Heart rate variability in patients with recurrent syncope

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Abstract

Introduction: The autonomic nervous system participates in the pathophysiology of vasovagal syncope. The disturbances in the autonomic nervous system can be measured by heart rate variability (HRV). The aim of the study was to assess the usefulness of HRV spectral analysis during HUTT in patients with recurrent syncope.
Material and methods: 170 patients with syncope were divided into: positive head-up tilt testing (HUTT) (group I) n=129 and negative HUTT (group II) n=41. The control group comprised 19 healthy volunteers. In all the history was taken, especially with data about syncope and coexisting diseases. Physical examination, 12-lead rest ECG, 24-hour Holter ECG and HRV spectral analysis during HUTT were also performed.
Results: Analyzed groups differed in number of syncope, presence of prodromal symptoms ($p<0.05$) and typical vasovagal history ($p<0.00000$). In non-vasovagal patients there was significantly more hypertension, ventricular arrhythmia of IV b class pro Lown and conduction AV blocks ($p<0.05$). In all analyzed phases of HUTT there were significant differences of sympathetic and parasympathetic activity between vasovagal patients, non-vasovagal and controls. Changes of a component's activity in the autonomic nervous system related to the tilting differentiated VASIS groups.
Conclusions: HRV evidences disturbances of autonomic nervous system activity in patients with recurrent syncope. HRV spectral parameters at rest permit vasovagal patients to be separated from others suffering from syncope. HRV analysis requires further studies in patients with syncope.

Key words: syncope, autonomic nervous system, heart rate variability.

Introduction

Time domain and frequency estimation of heart rate variability (HRV) is used as a prognostic indicator of many cardiologic disorders, including coronary artery disease and heart failure [1-4]. HRV is a valuable and reproducible noninvasive method assessing changes in sympathovagal balance. A lot of authors have analyzed the maintenance of blood pressure and heart rate in reaction to the upright position during head-up tilt testing (HUTT) [5-7]. On the basis of these observations it is ascertained that tilting shows disturbances in the autonomic nerve system's homeostasis. Many studies have suggested a relation between HRV and the outcome of HUTT but still it is unclear and inaccurate [8-15]. HUTT extended by HRV analysis is not popular in clinical practice so far and is not the conventional evaluation for patients with syncope. However, HRV applied in evaluation of the HUTT results could disclose the type of reaction leading to syncope and might

identify persons susceptible to recurrent syncope. Time domain analysis shows RR variability and only some parameters reflect the vagal tone. Spectral analysis is able to detect the dynamic changes of a component's activity in the autonomic nervous system. Therefore in tilting patients we decided to estimate the short periodic spectral HRV parameters in response to orthostatic stress. Since discordant data about autonomic control during the tilt phases have been reported, the aim of the study was to assess the usefulness of HRV spectral analysis during HUTT in patients with recurrent syncope.

Material and methods

170 patients with history of repeated syncope (more than two episodes during the last six months) were enrolled and divided according to HUTT outcome: positive HUTT (vasovagal patients – group I) n=129; mean age 50.6±17.8 years, 0.37 males and negative HUTT (non-vasovagal patients – group II) n=41; mean age 50.0±18.3 years, 0.56 males. The control group (group III) comprised 19 healthy volunteers; mean age 49.8±17.9 years, 0.37 males.

According to the guidelines of the European Society of Cardiology [16, 17] in all the history was taken, especially with data about syncope and coexisting diseases, physical examination and 12-lead rest ECG. HUTT with Westminster protocol [18] was performed in the morning using an SP-1 tilt table with a foot support and straps. During HUTT the ECG was monitored continuously and blood pressure noninvasively with an automatic sphygmomanometer. If syncope did not occur in the passive phase of HUTT, it was followed by a 20-min pharmacological phase after the administration of sublingual nitroglycerin 400 mcg in spray (NTG). The results were considered positive in the case of syncope or presyncope associated with marked reduction of blood pressure and/or heart rate, according to the type of VASIS (Vasovagal Syncope International Study) reaction [19].

