

Age and gender as determinants of response to prolonged tilting in patients with syncope

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Abstract

Introduction: There are still many questions about factors and predictors of positive tilting. The main goal of the study was to identify an association between age and gender of syncopal patients and the outcome of head-up tilt testing (HUTT).

Material and methods: 470 patients (men 41%, mean age 46.5 ± 18.7 years) with recurrent syncope (more than 2 episodes in the last 3 months) were tilted and divided according to HUTT outcome: negative HUTT(-) and positive HUTT(+), and next according to type of Vasovagal Syncope International Study (VASIS): VASIS1 – mixed, VASIS2 – cardioinhibitory and VASIS3 – vasodepressor.

Results: HUTT(+) was observed in 300 patients (64%), including 172 cases of VASIS1, 47 of VASIS2 and 81 of VASIS3. HUTT(+) did not depend on age or gender of patients. Older age and male gender were positively associated with VASIS3 response (OR 1.02, CI 1.00-1.04, $p=0.015$ and OR 2.01, CI 1.14-3.54, $p=0.0015$ respectively). Time to syncope during passive tilting positively correlated with age of patients ($r=0.244$, $p=0.030$) and depended on VASIS reaction ($r=0.336$, $p=0.003$).

Conclusions: Positive result of tilting depends neither on age nor gender. Time to syncope onset during passive tilting is related to age and VASIS reaction. Older age and male gender are positively associated with VASIS3 response.

Key words: syncope, age, gender, tilting, VASIS response.

Introduction

Syncope is a common medical problem caused by many conditions, ranging from benign to potentially fatal. At present, head-up tilt testing (HUTT) is the one clinical examination recommended for unmasking susceptibility to neurocardiogenic syncope [1, 2]. Despite its increasing popularity, it is still not well standardized. There are still many questions about factors and predictors of positive tilting. Variations of the heart rate and blood pressure have a close relationship with age-related changes in cardiovascular and nervous system activities influencing the heart and vessels. Bloomfield et al. [3] reported different responses occurring during HUTT depending on age. Also Giese et al. demonstrated that the likelihood of a positive outcome to tilt table testing declines with age and showed among elders better tolerance of upright posture for a longer period before syncope than in younger subjects [4]. The older patients were less likely to develop syncope and relative bradycardia, and take longer to develop presyncope during HUTT. On the other hand, gender differences e.g. oestrogen hormones in women may also influence vascular kinetics and arterial stiffness [5, 6] and response to tilting. Therefore we hypothesized that the age and gender of patients are the most critical determinants of the outcome of HUTT.

The main goal of the study was to identify the association between age and gender of patients and type of response to tilting.

Material and methods

We enrolled in the study 470 consecutive patients (men 41%, mean age 46.5±18.7 years) with recurrent syncope (more than 2 episodes in the last 3 months) of unexplained aetiology after initial history, diagnosed in the Department of Cardiology, First Chair of Cardiology and Cardiac Surgery of the Medical University of Lodz. The main demographic and clinical characteristics of studied patients are shown in Table I. In all patients HUTT was performed using a tilt table (SP-1) with foot support and straps. The Westminster protocol was performed with 20 min of supine phase and next with passive tilting (45 min) at an angle of 60 degrees [7]. In case of a negative result of the passive tilting, pharmacological provocation with nitroglycerin (NTG) of 400 µg sublingually in the upright position was performed, followed by 20 min of active tilting [8]. Continuous ECG curve registration on a cardiomonitor and 3-lead digital Holter recorder, non-invasive blood pressure measurements at 3-min intervals and more frequently if symptoms developed, respiration rate analysis and blood saturation with pulseoximeter were made simultaneously during HUTT. A positive tilt test was defined as reproduction of clinical syncope accompanied by hypotension and/or relative bradycardia [1].

Patients were divided according to HUTT outcome: negative HUTT (HUTT(-)), positive HUTT (HUTT(+)), and next according to the type of Vasovagal Syncope International Study (VASIS) [9]:

- VASIS1 – mixed (blood pressure falls before the heart rate falls not less than 40 beats × min⁻¹ or less than 40 beats × min⁻¹ for less than 10 s with or without asystole of less than 3 s),
- VASIS2A – cardioinhibition without asystole (significant bradycardia with heart rate fall to less than 40 beats × min⁻¹ for more than 10 s but asystole of more than 3 s does not occur, blood pressure falls before the heart rate fall),
- VASIS2B – cardioinhibition with asystole (asystole occurs for more than 3 s, blood pressure falls coincidentally with or occurs before the heart rate fall), and
- VASIS3 – vasodepressor with hypotension without bradycardia (heart rate does not fall for more than 10% from its peak at the time of syncope).

