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Can the result of a tilt test be predicted in the first five minutes?

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Abstract

Background: *Head-up tilt testing (HUT) plays a pivotal role in the management of vasovagal syncope (VVS). Heart rate variability (HRV) is a well-known method used for noninvasive evaluation of autonomic nervous system activity. However, different results have been obtained in studies that have evaluated the HRV response to HUT in patients with VVS.*

Methods: *One hundred fourteen patients with recurrent VVS were enrolled in the study. According to the results of HUT, patients were divided into five groups: positive (n = 30) and negative (n = 23) Westminster; positive (n = 44) and negative (n = 11) Italian. Fourteen healthy volunteers with no history of syncope comprised the control group. Spectral indices of HRV variability were analyzed for three short-term intervals.*

Results: *Both protocols showed similar distribution of responses to tilt-testing. In the supine position, significant differences were observed between patients from groups 1, 2 and 3 in comparison with the control and Italian negative groups. They had significantly lower initial results of LF_1 [nu] and LF_1/HF_1 ratio, and higher HF_1 [nu] values. The onset of HUT in patients with positive Westminster protocol was characterized by an almost two-fold increase in LF [nu] and decrease in HF [nu] compared to all other patients. LF_2/HF_2 ratio in the Westminster positive group had increased more than five times since the baseline level, while during the last period, LF_3/HF_3 ratio had increased more than six times.*

Conclusions: *Patients with VVS have disturbed sympathovagal balance at rest. Our data suggests that the results of HUT could be predicted by analyzing the spectral parameters of HRV during the first five minutes of the test. The reaction to orthostasis in patients with syncope during the Westminster protocol was more severe compared to the Italian protocol group and the control group. Vasovagal response during the Italian protocol may be triggered by drug-induced vasodilatation.* (Cardiol J 2011; 18, 5: 521–526)

Key words: vasovagal syncope, head-up tilt test, heart rate variability

Introduction

Head-up tilt testing (HUT) plays a pivotal role in the management of vasovagal syncope (VVS) [1, 2]. Numerous protocols have been proposed for clinical practice since 1986 [3–5]. The Westminster protocol is the most popular due to its higher specificity, but it is less sensitive than the Italian one. On the other hand, a considerable shift of vegetative balance after sublingual nitroglycerin decreases the specificity of the Italian protocol [1–3, 6].

Heart rate variability (HRV) is a well-known method of noninvasive evaluation of autonomic nervous system (ANS) activity [7, 8]. Spectral analy-

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sis of HRV provides information on the power of RR-interval variations in the very low-frequency (VLF), low-frequency (LF) and high-frequency (HF) bands, and also sympathetic and parasympathetic interactions in cardiac rhythm control.

Different results have been obtained in studies evaluating HRV response to HUT in patients with VVS and healthy people [9–15]. Decreased HF [ms^2] and HF [nu], together with increased LF [nu] and LF/HF ratio have been observed after transition from the supine to the upright position in many of them [11, 13]. However, Kouakam et al. [12] observed a decrease of LF/HF ratio in patients with a positive result of HUT compared to those with a negative result.

Some studies have found no suppression of the sympathetic branch of ANS or rise in parasympathetic activity before a fall [12, 13]. Nevertheless, in the study of Takase et al. [10] the appearance of prodromal symptoms was accompanied by significantly increased LF [ms^2], HF [ms^2] and total power (TP) [ms^2] in middle-aged patients with VVS. Mehlsen et al. [13] showed that cardioinhibitory response was characterized by an increase in sympathetic activity (LF) and a decrease of HF just before a HUT-induced syncopal attack.

In the largest study, which enrolled 1,155 patients and was published by Virag et al. [15], the dynamics of HRV and blood pressure variability (LF_{RR} and LF_{SBP}) were able to predict a positive result of HUT with 95% sensitivity and 93% specificity, irrespective of the type of response.

The aim of our study was to assess the dynamics of spectral parameters of HRV during HUT performed by the Westminster and Italian protocols in patients with recurrent VVS.

Methods

Subjects

One hundred fourteen patients with recurrent VVS and who had suffered at least two falls during the previous 12 months, were enrolled in the study. All of them underwent medical examination according to the ESC guidelines [1, 2]. Then they were randomized to either the Westminster or the Italian protocol of HUT to evaluate HRV changes. None of the patients had carotid sinus hypersensitivity, arterial hypertension, diabetes, or coronary heart disease.

All the patients gave their consent to participate before enrollment in the study. The protocol was approved by the Research Committee of both hospitals.

