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Tilt testing and what you should know about it - Experience with 835 consecutive patients with syncope of unknown origin☆,☆☆

Christopher Gemein [a], Maike Roos [a], Anika Wolf [a], Nils Hermann [a], Augustin Kelava [b], Ritvan Chasan [a], Kay Weipert [a], Inga Helmig [a], Harilaos Bogossian [c], Christian W. Hamm [a,d], Thomas Neumann [d], Joern Schmitt [a], Damir Erkapic [a,*]

[a] Department of Cardiology and Angiology, University Hospital Giessen and Marburg, Justus-Liebig-University Giessen, Germany
[b] Hector Research Institute of Education Sciences and Psychology, Eberhard Karls University Tübingen, Germany
[c] Märkische Kliniken GmbH, Department of Cardiology and Angiology, Klinikum Lüdenscheid, Germany
[d] Kerckhoff Heart and Thorax Center, Department of Cardiology, Bad Nauheim, Germany

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ABSTRACT

Background: Numerous tilt testing protocols with and without a preceding passive phase or the administration of nitrates have already been investigated. However, a truely standardized method for the investigation does not yet exist.

Methods and results: A total of 835 consecutive patients who underwent tilt testing between January 2005 and March 2015 were included in this study. Results of a passive tilt test (PTT), a nitrate-stimulated tilt test (NSTT) with a preceding passive phase of 20 min, or an early nitrate-stimulated tilt test (ENSTT) without a preceding passive phase were compared and analyzed retrospectively in 735 patients. In addition, a further 100 consecutive patients were prospectively randomized 1:1 to compare NSTT and ENSTT. In the retrospective analysis, 38% of the patients in the ENSTT group had a positive test response compared with 45% in the NSTT group and only 27% in the PTT group ($p = 0.0002$). In the prospective study, 34% of the patients had a positive test response in the ENSTT group compared with 42% in the NSTT group ($p = 0.537$). The mean duration to a positive test response was significantly shorter in the ENSTT group (retrospective and prospective $p < 0.001$). The nitrate-stimulated groups did not differ significantly with respect to the hemodynamic characteristics of a positive test response (retrospective: $p = 0.773$; prospective: $p = 0.086$).

Conclusion: Due to the rate of positive test response being comparable to other protocols and its significantly shorter test duration, nitrate-stimulated tilt testing without a preceding passive tilt test may be favored for use in a busy clinical practice.

1. Introduction

Syncope is defined as a sudden and temporary loss of consciousness due to transient cerebral hypoperfusion [1]. The most frequent type is neural reflex syncope, in particular vasovagal syncope (VVS), followed by syncope due to cardiac causes [2,3,4,5]. The underlying pathomechanism of reflex syncope is an autonomic dysregulation followed either by peripheral vasodilatation (vasodepressed type), symptomatic bradycardia (cardioinhibitory type), or a mixed type with characteristics of both mechanisms [1,6,7,8,9,10]. Tilt testing is an established diagnostic tool to confirm suspected reflex syncope in selected patients [1,10,11]. In general, the specificity of tilt testing is relatively high; thus, a positive tilt test result is rated as diagnostically evident [10]. However, there is no uniform standard for performing tilt tests, and several methods with or without drug stimulation or preceding passive tilt phase as well as different tilt angulations, durations of the passive tilt phase, or drug provocation regimens are used.

The aim of this study was to compare different tilt test protocols in a retrospective and a prospective randomized manner in a “real-world” patient cohort with syncope of unknown origin.

Abbreviations: CI, confidence interval; ECG, electrocardiogram; ENSTT, early nitrate-stimulated tilt test; NSTT, nitrate-stimulated tilt test; OR, odds ratio; PTT, passive tilt test; VVS, vasovagal syncope; s.l., sublingual.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

☆☆ All authors declare: No conflict of interest.

* Corresponding author at: University Hospital Giessen and Marburg, Justus-Liebig-University Giessen, Department of Cardiology and Angiology, Klinikstrasse 33, 35392 Giessen, Germany.
E-mail address: damir.erkapic@innere.med.uni-giessen.de (D. Erkapic).

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2. Material and methods

The protocol of this study conforms to the ethical guidelines of the Declaration of Helsinki and was approved by the Medical Ethics Committee of the Justus Liebig University of Giessen, Giessen, Germany.

