

# The effects of gender and test protocol on the results of head-up tilt test in patients with vasovagal syncope

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## Abstract

**Background:** Head-up tilt testing (HUTT) is a well-established method for the diagnosis of reflex syncope. Some controversies exist whether gender and HUTT protocol influence HUTT results.

**Aim:** To analyse the results of HUTT in patients with syncope in relation to their gender and used protocol of HUTT.

**Methods:** We retrospectively analysed data of 537 consecutive patients (313 women and 224 men), aged 13-79 years with history of neurally-mediated syncope referred to HUTT. The cardiogenic and neurological aetiology of syncope was excluded in all patients based on previous examination. In 375 patients standard HUTT (STD HUTT), according to the Westminster protocol, was used. In 257 patients in whom STD HUTT was negative, HUTT was continued with pharmacological provocation using isoproterenol intravenous infusion – 114 patients (ISO HUTT) or sublingual nitroglycerin – 143 patients (NTG HUTT). In the remaining 162 patients HUTT was performed according to the Italian protocol (ITL HUTT). The HUTT results were classified according to the VASIS scale.

**Results:** Female gender dominated, however, syncope was induced in a similar proportion of women and men (77.3 vs. 70.5%, NS). There were also no significant differences in the type of vasovagal response (VVR) to HUTT between women and men. Mixed type of VVR was the most frequent after isoproterenol provocation (ISO HUTT), whereas cardioinhibitory type of VVR was the most frequent after nitroglycerin provocation (NTG HUTT).

**Conclusions:** There is no significant relationship between gender and the result of HUTT. The type of VVR is related to HUTT protocol – cardioinhibitory response is more frequent following nitroglycerin administration in comparison to standard protocol and HUTT with isoproterenol provocation.

**Key words:** tilt testing, protocol, vasovagal syncope, gender

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## Introduction

Syncope is a common clinical problem responsible for 1-6% of admissions to hospital wards. About 40% of people faint at least once in their lives and about 10% of them experience recurrence of syncopal episodes [1-4]. Neurally-mediated syncope is the most frequent mechanism of loss of consciousness, especially in patients without organic heart disease [2, 3]. Head-up tilt test (HUTT) is a basic diagnostic tool in the evaluation of patients with vasovagal syncope (VVS) [2, 3]. It has been shown that different HUTT protocols (variable duration of test, tilt angle or used pharmacological provocation) have an impact on the HUTT results [2, 3, 5-7]. Also patient's gender may influence HUTT results although the majority of investigators did not find such a relationship [8-12].

The aim of our study was to assess the effects of gender and test protocol on the results of HUTT and type of vaso-vagal response (VVR) in patients with neurally-mediated syncope.

## Methods

### Patients

We performed retrospective analysis of data concerning 537 consecutive patients (313 women and 224 men), aged 13-79 years (mean  $45.6 \pm 17.6$  years), diagnosed because of syncope in the Coronary Disease Department. The mean number of syncopal episodes was 3.13 (1-16), and presyncopal episodes – 11.1 (2-35). The mean time from the first faint to HUTT was 4.6 years (1.5-17). One hundred six (19.7%) subjects experienced injury during syncopal spell.

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Based on initial examination (history of syncope, physical examination, 12-lead ECG and blood pressure in supine and upright position) in all patients were diagnosed as having VVS as probable or certain cause of lost of consciousness. All these patients were referred to HUTT for a definite diagnosis or confirmation. The cardiogenic or neurological aetiology of syncope was excluded on the basis of performed additional examinations if we suspected that aetiology. The clinical characteristic of patients is shown in Table I and concomitant disorders are listed in Table II.

