AGE AND GANDER DIFFERENCES IN THE TILT TABLE TEST RESULTS

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Abstract

Syncope is a medical term used for the sudden and most often short-lived loss of consciousness which is the result of brain hypoxia due to reduced blood flow. Syncopes are divided into three groups; reflex syncope, orthostatic hypotension and cardiac syncope. Vasovagal syncope is diagnosed by typical anamnestic information and head-up tilt table test. In the general population, the annual number of syncope episodes is 18.1–39.7 per 1000 patients, with similar incidence between genders. Significant increase in the incidence of syncope in observed after 70 years of age. The aim of our study was to investigate the differences in head- up tilt table test results between genders and different age groups of patients. The study was conduct in 969 consecutive patients from University Hospital Center Sisters of Charity and University Hospital Center Zagreb between 2014 and 2018. Patients were analyzed and compared according to demographic data (age and gender) and test results (positive or negative) with specific response (cardio-inhibitory, vasodepressor or mixed). The test was positive in 309 (31.8%) of all evaluated patients, with u specific responses; 182 (59%) vasodepressor, 29 (9%)
cardioinhibitory and 99 (32%) mixed response. Age resulted in being a strong negative predictor for head-up tilt-test. With each year of age, the probability of a positive test decreased by 3%. Gender presented as a trend rather than a significant factor. Accordingly, the question is whether the head-up tilt-test should at all be needed for patients older than 65 years of age.

Keywords: reflex syncope, vasovagal, tilt test

1. Introduction

Syncope is a medical term used for the sudden and most often short-lived loss of consciousness, which may lead to falling. They are usually the result of brain hypoxia due to reduced blood flow and transient global cerebral hypo-perfusion. Depending on etiology, prognosis and therapy, there are three types of syncopes; orthostatic hypotension, reflex syncope and cardiac syncope (rhythm disorders). The most frequent type of reflex syncope is vasovagal syncope (neurocardiogenic) that occurs after prolonged standing. The vasovagal syncopes are divided into three groups: cardio-inhibitory, vasodepressor, and mixed syncope.

It is quite often for vasovagal syncope to reoccur in patients who are experiencing high levels of stress, fear, pain and fatigue. Following symptoms may precede a syncope: pallor, diaphoresis, nausea, visual blurring, light headedness and tinnitus. Loss of consciousness that does not match previously described symptoms should be considered as "pseudosyncope". Convulsion, epilepsy, poisoning, hypoglycemia and hypoxia may lead to such events with symptoms like cyanosis, tongue biting and a prolonged postictal state which favor an epileptic seizure according to Kein et.al [4].

In the general population, the annual number of syncope episodes is 18.1–39.7 per 1000 patients, with similar incidence between genders. Significant increase in the incidence of syncope in observed after 70 years of age

with 19.5 per 1000 patients after the age of 80. The annual mortality, according to Rose M.et al., depends on the cause of syncope, therefore it is 18-33% in cardiac cause, and between 0-12% in non-cardiac cause [10]. Head-up tilt-test (HUTT) is considered as the golden standard for diagnosing of reflex syncope (ESC Guidelines), especially a hypotensive (vasodepressive) tendency, in patients with unconfirmed diagnose by initial evaluation and for evaluation of orthostatic hypotension [1]. Some studies (Ghariq et al.) suggest that there are sex-specific pathophysiological differences in syncope onset that effect head-up tilt-test results with more vasovagal syncope inductions in men in first phase of testing (without nitroglycerin) opposite to women with more vasovagal syncope inductions in second phase of testing (with nitroglycerin) [3]. Also changes in blood pressure drop were noticed in tilt test results in elderly patients especially in connection with frailty, slowness and weakness that were associated with orthostatic hypotension with significant decrease of blood pressure after the first minute of testing [6]. Orthostatic hypotension was more significant, by Kocyigit et al., in terms of falls and dementia in older adults than orthostatic hypertension [5].

The aim of this study was to identify and measure the effect of age and gender on positivity of HUTT in patients who have already had at least one syncope prior to the test.

