



# GENDER RELATED DIFFERENCES IN ACTIVE RENIN, ALDOSTERONE AND BIG ENDOTHELIN CONCENTRATION DURING HEAD-UP TILT TESTING IN PATIENTS WITH ISOLATED VASOVAGAL SYNCOPE



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**Abstract:** Introduction and objective: Neuroendocrine dysregulation seems to play the main role in liberation of abnormal vasovagal reflex, and the pathomechanism can be gender-related. The aim of the study was to assess changes in concentration of active renin (R), aldosterone (A) and big endothelin (BE) at rest and tilting in patients with vasovagal syncope in reference to gender and result of the head-up tilt test (HUTT). Material and methods: Study involved 133 patients with syncope. In all HUTT were performed. Concentrations of the analyzed hormones were measured at the last minute of the rest, at the 10th minute of tilting and at the end of the test. An aldosterone/renin ratio (A/R) was calculated for each of the phases. Results: HUTT(+) was observed in 87 subjects (65%). During tilting a gradual increase of R and A was observed. The highest A/R was present in women HUTT(-) ( $p=0.040$ ), contrary to non-fainting men in which decrease of A/R was accompanied with the highest absolute values at the end of the test ( $>18.6$  pg/ml and A/R ratio at the end of the test  $<2.53$  revealed to be independent predictors of syncope during tilt. The increase of R concentration during tilting  $<1.26$  fold and the lack of increase of A predicted syncope during passive phase. In men, A concentration at the end of the test  $<44.0$  pg/ml and the increase of A during tilting less than 2.10 fold, independently predicted positive result. None of analyzed parameters was pointed as an independent factor of syncope during passive phase. Conclusions: The activity of the vasoactive hormones is different in women and men and can determine the result of the test and the tolerance to passive tilting.

**Key words:** vasovagal syncope, head-up tilt test, aldosterone, renin, big-endothelin.

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## INTRODUCTION

According to actual guidelines, syncope is defined as „transient loss of consciousness (TLOC) due to cerebral hypoperfusion, characterized by a rapid onset, short duration, and spontaneous complete recovery” [1]. In the general population of patients diagnosed due to the syncope, more than 37% episodes are caused by pathological vasovagal reflex syncope (VVS) [2]. They concern mostly the young persons without structural heart disease. The main diagnostic tool of VVS is detailed anamnesis and head-up tilt test (HUTT) that allows to reproduce VVS in the controlled conditions [3, 4].

Short-term blood pressure regulation is a result of detailed cooperation between humoral and autonomic nervous systems. The increase of sympathetic activity is expressed by increase of catecholamine concentration, activation of a renin – angiotensin – aldosterone system (RAS) [5] and other vasoactive hormones, including endothelin 1 (ET-1) or its precursor big endothelin (BE). Neuroendocrine dysregulation seems to play the main role in liberation of abnormal vasovagal reflex, and the pathomechanism can be different in men (M) and women (W).

Female steroids hormones have significant influence on blood pressure regulation, that's why differences in RAS activity before and after menopause are observed [6].

The primary objective of the study was to assess changes in concentration of active renin, aldosterone and big endothelin at rest and at prolonged tilting in patients with isolated vasovagal syncope in relation to gender.

The additional aim was to determine hormonal parameters that could be useful in prediction a result of the head-up tilt test.

## METHODS

### Study population

The initial assessment involved consecutive patients presenting symptoms suggesting VVS and qualified for the HUTT after exclusion of other cardiac, neurological or endocrine disturbances. To avoid a potential influence of additional factors all patients with chronic comorbidities (including cardiac pacing) or taking any medicines in the last 8 weeks prior to testing (including nonsteroidal anti-

inflammatory drugs and hormonal contraceptives) were excluded from recruitment. Finally 133 persons with isolated VVS were enrolled.

The study was conducted according to Good Clinical Practice guidelines and Declaration of Helsinki, with the approval of local Ethics Committee RNN/170/05/KE. All subjects gave written informed consent to participate in the study.