### Tilt testing

All patients underwent HUTT according to the European Society of Cardiology guidelines [2, 3]. The test

was preceded by at least 20 min supine phase. In 375 patients a standard HUTT (STD HUTT), according to the Westminster protocol (passive tilting at 60 degrees by over 45 min) was performed. The tilt test was continued in 257 patients with negative STD HUTT using pharmacological provocation (active phase tilting) [2, 3, 5] – 114 subjects received intravenous infusion of isoproterenol in a dose of 1-5 µg/min (ISO HUTT) [2, 3, 5] whereas sublingual nitroglycerin in a dose of 0,4 mg was administered to 143 patients (NTG HUTT). The remaining 162 patients underwent HUTT according to the Italian protocol (ITL HUTT): passive phase – 60 degrees over 20 min, followed by an active phase at 60 degrees over 15 min after sublingual administration of 0.4 mg of

**Table I.** Clinical characteristic of patients

	All group n = 537	Type of HUTT				p
		STD n = 375	ISO n = 114	STD n = 143	ITL n = 162	
Women, n (%)	313 (58.3)	213 (56.8)	76 (65.0)	88 (61.5)	100 (61.2)	0.17
Age (± SD) [years]	45.6 ± 17.6	44.3 ± 17.8	44.3 ± 17.8	49.6 ± 17.6	41.7 ± 15.9	0.24
Mean number of syncopal episodes (IQR)	3.2 (2-16)	3.4 (2-16)	3.5 (3-16)	3.3 (2-15)	3.1 (2-14)	0.43
Mean duration of disorder (range) [years]	4.6 (1.5-17)	4.8 (2.3-17)	4.1 (1.9-16)	4.3 (1.8-16)	4.9 (2.1-17)	0.76
Syncope related trauma [%]	19.8	21.1	20.5	18.9	17.8	0.11
Presyncope [%]	7.4	9.5	8.9	9.5	6.7	0.27
Orthostatic hypotension, n (%)	4 (1.6)	0 (0)	1 (2.3)	1 (1.4)	2 (4.4)	0.12

**Table II.** Concomitant disorders

Disorder	Total n (%)	Disorder	Total n (%)
Arterial hypertension	178 (33.1)	Peripheral arterial disease	9 (1.7)
Coronary artery disease	108 (20.1)	Instability of cervical spine	29 (5.4)
History of myocardial infarction	22 (4.1)	History of stroke	2 (0.4)
Previous PCI	21 (3.9)	Subarachnoidal bleeding	4 (0.7)
Previous CABG	3 (0.6)	Vertebro-basal insufficiency	4 (0.7)
Lown 1-3 ventricular ectopic beats	35 (6.5)	History of TIA	5 (0.9)
Episodes of bradycardia	42 (7.8)	History of subdural hematoma	1 (0.2)
Mitral valve prolapse	21 (3.9)	Intracranial aneurysm	1 (0.2)
Paroxysmal 1 <sup>st</sup> type 20 AV block	15 (2.8)	Migraine	9 (1.7)
Preexcitation syndrome	2 (0.4)	Microprolaktinoma	1 (0.2)
Paroxysmal atrial fibrillation	21 (3.9)	Epilepsy	11 (2.0)
Diabetes mellitus	17 (3.2)	Somatisation disorders	3 (0.6)
Metabolic syndrome	9 (1.7)	Depression	33 (6.1)
Sleep apnea syndrome	3 (0.6)	COPD	12 (2.2)
History of pulmonary embolism	2 (0.4)	Varices	25 (4.7)
Surgically corrected CHD	6 (1.1)	Bronchial asthma	9 (1.7)

nitroglycerin [2, 3, 7]. The ECG, blood pressure and blood saturation were continuously monitored during HUTT.

A HUTT was defined positive when characteristic haemodynamic responses occurred during tilting in association with reproduction of syncope. The haemodynamic response to HUT was classified according to the VASIS classification [2, 3, 5]:

- Type 1 or mixed: BP fall precedes bradycardia and heart rate falls but not below 40 beats per minute (bpm) or < 40 bpm for < 10 s with or without asystole of < 3 s at the time of syncope.
- Type 2A: cardioinhibition of < 40 bpm for more than 10 s without asystole of more than 3 s. Blood pressure falls before heart rate falls.
- Type 2B: cardioinhibition with asystole of more than 3 s, and BP fall coincides with or occurs after the fall in heart rate.
- Type 3: vasodepressor. Heart rate does not fall more than 10% below baseline.