2. Materials and methods

2.1 Study design: This study was performed in 969 consecutive patients in University Hospital Center Sisters of Charity and University Hospital Center Zagreb, between 2014 and 2018. The HUTT was performed at the Department of Cardiology at both sites based on the recommendation of the attending doctor of each patient. The investigation was performed in accordance with ethical standards of Helsinki Declaration and approved by ethical committee of both institutions involved. Patients were included in the study independently based on anamnestic information of prior syncope episode.

Patients were analyzed and compared according to their baseline demographic data (age and gender), HUTT results (positive or negative), and responses defined and classified by the Vasovagal Syncope International Study (VASIS) criteria [8].

2.2 HUTT Definition: HUTT was defined as positive when syncope occurred, with associated hypotension and/or bradycardia. This classification was done according to Vasovagal International Study Investigators [8,14].
1. Mixed = heart rate decreases but remains >40 beats/min or <40 beats/min for <10 s and without asystole for <3 s. Blood pressure falls before heart rate decreases.
2. Cardio-inhibitory =heart rate decreases <40 beats/min for >10 s or asystole >3 s. Blood pressure falls before or after heart rate falls.
3. Vasodepressor = heart rate does not decrease more than 10% from peak value at time of syncope. Fall in blood pressure alone accounts for syncope.
   For the purposes of this study, hypotension was defined as a fall in systolic blood pressure of 50 mm mercury.

The inability of the patient to perform the test due to nausea and vomiting was considered as exclusion criteria for our study.

2.3 HUTT Protocol: The HUTT was performed in accordance with the European Society of Cardiology (ESC) Guidelines for the diagnosis and management of syncope (version 2009.).[14]Patients were in horizontal position for 20 minutes before the test started. Electrocardiographic (ECG) recording and monitoring of blood

pressure (BP) and heart rate (HR) were recorded every 5 minutes. Patient was positioned vertically for 60 minutes (or until syncope occurred) with ECG recording and repetitive measurements of BP and HR were preformed every 5 minutes and nitroglycerin was administered sublingually after the first 30 minutes when necessary. Afterwards, patients were put into a horizontal position.

3. Statistical analysis

Continuous data (age) was expressed by median and interquartile range as appropriate. Categorical values were expressed in absolute values and relative frequencies and compared by the χ^2 test. Continuous variables were compared by Mann-Whitney Test. Uni- and multi-variant logistic regression models were created using logistic regression. The receiver operator characteristic curve was evaluated to determine c-statistics describing the predictive ability of the model for study outcomes. Predictive values were calculated for positive predictive value (PPV), negative predictive value (NPV), sensitivity, specificity and accuracy. Two-sided statistical tests were evaluated using SPSS V.23 (IBM SPSS Statistics) with a p value of ≤0.05 designated as statistically significant. The model analysis was performed in Orange V 2.7 (University of Ljubljana, Slovenia).

4. Results

Head up tilt test was performed on a total of 969 patients. The HUTT was positive in 309 (31.8%) of all evaluated patients, of which 182 (59%) had vasodepressor, 29 (9%) cardioinhibitory and 99 (32%) mixed response. Depending on gender, there was a difference: women (219/630), men (90/339), chi-square = 6.845, P = 0.009. Women were younger than men, median (IQR) 35 (20-56) vs 42 (24-61), Mann-Whitney test P = 0.006. These data put into logistical regression result in OR 0.9703 CI 0.9631-0.9775 for age and only OR 0.7412 CI 0.5477-1.0031 for sex - which means that sex is quite significant but it is still more likely that difference in outcome was due to age differences.

Table 1. Baseline characteristics of patients undergoing HUTT

	HUT positive (n=309)	HUT negative (n=660)	p
age(median, (IQR))	24 (16-47)	42.5 (26-61)	<.0001*
male sex (n, (%))	90 (29.1%)	249 (37.7%)	0.009**

(* Mann-Whitney Test, ** Chi-Square Test)

Table 1 presents positive HUTT results in patients by age and gender distribution. Results for age distribution were compared by Mann-Whitney Test and for gender distribution by Chi-Square Test.