### Head-up tilt test

The diagnostic HUTT was performed on the morning, in slightly darkened room. The participants were asked not to smoke tobacco, not taking alcohol, caffeine or other psychoactives during 12 hours prior to the HUTT. Changes in body position were made with the use of table tilt testing SP-1 the feet supported and the straps placed at the height of the knees and chest. HUTT according to extended Westminster protocol included a 30-minute resting phase and 45-minute tilting at an angle of 60 degrees. If there was a negative response to passive tilting, pharmacological provocation with an aerosol of glyceryl trinitrate (GTN) were administered sublingually in a dose of 0.4mg and tilting continued for a further 15 minutes. The HUTT result was considered positive in the occurrence of syncope or presyncope with sudden hypotension and/or bradycardia, and was evaluated according to the international VASIS classification [7].

During the HUTT heart rate (HR) and blood pressure (BP) were continuously monitored with the use of Spacelabs Medical 90369 Patient Monitor, and subsequently analyzed offline (HR were calculated as an average of a 30-second period). The used set included the module to noninvasive automatic blood pressure measurement in a 1-minute intervals.

A study group were divided according to the HUTT result (HUTT(+)- positive HUTT; HUTT(-)- negative HUTT) and then according to the phase in which the syncope has occurred (passive vs GTN). Independent analysis for W and M were done.

### Hormonal analysis

An active renin (R) and aldosterone (A) concentrations were measured three times: at the last minute of the rest (R1, A1), the 10th minute of tilting (R2, A2) and at the end of the test (syncope or the end of tilting for HUTT(-)) (R3, A3). To avoid a renin activation the blood samples were directly centrifuged in ambient temperature, and then frozen in minus 80 degrees till final laboratory analysis. Immunoradiometric and radioimmunological method to measure of active renin and aldosterone concentration were used respectively.

An aldosterone/renin ratio (A/R) was calculated for each of the phases of the test.

A Big Endothelin (BE) concentration was measured three times: at the last minute of the rest (BE1), the 10th minute of tilting (BE2) and the end of the test (syncope or the end of HUTT(-)) (BE3). Blood samples were immediately placed on ice and centrifuged, and then frozen in minus

80 degrees till final laboratory analysis with immunoenzymatic method.

For an objective evaluation of variability of parameters assessed in subsequent stages of the tilt test, comparative analysis of the absolute values and also indicators of the dynamics of change (x $F$ ), with respect to the reference values were performed:  $xF(a/b) = F(a)/F(b)$ , where  $F(a)$  - the value of the analyzed parameter during phase,  $F(b)$  - the parameter value during the phase of being compared.

### Statistical analysis

Statistical analysis was performed using StatSoft STATISTICA software and MedCalc 20. Continuous variables were presented mean  $\pm$  SD and categorical variables as the absolute and relative frequencies (percentages). The distribution and normality of data were assessed by visual inspection and the Kolmogorov-Smirnov test. In the case of continuous variables t-Student's or U Mann-Whitney test was used to determine the significance of differences and the Chi-square test for categorical variables.

To find the relationship between continuous variables the evaluation of the linear correlation of Pearson (or Spearman) was performed.

From the analysis of ROC curves (Receiver Operating Curve) the cut-off values of the discriminative parameters were determined. Then, they were appointed for the final validation with use of univariate and multivariate logistic regression models for each of the sexes independently. A p value of <0.05 was considered significant.