Head-up tilt testing

HUT was performed during morning hours in a quiet room at a stable temperature. The tilting table was electrically driven and equipped with a footplate support. Following a rest period of 20 min in the supine position, each subject was tilted to 70° for a maximum of 40 min without the use of any provocative agents (Westminster protocol) or 400 μg of nitroglycerin spray was given sublingually after a 20 min drug-free phase (Italian protocol). If typical symptoms of pre-/syncope occurred during HUT, the patient was immediately returned to the supine position, and the test was terminated. A positive test was defined as the occurrence of syncope. Hemodynamic responses to HUT were classified according to the VASIS classification.

According to the results of HUT, patients were divided into five groups. Group 1 consisted of 30 patients (11 male, 19 female, mean age 28 ± 14 years) with positive result of HUT by the Westminster protocol. Group 2 included 23 patients (eight male, 15 female, mean age 32.0 ± 12.1 years) with a negative response to HUT by the Westminster protocol. Group 3 included 44 patients (15 male, 29 female, mean age 33.1 ± 11.4 years) with positive HUT by the Italian protocol. Group 4 included 11 patients (four male, seven female, mean age 32.5 ± 13.6 years) with negative HUT by the Italian protocol. Six patients were excluded from further analysis due to development of syncope after 2–9 min of HUT. Fourteen healthy age- and gender-matched volunteers with no history of syncope comprised the control group (five male, nine female, mean age 34.4 ± 14.4 years).

Heart rate variability

To clarify the autonomic state during HUT, power spectral analysis of HRV was performed according to the guidelines of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [7]. Spectral indices of HRV were computed by Fast Fourier analysis for three short-term intervals: the last 5 min before HUT in the supine position ('1st period'), the first 5 min of HUT ('2nd period'), and the last 5 min ('3rd period') before syncope or the end of HUT.

The power spectrum was calculated as high frequency (HF: 0.15–0.40 Hz), low frequency (LF: 0.05–0.15 Hz), and the ratio of LF to HF power (LF/HF). Measurement of LF and HF power components was made in absolute values of power [ms^2], and in normalized units [nu]. To measure the shift in autonomic balance for each period, the following ratios were also estimated: LF_2/LF_1 [ms^2], LF_2/LF_1

Table 1. Baseline characteristics of patients.

	Group 1 (n = 30)	Group 2 (n = 23)	Group 3 (n = 44)	Group 4 (n = 11)	Control group (n = 14)
Age	28.1 ± 14.4	32.0 ± 12.1	33.1 ± 11.4	32.5 ± 13.6	34.4 ± 14.4
Male	11 (36.7%)	8 (34.8%)	15 (34.1%)	4 (36.4%)	5 (35.7%)
Age at first syncope	15.8 ± 7.2	16.0 ± 5.5	16.1 ± 13.0	14.2 ± 11.2	
History of syncope (years)	12.3 (1–49)	16 (1–39)	12.7 (1–37)	14.8 (1–41)	
Last episode (months)	3.1	2.5	3.3	3.1	

Table 2. Hemodynamic parameters and responses to head-up tilt testing.

	Group 1 (n = 30)	Group 2 (n = 23)	Group 3 (n = 44)	Group 4 (n = 11)	Control group (n = 14)
HR_1 [bpm]	73 ± 16	65 ± 8	68 ± 14	68 ± 12	69 ± 10
HR_2 [bpm]	92 ± 19	79 ± 11	83 ± 17	78 ± 12	82 ± 12
HR_3 (bpm]		83 ± 15		86 ± 16	84 ± 14
SBP_1 [mm Hg]	114 ± 16	116 ± 10	117 ± 17	116 ± 12	110 ± 6
SBP_2 [mm Hg]	117 ± 11	116 ± 11	120 ± 17	118 ± 14	111 ± 8
SBP_3 [mm Hg]	69 ± 8*	115 ± 14	62 ± 10*	100 ± 8	110 ± 10
Responses to head-up tilt testing					
Type 1	19/63.3%		28/63.6%		
Type 2	2/6.7%		3/6.8%		
Type 3	9/30%		13/29.6%		

HR_{1-3} — heart rate during three periods; SBP_{1-3} — systolic blood pressure during three periods; *p < 0.05 *vs* control group

[nu], HF_2/HF_1 [ms^2], HF_2/HF_1 [nu], LF_3/LF_1 [ms^2], LF_3/LF_1 [nu], HF_3/HF_1 [ms^2], HF_3/HF_1 [nu].