24-hour Holter ECG and HRV spectral analysis during HUTT were also performed. The short-periodic HRV spectral analysis was made during HUTT at rest (rest), tilting (tilting) and during the first 5 minutes of upright position (5' tilting). The three-lead digital ECG recorder was processed using the Oxford Holter analyzer. The spectral parameters of HRV were calculated with Fast-Fourier analysis for each interval. The spectral power was evaluated quantitatively and expressed in normalized units (n.u.), with measurement of frequency ranges: LF (0.06-0.15 Hz), which mainly gives a measure of sympathetic activity, and HF (0.15-0.40 Hz), which reflects solely parasympathetic activity. To cancel out the influence of parasympathetic activity on LF, the LF/HF index was calculated. This ratio provides a measure of the sympathovagal balance [20]. Normalized units were calculated as follows:

LF n.u. = LF/TP – VLF x 100 and HF n.u. = HF/TP – VLF x 100 (TP – total power, VLF – very low frequency below 0.03 Hz).

All the patients and normal controls gave their written informed consent to the investigation. The study was approved by the local Ethics Committee.

Statistical analysis

A descriptive statistical analysis of the data was made. Continuous variables that did not show a normal distribution were analyzed with the Mann-Whitney test. Statistical comparisons between groups were made using paired and non-paired tests. Qualitative data expressed as percent were compared by χ^2 test with Yates correction. The univariate analysis was performed. Tests were two-sided. Data are presented as mean value ± standard deviation. Two-sided P value <0.05 was considered as statistically significant. Data were analyzed with Statistica 5.0 PL (StatSoft Poland) software.

Results

The main demographic, clinical and electrocardiographic characteristics of studied patients are shown in Table I. During HUTT syncope was induced in 129 patients (f=0.759) and in 3 subjects from the control group (f=0.158). From the passive phase of HUTT symptoms resulted in 37 patients (f=0.287) and after NTG provocation in 92 patients (f=0.713). According to the VASIS classification mixed vasovagal reaction (VASIS 1) was observed in 74 patients, cardiodepressive (VASIS 2) in 27 and vasodepressive one in 28 subjects.

Analyzed groups differed in number of syncope ($p<0.05$), presence of prodromal symptoms ($p<0.05$) and typical vasovagal history ($p<0.00000$) (Table I). In non-vasovagal patients hypertension frequently appeared ($p<0.05$). There were no significant differences between these two groups with regard to age, body mass index, prevalence of coexisting: coronary artery disease, diabetes, paroxysmal atrial fibrillation, sinus bradycardia or depression (Table I). From ECG abnormalities in non-vasovagal patients frequently were recorded in 24-hour Holter ECG ventricular arrhythmia of IV b class pro Lown (nonsustained ventricular tachycardia) and conduction AV blocks ($p<0.05$). A paroxysmal type I and II second degree AV block was reported in 5% of cases and complete AV block in 4%. Persistent first degree AV block was documented by standard ECG in 4% of cases. The most frequent block was persistent block in the bundle branches in 11% of cases with majority of left bundle block.

In all analyzed phases of HUTT there were significant differences in LF activity ($p<0.05$) between vasovagal patients, non-vasovagal and controls (Figures 1, 2). At rest, the highest activity of LF was

Table I. Characteristics of the study groups

	Group I n=129	Group II n=41	Group III n=19	p
Mean age [years]	50.6±17.8	50.0±18.3	49.8±17.9	>0.05
BMI [kg/m2]	25.9±4.7	26.3±5.1	24.1±3.2	>0.05
Number of syncope	3.3±3.4	2.1±2.6	–	<0.05
Typical vasovagal history [f]	0.81	0.12	–	<0.00000
Prodromal symptoms [f]	0.74	0.49	–	<0.05
Sinus bradycardia [f]	0.15	0.22	–	>0.05
Paroxysmal AF [f]	0.04	0.10	–	>0.05
Conduction blocks [f]	0.11	0.24	–	<0.05
Ventricular arrhythmia of IV b class pro Lown [f]	0.05	0.18	–	<0.05
Coronary artery disease [f]	0.39	0.39	–	>0.05
Hypertension [f]	0.21	0.38	–	<0.05
Diabetes [f]	0.07	0.08	–	>0.05
Depression [f]	0.04	0.10	–	>0.05

f – fraction, BMI – body mass index, AF – atrial fibrillation

observed in control subjects and the lowest in non-vasovagal patients (p<0.01). In contrast to non-vasovagal patients there was a significant rise in LF activity related to the tilting in vasovagal patients and the control group (p<0.05), the highest in the latter subjects. Changes of LF activity related to the tilting differentiated VASIS groups. In contrast to VASIS 1 and VASIS 2, in VASIS 3 (vasodepresssor reaction) we found similar activity of LF at rest and after tilting (Figure 2).