2.1. Inclusion and exclusion criteria

Patients with a history of singular or recurrent syncope of unknown origin with indication for tilt testing according to current guidelines were eligible for this study [1]. All patients signed informed consent for undergoing a tilt test and for independent participation in the prospective randomized part of the study. Prior to enrolment, structural heart disease was excluded, and anamnesis, clinical examination, 12-lead electrocardiogram (ECG) and blood pressure measurements were inconclusive regarding other potential causes of syncope. In selected patients, previous examinations were supplemented by echocardiography, treadmill ergometry, long-term ECG, or even coronary angiography, if clinically indicated. Exclusion criteria were: age < 18 years and >90 years; pregnancy; previous tilt training after diagnosis of reflex syncope; contraindication for nitrate stimulation; unwillingness or inability to give informed consent for the prospective study; and participation in other studies, which may potentially conflict with this study.

2.2. Tilt test examination and different tilt testing protocols

All tilt test examinations were executed in the outpatient clinic of the University Heart Center Giessen. The tests were performed on a customized tilt table (Vario-Line Kipptisch HV, Beka Hospitec, Wetzlar, Germany). All patients had fasted for at least 4 h before tilt testing. Peripheral venous access (Vasofix Safety, B. Braun, Melsungen, Germany) was obtained for safety reasons. Before and during examinations, continuous ECG monitoring, pulse-wave oxymetry, and non-invasive blood pressure monitoring with measurements every 2 min were performed (IntelliVue-MP30, Philips Healthcare, Amsterdam, The Netherlands). In this study three different tilt test protocols with or without nitrate stimulation were compared retrospectively followed by a prospective comparison of two protocols with nitrate stimulation. In all protocols, a pre-tilt phase was maintained for at least 20 min after peripheral venous access with the patient lying supine on the tilt table without any disruption. Thereafter, either a passive tilt test (PTT) with a tilt angle of 70° and a duration up to 45 min [15,16] or a nitrate-stimulated tilt test was performed. Two different protocols were applied for the latter type of tilt test: either 1) a nitrate-stimulated tilt test according to a modified "Italian protocol" (NSTT) [1,12] recommended by the guidelines [1] that is composed of a passive tilt phase of 20 min (tilt angle 70°) followed by a further observation time of 16 min after sublingual (s.l.) administration of 0.4 mg glycerol trinitrate ("Nitrolingual akut Spray", Pohl-Boskamp, Hohenlockstedt, Germany) and therefore a total tilt time of 36 min; or 2) an early nitrate-stimulated tilt test (ENSTT) without a preceding passive phase and immediate nitrate administration (0.4 mg s.l.) after reaching the tilt angle of 70° in patients with a systolic blood pressure ≥ 100 mm Hg followed by an observation time of up to 16 min [14].

All patients who met the inclusion criteria and had tilt testing at our center between January 2005 and November 2013 were included in the retrospective analysis. The choice of tilt testing protocol (PTT, NSTT, or ENSTT) was at the discretion of the investigator. All data were prospectively entered into a central database and analyzed retrospectively. In the prospective part of the study (from February 2014 to March 2015) patients were randomized 1:1 via a sealed envelope system into either the ENSTT or the NSTT protocol group. The study endpoint was defined as a positive test response consisting of syncope or pre-syncope due to either reflex hypotension (vasodepressory) with a systolic blood pressure decrement of at least 60% or below 70 mm Hg or bradycardia (cardioinhibitory) with a heart rate below 40 beats per minute or asystole or a mixed type according to known classifications [17,18,19]. The main focus in this study was the proportion of positive test response, the time to positive test response, and the distribution of VVS types for all tilt testing protocols.

2.3. Statistical analysis

Statistical analysis was performed with SPSS software version 22.0 (IBM Inc., Armonk, NY, USA). All data are expressed as mean ± SD for normally distributed continuous variables or as median (interquartile range [IQR]) for non-normally distributed data. Categorical data are reported as numbers and percentages. Total tilt test times or times until occurrence of study end points are presented in a descriptive manner. Similarly, differences between the patient groups in terms of age, sex, blood pressure, heart rate, type of reflex syncope, or additional diseases are presented descriptively. Comparisons between variables were performed by using an independent Student's *t*-test, Mann–Whitney *U* test, or chi-square test depending on the class of analyzed data and possible direction of causality. Cox regression analysis was performed to determine independent predictors of positive tilt test response, and the impact of the different variables was valued by their individual coefficient, odds ratio, and 95% confidence interval. A p value of <0.05 was considered to be statistically significant.

