What is the optimal duration of the TILT after administration of 0.4 mg nitroglycerin spray?

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Abstract
Performing a head-up tilt test can be of great value for the diagnosis of vasovagal syncope. The European Society of Cardiology recommends a drug challenge phase duration of 15 to 20 minutes, with either Isoprenaline or Nitroglycerin administration.

We sought to investigate the outcome of a ten-minute active phase with Nitroglycerin in patients suspected of vasovagal syncope and determine the percentage of loss in the positivity rate, using this short duration approach.

We consecutively enrolled patients presenting with syncope undergoing the head-up tilt test (HUTT), with a clinical suspicion of vasovagal syncope between the years 2009 to 2019. The HUTT consisted of 2 successive phases: passive and active. During the passive phase, the patients were tilted at 70° for 20 minutes. If negative, the test was then administered after administration of 0.4mg of sublingual Nitroglycerin. Applying the (VASIS) Vasovagal Syncope International Study classification of the vasovagal syncope international study and comparing for age and gender, positive responses were categorized into 3 types.

A number of 306 patients (age = 43.5 ± 20.3; male = 140 [45.7%]) with suspected vasovagal syncope, undergoing HUTT, were enrolled in the years of 2009 to 2019. Of those, 245 [80.2%] presented a positive test, with 200 patients [82.0%] during the being positive during the active phase of the test. The results were as follows: 116 subjects [47.2%] presented with a mixed response (VASIS I), 52 [21.3%] showed a cardio inhibitory response (VASIS II), and 77 [31.5%] displayed a vasodepressor response (VASIS III). We found no relationship between the type of syncope with neither gender, nor age of the patient. Three minutes represented the median time to positivity, after Nitroglycerin administration. The time distribution showed a peak incidence appearing between minutes 3 and 5, ranging from 1 to 20 minutes. Only 3 patients tested positive after minute 10.

Shortening the active phase to 10 minutes would result in a positivity rate loss of 1.5%.

Abbreviations: ECG = electrocardiogram, HUTT = head-up tilt test, VWS = vasovagal syncope.

Keywords: head-up tilt test, VASIS, vasovagal syncope

1. Introduction
Syncope is a sudden and transient loss of consciousness, arising from cerebral hypoperfusion. The most frequent type is represented by vasovagal syncope and has been estimated to constitute 40% of all syncopal episodes evaluated in the outpatient clinic.[1] Vasovagal syncope (VVS) characteristically manifests due to an excessive vagal tone, associated with sympathetic withdrawal. The head-up tilt test (HUTT) is a practical tool in the diagnosis and management of vasovagal syncope.[2-5] It consists of 2 consecutive phases: passive and active. During the passive phase, the patient is tilted at 70° for 20 minutes and, if negative, the active phase is initiated with 0.4mg of sublingual Nitroglycerine for another 20 minutes.

Our aim was to determine whether a 10-minute long active phase with Nitroglycerine is sufficient in obtaining a positive test in patients with suspected vasovagal syncope.

2. Objectives
In this study, we investigated the outcome of a 10-minute long active phase with Nitroglycerin in patients with suspected vasovagal syncope, hospitalized in a Cardiac Rehabilitation Department. Using this short duration active phase, we furthermore intended to determine the percentage of loss in positivity rate.

3. Methods

3.1. Study population
Upon approval by the Ethics Committee of the Rehabilitation Hospital Cluj-Napoca, Romania, a total number of 306 patients with suspected VVS participated. These subjects underwent HUTT between January of 2009 and May 2019. During this period, 245 patients exhibited a positive response, defined as follows: evidence of syncope in association with hypotension, bradycardia or both.[5,12,13]
Inclusion criteria represented patients with vasovagal syncope being in sinus rhythm. Informed consent was obtained from all subjects, before enrolment.

Exclusion criteria comprised arrhythmias, other than sinus rhythm, patients implanted with a pacemaker/defibrillator, heart failure New York Heart Association III/IV, hemiparesis/hemiplegia, age over 80, structural causes of syncope, such as left ventricular outflow tract obstruction, or mitral stenosis. Additionally, patients with carotid hypersensitivity were excluded by performing carotid sinus massage (CSM) in those over 60 years of age. In case of a positive CSM, we did not commence with HUTT.