The exceptions to this classification are:

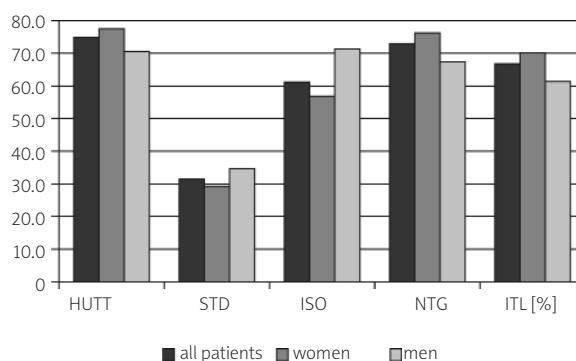
- chronotropic incompetence when the heart rate rise during upright tilt is < 10%;
- postural tachycardia syndrome, when there is an excessive heart rate rise to > 130 bpm at the beginning of HUTT and through its duration before syncope.

### Statistical analysis

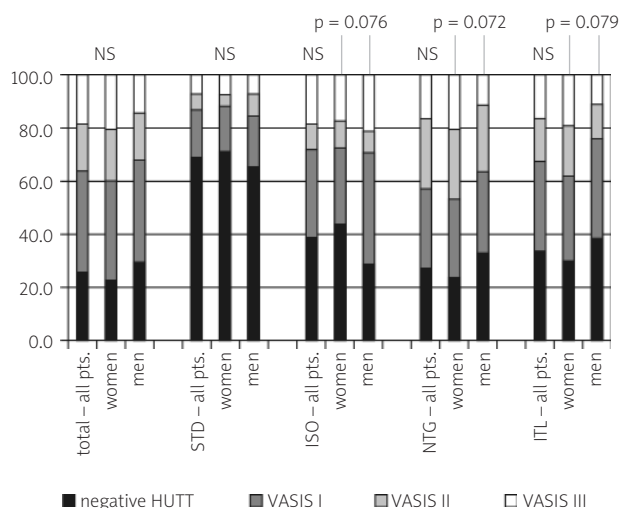
Continuous variables are expressed as mean  $\pm$  standard deviation for normally distributed variables and median with inter-quartile range (IQR) for non-normally distributed variables. Categorical variables are presented as numbers and percentages. The statistical significance of differences between analysed parameters was performed with the use of the  $\chi^2$  test or Student t-test for normally distributed variables and non-parametric test for not normally distributed parameters. A p value < 0.05 was considered statistically significant.

## Results

Positive result of HUTT was observed in 400 (74.5%) patients. Using STD HUTT the percentage of positive results was the lowest - 31.5%. The application of pharmacological provocation increased the number of positive HUTT: ISO HUTT - to 61.4%, NTG HUTT - to 72.2% and ITL HUTT - to 66.7%. We did not observe significant differences in the occurrence of syncope during HUTT between women and men, both in all group (77.3 vs. 70.5%) and in case of using each of HUTT protocols (STD HUTT: 29.1 vs. 34.6%,  $p = 0.29$ ; ISO HUTT: 56.6 vs. 71.1%,  $p = 0.68$ ; NTG HUTT: 76.1 vs. 67.3%,  $p = 0.17$  and ITL HUTT: 70.0 vs. 61.3%,  $p = 0.58$ ). The prevalence of positive HUTT according to gender and HUTT protocol is shown in Figure 1, and the type of VVR in relation to gender and HUTT protocol is depicted in Figure 2.



