

Is heart rate recovery index a predictive factor for cardioinhibitory syncope?

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Abstract

Background: Cardioinhibitory syncope is related with excessive bradycardia or asystole due to parasympathetic response.

Aim: We investigated whether patients with cardioinhibitory syncope have higher heart rate recovery index (HRRi) considered as a parasympathetic system activation in exercise stress testing (EST) than in those with other neurogenic syncope forms.

Methods: A total of 262 patients who had neurogenic syncope documented by head-up tilt test (HUTT) and 199 healthy control individuals were examined. A maximal EST was applied to all patients after the HUTT. The HRRi was obtained by subtracting the heart rate that was measured at the first (HRRi-1), second (HRRi-2), and third minute (HRRi-3) of the recovery period from the maximal heart rate that was measured during the test.

Results: Eighty patients had cardioinhibitory syncope, 118 patients had vasodepressor syncope, and 64 patients had mixed-type syncope. The HRRi-1 was higher in patients with syncope (43.3 ± 7.7) compared to the control group (34.5 ± 4.8 ; $p < 0.001$). Post hoc analysis showed that among the syncope groups, there was no difference between patients with vasodepressor syncope (42.2 ± 7.6) and those with mixed type syncope (40.7 ± 4.1) in terms of HRRi-1 ($p = 0.420$). However, patients with cardioinhibitory syncope (47 ± 8.7) had a higher HRRi-1 than vasodepressor and mixed-type syncope groups ($p < 0.05$). The threshold value of the HRRi-1, which can be used for the prediction of cardioinhibitory syncope development, was determined to be 41 with 75% sensitivity and 72% specificity.

Conclusions: The HRRi-1 was higher in patients with cardioinhibitory syncope compared to the controls. The HRRi-1 has the predictive feature of differentiating cardioinhibitory syncope from other syncope types.

Key words: neurogenic syncope, cardioinhibitory syncope, heart rate recovery index, exercise stress test

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INTRODUCTION

Syncope is a very common clinical finding and is observed in 6% of patients who are admitted to hospital and 3% of patients in the emergency unit [1]. Neurogenic syncope is the most common type of syncope [2]. Even though the pathophysiological mechanism of neurogenic syncope has not yet been precisely determined, uncontrolled and excessive response of the autonomic nervous system is the mostly accepted theory. Excessive activation of the parasympathetic system, which occurs depending on the increased activation of the sympathetic nervous system response, leads to bradycardia and hypotension and thus leads to neurogenic syncope [3, 4]. Due to excessive activation of the parasympathetic system, syncope can

develop in some patients because of vasodilatation-induced hypotension, while in other patients, syncope can develop because of excessive bradycardic response. Furthermore, syncope can develop in some patients due to a combination of vasodilatation and bradycardia. The response of the parasympathetic system during syncope is generally determined using the head-up tilt test (HUTT) [5]. The HUTT is the most commonly used test for differentiation of neurogenic syncope forms. However, there is no other simple and practical test that can distinguish the neurogenic syncope types.

The heart rate recovery index (HRRi) is a parameter that is calculated by subtracting the recovery heart rate during the first minute after exercise from the maximal heart rate after

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a maximal or submaximal exercise stress test (EST). The HRRi that is measured at the first minute of the recovery phase shows the degree of parasympathetic system activation [6].

It is shown that the HRRi is higher in patients who have neurogenic syncope compared to the normal population. In addition, it is determined that the HRRi is a predictive factor for neurogenic syncope [7]. However, there is insufficient information whether the HRRi is different between syncope forms, and if so, it is not known whether HRRi can distinguish neurogenic syncope types. Cardioinhibitory syncope is related with excessive bradycardia or asystole due to parasympathetic response. Based on this data we hypothesised that patients with cardioinhibitory syncope should have higher HRRi considered as parasympathetic system activation in EST.

In this study, we examined whether HRRi, which is considered as a marker for parasympathetic nervous system activation in EST, is higher than other in syncope types and in the healthy population.

METHODS

Patients who had syncope two times in the last six months and documented neurogenic syncope by HUTT were included in the study. Before HUTT, the health status of all patients was recorded, and cardiac and neurological physical examination, 12-lead electrocardiogram, transthoracic echocardiography, orthostatic blood pressure, serum glucose, and electrolyte measurements were performed. In this way, patients who had structural and organic disease-mediated syncope were excluded from the study. Moreover, patients who were smoking and who had coronary artery disease, heart failure, atrial fibrillation, cerebrovascular disease, epilepsy, diabetes mellitus, chronic renal failure, rheumatic disease, or permanent pacemaker were excluded from the study. Approval was obtained from the local Ethics Committee for this study. Written, informed consent was also obtained from all patients. The study was conducted in accordance with the Helsinki Declaration.

