ORIGINAL ARTICLE

Parameters of Heart Rate Variability Can Predict Prolonged Asystole before Head-Up Tilt Table Test

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Background: We aimed to evaluate whether heart rate variability (HRV) could predict prolonged asystole before head-up tilt table test (HUTT) by comparing time domain HRV parameters of patients with type 2B vasovagal syncope (VVS) and patients with other types of VVS.

Methods: Ninety-eight patients who examined with 24-hour Holter electrocardiogram monitoring before HUTT and diagnosed with VVS were enrolled. Patients were divided into two groups in accordance with their VVS type as group 1 (n = 43) consisting of patients with type 2B VVS and group 2 (n = 57) consisting of patients with other types of VVS. Time domain HRV parameters (SDNN, SDANN, SDNN index, RMSSD, pNN50) of two groups were compared. ROC curve analysis was performed to predict best cutoff values that could prognosticate occurrence of prolonged asystole during HUTT.

Results: SDNN, SDANN, SDNN index values were significantly longer for group 1 compared to group 2 (P = 0.009, P = 0.006, P = 0.004; respectively). While a SDNN cutoff value of ≥ 151 ms predicted occurrence of type 2B VVS before HUTT with 69% sensitivity and 56% specificity, a SDANN value of ≥ 164 ms had 47% sensitivity and 87% specificity and a SDNN index value of ≥ 102 ms showed 40% sensitivity and 85% specificity.

Conclusions: In our study, we tried to demonstrate prediction of prolonged asystole by analyzing HRV parameters before HUTT. We found out that time domain HRV parameters were longer in patients with type 2B VVS than patients with other types of VVS. Our results need to be supported by extensive studies.

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vasovagal syncope; heart rate variability; tilt table test

Neurally mediated reflex syncope, commonly referred as vasovagal syncope (VVS), is the most common cause of transient loss of consciousness in young population resulting from abnormal response of cardiovascular reflexes to a trigger.^{1,2} Head-up tilt testing (HUTT) enables reproduction of a neurally mediated reflex in laboratory setting and helps to identify VVS subtypes classified in accordance with specific patterns of heart rate and blood pressure during the test.³ When a reflex is induced, the responses are classified as car-

dioinhibitory, vasodepressor, or mixed according to predominance of decreased components.⁴ Type 2B VVS, a subgroup of cardioinhibitor type VVS, is associated with long-term asystole that lasts for 3 seconds. The pathophysiology of prolonged asystole in type 2B VVS is thought to be resulted from hypersensitivity to the parasympathetic effect on sinus node.

The cyclic changes in a given time at sinus rhythm are defined as heart rate variability (HRV). HRV is affected by the sympathetic and

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parasympathetic stimuli and evaluated as an indicator of cardiac autonomic tone.⁵ Measurement of HRV is a noninvasive approach based on ECG monitoring which provides an indirect assessment of cardiovascular autonomic control.⁶⁻⁸ In this study, we aimed to find out whether prolonged asystole can be predicted with time domain parameters of HRV before HUTT by comparing time domain HRV measures of patients with type 2B VVS and patients with other types of VVS.

METHODS

Study Population

The recordings of patients who presented with complaint of syncope between January 2009 and June 2012 were reviewed. Patients with syncope who were considered to have VVS on initial assessment and normal neurological and cardiovascular examinations without evidence of pre-excitation, long and short QT syndromes or Brugada syndrome in 12-lead electrocardiogram (ECG) were enrolled to this study. The study population consisted of 98 patients (38 males and 60 females) without any echocardiographic evidence of structural heart disease in their 24-hour Holter ECG monitoring before a positive HUTT result. Based on their HUTT results patient population was divided into two groups for a comparison of time domain HRV measures as follows: patients showing type 2B VVS (group 1, n = 43) and patients showing a response beyond type 2B VVS (group 2, n = 55).