## RESULTS

### Head-up tilt test result

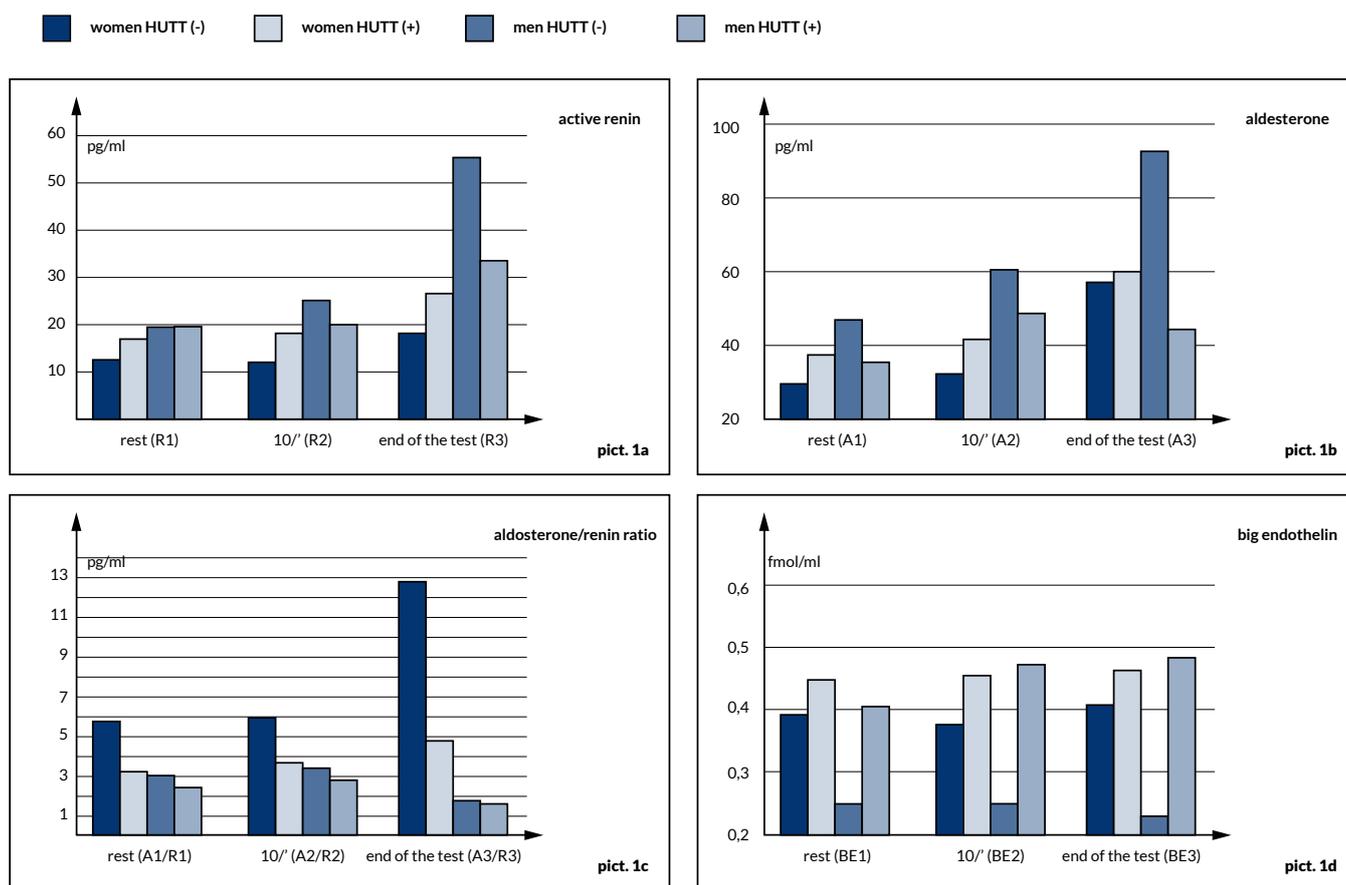
In group of 133 patients (W 84 (63%); mean age  $36.8 \pm 16.5$  years; modal 22 years) which were enrolled, the positive result of HUTT was observed in 87 subjects (65%). There were no sex differences in relation to the percentage of positive results ( $p=0.103$ ) nor to the phase of HUTT in which syncope was occurred ( $p=0.881$ ).

### Resting hormonal activity and age

Resting mean values of analyzed hormones were similar in M and W. The trend to lower R and higher BE in W was noted (table 1).

In W significant decrease of R for 0.16 pg/ml for each year was observed ( $R(\text{pg/ml})=21.31-0.1558*\text{age}$ ;  $p=0.036$ ); this trend was not noted in M. Significant negative correlations of age and A in both groups were observed (W:  $A(\text{pg/ml})=52.42-0.4639*\text{age}$ ;  $p<0.0001$ ; M:  $A(\text{pg/ml})=54.78-0.4214*\text{age}$ ;  $p=0.043$ ). Significant positive correlation between age and A/R ratio in W and negative trend in M were also found (W:  $A/R=1.1+0.0727*\text{age}$ ;  $p=0.039$ ; M:  $A/R=3.742-0.032*\text{age}$ ;  $p=0.055$ ). Insignificant influence of age for BE was noted.