VASIS2 groups A and B did not have enough patients for statistical analysis, so in the subsequent part of the study they were analyzed together as the VASIS2 group.

The exclusion criteria were: co-morbidities, current medicament therapy and pre-syncope in HUTT. Everyone signed the voluntary agreement form before enrolment in the study. Protocols used received the Local Bioethics Committee's approval.

Statistical analysis

A descriptive statistical analysis of the data groups was performed. Demographic data between the groups were compared with Student's *t* test. Comparisons between groups were made using Mann-Whitney U test for continuous variables that did not show a normal distribution and the Chi-square test for categorical variables. Spearman rank correlations were calculated. The relationship between a set of independent and dependent variables was computed with nonlinear estimation procedures via logistic regression analysis (quasi-Newton method). To the multivariate model were introduced: age, gender, results of the HUTT, VASIS response and HUTT phase of syncope development (passive, NTG). Two-sided *p* value <0.05 was considered as statistically significant. Data were analyzed with Statistica 5.0 PL (StatSoft Poland) software. Data are presented as mean ± SD and absolute numbers or decimal fractions.

Results

Positive result of the HUTT was observed in 300 patients (64%), including 172 cases of VASIS1, 47 of VASIS2 and 81 of VASIS3. In 80 patients (*f*=0.27) syncope was observed during passive tilting. The results of tilting are shown in Table II. During passive tilting VASIS3 was observed more often in comparison to other VASIS types (*r*=0.135, *p*=0.019) and frequently in men and older patients (*r*=0.162,

Table I. Patients' characteristics (mean ± SD)

	HUTT(+) n=300	HUTT(-) n=170	Value P
Age (year)	46.2±18.5	47±19.11	>0.05
Men	116	74	>0.05
Women	184	96	>0.05
No. of syncope	3.5±4.7	3.8±8.7	>0.05
Systolic blood pressure (mm Hg)	123.1±16.4	126.0±13.1	>0.05
Diastolic blood pressure (mm Hg)	80.5±9.1	81.7±7.4	>0.05
Heart rate in the rest (bpm)	61.3±14.7	63.5±15.8	>0.05
LV EF (%)	69.8±12.3	71.4±10.6	>0.05

HUTT(+) – positive result of the head-up tilt test

HUTT(-) – negative result of the head-up tilt test

bpm – beats per minute

LV EF – ejection fraction of left ventricle

SD – standard deviation

Table II. Age, gender and passive phase of used protocol with the time to reproduced syncope in relation to VASIS response (mean \pm SD and fraction)

	Age (year)	Men n (f)	HUTT(+) passive n (f)	Time to syncope (min)
VASIS1 n=172	43.9 \pm 18.1	55 (0.32)	37 (0.22)	17.08 \pm 10.42
VASIS2 n=47	47.6 \pm 19.1	21 (0.45)	15 (0.32)	18.00 \pm 9.18
VASIS3 n=81	50.2 \pm 18.4	40 (0.50)	28 (0.35)	24.56 \pm 9.72
P				
VASIS1 vs. VASIS2	>0.05	>0.05	>0.05	>0.05
VASIS1 vs. VASIS3	<0.05	<0.01	<0.05	<0.001
VASIS2 vs. VASIS3	>0.05	>0.05	>0.05	<0.001

HUTT(+) – positive result of the head-up tilt test
HUTT(+) passive – positive result of passive tilting
HUTT(-) – negative result of the head-up tilt test
VASIS1 – mixed reaction
VASIS2 – cardioinhibitory reaction
VASIS3 – vasodepressor reaction
time to syncope – time to syncope onset during passive tilting (min)
SD – standard deviation
f – fraction

$p=0.005$ and $r=0.149$, $p=0.009$ respectively) (Table II). Time to syncope development during passive tilting was positively correlated with age of patients ($r=0.244$, $p=0.030$) and was different in relation to VASIS reaction (Table II) ($r=0.336$, $p=0.003$): the shortest in VASIS1 and the longest in VASIS3 ($p=0.000$).