24-Hour Holter Electrocardiography

All patients were monitored for 24 hours by ECG Holter system (Lifecard CF Digital Recorder, Del Mar Reynolds Medical Ltd, Hertford, United Kingdom) average of 8 days before HUTT. ECG holter was performed on an outpatient basis, not during a hospitalization to evaluate routine daily interaction. Holter ECG recordings were transferred to a computer program (World Holter System, V 6:15 SP4, Del Mar Reynolds Medical Ltd.) and analyzed. Before analyzing the data, recordings were preprocessed and artifacts were excluded from analysis with visual examination of the recordings by a cardiologist. The lowest and highest heart rate and time domain HRV

parameters including RMSSD (square root of mean squared differences of successive normal-to-normal [NN] intervals), NN50 (number of pairs of adjacent NN intervals differing by more than 50 ms in entire recording), pNN50 (proportion derived from dividing NN50 by total number of all NN intervals), SDNN (standard deviation of all NN intervals), SDANN (standard deviation of averages of NN intervals calculated over 5-minute periods of entire recording), SDNN index (mean of standard deviation derived from 5-minute NN intervals over entire recordings) were calculated in accordance with the previous guidelines published by European Society of Cardiology.⁹

Head-Up Tilt Table Test Protocol

Head-up tilt table testing was performed for each patient on an electrically driven tilt table after 8 hours of fasting in accordance to the Westminster protocol. Blood pressure was measured with a sphygmomanometer in every 5 minutes. Heart rhythm was monitored continuously during the test. Following a rest period of 20 minutes in the supine position, each subject was tilted to 70° for a maximum of 45 minutes without any provocative agent usage. In case the test had remained negative for 45 minutes, 0.4 milligram of sublingual nitroglycerine was administered for 15 minutes in upright position. A positive test result was defined with development of syncope or presyncope induced by reflex hypotension/bradycardia or delayed orthostatic hypotension. Hemodynamic responses to tilt table test were classified in accordance with the VASIS classification as type 1 mixed, type 2A (cardioinhibition without asystole), type 2B (cardioinhibition with asystole), and type 3 (vasodepressor).⁴ When asystole is induced during HUTT, its duration was analyzed from ECG recordings obtained during the test.

Statistical Methods

All statistical analyses were performed using SPSS version 15.0 for Windows, (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL, USA). Continuous variables were expressed with mean $\pm$ standard deviation (SD) while categorical data was described with numbers. Categorical variables were analyzed using chi-square test. Kolmogorov-Smirnov test was performed to test normality.

Table 1. Baseline Characteristics of the Study Population

	Patients (n:98)
Age year $\pm$ SD	31.5 $\pm$ 15.9
Men n, (%)	38 (38.7)
BMI kg/m ² $\pm$ SD	24.2 $\pm$ 2.4
Ejection fraction % $\pm$ SD	60.2 $\pm$ 2.1
Type of VVS	
Type 1 n, (%)	26, (26.5)
Type 2A n, (%)	1, (1.0)
Type 2B n, (%)	43, (43.8)
Type 3 n, (%)	28, (28.5)

Continuous data are expressed as mean $\pm$ SD, categorical data are expressed as n(%).
VVS, vasovagal syncope; BMI, body mass index; SD, standart deviation.

Statistically significant differences between two groups of continuous variables were assessed using independent t-test and Mann-Whitney U test, as appropriate. Differences between groups were considered statistically significant when P value was <0.05. Receiver operating characteristics (ROC) curve analysis was performed to identify best cut-off values of HRV parameters for prognosticating occurrence of type 2B VVS during HUTT.

RESULTS

Demographic characteristics of the study population are presented in Table 1. According to the observed responses during HUTT, there were 26 patients with type 1 VVS, 1 patient with type 2A VVS, 43 patients with 2B VVS, and 28 patients with type 3 VVS among 98 patients. Among patients showing type 2B VVS, females (n = 22) had a longer asystole duration compared to males (n = 21) (6.2 $\pm$ 3.0 seconds vs 4.0 $\pm$ 1.2 seconds, P = 0.045). Table 2 displays the baseline characteristics of two groups. Two groups were well-matched in terms of age, gender, blood pressure, and left ventricular ejection fraction (Table 2). Comparisons of results obtained from 24-hour Holter ECG monitoring are shown in Table 3. The SDNN, SDANN, and SDNN parameters were significantly longer in group 1 compared to group 2 (P = 0.009, P = 0.006, P = 0.004, respectively). In spite of not being statistically significant, patients in group 1 had higher RMSSD and pNN50 values compared to patients in group 2 (P = 0.158, P = 0.257; respectively). The maximum heart rate recorded during 24-hour Holter ECG monitoring