3. Results

3.1. Retrospective comparison of passive versus nitrate-stimulated tilt testing protocols

A total of 735 patients were included in the retrospective analysis. Of these, 277 (38%) underwent PTT (56% male, mean age 57 ± 20 years), 175 (24%) underwent NSTT (49% male, mean age 50 ± 20 years) and 283 (38%) underwent ENSTT (51% male, mean age 58 ± 20 years). The detailed patient characteristics of the retrospective analysis are displayed in Table 1A. In the PTT group, 74 patients (27%) had a positive test response compared with 79 patients (45%) in the NSTT group and 107 patients (38%) in the ENSTT group (p = 0.0002; Fig. 1A). Thus, nitrate-stimulated tilt testing was associated with a significantly higher response rate. Analysis of the hemodynamic characteristics of positive test responders showed that the PTT, NSTT, and ENSTT groups differed significantly regarding vasodepressory (58% vs. 50% vs. 72%), cardioinhibitory (8% vs. 10% vs. 5%), or mixed response (34% vs. 40% vs. 23%; p = 0.043) (Fig. 1B). The time until occurrence of a positive test response also varied significantly between the groups: the NSTT group required a mean duration of 27 ± 9 min, the PTT group 22 ± 12 min, and the ENSTT group only 14 ± 7 min, and (p < 0.001)

Table 1
Patient characteristics. PTT = passive tilt test, NSTT = nitrate-stimulated tilt test, ENSTT = early nitrate-stimulated tilt test, BMI = body mass index, LVEF = left ventricular ejection fraction, RR = blood pressure, ACE = angiotensin converting enzyme, ARB = angiotensin receptor blocker, TIA = transient ischemic attack, bpm = beats per minute, SD = standard deviation.

	A: Retrospective cohort				B: Prospective cohort		
	PTT (n = 277)	NSTT (n = 175)	ENSTT (n = 283)	p-Value	ENSTT (n = 50)	NSTT (n = 50)	p-Value
Age (y mean ± SD)	57 ± 20	50 ± 20	58 ± 20	<0.00001	43 ± 22	44 ± 20	0.788
Female gender (%)	44	51	49	0.238	66	62	0.835
BMI (mean ± SD, kg/m^2)	26 ± 4	26 ± 5	26 ± 5	0.286	25 ± 4	26 ± 5	0.287
Prodromi in history (%)	52	55	51	0.613	88	90	1.0
RR systolic (mean mm Hg ± SD)	130 ± 21	123 ± 15	141 ± 20	<0.00001	127 ± 18	123 ± 17	0.896
RR diastolic (mean mm Hg ± SD)	71 ± 13	71 ± 11	76 ± 13	<0.00001	71 ± 10	72 ± 14	0.738
Heart rate (mean bpm ± SD)	66 ± 12	66 ± 11	67 ± 12	0.537	68 ± 11	69 ± 12	0.738
LVEF (% mean + SD)	63 ± 10	64 ± 6	64 ± 9	0.45	63 ± 4	61 ± 7	1.0
Coronary heart disease (%)	40	14	35	<0.00001	16	12	0.773
Heart failure (%)	13	3	11	0.001	0	4	0.475
Hypertension (%)	53	38	58	0.0002	28	42	0.208
Diabetes mellitus (%)	12	10	12	0.816	14	8	0.523
Renal dysfunction (%)	20	7	17	0.0007	8	8	1.0
Previous stroke/TIA (%)	12	3	6	0.002	12	0	0.035
Betablockers (%)	44	26	43	0.0003	18	22	0.802
ACE inhibitors/ARB (%)	44	26	43	0.0003	26	32	0.659
Calcium antagonists (%)	18	12	24	0.007	4	14	0.162
Diuretics/spironolactone (%)	33	23	35	0.018	16	24	0.453
Nitrates (%)	5	2	6	0.152	4	0	0.475

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