-sided P value less than 0.05 was considered significant. All statistics were done in SAS 9.1.3 (SAS Institute Inc, Cary, NC).

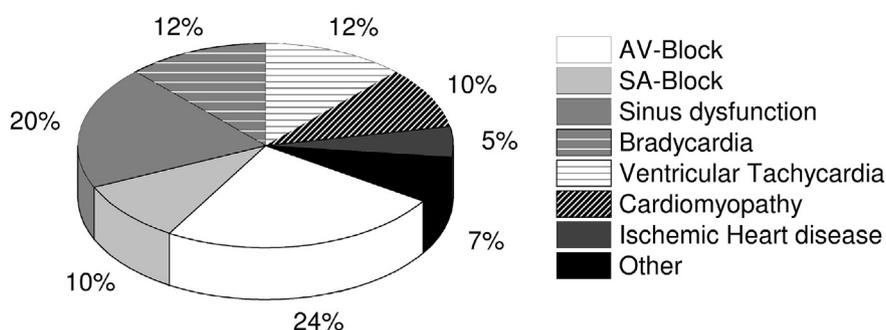
## Results

A total of 41 patients were included with a mean age  $64 \pm 17$  years (range 16–85 years) and 66% were men (Table 1).

Symptoms that lead to referral for tilt table testing included syncope in 61% and pre-syncope including vertigo or suspected orthostatic hypotension in 39%. Indications for PM implantation in the included population are shown in Fig. 1, with the majority of patients having received pacemakers due to AV-block, SA-block, or sinus node dysfunction. Patients with ventricular tachycardia or cardiomyopathy all had received an ICD (ICD\_V, single ICD\_D). None of the patients had received PM specifically for neurocardiogenic syncope. Two patients had prophylactic ICD pacemakers due to ischemic heart disease and left ventricular dysfunction. Three patients with other indications all had DDD-pacemakers due to bundle branch block (triphasic/right) and one due to suspected sinus caroticus syndrome.

The outcome of tilt table testing is shown in Fig. 2. Overall, 54% of patients had a positive response. Vasodepressor or orthostatic hypotensive response was the most prevalent accounting for 39% of all patients and 72% of patients with positive test.

In 6 patients that predominately had sinus rhythm, a cardioinhibitory or mixed response was seen with activation of pacing that could not prevent syncope or significant BP/HR drops. The pacemakers were activated due to bradycardia associated with BP drop in 3 patients with mixed response, one patient had second degree AV-block in association with BP drop (mixed response), one patient developed third degree AV-block and one patient had 15 s asystole (no



**Fig. 1 – Indications for pacemaker therapy in the included population.**

atrioventricular conduction or ventricular escape with atrial pacing in AAI- Fig. 3).

Of the nine patients who were paced throughout the test 5 had a normal test, 3 patients had orthostatism and one had vasodepressor response. Of the four patients who had intermittent but predominately paced rhythm, 2 had a normal test and 2 had vasodepressor response.

Among the patients that predominately had sinus rhythm, 11 patients had a normal test with no or very limited pacemaker activity and eight patients had vasodepressor responses with no bradycardia and no pacemaker activity in relation to BP drop. Most of these patients had compensating increase in HR as the BP dropped.

There were no significant differences between the results of HUT with respect to pacing mode (Fisher's exact test  $p = 0.28$ , Table 1), although all patients with atrial pacing systems had a positive test ( $n = 3$ ). In two patients, a cardioinhibitory response was seen despite functioning pacing systems, one with 2:1 AV-block with heart rate  $<40$  bpm (pacing starts after 5 s) and one with "functional" total AV-block with no atrioventricular conduction of atrial pacing (Fig. 3).

There were no differences between the groups with positive tests and negative tests regarding age, gender, baseline values, daily fluid intake or pacing rhythm at rest (Table 1).

Patients who had PM implanted due to AV-block, sinus node dysfunction/SA-block or all other indications as a group did not differ in outcome of HUT ( $p = 0.18$ , Fisher's exact test). Symptoms and/or syncope occurred after 21 min (range 1–27 min), with the majority seen after nitroglycerine provocation (90%). In all positive tests, the BP started to drop before any decrease in HR was seen. In the group with positive tests, the PM was constantly active during the whole test in 6 patients, the PM was activated at syncope (but not preventing positive outcome) in 7 patients and no PM activity was apparent in 9 patients.

### Discussion

The main finding in our study was that HUT in patients with implanted pacemakers referred for postural symptoms or possible syncope had a high diagnostic yield. We found that the response to HUT was primarily one of vasodilatation or postural hypotension. Some patients showed significant reductions in heart rate despite normal functioning pacemaker. Thus, HUT provided valuable clinical information in pacemaker patients and could lead to revised device- or medical management.

