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Heart rate variability and heart rate turbulence in patients with vasovagal syncope

Aim	The autonomic nervous system plays an important role in the pathogenesis of vasovagal syncope, but studies on the effect of basal autonomic tone have found confusing results. The aim of this study was to investigate the effect of basal autonomic functions, as assessed by heart rate variability (HRV) and heart rate turbulence (HRT), in patients with vasovagal syncope.
Material and methods	Patients who underwent head-up tilt test (HUTT) due to unexplained syncope and who had a 24-hr Holter ECG recording in the same period were retrospectively analyzed. Patients with diabetes, a history of myocardial infarction, heart failure, orthostatic hypotension, atrial fibrillation, or use of vasoactive drugs, such as beta blockers, were excluded from the study. 161 patients who met these criteria were included in the study. Time domain HRV parameters from Holter ECG recordings and HRT parameters from patients with sufficient number of ventricular premature contractions were measured.
Results	The age of the patients varied from 16 to 75 yrs (mean: 44.8±18.5 yrs). HUTT results of 60 (37.2%) patients were evaluated as positive. There were no significant differences in the basal demographic, clinical, or laboratory findings of the tilt-positive and tilt-negative patient groups. Likewise, there were no significant differences between the time domain HRV parameters and HRT parameters of both groups.
Conclusion	HRV and HRT parameters reflecting basal autonomic function were not different between HUTT positive and HUTT negative patient groups. These findings suggest that basal autonomic functions have no effect on vasovagal syncope pathogenesis.

Keywords	Vasovagal syncope; tilt-table test; holter ECG; autonomic nervous system
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Introduction

Syncope is the sudden loss of consciousness, associated with inability to maintain postural tone, with immediate and spontaneous recovery without requiring electrical or chemical cardioversion. Most common is neurocardiogenic syncope, which is also known as vasovagal syncope (VVS), and which accounts for one-third of all cases of syncope [1].

The head-up tilt test (HUTT) aims to replicate neurally mediated, orthostatic syncope in the laboratory environment [2]. Studies during tilt testing showed that the autonomic nervous system (ANS) plays a key role in the mechanism of VVS. Tilting to the upright position causes lower body pooling of blood. This increases peripheral sympathetic nerve activity, resulting in vasoconstriction and an increase in heart rate to maintain blood pressure and optimal cardiac output [3]. However, decreased venous return causes a decrease in cardiac preload and cardiac output. In patients with VVS, this leads to a further increase in reflex-mediated sympathetic stimulation of the ventricular myocardium, which, in turn, increases ventricular C-fiber afferent traffic to medullary vasomotor centers. Before syncope, an increase in parasympathetic tone causes a bradycardic response, and a sudden loss of peripheral sympathetic tone causes hypotension [3, 4]. Since the peripheral sympathetic tone of the patient is disturbed in orthostatic syncope, a progressive decrease in blood pressure is observed from the beginning of the HUTT [3].

Heart rate variability (HRV) and heart rate turbulence (HRT) parameters, as obtained from 24-hr Holter electrocardiogram (ECG) recordings, have been shown to play a role in the prediction of arrhythmic death in patients with heart failure and in those with a history of myocardial infarction. HRV is a measure of the ANS effects on the sinoatrial node, and HRT is indicative of baroreceptor sensitivity [5, 6]. Power spectral analysis of heart rate during HUTT revealed the role of the ANS in VVS pathophysiology

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[7]. However, conflicting data are found in the literature regarding the basal autonomic tone as assessed by HRV in VVS, a factor that may impact the response to HUTT [8, 9]. In this study, we evaluated the effects of basal autonomic function as measured by HRV and HRT in VVS patients.

Material and Methods

This study was approved by the local ethics committee. Patients who underwent HUTT between 2015 and 2020 for suspected VVS and had 24-hour Holter ECG recordings before HUTT were identified from the hospital database. Those patients with a previous history of myocardial infarction, coronary artery disease, heart failure, diabetes mellitus, atrial fibrillation, neurological disorders, or using beta-blockers were excluded. Patients with orthostatic hypotension, defined as a decrease in systolic blood pressure of at least 20 mmHg or diastolic blood pressure of at least 10 mmHg in the first 3 min of HUTT, were excluded since its effect on HRV was shown in a prior investigation [10]. 161 patients who met the study criteria were included in the study. HUTT records and Holter ECG records of those patients were evaluated.