Statistical analysis

Statistical analysis was performed using Statistica 7.0 software package (Statsoft). The distribution of normality was examined. When data were distributed normally, statistical comparisons among variables were made with two-sided unpaired *t* tests. If data were inhomogeneous, Wilcoxon Mann-Whitney and χ^2 tests were used for comparison between groups. A two tailed p value < 0.05 was considered statistically significant. Continuous data are expressed as mean ± one standard deviation. When distributional assumptions were in doubt, medians were calculated.

Results

Baseline characteristics are presented in Table 1. There was no significant difference between the groups in terms of mean age, sex, age at first syncope, or frequency of syncope.

Hemodynamic parameters at rest were also the same between the groups (Table 2). Heart rate rose more prominently, but insignificantly, in the Westminster positive group only. Both protocols showed similar distribution of responses to tilt-testing. In the Westminster positive group, a type 1 (mixed) reaction, according to the VASIS classification, was observed in 19 patients, two patients had cardioinhibitory reaction, while the remaining nine patients showed type 3 (vasodepressor) response. A positive result was registered on average after 20 min of HUT (median 19.9 [10–38] min). In the Italian positive group, a type 1 (mixed) response was observed in 28 patients, three patients had a cardioinhibitory reaction, and 13 patients showed type 3 (vasodepressor) response. A positive reaction was registered 4 min after sublingual nitroglycerin administration (median 3.9 [2–7] min). All healthy persons from the control group gave a negative reaction to HUT by the Westminster protocol.

There were no differences in LF, HF, or LF/HF initially (Table 3) between the groups, if they were calculated in absolute values of power [ms^2].

Table 3. Initial values of heart rate variability in absolute values of power [ms^2].

	LF_1 [ms^2]	HF_1 [ms^2]	TP_1 [ms^2]
Group 1	489 (299; 949)	482 (212; 1,633)	1,982 (1,327; 4,676)
Group 2	716 (360; 1,405)	438 (276; 1,259)	2,812 (1,525; 5,978)
Group 3	689 (284; 1,065)	406 (181; 1,163)	2,188 (900; 3,722)
Group 4	591 (229; 1,952)	409 (164; 785)	2,897 (1,325; 3,029)
Control group	752 (384; 1,617)	441 (88; 576)	2,640 (1,681; 5,448)

LF — low-frequency; HF — high-frequency; TP — total power

Table 4. High-frequency (HF) values within three periods of head-up tilt testing.

	HF_1 [ms^2]	HF_2 [ms^2]	HF_3 [ms^2]
Group 1	482 (212; 1,633)	149 (58; 365)*	134 (59; 253)
Group 2	438 (276; 1,259)	229 (121; 494)*	208 (67; 670)
Group 3	406 (181; 1,163)	156 (78; 238)*	50 (25; 149)*
Group 4	409 (164; 785)	141 (126; 477)*	178 (18; 263)
Control group	441 (88; 576)	299 (60; 527)*	124 (34; 430)

*$p < 0.05$ within the group

The amplitude of HF variability decreased dramatically in all patients with VVS and controls during two periods of active HUT. However, no significant difference was observed between the groups (Table 4). Meanwhile, the behavior of the LF component of HRV was unpredictable: LF amplitude increased in 50–69% of patients with VVS, but at the same time it showed opposite direction in up to 42% of them (Fig. 1A). The dynamics of TP amplitude was roughly similar to LF (Fig. 1B).

LF [nu], HF [nu] and LF/HF changes during HUT are presented in Table 5. In the supine position, statistically significant differences were observed between patients with VVS from groups 1 through 3 in comparison with the control and Italian negative groups. They had significantly lower initial results of LF_1 [nu] and LF_1/HF_1 ratio, and higher HF_1 [nu] values. Interestingly, patients from groups 1 through 3 had similar baseline values of HRV irrespective of the final result of the test, whereas the data of patients from the Italian negative group was almost identical to that from patients from the control group.

The onset of HUT in patients with a further positive response to the Westminster protocol was characterized by an almost two-fold increase of LF [nu] compared to all other patients and healthy volunteers (Table 6). HF_2 [nu] level decreased during the first five minutes in the upright position compared to HF_1 in the vast majority of patients, but only the Westminster positive group of patients showed more than a two-fold decrease of HF component; therefore they had the highest LF_2/HF_2