**Table 1 – Baseline data for whole population and population stratified according to tilt table.**

	Total	Tilt test outcome		p-value
	N = 41	Positive	Negative	
		N = 22	N = 19	
	Mean ± SD	Mean ± SEM	Mean ± SEM	
Age (years)	64 ± 17	62 ± 3.9	65 ± 3.8	P = 0.58
Gender (% male)	66%	59%	74%	P = 0.33
Resting				
Systolic BP (mmHg)	123 ± 25	126 ± 5.3	120 ± 5.7	P = 0.42
Diastolic BP (mmHg)	73 ± 18	75 ± 3.8	71 ± 4.2	P = 0.45
Heart Rate (bpm)	71 ± 10	69 ± 2.1	72 ± 2.2	P = 0.36
Left Ventricular ejection fraction (%)	49 ± 6	51 ± 5	47 ± 7	P = 0.06
Daily fluid intake (l/day)	2.0 ± 0.8	2.1 ± 0.2	1.8 ± 0.2	P = 0.30
Paced rhythm at rest	37%	31%	42%	P = 0.50
Pacing Modality				P = 0.28
Atrial (No.)	3	3	0	
Ventricular (No.)	20	9	11	
Dual (No.)	18	10	8	

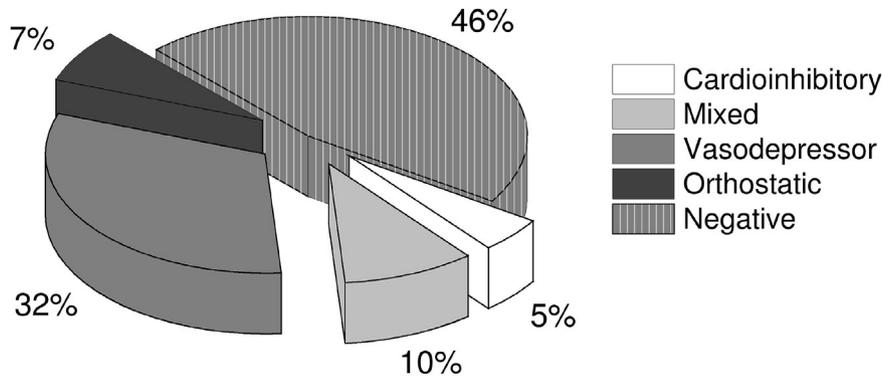


Fig. 2 – Tilt table outcomes according to current guidelines.

In a review of 46 patients with recurrent syncope after implantation of VVI pacemakers by Pavlovic et al. [15], a thorough work up including HUT could identify a cause of syncope in 70% of patients, primarily due to abnormal HUT. In their series, 63% of patients had a negative HUT, compared to 46% in our study – a difference that could be attributed to differences in protocols (passive vs. nitroglycerine) as addition of nitroglycerine provocation increases the diagnostic yield and the test sensitivity [16]. Vasodepressor reaction with hypotension leading to syncope was seen in 34%, directly comparable to our result of 32%. At one year follow-up, Pavlovic et al. observed that most patients continued to experience syncope, except one patient where the PM was replaced due to exit block. Only rarely was PM dysfunction the underlying cause of syncope (6%) [15]. Similar results were seen in patients with sick sinus node syndrome. In 70% of cases, recurrent syncope could be explained by vasovagal responses (18%), orthostatic hypotension (26%), arrhythmias (17%), ischemia (3%) or pacemaker dysfunction (7%) [17]. Keim et al. [18] reported a series of eight patients with pacemaker and recurrent

syncope. In all patients, the tilt test was positive with 50% pure vasodepressor, 38% mixed and 12% cardioinhibitory responses, thus with a distribution of positive tests being somewhat similar to our results.

Cardiac pacing has been suggested as treatment of recurrent syncope, and initial open label trials (comparing pacing to medical therapy or no therapy) were encouraging [7,8,11]. However, two truly blinded trials (pacing vs. sensing only) could not demonstrate any effect of cardiac pacing on syncope recurrence [6,9]. The recurrence rate for syncope in patients with PM varies considerably (0–78%) depending on mode of pacing [5–11]. Although pacing can address the cardioinhibitory component of reflex syncope, the vasodilatation and hypotension associated with reflex syncope remains unmanaged. In a recent trial, PM implantation was guided by implantable loop recorders, selecting only patients with spontaneous asystole. Using this approach pacing reduced the syncope recurrence. However, 25% still experienced syncope in the pacing arm of the study despite active pacing [5]. The syncope mechanism in these patients with pacemaker but recurrent syncope was not further described.

