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Reproducibility of Tilt-table Test with Different Dosages of Sublingual Nitroglycerin

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ABSTRACT

Reproducibility of tilt-table test potentiated with sublingual nitrate is significant since it is directly related to diagnostic accuracy of the test. Nitrates shorten the test time and increase the sensitivity of the test. However the effects of different nitrate dosages on reproducibility have not been reported. Therefore we aimed to investigate the effects of 400 mcg, 800 mcg, and 1200 mcg sublingual nitroglycerin on reproducibility of tilt-table test.

All patients undergoing tilt-table test at our hospital due to suspected syncope evaluated and patients giving consent included. First group received 400 mcg, second group received 800 mcg, and third group received 1200 mcg sublingual spray nitroglycerin. Patients underwent a second test with a same protocol within 1-7 days following the initial test.

Overall 189 patients included in this study. All of the patients in the first (n=62) and the second group (n=66) completed the initial test whereas 2 patients in the third group (n=65) terminated the initial test due to severe headache related to nitroglycerin. Five patients in the third group gave exaggerated response. The overall reproducibility of tilt-table test was 81.9%, 88.9%, 82.1%, in the first, second, and third group, respectively. There was no statistically significant reproducibility difference between groups.

The reproducibility of tilt-table test is similar with different dosages of sublingual nitroglycerin; however 1200 mcg nitroglycerin has more frequent side effects and exaggerated response.

Key Words: Tilt Table Test, syncope, nitroglycerin, reproducibility

Introduction

Tilt-table test (TT) potentiated with a pharmacological agent has higher sensitivity than TT performed without stimulation (1-4). Intravenous isoproterenol was the first agent used widespread for pharmacological stimulation, however, due to side effects and administration route sublingual nitrates superseded the isoproterenol (5). Sublingual nitrates well tolerated, have infrequent side effects, widely available and readily administrated. Tablet formulation of sublingual nitrates has different bioavailability and its maximal plasma levels are achieved relatively late. On the other hand sublingual spray nitroglycerin (NTG) is not affected by the dryness of mouth and has no presystemic clearance and achieves maximal plasma levels within several minutes (6).

Usefulness of any test is strongly related to the reproducibility of the test. Reproducibility of TT has been reported to range in a wide variation (7-11). The wide variation of TT reproducibility may be related with different test protocols, patient populations, and pharmacological stimulation. Since TT is not recommended for therapeutic aims reproducibility of TT is significant because of concerns about diagnostic accuracy of TT for syncope. The effects of different dosages of nitrates on reproducibility of TT are not well known. There is a lack of data if reproducibility is dose-dependent. In this study we aimed to investigate the effects of different sublingual NTG doses on reproducibility of TT in a patient group who had suspected recurrent syncopal episodes and were initially assessed and selected carefully.

Material and Methods

Suspected syncope patients are comprehensively evaluated at our cardiology department. A detailed history is taken, a careful physical examination including supine and standing BP measurements, 12-lead electrocardiogram (ECG), transthoracic echocardiography (TTE) are performed for all patients. If the diagnosis is not clear with the initial assessment 24-hour rhythm Holter, carotid

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ultrasound, neurology consultation and TT are the second line tests.

All patients who underwent TT due to suspected syncope between May 2017 and April 2019 at our hospital were evaluated to participate in the study. All patients included had normal ECG and normal TTE. Patients who referred to TT due to only one syncopal or presyncopal episode and patients younger than 18 years, patients who underwent to first TT after 30 days of last suspected syncope episode and patients receiving vasoactive medication were excluded.

All tests were performed between 10:00 am and 12:00 am at our laboratory. The laboratory room is quiet, dim, and at a comfortable temperature. Patients underwent test after at least 4 hours of fasting. Nicotine, caffeine and alcohol were omitted for 24 h prior to testing. At the beginning of each procedure, the demographic and clinical data of the patient were recorded, as well as the test indication. TT protocol was as follows: First of all, patient is placed supine on tilt table and secured with protective straps to avoid falls. The patient rests supine for 10 minutes. Thereafter, the table is raised up to 70 °. If there is no syncope within 20 minutes, it was followed by a pharmacological phase lasting 15 min after the administration of sublingual nitroglycerin in aerosol (8). Tilting was maintained until a positive result was obtained, intolerance due to other causes was detected, or the protocol concluded (a total of 45 min). The ECG was monitored continuously during the procedure. BP was measured noninvasively with an automatic sphygmomanometer every 3 min, or more frequently if symptoms or bradycardia appeared. In order to exclude carotid sinus hypersensitivity, carotid sinus massage is performed both in the supine position and in the early phase of upright position. The test was carried out by an experienced nurse with a cardiologist on call.