At rest, the highest parasympathetic activity was observed in vasovagal patients and the lowest in the non-vasovagal ones (p<0.001). Among the analyzed groups, a significant decrease in parasympathetic activity related to tilting was noted (p<0.001) (Figures 3, 4), the highest in the vasovagal patients and the lowest in non-vasovagal patients. Changes in HF activity related to tilting differentiated VASIS groups. In contrast to VASIS 1 and VASIS 3, in VASIS 2 (cardiodepressive reaction) we found during the first five minutes of the tilting a rise in HF activity (p>0.05).

In the LF/HF index at rest, tilting and the first 5 min of tilting we observed no differences between analyzed groups (p>0.05). The highest rise in LF/HF related to the tilting was typical for the control group (p<0.05) and the lowest one for non-vasovagal patients (p<0.01) (Figures 5, 6). Changes in the LF/HF index related to the tilting differentiated VASIS groups. In contrast to VASIS 1 and VASIS 3, in VASIS 2 this index still rose in the first 5 minutes of tilting (p<0.05).

A summary of the HRV analysis is presented in Table II.

Discussion

The main findings of this study were the differences in activity of components of the autonomic nervous system measured by spectral HRV related to HUTT results in analyzed of patients with recurrent syncope. We analyzed HRV parameters not only, as it was done in prior studies, in patients with positive versus negative tilt testing, but also with regard to VASIS

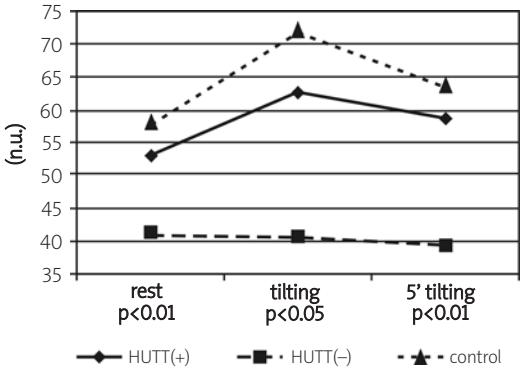

Figure 1. Mean value of LF in normalized units [n.u.] during the head-up tilt test (HUTT)

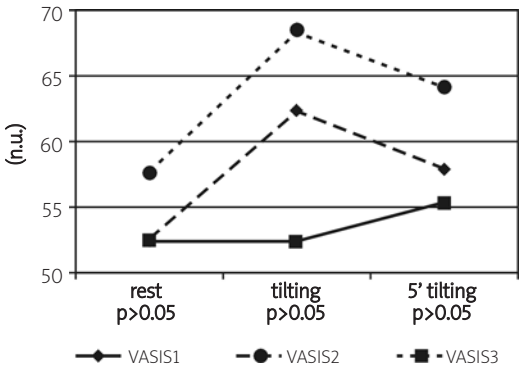

Figure 2. Mean value of LF in normalized units [n.u.] during the head-up tilt test in VASIS groups

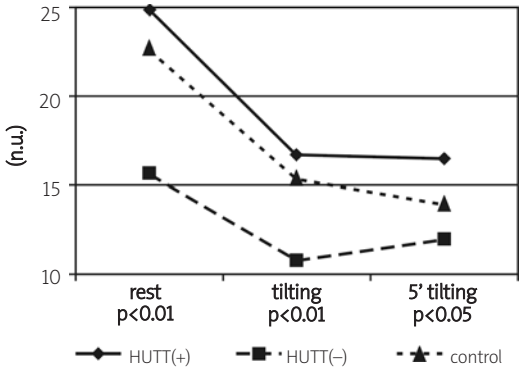

Figure 3. Mean value of HF in normalized units [n.u.] during the head-up tilt test (HUTT)