HUTT protocol

All HUTTs followed the same protocol. HUTTs were performed on an electrically powered table with a footboard, between 9 am and 12 am, after at least 8 hr of fasting, and in a quiet, dimly lit room. The ECG was continuously monitored during the test. Blood pressure was measured noninvasively with an arm sphygmomanometer in the supine position, 1, 3, and 5 min after the tilt, and then every 5 min and also in the presence of any clinical symptoms. After 10 min of rest in the supine position, the table was raised to a 70-degree angle. If the test ending criteria were not reached, sublingual 400 mcg nitroglycerine was administered at 20 min. After the sublingual nitroglycerine, the 70-degree slope position was continued for another 15 min [11]. The HUTT was continued until complete unconsciousness occurred, or acute arrhythmia developed, or the patient felt significantly uncomfortable, or the protocol was completed. HUTT results were evaluated according to the VASIS classification [12].

Positive results were classified as: Type 1 (Mixed), heart rate and blood pressure decreased together, but the heart rate remained above 40 bpm; Type 2a (Cardioinhibition without asystole), heart rate below 40/min without asystole longer than 3 sec; Type 2b (Cardioinhibition with asystole), decreased heart rate with asystole for longer than 3 sec; Type 3 (Vasodepressor), rapid blood pressure drop during syncope, with heart rate not dropping more than 10/min from baseline. Tests with other results were evaluated as negative.

Holter ECG

24-hr Holter ECG recordings were obtained before HUTT with 3-channel digital recorders. Records of at least 20 hr were included in the study. Records were carefully evaluated manually for potential artifacts and then processed. Time-domain HRV and HRT parameters were measured with Cardioscan Premier 12 software (DM Software, NV, USA). Five time-domain indexes of HRV have measured:

- 1) the square root of the mean squared differences of successive normal-to-normal (NN) intervals (RMSSD);
- 2) the standard deviation (SD) of all NN intervals (SDNN);
- 3) the mean of the deviation of the 5-min NN intervals over the entire recording (SDNN index);
- 4) the SD of the average NN intervals calculated over a 5-min period of the entire recording (SDANN);
- 5) the proportion of adjacent RR intervals differing by >50 ms in the 24-hr recording (pNN50) [6].

HRT was analyzed in 62 patients with sufficient ventricular premature beats on the 24-hr Holter ECG recordings. The measured HRT parameters were turbulence onset (TO) and turbulence slope (TS), which have been detailed in previous publications [5]. In previous studies, TO less than 0% and TS greater than 2.5 ms were identified as normal values [13]. According to these values, the HRT category was determined:

- 1) HRT category 0, individuals with normal TO and TS;
- 2) HRT category 1, individuals with either TO or TS abnormal;
- 3) HRT category 2, individuals with both TO and TS abnormal [5].

Statistical analysis

Statistics Program for Social Sciences (SPSS for Windows 22, IBM Corp, NY, USA) was used for all statistical calculations. Nominal variables are presented as percentages and number of cases. Continuous variables are presented as mean±standard deviation (SD) or as the median and interquartile intervals. Data were tested for normal distribution with the Kolmogorov-Smirnov test. χ^2 tests were used for categorical comparisons between the two groups. Continuous variables were compared using Student's t-test and Mann-Whitney U test where applicable. HRT categories were compared using one-factor ANOVA. All significance tests were two-tailed. Statistical significance was defined as $P < 0.05$.

Results

The study included 161 patients aged between 16-75 yrs (mean: 44.8±18.5 yrs), 77 (47.8%) of whom were male. HUTT results of 60 (37.2%) patients were evaluated as positive. 35 (58.3%) of the positive

results were type 1, 7 (11.7%) were type 2a, 5 (8.3%) were type 2b, and 13 (21.7%) were type 3. The clinical, demographic, laboratory, and echocardiographic findings of the patients are shown in Table 1. When the patients' characteristics were compared according to the HUTT results, older patients, more females, and more smoking patients were found in the tilt positive group, but these differences did not reach statistical significance (p: 0.109, 0.063, 0.059, respectively). With regard to other characteristics, there were no significant differences between the two groups (Table 1).

The HRT of 39 patients in the HUTT negative group and of 23 patients in the HUTT positive group could be calculated. In patients with HRV data, plasma cholesterol and creatinine level were higher in the HUTT positive group (p: 0.024, 0.044, respectively). No other clinical or laboratory findings were different between groups (Table 2).

The 24-hr Holter ECG data are presented in Table 3. No time-domain HRV parameters differed between the two groups. TO and TS values were similar in both groups. When HRT categories were compared, no difference was found between the groups (Table 3).

Discussion

In this study, we found that basal autonomic functions, as evaluated with HRV and HRT, have no effect on HUTT results in patients with VVS. Although many studies have evaluated HRV in this patient group, as far as we know, this study is the first that examined HRT parameters. HRT reflects the baroreflex-mediated response of the sinus node after a ventricular premature beat. Thus, HRT provides information about the ANS [5]. Iacovelli et al examined baroreflex sensitivity in 97 patients with unexplained syncope [14]. 37 patients had a positive tilt test before nitroglycerin, and in this group, baroreflex sensitivity did not differ from that of the negative group. However, patients with syncope after nitroglycerin had lower baroreflex sensitivity and baroreflex effectivity index.