First group of patients were given 400 mcg NTG, second group of patients were given 800 mcg NTG and third group of patients were given 1200 mcg NTG. Patients with arterial tension over 120/80 mmHg included in the third group because of highest NTG dose. A second TT was performed within 1-7 days following the first test. Same test protocol used in the second test.

A positive response TT for vasovagal response was defined Type 1- mixed, Type 2- cardionhibitory, and Type 3-vasodepressor (12). An exaggerated response to nitrates was defined as a gradual development of symptoms, as a consequence of progressive (occurring >5 min) decrease in BP along with only a slight reduction (<30%) or no change in the heart rate (1).

The study complies with the Declaration of Helsinki and local ethics committee approved the study.

Statistics: The data of the study was analyzed in SPSS 17.0. Descriptive statistics are given as frequency, average with standard deviation and median with minimum and maximum values. Chi-square test was used to compare categorical variables. The variables that do not have normal distribution were compared across the groups using the Mann Whitney U-test. For more than two measurement groups Kruskal Wallis test is used and those with significant results, independent two groups comparisons were performed by Mann Whitney-U test and Bonferroni correction. The distribution of normality was analyzed by the Shapiro-Wilk test. $P<0.05$ is considered to be statistically significant.

Results

A total of 189 patients (101 female, 53.4%and 59 male, 46.6%) aged 18-58 years, (mean±sd: 31.68± 8.72, median: 30) were included in this study. The number of syncopal episodes per patient was 6.01±3.13 (median: 5, minimum: 2, maximum: 20). The number of syncopal episodes per patient within 30 days was 1.91±1.01 (median: 2, minimum: 2, maximum: 6).The reported duration of symptoms was 9.31±9.10 months (median: 6, minimum: 1-maximum 60). The time interval between two tests were 3.32±1.49 days (median: 3, minimum: 1, maximum: 7).

First group (n=62) received 400 μg NTG, second group (n=66) received 800μg NTG, and third group (n=63) received 1200 μg NTG. All of the patients in the first and second group completed the initial test, however two patients in the third group terminated the test due to severe headache following NTG administration. All of 189 patients completed the repeated test. There was no statistical difference between three groups according to age, gender, total syncope episodes, and basal heart rate however, systolic and diastolic arterial tension were higher in the third group due to study protocol (Table 1). Moderate or severe headache was seen in 30 (15.7%) patients. Headache related to NTG was seen in 5 (8.0%), 7(10.7%), 18 (28.6%) patients in the first, second and third group, respectively (p=0.09).

Table 1. Basal characteristics of patients

	400 μg	800 μg	1200 μg	p
Age, year, mean±SD	31.31±8.98	32.20±10.22	31.51±6.51	0.83
Gender				
Female,n (%)	38 (61.3)	29 (43.9)	34 (55.7)	0.13
Male, n (%)	24 (27.3)	37 (42.0)	27 (30.7)	
Total syncopal episodes,	6.37±0.44	6.45±0.38	6.23±0.34	0.24
Basal heart rate, mean±SD	67.84±1.03	69.53±0.54	68.08±0.66	0.60
Systolic BP, mmHg, mean±SD	122.12±1.98	125.63±1.86	131.09±1.44	0.018
Diastolic BP,mmHg, mean±SD	78.46±1.20	78.31±1.00	84.95±0.40	<0.001

Table 2. First and second tilt-table test results. (-) refers negative test result. (+) refers positive test result. (E) refers exaggerated response to nitrate. First parenthesis refers the first test and second parenthesis refers the second test

	Test results n,%					
	(-)/(-)*	(+)/(+)	(-)/(+)	(+)/(-)	(E)/(-)	p
NTG dose, μg						
400	34 (54.8)	16 (25.8)	4 (6.5)	7 (11.3)	(1.6%)	(0.31)*
800	42 (63.6)	14 (21.2)	5 (7.6)	2 (3.0)	3 (4.5)	
800	28 (45.9)	18 (29.5)	3 (4.9)	7 (11.5)	5 (8.2)	

*Kruskal Wallis test is used to compare the groups

Patients with positive response to the first test were 64 (33.9%), with negative response were 116 (61.4%) and with exaggerated response were 9 (4.8%). Patients with positive response to the second test were 60 (31.7%), with negative response were 129 (68.3%). Detailed test results are shown in table 2. The overall reproducibility of tilt-tablets was 81.9%, 88.9, 82.1, in the first, second, and third group, respectively. Overall, negative and positive reproducibility for each group is shown in table 3. There was no statistically significant reproducibility difference between groups.