**Figure 1.** Prevalence of positive result of HUTT according to applied protocol



**Figure 2.** The distribution of type of vaso-vagal response to orthostatic stress during HUTT in relation to gender and HUTT protocol

There were no significant differences in occurrence of type of VVR between women and men during head-up tilt test using 4 different protocols.

A non-significant trend towards more frequent occurrence of mixed type of VVR in men after isoproterenol provocation (42.1 vs. 28.3%,  $p = 0.076$ ) was observed. Similarly, a non-significant trend was observed regarding higher prevalence of vasodepressive response to orthostatic stress during NTG HUTT in women than in males (both NTG HUTT and ITL HUTT 19.7 vs. 11.1%,  $p = 0.09$ ) (NTG HUTT: 20.5 vs. 10.9%,  $p = 0.072$  and ITL HUTT: 19.0 vs. 11.3%,  $p = 0.079$ ). There was no difference in the frequency of cardioinhibitory response in relation to gender or HUTT protocol with pharmacological provocation.

Chronotropic incompetence during HUTT was present in 20 (3.7%) patients, including 3 subjects with negative HUTT, 4 with mixed VVR, 7 with cardioinhibitory VVR and 6 with vasodepressive VVR. Postural orthostatic tachycardia

during HUTT was observed in 2 (0.4%) patients with positive result of HUTT.

## Discussion

In our study a higher prevalence of women than males referred for syncope work-up was observed (1.4 – fold). Nevertheless, in our cohort VVS was induced with comparable frequency in both genders. The average incidence of a positive result of HUTT was as high as 74.5%. The application of tests with pharmacological provocation had a significant impact on HUTT results. Using STD HUTT the percentage of positive results was the lowest – 31.5%. Tests with pharmacological provocation had a higher percentage of positive results, ranging from 61.4% for test with isoproterenol to 72.7% for test with nitroglycerin. We did not observe any significant gender-related difference in the occurrence of positive result of HUTT, regardless of the HUTT protocol. These findings are similar to other studies in which no significant influence of gender on HUTT results was documented [8-12].

We performed the analysis of variation of response to orthostatic stress during HUTT in relation to gender and HUTT protocol. We observed non-significant trend to more frequent occurrence of mixed type vasovagal response in men after isoproterenol provocation. In contrast, females more often tended to reveal vasodepressive response to orthostatic stress in HUTT completed with NTG provocation. These findings may be explained by a relatively small number of patients diagnosed with pharmacologically supported HUTT in relation to the passive phase HUTT only. We did not observe significant differences in the frequency of cardioinhibitory response in relation to gender or HUTT protocol with pharmacological provocation. This issue has not been addressed in literature.

Interestingly, protocols with NTG administration more frequent caused cardiodepressive response in comparison to protocols only with passive phase or with isoproterenol administration. Lelonek et al. showed significantly smaller percentage of cardiodepressive response using the Italian protocol compared to the Westminster protocol with NTG provocation [13]. In our study all cardioinhibitory responses (IIA and IIB according to VASIS) were also more frequently observed in patients after standard passive Westminster HUTT completed with NTG provocation than in patients tested with Italian protocol (25.9 vs. 16.7%). Nevertheless, the prevalence of cardioinhibitory response with asystole more than 3 s (type IIB) was comparable: 15.4 vs. 14.8%. It confirms that nitroglycerin used for provocation during HUTT is responsible for more frequent cardioinhibitory response. Only a few studies dealt with this topic [14-16].

Although previous studies showed that the type of VVR during HUTT did not correlate with late outcome and had a low prognostic value in patients with neurocardiogenic syncope, there are some studies which document

a relationship between cardioinhibitory response during HUTT and potential benefit of cardiac pacing therapy [2, 3, 5, 17, 18]. Data coming from studies assessing VVS with implantable loop recorders illustrate that mechanisms causing spontaneous syncope are very often different to those induced by HUTT [19, 20]. Therefore, HUTT result (positive or negative) seems to be more important than the type of VVR during HUTT. Our data suggest that HUTT results should be interpreted according to the clinical context in association with symptoms, history of the disorder and circumstances of syncopal spells, especially that approximately 5% of patients have a false-positive HUTT result [2, 3, 5].