Head-up tilt test

The diagnosis for neurogenic syncope was confirmed using the HUTT test, which was performed in line with recommendations of the diagnosis and treatment of syncope from the European Society of Cardiology guidelines [8]. Patients were subjected to the test after a 4-h fasting period. Patients were kept in a passive supine position for 20 min after venous cannulation. Afterwards, patients were kept in an active position for 25 min on the test table, which was kept at an angle of 70°. A provocation test was applied to the patient at the active phase using sublingual nitroglycerine. Neurogenic syncope that developed during HUTT was classified according to the VASIS classification [9]. According to this classification, cardioinhibitory syncope develops when the heart rate is lower than 40/min for more than 10 s (type 2A) or when there is an asystole for more than 3 s (type 2B). Vasodepressor syncope

develops when the heart rate does not drop less than 10% during the syncope and when hypotension is observed before the syncope. Mixed-type syncope is observed when the heart rate does not drop to less than 40/min or drop to less than 40/min for less than 10 s with or without an asystole of less than 3 s following the fall in blood pressure during the syncope.

Exercise stress test

All patients were subjected to EST in order to calculate their HRRi. According to the Bruce protocol, it was ensured that all patients had at least 85% of the expected maximal heart rate ($220 - \text{age}$). A cool-down period was not used when calculating the HRRi. The HRRi was calculated by subtracting the heart rate values that were measured at the first (HRRi-1), second (HRRi-2), and third (HRRi-3) minute of the recovery phase of the test from the maximal heart rate value that was measured during the EST.

Statistical analysis

Statistical analyses were performed using SPSS 18 for Windows (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as mean \pm standard deviation (SD) and categorical variables were expressed as percentage (%). Kolmogorov-Smirnov test was used to determine whether or not the data of the study were normally distributed. Chi-square test was used to compare categorical values between groups. One-way ANOVA test was used in order to compare continuous variables. Intra-group differences were evaluated using Tukey post-hoc analysis. Independent Student t test was also used to compare the neurogenic syncope groups with each other. The value of the HRRi for predicting cardioinhibitory syncope was evaluated by using area under curve (AUC) in receiver operating characteristics (ROC) analysis. Statistical significance was accepted when the p value was less than 0.05 ($p < 0.05$).

RESULTS

There were 262 patients with neurogenic syncope and 199 control individuals in this study. Of the patients, 80 had cardioinhibitory syncope, 118 had vasodepressor syncope, and 64 had mixed type syncope. Fifty-six (7%) patients with cardioinhibitory syncope had type 2A and 30% of those had type 2B syncope. There was no difference between the syncope and control groups in terms of age, gender, height, weight, and body mass index (Table 1).

According to the EST that was performed in line with the Bruce protocol, exercise duration, maximal METs, maximal heart rate, and blood pressure values were similar between groups (Table 2).

HRRi values

HRRi-1 values were different between cardioinhibitory (47 ± 8.7), vasodepressor (42.2 ± 7.6), mixed syncope (40.7 ± 4.1), and control (34.4 ± 4.8) groups ($p < 0.001$).

Table 1. Characteristics of patients with syncope and control groups

Parameters	Cardioinhibitory syncope (n = 80)	Vasodepressor syncope (n = 118)	Mixed type syncope (n = 64)	Control group (n = 199)	P
Age [years]	28.2 ± 14.2	28.4 ± 8.5	28.6 ± 8.8	28.6 ± 9.7	0.993
Gender, female	28 (35%)	44 (37%)	22 (34%)	75 (38%)	0.950
Height [cm]	166 ± 9	165 ± 8	168 ± 9.4	165 ± 8.5	0.268
Weight [kg]	74 ± 15	71 ± 14.1	77 ± 17.3	74 ± 15	0.160
BMI [kg/m ²]	26.9 ± 5.3	26.1 ± 5.3	27.1 ± 4.9	26.9 ± 4.7	0.548

Data are presented as mean ± standard deviation or number (percentage); BMI — body mass index; N — number; SD — standard deviation

HRRi-2 values were different between cardioinhibitory (55 ± 8.7), vasodepressor (49 ± 9), mixed syncope (52.8 ± 5.3), and control (50.1 ± 8.2) groups ($p < 0.001$). In addition, HRRi-3 values were different between cardioinhibitory (64 ± 8.7), vasodepressor (58 ± 9), mixed syncope (61.8 ± 5.3), and control (57.7 ± 10.7) groups ($p < 0.001$). When comparing to neurogenic syncope groups between each other, patients with cardioinhibitory syncope had higher HRRi-1 values than other syncope types, while the HRRi-1 values of vasodepressor and mixed-type syncope patients were similar ($p = 0.142$). HRRi-2 and HRRi-3 values of the cardioinhibitory syncope group were similar to those of mixed type syncope groups but higher than those of vasodepressor syncope groups.