Discussion

This methodological study presents two main findings. Firstly, we found a high TT reproducibility with different doses of NTG in carefully selected suspected syncope patients. Although previous studies reported a wide range of reproducibility they had different protocols and patient groups (7-11). Our patients were carefully evaluated before ordering TT and they had recent syncopal episodes and the TT protocol that we used was with a high sensitivity. We believe that these factors resulted in high reproducibility.

Recently, concerns about diagnostic yield of TT in syncope patients are reported. Moreover European Society of Cardiology decreased its recommendation level from class I to class IIa for TT in patients with suspected syncope patients (13). TT is helpful to confirm a diagnosis of reflex syncope in patients following initial evaluation and to detect autonomic failure and orthostatic tachycardia syndrome (14-15). We found high reproducibility results for both positive and negative TT in a carefully evaluated patient group. Therefore we may recommend TT for diagnostic confirmation of suspected reflex syncope patients following initial diagnostic assessment.

Second main finding is about the effects of different dosages of NTG on reproducibility. Although we found a high overall reproducibility there was no statistically significant difference between different doses of NTG. Up to our knowledge there is no study in the literature reporting the effects of different dosages of NTG on TT reproducibility. In a study Timoteo et al. investigated TT with different NTG dosages in elderly patients. They divided patients in to three groups and they used 250 mcg, 375 mcg or 500 mcg NTG tablets (16). They found no difference between groups and concluded that the response to the NTG is not dose-dependent. Moreover they found no difference in the frequency of exaggerated responses to nitrates. Our study

Table 3. Positive, negative and overall reproducibility of patient groups

	Positive Reproducibility*, %	Negative Reproducibility **, %	Overall Reproducibility, %
NTG dose, μg			
400	69.6	89.5	81.9
800	87.5	89.4	88.9
1200	72.0	90.3	82.1

*Positive reproducibility refers positive response in both tests. ** Negative reproducibility refers negative response in both tests

presents significant results about reproducibility of TT with different NTG dosages.

In our study exaggerated response to nitrates were most frequent in the highest dose (1200 mcg) NTG group. Exaggerated response to nitrates may be defined as excessive vasodilator effects generated by nitrates. Differentiating this response from type 3 vasovagal syncope is significant due to these two conditions have similar definitions and it may lead to misdiagnosis.

Nitrates increase the sensitivity of TT with an accepted decrease in specifity. It is not clear by which mechanisms nitrates stimulate syncope. Venous pooling is assumed to be the main mechanism (17). Since the main effect of nitrates is venodilation, venous return diminishes and syncope is stimulated. Venous dilatation and mild arterial dilatation together may stimulate sympathetic tone. Increased sympathetic tone results in increasing ventricular contraction and this trigger the Bezold-Jarish reflex via mechanoreceptors. Other than hemodynamic and nuerohormonal effects, nitrates may have central action (18-19). In a study, NTG was directly injected in the nucleus tractus solitarii of rats which induced hypotension and bradycardia (20). Since the nitrates are lipid soluble they may cross to brain barrier and lead to central actions in humans.

Another significant result of our study is that although three different NTG dosages had similar reproducibility the side effects of NTG were more prevalent in patients receiving 1200 mcg NTG. Two patients could not complete the test due to severe headache. Another limitation with 1200 mcg NTG is arterial tension level. We initially determined an arbitrary level of blood pressure more than 120/80 mmHg in order to tolerate 1200 mcg NTG. We found no benefit of 1200 mcg NTG over 400 or 800 mcg NTG.

Although we believe that our study was well designed, still it has two important limitations. The number of patients in each group was relatively low. Further studies with more patients may reveal a significant reproducibility difference between different NTG dosages. A Second limitation is about patients' clinical characteristics. We included the patients who had high suspicion of recent and recurrent vasovagal syncope. Therefore our results may not represent the real world.

The reproducibility of TT is similar with different dosages of sublingual spray NTG, however 1200 mcg nitroglycerin has frequent side effects. Our study shows that 400 mcg or 800 mcg NTG might be preferred to 1200 mcg NTG for patients undergoing TT.

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