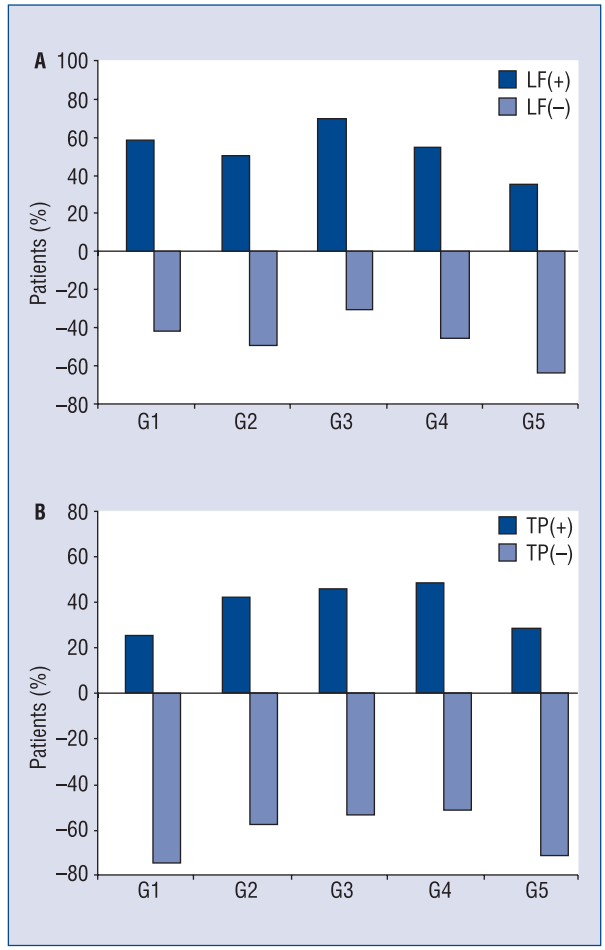

Figure 1. Behavior of low frequency (LF) [ms^2] component of heart rate variability (**A**) and total power (TP) [ms^2] during tilt testing in patients with syncope and healthy people (**B**).

Table 5. Heart rate variability (HRV) parameters [nu] at three stages of head-up tilt testing.

Group	LF_1	LF_2	LF_3	HF_1	HF_2	HF_3	LF_1/HF_1	LF_2/HF_2	LF_3/HF_3
1 (n = 30)	48.0 ± 17.2#	79.1 ± 12.1	80.8 ± 14.1	49.1 ± 17.1#	20.0 ± 11.0	14.0 ± 12.0#	0.9 ± 0.9#	5.4 ± 2.8#	6.2 ± 2.8
2 (n = 23)	50.9 ± 18.8#	65.7 ± 17.5	76.7 ± 12.8	46.0 ± 18.5#	32.3 ± 16.7	22.6 ± 12.1	1.1 ± 0.9#	2.5 ± 1.6	4.0 ± 2.1
3 (n = 44)	53.3 ± 17.2#	69.3 ± 17.2	79.3 ± 12.4	44.0 ± 17.2#	29.3 ± 14.0	19.0 ± 9.9	1.1 ± 0.9#	2.6 ± 1.9	4.8 ± 2.9
4 (n = 11)	63.3 ± 15.5	71.3 ± 17.4	83.8 ± 12.6	35.2 ± 15.3	27.0 ± 15.0	14.3 ± 8.9#	2.1 ± 0.8	4.3 ± 2.1	6.6 ± 2.7
Control (n = 14)	65.8 ± 10.1	74.9 ± 15.7	81.5 ± 8.8	33.6 ± 12.0	24.8 ± 13.8	18.1 ± 9.1	2.1 ± 0.8	3.9 ± 1.5	5.2 ± 2.7

LF — low-frequency; HF — high-frequency; #p < 0.05 *vs* control group

Table 6. Changes of low-frequency (LF) [nu] and high-frequency (HF) [nu] components during second and third periods of head-up tilt testing.

	LF_2/LF_1	LF_3/LF_1	HF_2/HF_1	HF_3/HF_1
Group 1 (n = 30)	1.91 ± 0.89*	1.94 ± 0.99**	0.47 ± 0.30*	0.40 ± 0.20
Group 2 (n = 23)	1.36 ± 0.62	1.73 ± 0.79	0.78 ± 0.36	0.58 ± 0.25
Group 3 (n = 44)	1.39 ± 0.60	1.66 ± 0.70	0.77 ± 0.35	0.51 ± 0.33
Group 4 (n = 11)	1.20 ± 0.49	1.44 ± 0.66	0.86 ± 0.40	0.51 ± 0.30
Control group (n = 14)	1.25 ± 0.25	1.28 ± 0.29	0.69 ± 0.34	0.53 ± 0.21

*p < 0.05 group 1 *vs* groups 2–5; **p < 0.05 group 1 *vs* 5

ratio. LF_2/HF_2 ratio in the Westminster positive group had increased more than five times since the baseline level, while in other groups a roughly two-fold increase was observed.