Post-hoc analysis shows that HRRi-1 values of patients with each syncope form were higher than the values of the control group ($p < 0.001$). There was no difference between patients who had vasodepressor syncope (42.2 ± 7.6) and patients who had mixed type of syncope (40.7 ± 4.1) in terms of HRRi-1 values ($p = 0.420$). However, HRR values of patients who had cardioinhibitory syncope (47 ± 8.7) were significantly higher than the other syncope groups (vasodepressor and mixed type syncope) ($p < 0.05$). While comparing the groups with each other, patients with cardioinhibitory syncope had higher HRRi-1 values than other syncope forms ($p < 0.001$). However, patients with vasodepressor and mixed-type syncope had similar HRRi-1 ($p = 0.142$).

ROC analysis shows that the threshold value of HRRi-1 for predicting neurogenic syncope development was 36 with 79% sensitivity and 62% specificity (AUC 0.832, 95% confidence interval [CI] 0.795–0.868, $p < 0.001$; Fig. 1). The threshold value of the HRRi-1 for predicting cardioinhibitory syncope development was determined to be 41 with 75% sensitivity and 72% specificity (AUC 0.796, 95% CI 0.746–0.846, $p < 0.001$; Fig. 2).

DISCUSSION

In this study, we determined that HRRi, as an index of parasympathetic tonus in EST, was higher in patients who had cardioinhibitory syncope compared to other patients who

had vasodepressor syncope or mixed-type syncope and the control group. Furthermore, it was also shown in this study that the HRRi can be used as a predictive factor for cardioinhibitory syncope.

Activation of the autonomic nervous system plays an important role in the pathophysiology of neurogenic syncope. However, the exact pathophysiological mechanisms responsible for neurogenic syncope have not been fully elucidated. After the initiating events of neurogenic syncope, complex haemodynamic changes occur, resulting in marked hypotension, bradycardia, and loss of consciousness [10]. Several theories have been presented to account for these haemodynamic changes, including ventricular theory [11], baroreflex dysfunction theory [12, 13], reduced blood volume theory, neurohumoral theories (epinephrine, serotonin, renin, vasopressin, b-endorphin, endothelin, and nitric oxide), and active vasodilation theory, which could not clearly delineate the mechanism for neurogenic syncope [10]. Nevertheless, we can suggest that irrespective of sympathetic system response (increase or decrease), excessive parasympathetic system activation can lead to excessive bradycardia in some syncope forms, although mainly in cardioinhibitory syncope. However, in vasodepressor syncope, excessive parasympathetic system activation mainly affects vascular beds, in contrast to cardioinhibitory syncope. Although bradycardia can be seen in mixed-type syncope, heart rate drop is not evident as seen in cardioinhibitory syncope.

The pathophysiological roles of the autonomic nervous system in syncope and cardiovascular events have always been subjects of curiosity. Recently, EST has been primarily used in the evaluation of normal and pathophysiological modulation of the autonomic nervous system [14]. Sympathetic nervous system activation occurs during exercise and thus there is an increase in cardiac output, heart rate, cardiac contractility, alveolar ventilation, and venous return [15]. Activation of the sympathetic system is lost and parasympathetic system activation occurs during the recovery stage of EST. The heart rate and blood pressure return to normal in a few minutes, depending on the activation of the parasympathetic system. The increase in parasympathetic system activation

Table 2. Exercise test results of patient and control groups

Parameters	Cardioinhibitory type syncope (n = 80)	Vasodepressor type syncope (n = 118)	Mixed type syncope (n = 64)	Control group (n = 199)	P*	P**	P#	P##
Maximum METS	14.4 ± 2.2	14.1 ± 1.8	14.6 ± 1.27	14.4 ± 0.9	0.172	0.295	0.514	0.051
Exercise duration [min]	14.4 ± 1.8	14.9 ± 2.7	14.6 ± 2.5	15.2 ± 2.7	0.092	0.140	0.650	0.399
Maximal heart rate [bpm]	192 ± 14.7	195 ± 9.1	194 ± 8.9	194 ± 9.7	0.157	0.05	0.205	0.630
Maximal systolic BP [mmHg]	170 ± 8	171 ± 8.6	170 ± 8.9	170 ± 8	0.741	0.453	0.784	0.699
HRRI-1	47 ± 8.7	42.2 ± 7.6	40.7 ± 4.1	34.4 ± 4.8	< 0.001	< 0.001	< 0.001	0.142
HRRI-2	55 ± 8.7	49 ± 9	52.8 ± 5.3	50.1 ± 8.2	< 0.001	< 0.001	0.082	0.002
HRRI-3	64 ± 8.7	58 ± 9	61.8 ± 5.3	57.7 ± 10.7	< 0.001	< 0.001	0.082	0.002