### Hormonal activity during HUTT in relation to the result of tilting

**Table 1. Resting hormonal activity in women and men**

	Women (n=84)	Men (n=49)	p
R (pg/ml)	15.36±11.67	19.47±11.46	0.050
A (pg/ml)	34.70±19.98	40.48±22.48	0.127
A/R	3.88±5.53	2.63±1.74	0.127
BE (fmol/ml)	0.43±0.24	0.35±0.27	0.089

A - aldosterone

A/R - aldosterone/renin ratio

BE - Big Endothelin

R - renin

During tilting a gradual increase of R and A in all subgroups were observed (picture 1a, 1b). The highest absolute values at the end of the test were noted in M HUTT(-) ( $p < 0.001$ ) accompanied with decrease of A/R ratio, while the highest A/R ratio was present in W HUTT(-) ( $p < 0.05$ ) (picture 1c). M HUTT(-) were also characterized with the lowest BE activity during all the HUTT phases ( $p < 0.01$ ) (picture 1d).

In W, R concentration after 10 minutes of tilting (R2), A/R ratio at the end of the test (A3/R3) and coefficient of dynamics of BE concentration from the 10th minute of tilting to the end of the test (xF BE(3/2)) differentiated groups of HUTT(-) and HUTT(+). The R concentration at the end of the test (R3), coefficients of dynamics of R and A concentration from basal to the end of the test (xF R(3/1), xF A(3/1)) and from 10th minute of tilting to the end of the test (xF R(3/2), xF A(3/2)) differentiated sub-

cts in which syncope occurred during passive tilting and after GTN.

In M, positive result of HUTT was related to RAS activity during syncope (R3, xF R(3/1), xF R(3/2), A3, xF A(3/1), xF A(3/2)) and BE activity during tilting (BE2). None of the parameters revealed to distinguish M HUTT(+) that fainted during passive and GTN phase. Significant differences between subgroups, for both sexes independently, are summarize in table 2.

### Predictors of positive HUTT

The ROC analysis allowed to identify cut-off values of the parameters presented in table 2. Then, as binary variables, they were incorporated into multivariate logistic regression models. In W, R2 concentration over 18.61 pg/ml (ROC: 0.757; percent of cases correctly classified: 73.81%) and A3/R3 ratio lower than 2.53 (ROC: 0.708; percent of cases correctly classified: 71.43%) revealed to be independent predictors of syncope during HUTT (table 3).

In M, A concentration at the end of the test (A3) below 44.05 pg/ml (ROC: 0.753; percent of cases correctly classified: 75.51%) and the increase of A during tilting (xF A(3/2)) less than 2.10 (ROC: 0.709; percent of cases correctly classified: 73.47%), independently predicted HUTT(+) (table 4).

### Predictors of syncope during passive phase of HUTT

**Table 2. Significant differences of hormonal activity during prolonged tilting according to the result of head-up tilt test in females and males groups**

	women HUTT(+) (n=60)	women HUTT(-) (n=24)	p
R2 (pg/ml)	18.36±13.83	11.57±7.29	0.025
A3/R3	4.71±12.11	12.71±22.92	0.040
xF BE(3/2)	1.11±0.34	1.93±2.63	0.027
	women HUTT(+) GTN (n=36)	women HUTT(+) passive (n=24)	p
R3 (pg/ml)	33.51±20.63	17.49±11.27	0.001
xF R(3/1)	2.82±2.87	1.3±0.60	0.014
xF R(3/2)	1.97±1.00	1.33±0.77	0.010
xF A(3/1)	1.87±0.86	1.4±0.79	0.036
xF A(3/2)	1.69±0.76	1.29±0.67	0.041
	men HUTT(+) (n=27)	men HUTT(-) (n=22)	p
R3 (pg/ml)	33.40±21.03	54.67±18.76	<0.001
xF R(3/1)	2.23±2.15	3.4±1.53	0.036
xF R(3/2)	1.82±0.97	2.69±1.65	0.024
A3 (pg/ml)	43.09±32.76	92.65±65.02	0.001
xF A(3/1)	1.29±0.71	2.2±1.51	0.007
xF A(3/2)	1.07±0.51	1.72±1.0	0.004
BE2 (fmol/ml)	0.479±0.35	0.251±0.19	0.012
	men HUTT(+) GTN (n=17)	men HUTT(+) passive (n=10)	
	No significant differences		