Table 2. Logistic regression models

Univariate logistic regression model

Variable	Odds ratio	95% Confidance interval
Age	0.9698	0.9626-0.9770
Multivariate logistic regression model		
Variable	Odds ratio	95% Confidance interval
Age	0.9703	0.9631-0.9775
Sex	0.7412	0.5477-1.0031

Table 2 presents odds ratio results with 95% confidence interval for age and sex variables using univariate and multivariate logistic regression model.

Table 3. Logistic regression model analysis

	Classification accurasy	Sensitivity	Specificity	Area under the ROC curve	PPV	NPV
ULRM	70 %	16.8%	95%	0.676	61%	74.7%

Table 3 presents accuracy, sensitivity, specificity, area under the ROC curve, positive and negative predictive value using univariate logistic regression model analysis.

5. Discussion

Our study is among the first with a very broad spectrum of patient age; the youngest patient was 7 years old and the oldest was 87 years old at the time of the examination. Furthermore, all relevant studies have provided data for selected age groups. In our research, we observed the relationship between positive HUTT outcomes in women and men as well as the impact of age (Table 1).

In study conducted by Pietrucha et al. there was no significant gender differences in the type of vasovagal response to HUTT, they consider that the HUTT protocol differences are mostly related with vasovagal response [9]. Naqvi et al. have also shown that there is no significant difference in the frequency of responses to HUTT between the gender groups [7]. Ghariq et al. in their study showed more vasovagal syncope inductions in men in first phase of testing (without nitroglycerin) opposite to women with more vasovagal syncope inductions in second phase of testing (with nitroglycerin) [3]. Only gender differences in HUTT results reported by Suryanarayana P.G. et al. were ECG changes during the testing primarily in women of yet unknown clinical significance [13]. In our study gender presented as a trend rather than a significant factor.

The potential reason why age is important in HUTT positivity is primarily the possibility of a hyperactive vasodepressor effect of vagus nerve in young people. The explanation might lay in physiological aging which results in reduction of the sympathetic-parasympathetic control of cardiac rhythm. Compared to the older population, where there is a much wider range of causes of syncope due to comorbidities, younger persons prevalence of other causes of syncope are significantly lower in comparison with the vasovagal reaction. Steward et al. have explored pathophysiological mechanisms of vasovagal syncopes in young adults and have

shown predominant effect of systemic vascular resistance drop caused by impaired splanchnic vasoconstriction [12]. In our study age resulted in being a strong negative predictor (NPV 74,7%) for HUTT with the probability of a positive test decreasing by 3% with each year of age. Elderly patients have high prevalence of syncope. Diagnosing syncope is not always an easy task, considering the comorbidities those patients usually have. Analysis of Framingham has shown that the incidence of syncope becomes exponential in elderly patients especially when they are above 80 years of age [11]. The majority of patients in this age group will display a dysautonomic hemodynamic response which results in hypotensive reaction during HUTT. Kocyigit et al. noticedchanges in blood pressure drop were connected with physical state of elderly patients, so frailty, slowness and weakness that were associated with orthostatic hypotension with significant decrease of blood pressure after the first minute of testing [6].

A meta-analysis evaluating the CHADS2 and CHA2DS2-VASc scores reported some of the best c-statistics for these scores at 0.685 and 0.675, respectively, although these values suggest limited predictive ability for stroke [2]. According to C- statistic, age is more significant for negative HUTT than in CHADS2 and CHA_2DS_2-VASc for thromboembolic incidents in patients with atrial fibrillation (Table 3).

6. Conclusions

Age resulted in being a strong negative predictor for HUTT. With each year of age, the probability of a positive test is decreased by 3%.Therefore we consider that vascular stiffness in elderly patients and orthostatic hypotension is the main cause of syncope whereas in the young, do to systemic vascular resistance drop, vasovagal syncope is the most often cause of syncope. While gender is presented as a trend rather than a significant factor. Accordingly, the question is whether the HUTT should at all be needed for patients older than 60 years of age. Other diagnostic methods could benefit more in this group of patients; 24h ambulatory blood pressure monitoring and 24h electrocardiogram holter monitoring in detecting orthostatic hypotension and bradyarrhythmia. In the end it is important to remember that ultimately the negative HUTT does not guarantee that the person doesn't has a vasovagal syncope.

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