Many studies have examined HRV parameters in VVS. While some of these studies examined 24-hr HRV parameters, others made instant HRV measurements during the tilt test. Time-domain measurements are more advantageous in 24-hr HRV evaluations, whereas frequency domain measurements are more advantageous when measuring for short periods [6]. Klemenc et al measured the frequency domain HRV parameters and baroreflex sensitivity of 105 patients who underwent HUTT [15]. While there was no significant differences among resting parameters of positive and negative patients, significant differences were

Table 1. Baseline characteristics and echocardiographic and laboratory findings of all patients

Variables	HUTT Negative (n = 101)	HUTT Positive (n = 60)	p
Age, years	42.8±17.8	48.1±19.3	0.109
Gender, male/female	54 (53.4)/ 47 (46.6)	23 (38.3)/ 37 (61.7)	0.063
Current smoking	5 (4.9)	8 (13.3)	0.059
Hypertension	24 (23.7)	15 (25.0)	0.859
Plasma Glucose, mg/dl	96.4±32.0	101.1±30.4	0.184
Total cholesterol, mg/dl	1911±41	199±47	0.775
Triglycerides, mg/dl	119±56	128±79	0.946
Serum Creatinine, mg/dl	0.79±0.17	0.81±0.21	0.773
Hemoglobin, g/dl	13.5±1.5	13.5±1.1	0.962
Systolic blood pressure, mm Hg	128±18	126±15	0.773
Mean heart rate, beats/min	76.2±11.1	76.1±11.0	0.909
Left ventricular diastolic diameter, mm	44.6±8.5	43.5±7.8	0.220
Interventricular septum thickness, mm	9.4±3.6	10.0±6.5	0.507
Ejection fraction, %	64.1±4.8	62.4±9.5	0.393
Left atrial diameter, mm	33.9±5.9	33.4±7.3	0.435

Data are mean±standard deviation or number (percentage). HUTT, head-up tilt test.

Table 2. Baseline characteristics and echocardiographic and laboratory findings of HRT patients

Variables	HUTT Negative (n = 39)	HUTT Positive (n = 23)	p
Age, years	51.8±16.5	57.7±17.9	0.162
Gender, male/female	21 (53.8)/ 18 (46.2)	13 (56.5)/ 10 (43.5)	0.838
Current smoking	1 (2.6)	2 (8.7)	0.277
Hypertension	20 (51.3)	7 (30.4)	0.110
Plasma Glucose, mg/dl	103.4±35.0	104.0±31.4	0.973
Total cholesterol, mg/dl	200±41	205±58	0.024
Triglycerides, mg/dl	126±58	112±37	0.614
Serum Creatinine, mg/dl	0.83±0.19	0.90±0.24	0.044
Hemoglobin, g/dl	13.6±1.3	13.8±1.1	0.724
Systolic blood pressure, mm Hg	133±20	131±11	0.778
Mean heart rate, beats/min	73.6±11.2	73.6±8.7	0.545
Left ventricular diastolic diameter, mm	44.0±11.8	44.4±11.1	0.569
Interventricular septum thickness, mm	9.3±4.5	8.1±5.1	0.285
Ejection fraction, %	62.3±5.1	61.7±8.1	0.928
Left atrial diameter, mm	35.5±6.5	36.9±6.1	0.754

Data are mean±standard deviation or number (percentage). HUTT, head-up tilt test.

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Table 3. Comparison of 24-h Holter electrocardiographic, heart rate variability, and heart rate turbulence data

Variables	HUTT Negative (n= 101)	HUTT Positive (n= 60)	P
Recording time, hr	23.2±1.7	23.3±0.80	0.767
Mean RR interval, ms	787 (721/876)	802 (716/877)	0.590
Heart ravariability parameters			
SDNN, ms	133 (110/168)	133 (98/159)	0.218
SDNN index, ms	57 (41/73)	51 (41/66)	0.181
SDANN, ms	120 (95/153)	121 (91/139)	0.230
RMSSD, ms	33 (23/42)	30 (23/43)	0.999
pNN50, %	10 (3/17)	7 (3/17)	0.930
Heart rate turbulence parameters			
Number of patients	39	23	–
Turbulence onset, %	-1.36 (-2.97/1.13)	-1.24 (-3.05/0)	0.403
Turbulence slope, ms/RR	7.8 (4.5/14)	7.6 (3.9/19.7)	0.899
Heart rate turbulence category			
category 0	27 (69.2)	15 (65.2)	0.911
category 1	8 (20.5)	7 (30.4)	
category 2	4 (10.2)	1 (4.3)	