A – aldosterone  
BE – Big Endothelin  
HUTT(+) – positive head-up tilt test  
HUTT(-) – negative head-up tilt test  
GTN – glyceryl trinitrate  
R – renin  
xF – indicators of the dynamics of change  
1 – concentration at rest  
2 – concentration after 10 minutes of tilting  
3 – concentration at the end of the test (syncope or the end of negative test)  
(detailed description of abbreviation was presented in methodology of the study)

In W the increase of R concentration during tilting (xF R(3/2)) below 1.26 (ROC: 0.833; percent of cases correctly classified: 83.33%) and the lack of increase of A (xF A(3/2) ≤ 1) (ROC: 0.847; percent of cases correctly classified: 86.67%) predicted syncope during passive phase (table 5). In M none of analyzed parameters was pointed as an independent factor of HUTT(+) during passive tilting.

**Table 3. Results of univariate and multivariate logistic regression distinguishing women with positive and negative head-up tilt test**

Factors	OR	-95% CI	+95% CI	p
Univariate analysis				
R2 > 18.61 (pg/ml)	6.37	1.37	29.70	0.018
A3/R3 ≤ 2.53	6.00	2.06	17.47	0.001
Multivariate analysis				
R2 > 18.61 (pg/ml)	5.77	1.17	28.48	0.031
A3/R3 ≤ 2.53	5.62	1.86	16.93	0.002

A3/R3 – aldosterone/renin ratio at the end of the tilting (syncope or the end of negative test)  
R2 – renin concentration at 10th minute of the tilting

**Table 4. Results of univariate and multivariate logistic regression distinguishing men with positive and negative head-up tilt test**

Factors	OR	-95% CI	+95% CI	p
Univariate analysis				
R3 ≤ 37.51 (pg/ml)	10.69	2.74	41.74	0.001
xF R(3/1) ≤ 2.05	9.33	2.53	34.43	0.001
xF R(3/2) ≤ 2.32	4.20	1.22	14.45	0.023
A3 ≤ 44.05 (pg/ml)	9.33	2.53	34.43	0.001
xF A(3/1) ≤ 1.35	6.33	1.81	22.11	0.004
xF A(3/2) ≤ 2.10	21.67	2.48	189.10	0.005
BE2 > 0.40 (fmol/ml)	8.36	1.61	43.27	0.011
Multivariate analysis				
A3 ≤ 44.05 (pg/ml)	7.67	1.65	35.67	0.009
xF A(3/2) ≤ 2.10	11.54	1.14	117.00	0.039

A – aldosterone  
BE – Big Endothelin  
R – renin  
xF – indicators of the dynamics of change  
1 – concentration at rest  
2 – concentration after 10 minutes of tilting  
3 – concentration at the end of the test (syncope or the end of negative test)  
(detailed description of abbreviation was presented in methodology of the study)

## DISCUSSION

Recurrent syncope is an important diagnostic and therapeutic problem of high prevalence in the general population. The greatest amount of information on the epidemiology of syncope can be found in the Framingham study, with all limitations due to studied population, in which 3.5% of women and 3% of men experienced at least one syncope episode in their lifetime [8]. Due to various conditions and comorbidities the pathomechanisms trig-

**Table 5. Results of univariate and multivariate logistic regression distinguishing women with syncope occurred during passive tilting and pharmacological provocation**

Factors	OR	-95% CI	+95% CI	p
<b>Univariate analysis</b>				
R3 ≤ 14.90 (pg/ml)	5.83	1.87	18.25	0.002
xF R(3/1) ≤ 1.54	8.85	2.48	31.53	0.001
xF R(3/2) ≤ 1.26	25.00	6.25	99.96	<0.001
xF A(3/1) ≤ 1.09	16.00	4.18	61.22	<0.001
xF A(3/2) ≤ 1.00	51.00	9.32	278.96	<0.001
<b>Multivariate analysis</b>				
xF R(3/2) ≤ 1.26	7.45	1.44	38.55	0.017
xF A(3/2) ≤ 1.00	18.91	2.98	120.07	0.002

A - aldosterone

R - renin

xF - indicators of the dynamics of change

1 - concentration at rest

2 - concentration after 10 minutes of tilting

3 - concentration at the end of the test

(detailed description of abbreviation was presented in methodology of the study)

gering syncope has not yet been clearly established. There is evidence that its pathophysiological basis in men and women may not be the same [6]. The results of our study show that different activity of RAS and BE in response to tilting can be crucial. It can be explained by the important role of these hormones in short- and long-term regulation of blood pressure. Changing the position of the body leads to decrease of venous return, decompression of high-pressure baroreceptors of the aortic arch and carotid body, resulting in disinhibition of the sympathetic nerve fibers (type C1) activity. On the other hand, catecholamines released from sympathetic endings are major activators of RAS. In case of functional disorders of any of the components of neurohumoral reflex, hemodynamic imbalance may occur. Unambiguous determination of the cause-and-effect relationship is often impossible to perform.