By logistic regression analysis, positive result of tilting did not depend on age or gender of patients, but older age and male gender correlated with VASIS3 (OR 1.02, CI 1.00-1.04, $p=0.015$ and OR 2.01, CI 1.14-3.54, $p=0.00151$ respectively).

Discussion

In the present study, we tried to determine the connection between age and gender of patients and type of response related to tilting in a large group of patients with unexplained syncope. The effect of age on the HUTT result is controversial. Previous studies [4, 10, 11] reported that positive tilting response declines with age. On the other hand, Bloomfield et al. [3] demonstrated a higher than expected incidence of neurocardiogenic syncope in 133 older patients over 65 with no sex preponderance. Similarly, McGavigan et al. [12] in a large study of 590 patients did not find an age-related decline in positive results to tilting.

The main findings of this study were similar to those of other authors [12-14]. We could not find any predictive value of age or gender for the positive response to tilting. In a study by Kochiadakis et al. [15] and Kazemi et al. [16] age predicted a different type of syncopal response to HUTT – VASIS1 or VASIS2 in the young and VASIS3 in the older patients. Although age and gender did not predict positive tilting results in our study, age significantly influenced response type and time to

syncope development. Similarly to previous studies [12, 15, 16], in this research older age was strongly correlated with pure vasodepressor reaction. Like other authors [4, 17], we showed that time to reproduced syncope was also positively associated with age of patients and type of VASIS reaction, so the highest sensitivity of passive tilting was in the vasodepressor group. This is of great importance since the investigators shorten the passive phase of HUTT or perform the HUTT without a preceding passive tilt phase [18]. Moreover, the haemodynamic syncopal patients seem after NTG provocation studies to be not identical to those in whom syncope occurs during the passive tilting [19]. Our results are in contrast with those of McGavigan et al. [12], who reported no age influence on the time to syncope development during tilting.

Although traditionally women are more susceptible to orthostatic intolerance [20], the current study supports McGavigan's report [12] of no relation between gender and positive tilting and time to syncope development. Intriguingly, in our results male gender was associated with vasodepressor reaction. The mechanism of male gender influence on VASIS response to tilting is unknown; there may underlie a cardiac anatomical sex differences (e.g. greater, more distensible left ventricles in men [21]). In women the oestrogen hormones affect arterial distensibility and arterial stiffness and may affect blood flow velocity in arteries [22]. These differences between men and women may affect the response to orthostatic stress.

The different clinical pattern of neurally-mediated reflex syncope observed in younger and older patients could be a result of several mechanisms [4, 17, 23-26], including:

- 1) stronger activation of the autonomic system during syncope triggered by emotional stimuli (typical of younger patients) compared to syncope triggered by peripheral receptors (typical of older patients),
- 2) an age-related structural change in the heart and/or autonomic nervous system, which are unable to make the appropriate compensatory heart rate changes for the stress induced by tilt testing,
- 3) a smaller increase in circulating epinephrine levels when upright, and
- 4) the pharmacodynamic response to the vasodilating effect of NTG is greater in older patients, because of the relative dehydration typical of this group [2, 22].

The response to prolonged orthostatic stress is the increase of venous pooling and falls of venous return to the right ventricle and an increase in ventricular inotropy, which causes activation of mechanoreceptors. Age-associated physiological changes in baroreflex sensitivity, cerebral blood flow and intravascular volume regulation with reduction in ability to preserve sodium and water as well as autonomic dysfunction influence the response to orthostatic stress [27]. Older patients often have relative dehydration (reduced drinking of liquids and a diminished ability of the kidneys to conserve sodium when intake is restricted and plasma renin and aldosterone responses may be diminished, leading to difficulties in maintaining fluid balance [28]), which has an impact on venous volume and an inherent predisposition to the activation of mechanoreceptors [1, 2, 22]. Ageing alone has been associated with the diminution of cerebral blood flow [27]. Therefore in older patients we should avoid hypoperfusion of the central nervous system, caused by NTG in the active phase of HUTT, using prolonged passive tilting.

There are limitations to this study. In our institution the protocol of HUTT does not allow for beat-to-beat blood pressure monitoring. The second limitation of the study was the lack of a control group.

In conclusion positive result of tilting depends neither on age nor gender. Time to syncope during passive tilting is related to age and VASIS reaction. Older age and male gender are positively associated with VASIS3 response.

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