Table 2. Comparison of Baseline Patient Characteristics between Two Groups

	Group 1 (n = 43)	Group 2 (n = 55)	P
Age years $\pm$ SD	31.6 $\pm$ 14.3	32.7 $\pm$ 16.7	0.362
Gender			
Male n (%)	21 (48.8)	17 (30.9)	0.122
Female n (%)	22 (51.2)	38 (69.1)	
Blood pressure			
SBP mmHg $\pm$ SD	115.3 $\pm$ 10.8	115.2 $\pm$ 8.1	0.425
DBP mmHg $\pm$ SD	69.4 $\pm$ 5.3	73.2 $\pm$ 5.1	0.627
Ejection fraction % $\pm$ SD	60.3 $\pm$ 1.7	60.2 $\pm$ 1.9	0.972

Continuous data are expressed as mean $\pm$ SD, categorical data are expressed as n (%).
SBP, systolic blood pressure; DBP, diastolic blood pressure; SD, standard deviation.

Table 3. Comparison of Heart Rate Variability (HRV) Parameters between Two Groups

	Group 1 (n = 43)	Group 2 (n = 55)	P
Lowest HR bpm $\pm$ SD	52.7 $\pm$ 6.3	55.1 $\pm$ 6.7	0.157
Highest HR bpm $\pm$ SD	120.2 $\pm$ 25.5	132.8 $\pm$ 26.0	0.023
SDNN ms $\pm$ SD	161.8 $\pm$ 38.3	142.3 $\pm$ 27.9	0.009
SDANN ms $\pm$ SD	149.1 $\pm$ 42.1	130.4 $\pm$ 32.4	0.006
SDNN index ms $\pm$ SD	84.8 $\pm$ 31.7	70.1 $\pm$ 19.6	0.004
RMSSD (ms)	56.1 $\pm$ 26.5	48.1 $\pm$ 15.1	0.158
Pnn 50 (%)	17.0 $\pm$ 12	14.1 $\pm$ 8.4	0.254

Continuous data are expressed as mean $\pm$ SD, categorical data are expressed as n (%), statistically significant P value is <0.05 (bold P values). HR, Heart rate; bpm, beat per minute; ms, millisecond; SDNN, standard deviation of all NN intervals; SDANN, standard deviation of the averages of NN intervals calculated over 5-minute periods of the entire recording; SDNN index, mean of the standard deviation of the 5-minute NN intervals over the entire recordings; RMSSD, square root of mean squared differences of successive normal to normal (NN) intervals.

Table 4. Predictors of Prolonged Asystole in Patients with Type 2B Vasovagal Syncope (VVS)

	Threshold	Sensitivity (95% CI)	Specificity (95% CI)	P
Highest HR	141 bpm	81% (65.9–91.4)	47% (33.7–62.2)	0.010
SDNN	151 ms	69% (52.9–82.4)	58% (44.1–71.3)	0.013
SDANN	164 ms	47% (32.0–63.6)	87% (75.5–94.7)	0.003
SDNN index	102 ms	40% (25.6–56.7)	85% (73.3–93.5)	0.048

HR, Heart rate; bpm, beat per minute; ms, millisecond; CI, Confidence interval; SDNN, the standard deviation of all NN intervals; SDANN, standard deviation of the averages of NN intervals calculated over 5-minute periods of the entire recording; SDNN index, mean of the standard deviation of the 5-minute NN intervals over the entire recordings.

was significantly higher in group 2 compared to group 1 ($P = 0.023$) (Table 3). According to the results of ROC analysis, a 141 bpm or lower maximal heart rate obtained during 24-hour Holter ECG predicted occurrence of type 2B VVS before a HUTT with 81% sensitivity and 47% specificity. A SDNN value of 151 ms or longer had 69% sensitivity and 58% specificity, whereas a SDANN value of 164 ms or longer had 47% sensitivity and 87% specificity and a SDNN index value of 102 ms or longer had 40% sensitivity and 85% specificity in prediction of type 2B VVS (Table 4).

DISCUSSION

The present study suggests that patients with type 2B VVS have significantly longer SDNN, SDANN, and SDNN index values but lower maximum heart rate values compared to those patients with other types of VVS as shown in 24-hour Holter ECG monitoring. Occurrence of type 2B VVS during HUTT can be predicted by HRV parameters before performing HUTT. Females with type 2B VVS have longer asystole durations than males with type 2B VVS during HUTT.