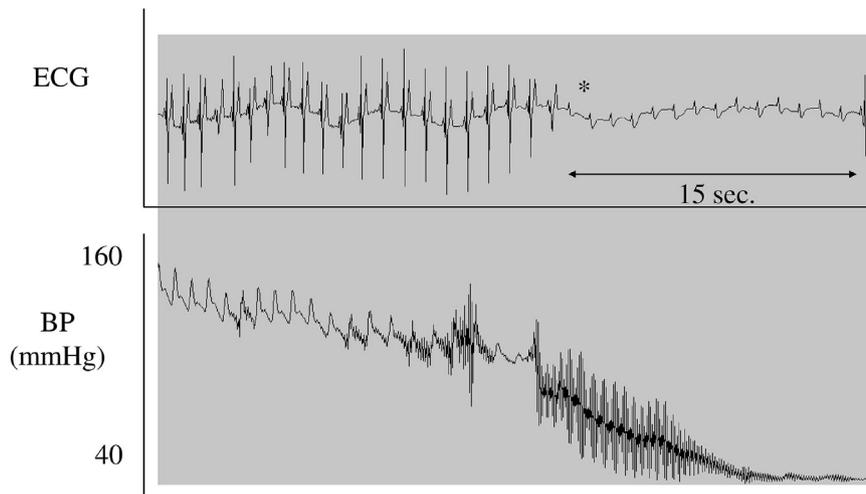


Fig. 3 – Sixty-four year old male who had an AAI-pacing system implanted due to recurrent syncope and suspected sinus node dysfunction with bradycardia. Continuously ECG and blood pressure tracing at time of syncope shows technical asystole with atrial pacing artefact/atrial activation without atrioventricular conduction (\*) for 15 s leading to hypotension and syncope. There was spontaneous restoration of atrioventricular conduction upon tilting down to horizontal position.

Our results support the notion that a vasovagal etiology is likely, but other reasons should not be ruled out in advance, and a HUT might be an appropriate way of acquiring both clinical and patient-orientated reassurance.

Some patients with a negative HUT were paced continuously throughout the procedure, with no significant change in heart rate or blood pressure. As these patients were completely dependent on their pacemaker, any cardioinhibitory or mixed response was not possible. However, this could be due to the fact, that their HR had a very limited frequency span – i.e., 50–80 bpm, thus, never qualifying for cardioinhibitory or mixed response. Whether these patients were “protected” from cardioinhibitory response or simply did not have reflex syncope is thus speculative.

We could not demonstrate any difference in tilt table outcome according to pacing mode, although all only atrial paced patients had a positive outcome. Firstly, this could be attributed to the highly selected population (patients with PM and syncope referred to syncope unit), and secondly, to the limited number of patients preventing any evident effect of pacing mode. Multiple reports suggest differences between pacing protocols and recurrence of syncope, with DDD pacing being superior to DDI [19] and DDD-CLS pacing being superior to DDI [10].

A number of studies have suggested value of performing HUT in the evaluation of patients with PM and recurrent syncope [15,17,18,20]. In the INVASY and VASIS studies [7,10], HUT performed after PM implantation in a fraction of patients was not a predictor of clinical recurrence. In the paced group in the VASIS study [7], five patients had a positive test without pacemaker activation (HR remained above 45 bpm) and five had positive tests despite pacemaker activation – similar to our results. In patients with negative HUT and PM, the PM was activated and possibly prevented syncope only in one patient [7].

Thus, the value HUT for diagnosis of recurrent syncope in PM patients seems well established. However the predictive value of positive HUT after PM implantation is still not clear.

When comparing the outcome of our PM patients with a large series of patients from our own syncope clinic, more patients with PM required nitroglycerine provocation for a positive result (90% vs. 68%) [13]. There was no difference in the fraction of cardioinhibitory, mixed or vasodepressor among positive responses and the diagnostic yield was similar (54% in our series, 64% in the reference population). The time to syncope in our study was marginally increased compared to findings by others [13,21]. In the INVASY study, the time to syncope/pre-syncope in 22 patients with pre-syncope symptoms was increased from a mean of 14 min–20 min suggesting that CLS-pacing support prevented asystole and prolonged the time to hypotensive symptoms [10]. One can speculate that the pacemakers provided some sort of support, postponing the time to syncope and thus, more patients requiring nitroglycerine. Whether more patients experienced vasovagal response due to nitroglycerine or if the test was false positive is also speculative – as mentioned compared to our other patients without pacemakers we could not see an over reporting of vasovagal outcomes and test was only considered positive if the symptoms were similar to real life events.

## Limitations

The study included highly selected population from a single center. Still the findings are in line with earlier reports from patients with pacemakers. The diagnostic yield is also in line with previous experience in our unit.

We have not conducted a full work up on patients, and can therefore not definitely claim that their syncope was related to hypotensive responses. However, all pacemakers were normally functioning and tests were only declared positive if the patient experienced symptoms during tilt test similar to their real life events.

We did not study the effect of specific pacing mode or advanced pacing algorithms due to limited number of patients in each category. The literature suggests that closed-loop stimulation pacing is superior to regular dual chamber pacing algorithms in preventing vasovagal syncope.

## Conclusion

In PM patients referred for HUT due to recurrent syncope/pre-syncope 54% had a positive result. Vasodepressor or orthostatic hypotensive response was the most prevalent outcome but mixed or cardioinhibitory responses were also seen – adding diagnostic information that could help to optimize either device or medical management. Pacing mode, pacing indication and baseline data did not differ between patients with and without positive HUT. The added value of HUT in managing PM patients experiencing recurrent syncope seems feasible with a high diagnostic yield and adding potentially valuable clinical information about the patients' mode of syncope.

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