#### Age and gender related differences in resting hormonal activity

Analyzing resting hormonal activity we observed the association of the resting concentrations of R with age, but only in W. This phenomenon can be related to more pronounced hormonal and hemodynamic changes in aging females. Pecher-Bertschi et al. [6] reported a different profile of arterial pressure regulation in groups of W before and after menopause. Jacob et al [9] observed higher level of aldosterone and plasma renin activity in women with constitutional hypotension both supine and tilting.

In our study there was no effect of age and gender on the initial concentration of BE, but the significant differences in the activity of the RAS, catecholamines and other vasoactive hormones in relation to age and gender were observed among healthy subjects [6].

#### RAS dynamics during tilting

Another issue is intensity of activation of the RAS in patients with syncope. In the group of patients prone to hypotension (both young and elderly), there is a subgroup with the initial low plasma renin activity, which does not increase during syncope [7]. Therefore, in our analysis we scoped on the dynamics of hormonal activity. We identified different patterns of neurohormonal regulation in M and W, as well as for passive and GTN provoked syncope.

In response to the tilting we expected the increase of the R and A concentration as that was reported previously [10,11]. Indeed, Grasser et al. [12] noted nearly 3-fold increase in R during tilting, however not accompanied by an increase of A concentration. The authors explained the results by delay in the activation of the RAS axis.

In our study the relation of A and R revealed to be clinically important, especially in W. In W HUTT(+) a growth of R resulted in relatively lower increase in the concentration of A (A/R ratio) in comparison to W HUTT(-). The detailed analysis showed that high R activity during first 10 minutes of tilting can predict syncope generally (regardless of the phase, table 3), but low final R activity and RAS dynamics favors syncope just during passive phase (table 5). That suggests that high activation of RAS can prevent syncope during passive test but can predispose to VVS after GTN.

In men a reaction of RAS turned out to be also important. In M HUTT(-) significantly higher values of R and A were observed, rising in the course of prolonged tilting. Despite the highest absolute values of both RAS components, the A/R ratio has declined to the value noted in M HUTT(+), in which A, lower just at the beginning, did not increase in response to R. Thus, similarly as for women, the RAS compensatory function was blunted (the strong predictive condition of syncope was the final A below 44.05 pg/ml and only slight increase during tilting). None of the analyzed parameters allowed to identify the test phase in which the syncope would occur.

These results may indicate the presence of additional pathways modulating adrenal response to R in men and women that participate in the syncope triggering. A pathomechanism of hypotension may also be different in case of passive tilting and after GTN admission, what in our study was clearly shown in women, although Nilsson et al. did not observe difference in resting concentrations or at 3 minutes of HUTT after adjustment for age and gender [13].

#### Role of endothelin in the response to tilting

Another important element of the neurohormonal regulation of blood pressure is ET-1. In our study, we used BE concentration assays. BE is a precursor to ET-1, and thanks to the greater stability of the molecule, the risk of pre-laboratory errors is reduced. The evaluation of BE change during tilting, that we performed, was justified by both: association of endothelial function with RAS and additional independent input of endothelin on cardiovascular hemodynamics. The increase in blood pressure is directly dependent on the endothelin's dose