In recent studies, patients diagnosed with VVS were shown to have significantly increased time domain HRV parameters compared to healthy individuals.^{10,11} Arslan et al. investigated HRV parameters in 33 patients with a typical history of VVS who were scheduled for HUTT. In spite of not being statistically significant, the patients with a positive HUTT results had higher NN50, pNN50, RMSSD, and SDNN index values compared to the control group. They suggested that an increased parasympathetic tonus reflected by higher HRV parameters was associated with HUTT positivity in patients with syncope.¹⁰ Salamah et al. also showed significantly increased time domain HRV

parameters in patients with VVS.¹¹ However, these studies have not investigated HRV parameters in different types of VVS. Unfortunately, there are a limited number of studies which assessed HRV parameters among patients with different types of vasovagal syncope. In a study assessing the correlation between time and frequency domain HRV indices and HUTT-induced asystole, no difference was detected between patients with prolonged asystole and patients with a positive HUTT result and no prolonged asystole. However, while 115 patients had a positive HUTT result in this study, only 6 of them showed prolonged asystole during the test.¹² The most extensive study to date, which enrolled 1155 patients, the dynamics of HRV were able to predict a positive result of HUTT with 95% sensitivity and 93% specificity, irrespective of the type of response.¹³ However, in this study a simultaneous analysis of RR interval and systolic blood pressure trending in early stages of HUTT was used in HUTT positivity prediction.

Baroreflex Sensitivity (BRS) is an important indicator which can noninvasively evaluate autonomic balance of heart similar like HRV parameters. Just as HRV, BRS also changes in several cardiac conditions. In previous studies BRS was shown to have decreased in post-myocardial infarction, hypertension and heart failure.^{14–16} The correlation between VVS and BRS were evaluated in several studies and inconsistent results were obtained. Impact of BRS on controlling heart rate in VVS was not clearly demonstrated in studies^{17–20} while in some of them it was decreased^{21,22} and in several studies it was increased.^{23,24} In a study conducted by Sneddon et al., temporal and spectral analysis of heart rate variability and high pressure baroreceptor testing measurements were performed during tilt test for evaluation of vagal activity in syncope etiology. No significant differences found between the groups in any of the temporal or spectral measures of heart rate

variability and mean high pressure baroreceptor sensitivity.²⁰ Status of BRS in vasovagal syncope should be clearly enlightened with further studies just as status of HRV.

In this study we evaluated time domain HRV parameters using 24-hour Holter ECG monitoring, a simple and widely available method which is used in daily routine practice to exclude arrhythmogenic causes of syncope. To the best of our knowledge, a study predicting prolonged asystole based on assessment of HRV parameters in patients with type 2B VVS is lacking in the literature. We detected higher SDNN, SDANN, SDNN index values in patients with type 2B VVS than patients with other types of VVS, suggesting presence of a higher sensitivity to the effects of autonomic nervous system in these patients compared to patients with other types of VVS. The highest heart rate value recorded during 24-hour Holter ECG monitoring in type 2B VVS was lower than the other group in our study. This might suggest that sinus node parasympathetic dominance prevents achievement of higher heart rate values in patients with type 2B VVS. Park et al. examined time and frequency-based HRV parameters of 637 healthy individuals. They suggested that sympathetic effects are more dominant in the middle-aged men compared to women.²⁵ In our study, the average length of asystole was significantly longer in women compared to men ($P = 0.045$). This could be interpreted as parasympathetic dominance in women is longer than men during occurrence of type 2B VVS.

CONCLUSIONS

Females with type 2B VVS have longer asystole durations than males, indicating higher sensitivity to the effects of parasympathetic nervous system. HRV parameters are helpful in identification of patients with type 2B VVS. Prolonged asystole during HUTT could be predicted with analyses of SDNN, SDANN and SDNN parameters before the test. We considered that higher sensitivity and specificity ratios would appear in prospective studies designed with more patients.

Limitations

Our study has several limitations. We could not explain the reason why significant difference can not be obtained for other parameters (RMSSD,

pNN50). Since Holter results of hospitalized patients are unaffected from daily physical activity they would provide more reliable data. Our results need to be confirmed by extended, prospective studies with hospitalized patients. We investigated only time domain HRV indices of patients with VVS. However, studying the frequency domain HRV parameters would also provide additional valuable data.

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