Before the development of syncope or the end of HUT (the 3rd period), LF_3 [nu] reached maximal level in all groups, although without any difference between them. HF_3 [nu] amplitude decreased in all patients, but it was significant only in those with positive result of HUT by the Westminster protocol and negative to the Italian protocol. LF_3/HF_3 ratio again increased in all groups without significant difference between them. Nevertheless, LF_3/HF_3 ratio increased more than six times in patients with positive HUT by the Westminster protocol, while in the other groups it did not even reach the level observed in the Westminster positive group after the onset of HUT.

Discussion

Heart rate variability has often been evaluated in patients with VVS at rest, during daily activities, and directly before syncope [9–21]. These studies have aimed not only to reveal the mechanisms of syncope or predict the results of HUT, but also to select the most effective treatment for VVS. However, analysis of HRV during tilt testing is difficult, owing to instability periods and data interpretation problems, leading to the contradictory results and conclusions of the aforementioned studies. Some investigators did not find significant differences in baseline HRV parameters among patients with various types of VVS [12, 13], and also between VVS patients and healthy people [21]. Meanwhile, other researchers have described higher levels of sympathetic or parasympathetic activity in patients with VVS compared to healthy people [15–17, 20]. There is a point of view that a positive result of HUT in patients with recurrent VVS can be predicted by increased tone of the parasympathetic part of the ANS at baseline [18, 19].

Many studies have shown a reduction of LF and HF in absolute values of power [ms^2] in the upright position along with increases of LF [nu] and LF/HF ratio [13, 21]. Only one paper has reported a decrease of LF/HF ratio in patients with VVS during orthostatic phase of the positive HUT compared to those having a negative result [12].

We were unable to predict a positive response of HUT if HRV was expressed in [ms^2] due to the unpredictable behavior of LF and TP components, whereas HF [ms^2] amplitude significantly decreased during each of the three stages of HUT in all patients enrolled in our study, although without any difference between all five groups.

On the other hand, patients with recurrent VVS and positive HUT by the Westminster protocol showed significantly lower initial results of LF [nu] and a higher level of HF [nu], which indicates increased baseline tone of the parasympathetic branch of ANS. In the upright position, the sympathetic tone of ANS increased in all patients, including healthy volunteers, but the shift was more prominent only in the Westminster positive group. They

also had higher values of LF_2/HF_2 and LF_2/LF_1 ratio. Parasympathetic activity dropped off during the orthostatic phase, but, again, in patients with positive HUT by the Westminster protocol it presented the most evident dynamics — the minimal level of HF_2/HF_1 [nu] between all the groups.

Analysis of HRV parameters before syncopal fall in our study did not allow us to conclude that the main reason for the positive result of HUT was additional changes of sympathetic or parasympathetic tone during the last 5 min of the test. This data is in line with most previous works [11–13] with one exception [18]. However, it is reasonable to take into consideration the fact that the maximal LF_3/HF_3 ratio in our study was registered in Westminster positive and Italian negative patients. In the other three groups, it was lower than observed in patients with positive Westminster protocol during the first 5 min of the test.

Unexpectedly, we failed to reveal any additional vegetative abnormalities before syncope in patients with positive result by the Italian protocol. Presumably, vasovagal response in these patients was triggered by drug-induced vasodilatation, because changes of vegetative balance during HUT did not significantly differ from the control group. This fact partially supports the opinion of inadequacy of nitroglycerin stimulation of VVS.

Limitations of the study

Fast Fourier transformation was used in our study to assess HRV dynamics despite the fact that the first 5 min of HUT cannot be considered as a stationary period. Moreover, the same limitation can be applied to the last 5 min before syncope. We also did not control respiratory frequency during the whole test.

Nevertheless, despite these limitations, we assume that HRV analysis during HUT contributes to a better understanding of the pathophysiology of VVS, and may be considered as the method of choice in predicting success during tilt-training programs.

Conclusions

Almost all patients with recurrent VVS have disturbed sympathovagal balance at rest. Our data suggests that the results of HUT could be predicted by the analysis of spectral parameters of HRV during the first 5 min of the test. Although the development of syncopal attack in patients susceptible to VVS begins during the first 5 min, it only becomes clinically evident later on.

Reaction to orthostasis in patients with syncope during the Westminster protocol was more severe compared to the Italian protocol group and the control group. Vasovagal response during the Italian protocol may be triggered by drug-induced vasodilatation.

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