3.2. HUTT

After a 10-minute rest period in the supine position, patients were tilted to 70° on an electric tilt table using a supportive foot plate and straps for up to 20 minutes or until a positive response was elicited. If no response could be obtained during the passive phase, the active phase, with Nitroglycerin, was initiated while maintaining the same 70° upright posture as in the passive phase. Aerosolized droplets of Nitroglycerin 0.4 mg were administered sublingually (commercial name: Nitromint spray Egis Pharmaceuticals, Hungary). Upon obtaining a positive response, the table was returned swiftly into a horizontal position. Continuous monitoring of the cardiac rhythm was applied throughout testing and blood pressure measurements were taken every 5 minutes, in the passive phase, and every minute, in the active phase.

Previous studies classified the pattern of a positive response during HUTT into 3 categories: vasodepressor type, cardioinhibitory type, and mixed type.\(^{[12][13]}\) The vasodepressor type response was defined by a diminution in the systolic blood pressure <80 mm Hg, without a significant decrease in the heart rate. Sinus arrest or bradycardia characteristically represented the cardioinhibitory type. Asystole was defined as a pause lasting longer than 2 seconds. The mixed type included both hypotension and bradycardia.

3.3. Statistical analysis

We obtained means for continuous variables and frequencies for categorical variables. Comparisons between groups were made using Mann-Whitney U test and categorical variables were tested applying Chi-square. T test was used for the comparison of 2 parametrical groups. A P-value <.05 was considered statistically significant. All data were analyzed using SPSS version 21. In case of missing data, we utilized the missing data analysis provided by the SPSS program.

4. Results

Three hundred six subjects were analyzed. The mean age was 43.5 +/- 20.3; and the sex ratio was 54.3% to 45.7% female/male (Table 1). Upon performing HUTT, 245 patients (80.2%) tested positively. Of those, 18% elicited a response during the passive phase and 82% during the active phase. With 116 patients (47.2%), mixed type VVS was most frequently observed, followed by the vasodepressor type, with 77 patients (31.5%). Cardioinhibitory type VVS was seen in 52 patients (21.3%) (Table 2).

There was no statistically significant correlation between the age of the patient and the VASIS group of response (\(P=\text{.216}\)). Furthermore, we found no statistically significant correlation between the sex of the patient and the occurrence of vasovagal syncope in a 1-sample binominal test (\(P=\text{.206}\)).

A tilt test with 20 minutes of active phase found 245 positive results (80.2%) out of 306 performed. During the passive phase, 45 patients presented with episodes of syncope. The number of episodes increased to 200 in patients undergoing the active phase. In the second phase of testing, the median time to syncope after Nitroglycerin was 3 minutes (interquartile range [IQR] 3–4 minutes). A distribution in time shows the peak incidence, which we observed between minutes 3 and 5 after Nitroglycerine administration, overall ranging from 1 to 20 minutes (Fig. 2).

Following a 10-minute duration of tilting, the test was positive in 197 of the 200 cases (98.5%). After surpassing the 10-minute mark, only 3 subjects elicited a positive response (after 15 minutes in 2 patients and after 20 minutes in 1 patient). In consequence, by decreasing the active phase to 10 minutes we would miss 3 out of 200 patients (1.5%) who tested positive during the active phase or, in other words, 3 out of 306 test subjects (0.98%) (Fig. 1). A pattern was observable in the 45 patients presenting syncope during the passive phase, showing an increase in episodes as the minutes passed. Contrasting these findings is the median time to syncope during the active phase, where the event primarily occurred between minutes 3 and 5 (Figs. 2 and 3). The median time to syncope after Nitroglycerin within the mixed group was 4 minutes, (IQR 3–4 minutes), 3 minutes in the vasodepressor group (IQR 3–3 minutes) and in the cardioinhibitory group (IQR 2–4 minutes), respectively.

An independent sample \(T\) test revealed an insignificant difference of positivity between a 10-minute or 15-minute active phase (\(P=.08\)). However, the same test showed a significant difference of positivity (\(P=\text{.01}\)) between the 5-minute and a 15-minute test. Therefore, the 10-minute active phase seems appropriate for a short duration tilt-test. Reduction of the active phase to 10 minutes would result in a loss of 1.5% of the positivity rate or 0.98% of patients with suspected vasovagal syncope.

5. Discussion

Our study showed that reducing the active phase to 10 minutes would result in a loss of 1.5% in the positivity rate or 0.98% of patients with suspected vasovagal syncope. Therefore,
Figure 1. Flowchart of the patients that performed tilt test. Duration of the passive and active phase.

Figure 2. Time to syncope during passive phase. The longer time of the phase, the higher number of patients with syncope during the phase.
10 minutes after administration of Nitroglycerin would be sufficient to obtain a positive tilt test and proved prolongation of the test to be redundant.