Data are mean±standard deviation or median (25%/75% interquartile range) or number (percentage). HUTT, head-up tilt test; pNN50, the proportion of adjacent RR intervals differing by>50ms in the 24-hr recording; RMSSD, the square root of the mean squared differences of successive normal-to-normal intervals; SDANN, the standard deviation of the average normal-to-normal intervals calculated over the 5-min period of the entire recording; SDNN, the standard deviation of all normal-to-normal intervals; SDNN index, the mean of the deviation of the 5-min normal-to-normal intervals over the entire recording.

petected during tilt and before syncope. However, the researchers could not obtain from these data a statistical model for the predicting syncope. Shim et al compared HRV parameters of 23 children with VVS and 23 healthy controls [16]. They found significantly higher time-domain HRV parameters in the VVS group and concluded that these patients have decreased sympathetic tone and increased vagal tone. Lazzeri et al evaluated 44 patients with syncope [17]. RMSSD and SDANN values were lower in patients with vasodepressor type syncope, but not in patients with cardioinhibitory type syncope. Arslan et al and Zygmunt et al studied 24 hr, time-domain HRV parameters in patients with VVS. In the study of Arslan et al, HRV parameters were significantly higher in tilt positive patients than in tilt negative patients or in healthy controls [9]. On the contrary, Zygmunt et al found significantly lower time-domain HRV parameters in the tilt positive group, compared with the tilt negative group [8].

Kochiadakis et al examined 42 patients with syncope, of which 14 had positive HUTT results [7]. Power spectral analysis of heart rate during the tilt test revealed that, in the tilt positive group, there was no change after tilt, but all HRV parameters increased before syncope. However, in the tilt negative group, there was a slight decrease in HRV parameters after tilt. In another study, Kochiadakis et al compared 60 patients with VVS to 20 control patients [18]. 24-hr HRV measurements were obtained, and the integrity of myocardial presynaptic nerve endings were evaluated with ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy. There was a significantly lower heart to mediastinum ratio with I–MIBG in syncopal patients. However, there were no differences in the time domain HRV parameters. The authors concluded that, since I–MIBG scintigraphy directly assesses adrenergic cardiac innervation, there was an imbalance in the cardiac autonomic system. Because HRV only shows end-organ response, it could not show this imbalance. These studies support our current findings.

Both HRV and HRT indirectly represent baseline ANS function. ANS dysfunction often causes neurogenic orthostatic hypotension as in diabetic autonomic neuropathy [19]. Therefore, patients with impaired HRV and HRT parameters should be expected to have orthostatic hypotension rather than VVS. The confusing results of previous studies may have been due to evaluation of orthostatic syncope as VVS.

Barsukov et al examined hemodynamics during HUTT of 72 patients with a history of VVS and of 32 healthy control patients [20]. They observed that 14 patients with positive HUTT had significantly lower cardiac output (CO) and increased total peripheral vascular resistance (TPVR) at rest. However, CO and TPVR did not differ from control values in the other patients with a history of VVS. These findings might not be due to different baseline autonomic functions in HUTT-positive patients. Since HUTT was performed

in a fasting state, the patients may have become dehydrated, which precipitates VVS. Dehydration also causes a decrease in CO and an increase in TPVR [21].

Although external autonomic innervation of the heart is thought to play a key role in the pathogenesis of VVS, this condition was seen in a patient after heart transplantation who would have lacked external cardiac autonomic innervation [22]. In recent studies, it has been determined that adenosine plays an important role in the pathogenesis of VVS, as well as central and peripheral baroreflex activity abnormalities. Saadjian et al examined the A_{2A} receptor gene polymorphism of 105 patients who underwent tilt testing for unexplained syncope [23]. The CC genotype was found to be significantly more common in patients with a positive tilt test. Also, spontaneous syncopal episodes were found more frequently in individuals with the CC genotype. Brignole et al administered theophylline, a non-selective adenosine receptor antagonist, to 16 patients with asystolic syncope [24]. With theophylline treatment, the average annual number of syncope episodes decreased from 2.6 to 0.4 [24]. In another report, Brignole et al suggested that adenosine plasma levels has a role in the different types of syncope [25]. These findings show that factors other than the ANS may have an important role in the pathogenesis of VVS.

Conclusion

This study found that HRV and HRT parameters did not differ in HUTT-positive and HUTT-negative patients who underwent testing due to unexplained syncope. These findings suggest that basal ANS functions, as assessed with HRV and HRT, have no role in the development of VVS.

Study limitations

The most important limitation of this study is its retrospective design. The mean age of the patients in our study was higher than that of VVS patients in the general population. Therefore, our findings may not reflect all VVS patients. The presence of structural heart disease in elderly patients was investigated in detail by examining the patient files. However, due to the retrospective nature of the study, some conditions may have been missed. HRT analysis could not be performed on a sufficient number of patients. Also, HRV was not measured during HUTT. Therefore, the instantaneous response of the patients to orthostatic stress could not be evaluated. These limitations could be overcome in a prospective study of a larger number of patients.

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