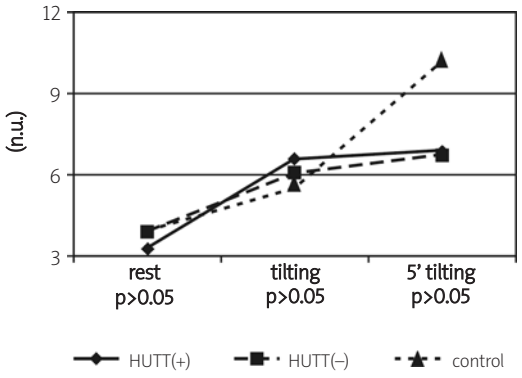

Figure 5. Mean value of LF/HF index during the head-up tilt test (HUTT)

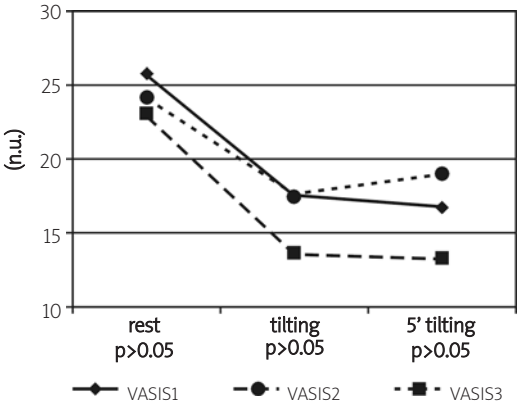

Figure 4. Mean value of HF in normalized units [n.u.] during the head-up tilt test in VASIS groups

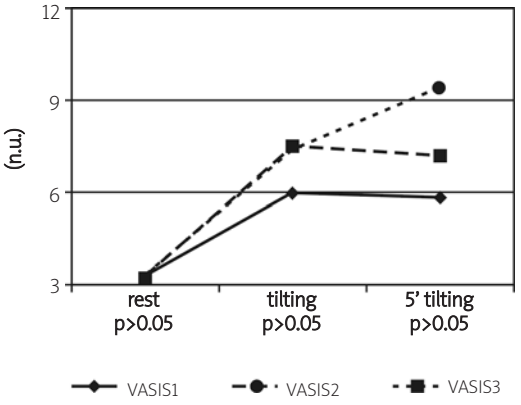

Figure 6. Mean value of LF/HF index during the head-up tilt test in VASIS groups

response. Already at rest HRV parameters permit patients with vasovagal syncope to be separated from patients suffering from syncope. These observations are similar to Piccirillo et al. [15], where the initial phase allowed patients with positive HUTT outcome to be differentiated, but they measured HRV parameters under controlled breathing. Baran et al. [11] performed a comparative analysis of the patients according to VASIS reaction, but unlike us he estimated time domain parameters, not indicating statistical significances. Our results show that the most typical HRV parameter for identification of patients with vasovagal syncope was high parasympathetic activity at rest.

There have already been attempts to explain the pathomechanisim of HRV [8-15]. The method of spectral analysis has proved to be the most stable parameter with the best reproducibility [21]. Our project limited to a few works with a small number of patients, trying to explain the autonomic nervous system activity changes due to reaction to prolonged tilt position during HUTT. Analysis made so far in a few vasovagal patient groups has not shown unequivocally correlations between HRV and HUTT outcome. In analyzed research differences in the activity of the autonomic system's components between vasovagal patients, non-vasovagal and controls were noted, similar to some data from the bibliography [8, 11]. Similar to Gielerak et al. [12] and Kochiadakis et al. [13] we found in healthy controls in response to tilting a drop in parasympathetic activity and a rise in LF/HF. In contrast to Kouakam [10], the rise in sympathetic activity expressed by LF/HF index in response to tilting was noted in all analyzed groups. Kochiadakis observed different trends of autonomic activity between the control group and patients with syncope [13]. In our research in all groups similar trends were noted. Very interesting are the dissimilarities of autonomic activity, expressed by HRV between VASIS patients. In response to tilting in all analyzed groups we observed a significant increase in LF activity except for vasodepressive patients (VASIS 3) and a significant decrease in HF activity except for cardiodepressive subjects (VASIS 2). These changes of activity of the autonomic nervous system's components identify two main types of vasovagal reaction. The increase in HF activity in the 5 min of the tilting in VASIS 2 patients suggests that