## Study limitations

In our study we did not evaluate specificity and sensitivity of HUTT in relation to applied protocol, thus – we observed only preselected patients – with certain or suspected VVS based on initial evaluation. Moreover, we did not have a reference (to HUTT) method for VVS diagnosis nor control group (patients without syncope).

## Conclusions

There is no significant relationship between gender and positive result of HUTT. The type of VVR is strongly related to the HUTT protocol (type of pharmacological provocation). Cardioinhibitory VVS is more frequent after nitroglycerin administration in comparison to passive tilting or HUTT with isoproterenol provocation.

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# Wpływ płci i zastosowanego protokołu na wynik testu pochyleniowego u pacjentów z omdleniami wazowagalnymi

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## Streszczenie

**Cel:** Ocena wpływu płci i rodzaju protokołu użytego podczas testu pochyleniowego (HUTT) na wynik badania i typ odpowiedzi wazowagalnej u osób z omdleniami neurokardiogennymi.

**Metody:** Badaniem objęto 537 kolejnych osób (w tym 313 kobiet i 224 mężczyzn) w wieku 13–79 lat (średnio 45,6 roku), zakwalifikowanych do testu pochyleniowego z powodu omdleń o prawdopodobnej etiologii odruchowej. Kardio- i neurogeną etiologię omdleń wykluczono na podstawie wcześniej przeprowadzonych testów diagnostycznych. U 375 osób wykonano standardowy test pochyleniowy (STD HUTT) wg protokołu westminsterskiego (pionizacja pod kątem 60° przez 45 min). U 257 osób z ujemnym wynikiem standardowego testu (STD HUTT) zastosowano przedłużoną pionizację z prowokacją farmakologiczną z użyciem: izoproterenolu (ISO HUTT) (wlew *i.v.* 1-5 µg/min) – 114 osób, lub nitrogliceryny (NTG HUTT) (0,4 mg podjęzykowo) – 143 osoby. U 162 osób wykonano test wg protokołu włoskiego (ITL HUTT) – faza biernej pionizacji 600 przez 20 min, następnie faza czynna – 15 min po podaniu 0,4 mg nitrogliceryny podjęzykowo. Test oceniano jako dodatni, jeżeli doprowadził do wystąpienia omdlenia z towarzyszącym spadkiem ciśnienia tętniczego krwi i/lub bradykardią (asystolią).

**Wyniki:** W badanej grupie przeważały kobiety, jednakże częstość występowania omdleń podczas testu pionizacyjnego nie różniła się istotnie pomiędzy kobietami i mężczyznami (77,3 vs 70,5%). Również częstość występowania poszczególnych typów odpowiedzi hemodynamicznej na pionizację podczas HUTT nie różniła się istotnie pomiędzy kobietami i mężczyznami. Mieszany typ odpowiedzi wazowagalnej podczas pionizacji stwierdzano częściej po prowokacji izoproterenolem (ISO HUTT), natomiast typ kardiodepresyjny występował częściej po prowokacji nitrogliceryną (NTG HUTT).

**Wnioski:** Częstość dodatniego wyniku testu pochyleniowego nie różniła się w zależności od płci. Na typ odpowiedzi wazowagalnej na pionizację ma wpływ zastosowany protokół badania (prowokacja farmakologiczna). Typ kardiodepresyjny odpowiedzi wazowagalnej istotnie częściej występował po prowokacji nitrogliceryną w porównaniu ze standardowym testem pochyleniowym oraz testem z zastosowaniem izoproterenolu.

**Słowa kluczowe:** omdlenie wazowagalne, test pionizacyjny, płeć, protokół testu

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