- 2-3-fold increase in the concentration of ET-1 causes a 19% increase in the value of blood pressure. Immediately after intravenous administration of endothelin, a decrease in blood pressure associated with the secretion of nitric oxide and of natriuretic peptides occurs, then there is a significant increase in arterial pressure, resulting from the increased vascular resistance, which is maintained for some hours [14]. Sex differences in endothelin 1 levels seems to be due to different transcriptional regulation of endothelin 1 and its metabolism from precursor to converting enzyme activity [15]. Males are also more prone to endothelin-induced vasoconstriction and increases in blood pressure than females [15]. In contrast, women experienced a greater increase in forearm blood flow in response to combined endothelin-A and endothelin-B receptor antagonism, supporting a hypothesis about more prominent role for endothelin-B receptor function in female [16]. However, the observations on endothelin dynamics in response to upright position are discordant. White et al. [17] in a group of 46 healthy subjects reported the increase in ET-1 during prolonged upright but only in those with a negative test result. The opposite results presented Magerkurth et al. [18], who observed significantly higher levels of endothelin in patients with HUTT(+) in both the supine and the upright position compared with HUTT(-). Similarly, Galletta et al. [19] found increased activity of endothelium with progressive peripheral vasodilation and significant bradycardia in patients with induced VVS. Interesting conclusions provided Kaufmann [20] that compared the relationship between the change in blood pressure and endothelin concentrations in healthy subjects, patients with primary autonomic failure, vasovagal syncope and diabetes. In healthy controls the concentration of endothelin increased while pressure was stable. In diabetics and patients with autonomic failure the decrease in blood pressure was not accompanied by the increase in ET-1, whereas in patients with VVS decrease in arterial pressure was associated with an increase in ET-1. Nilsson concluded that higher resting concentration of C-terminal -proET-1 predicts pronounced fall in SBP during first 3 minutes of HUTT [21]. Thus, the relation of endothelin to hemodynamics depends significantly on clinical state of the patient.

Our results revealed the other difference. The BE response to upright position in males and females was not uniform. Only in M the BE concentration differentiated patients according to the result of HUTT. Non-fainting M, in comparison with other subgroups, were characterized by significantly lower BE at all stages of the test. Moreover, the levels of BE in M HUTT(+) were similar as in W. However, in multivariate analysis BE activity did not reach the significant power to be independent predicting factor. It can be explained by strong relationship with RAS that probably dominates the control on vascular hemodynamics during HUTT.

It is difficult to clarify why low endothelial activity protects against syncope. It can be supposed that high BE release is an insufficient compensatory mechanism in case of RAS failure. Due to the prominent role played by the ET system in maintaining cardiovascular homeostasis, coupled with the ability of the ET system to interact with numerous other pathways involved in BP control,

more studies are needed to better define how the ET system regulates BP in both males and females. Besides the evaluation of changes in the concentration of BE during prolonged upright also requires further research because our analysis is the first of this kind in patients with recurrent syncope.

### Clinical implications

Our results indicate the different relation between renin-aldosterone axis and endothelin in males and females. They suggest modulating action of female hormones on neuroendocrine pathways, water and electrolytes balance [22, 23]. Resting neurohormonal evaluation did not revealed to be useful to predict response to prolonged tilting. However, the differences in dynamic changes of evaluated hormones provide some new insight into gender related differences in provoked fainting. Our observations may have some clinical value. The different response to orthostatic stress may result in a different efficacy of the management of recurrent syncope. The further studies evaluating the effect of the pharmacotherapy guide by the neurohormonal assessment could verify the clinical importance of our results.

### Limitations of work

The main limitation of our study is that we did not measure sex hormones and we do not take into account the current phase of the menstrual cycle in W, which can affect the neurohormonal regulation. We also did not measure arterial pressure in the continuous manner (by *beat to beat* method), which may impede the proper classification of the different types of vasovagal response. Thus, the analysis does not include the types of vasovagal reaction that can be characterized by specific neurohormonal patterns.

The methodological limitation can be the fact that we measured BE instead of ET-1. This assumption was justified by very short half-life of ET-1 and its low concentration in young subjects. Clearance of BE is much slower that limits the potential laboratory errors. For this reason we don't have possibility to direct comparing of our results to the other researches performed with using ET-1, what from the other hand can be treated as an innovative, positive aspect of our study.

Another limitation is, paradoxically, the high selectivity of the study group. Therefore our observations should be interpreted carefully for the general population, where fainting is frequently associated with hypertension, diabetes or other cardiovascular diseases.

### Conclusions

The RAS and endothelin are involved in the regulation of blood pressure in response to change in body position. The activity of these vasoactive hormones is different in women and men and can determine the result of the test and the tolerance to passive tilting. The observed differences in the activity of RAS and endothelin confirm the important contribution of hormonal dysregulation in the triggering a vasovagal reaction.

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