Table II. Values in normalized units of LF, HF, LF/HF and standard differences during HUTT: at rest (rest), tilting and in the first 5 min of tilting (5')

	Rest	Tilting	5'	p
		LF		
Vasovagal	53.6±17.8*	62.7±18.3*	58.7±22.8	*<0.0005
Non-vasovagal	40.6±19.9	40.5±18.9	39.2±21.5	>0.05
Control group	59.1±22.2	75.0±11.5	64.7±26.0	>0.05
VASIS1	52.6±17.9*	62.5±15.7*	57.9±20.8	*<0.001
VASIS2	57.6±16.6*	68.5±19.3*	64.1±23.1	*<0.05
VASIS3	52.5±18.5	52.5±18.5	55.3±27.1	>0.05
		HF		
Vasovagal	24.9±14.1*,**	16.7±12.7*	16.5±13.8**	*,**<0.001
Non-vasovagal	15.6±9.6*,**	10.7±8.9*	11.97±11.4**	*,**<0.05
Control group	24.0±16.4*	17.1±11.1	14.2±12.7*	*<0.05
VASIS1	25.8±13.8*,**	17.4±13.2*	16.8±13.3**	*,**<0.001
VASIS2	24.4±12.7	17.5±13.8	18.9±16.5	>0.05
VASIS3	23.0±16.1*	13.6±9.6*	13.2±12.2	*<0.05
		LF/HF		
Vasovagal	3.3±2.7*,**	6.6±5.6*	6.9±9.1**	*,**<0.001
Non-vasovagal	3.97±4.1*,**	6.1±4.6*	6.7±6.7**	*,**<0.01
Control group	3.97±2.83*	6.7±4.7	10.4±9.4*	*<0.05
VASIS1	3.3±3.2*,**	5.9±4.7*	5.8±5.5**	*<0.001 **<0.01
VASIS2	3.2±2.1*	7.4±7.1*	9.4±16.8	*<0.05
VASIS3	3.2±2.0*,**	7.5±6.2*	7.2±5.3**	*,**<0.01

parasympathetic tone plays the most important role in this type of vasovagal reaction.

This importance shows the necessity to differentiate the therapeutic methods on the basis of other pathological mechanisms triggering the vasovagal reaction. In our opinion the next stage should be the creation of a new vasovagal syncope classification according to autonomic system activity measured by HRV during prolonged upright position.

Similarly to Sagrista-Sauleda [22] and Kurbaan [23] our study confirmed that clinical data comprising markers for different aetiological categories of subgroups with recurrent syncope (vasovagal and non-vasovagal patients) and abnormal ECG (mainly ventricular arrhythmias and conduction blocks) had a higher rate in non-vasovagal subjects. In this study HUTT did not explain the reason for syncope in 24% of patients. In these patients syncope could be a consequence not only of the arrhythmias and conduction blocks but also of the side effects of the used medicaments (i.e. nitrates, diuretics, beta-blockers) on account of coexisting diseases. The high fraction of patients with negative results of HUTT necessitates extension of the diagnostic process to other methods, such as implantable loop recorder ILR [24, 25].

There are limitations of the study: 1) the lack of the respiratory frequency control and of the impact of the respiratory rate on the parasympathetic modulation, 2) the lack of randomization, 3) no comparison with others tests assessing the cardiovascular autonomic function in bearings of relations the last years indicated the independent sympathetic and parasympathetic modulation in the place of sympathovagal balance, and 4) the lack of analysis of the impact of the used medicaments on HRV parameters. Moreover, in our institution the protocol of HUTT does not allow for beat-to-beat blood pressure monitoring. We perform non-invasive blood pressure measurements at 3-min intervals and more frequently if symptoms develop.

Conclusions

HRV evidences disturbances of autonomic nervous system activity in patients with recurrent syncope. HRV parameters at rest permit patients with vasovagal reaction to be separated from patients suffering from syncope. HRV analysis requires further studies in patients with syncope.

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