Since the tilt test for vasovagal syncope is a time-consuming procedure, our study demonstrated that a shorter test duration will yield the same result as the classical approach. In addition to these findings, we observed an increased patient acceptance of the procedure, as well as decreased reported discomfort and anxiety. We believe that a 10-minute test increases patient compliance significantly.

Khan et al\[6\] performed HUTT testing on 100 patients with orthostatic intolerance and compared the results of the conventional and short duration protocols. The conventional protocol had a passive tilt phase of 30 minutes and a drug provocation phase of 20 minutes. The short duration protocol had both phases lasting 15 minutes, respectively, which could shorten the total test duration by 20 minutes. All patients underwent short duration HUTT procedure, with patients having a negative response undergoing the conventional HUTT after 1 week. The diagnostic yield of short duration and conventional HUTT was 53% and 63%, respectively, with no statistically significant difference between the 2 protocols. They concluded that a short duration approach is a suitable substitution for conventional HUTT, regarding time management.

Another possibility to shorten the test duration is represented by omitting the passive phase. Aerts and Dendale\[7\] performed tilt testing after direct administration of sublingual Nitroglycerine in an upright position on 38 patients and 31 control subjects. Sensitivity, specificity, and accuracy of the test were 82%, 84%, and 83%, respectively. They concluded that testing without the initial passive tilt phase provided an accurate, sensitive, and specific method to provoke vasovagal reactions in subjects clinically suspected of vasovagal syncope.

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In all of our subjects, the active phase was commenced with 0.4 mg of sublingual Nitroglycerine, which could decrease the duration of the test compared to a nonmedicated protocol. The study of Raviele et al\[8\] maintained the tilt 20 minutes after administration of 0.3 mg tablets of Nitroglycerin. Loss of consciousness appeared 7 to 8 minutes after dosing, with a range of 3 to 17 minutes. The clear advantage of this protocol is the redundancy for venous cannulation.

Sabri and Maghzian\[9\] conducted a study on 172 patients, referred for evaluation of unexplained syncope with ages ranging from 6 to 18 years (43 patients in the case group and 129 patients in the control group). The patients within the case group were tilted for 20 minutes (nonmedicated phase). If the results proved negative, the patient received 0.1 mg/kg isosorbide dinitrate sublingually in a supine position and the table was then tilted for a maximum of 20 minutes or until the test became positive (medicated phase). The patients in the control group were tilted to an angle of 65° for 40 minutes (conventional HUTT test protocol). The results showed that in 39.5% of the case group in the nonmedicated phase, and 44% in the medicated phase, elicited a positive response, and 62% of the control group showed a positive response. Similar to our study, the distribution of positive responses was greater during the medicated phase.

Furthermore, when using Nitroglycerine, the duration of the test decreases. Sabri and Maghzian also reported a mean
duration to symptom-development in the nonmedicated phase of 11 ± 6 minutes compared to 9 ± 3 minutes in the medicated phase. Authors concluded that the use of sublingual 0.1mg/kg ISDN as a provocative agent during tilt test is safe, with no major complications.

An aerosol formulation of Nitroglycerine has a better bioavailability than an oral one, with a more homogenous absorption, independent of the patient’s capacity of salivation and mastication, which may be impaired in older subjects. The dose used for aerosols is higher than the dose of oral Nitroglycerine (0.4mg), which further shortens the time to positivity. In the studies of Bartoletti\(^\text{[10]}\) and Del Rosso,\(^\text{[11]}\) the maximum time to syncpe during the active phase was 9 to 25 minutes after aerosol administration.

Limitations of our study are certainly the relatively small number of patients and the lack of testing patients between 40 and 60 years old for carotid hypersensitivity. Additionally, we did not prolong the duration of the passive phase over 20 minutes. By prolonging the duration to 40 minutes, more tests will become positive during the passive phase. Lastly, in our tilt protocol, we tilted the patients to 70°. It should be noted that a less steep angle of 65° may have resulted in a lower number of positive responses. A higher positive rate using a steeper tilt angle has been previously demonstrated in passive and medicated protocols.\(^\text{[12]}\)

In conclusion, shortening the active phase is a feasible substitution for conventional HUTT in order to save time. This new protocol offers a practical and easy-to-perform approach to diagnosing neurally mediated syncope. By diminishing procedure time, we lessen the burden of the test and expand its accessibility and usage, providing a positive alternative to the current diagnosis of patients with syncope.

**Author contributions**

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