Data are presented as mean ± standard deviation. BP — blood pressure; HRRI — heart rate recovery index; HRRI-1 — HRRI in first minute of recovery period; HRRI-2 — HRRI in second minute of recovery period; HRRI-3 — HRRI in third minute of recovery period; *p: one-way ANOVA testing for comparison between whole group; **p: comparison of cardioinhibitory and vasodepressor syncope groups by using student t test; #p: comparison of cardioinhibitory and mixed type syncope groups by using student t test; ##p: comparison of vasodepressor and mixed type syncope groups by using student t test

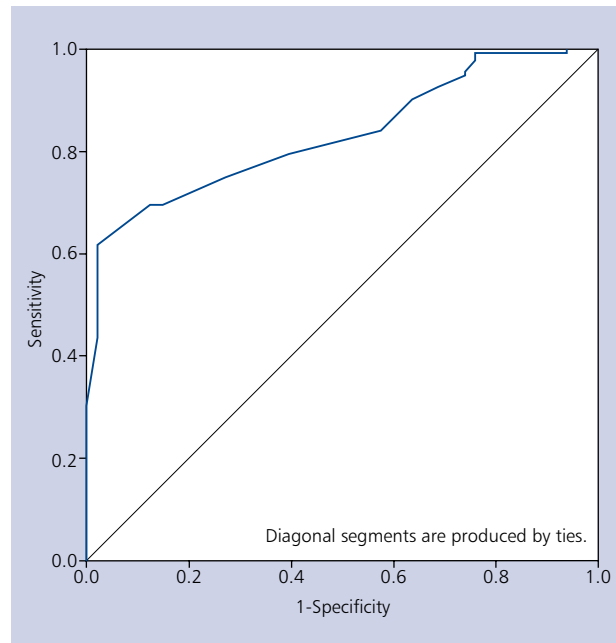


Figure 1. Receiver operating characteristics analysis: the threshold value of heart rate recovery (HRR) for predicting neurogenic syncope development was determined to be 36 with 79% sensitivity and 62% specificity

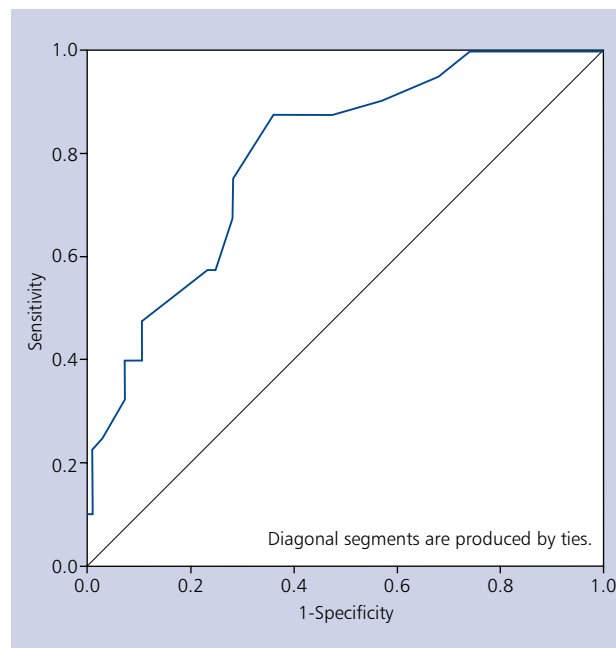


Figure 2. Receiver operating characteristics analysis: the threshold value of the heart rate recovery (HRR) index for predicting the cardioinhibitory syncope development was determined to be 41 with 75% sensitivity and 72% specificity

is very rapid in the first minute after the recovery period of exercise. In this phase there is a rapid decline in heart rate, depending on the strong parasympathetic response,

which is shown quantitatively with HRRi. Decreased HRRi was reported to be a mortality marker [16]. Furthermore, it is also a prognostic marker for various diseases such as coronary artery disease, heart failure, arterial hypertension, metabolic syndrome, and pulmonary hypertension [17–21]. Even though a low HRRi is generally associated with poor prognosis in cardiovascular disease, a high HRRi is firstly defined in patients who have syncope. Kocabas et al. [7] primarily detected that the HRRi value is higher in patients with neurogenic syncope. The HRRi threshold value was determined to be 35 with 81% sensitivity and 78% specificity, and the HRRi can be a predictive factor for neurogenic syncope. However, there are no data showing whether HRRi is different between syncope groups, due to a limited number of patients. In our study, HRRi-1 was higher in patients with cardioinhibitory syncope than the other syncope groups and the healthy population. However, HRRi-1 was not different between patients with vasodepressor and mixed type syncope. The threshold value for neurogenic syncope was determined to be 36 with 79% precision and 62% specificity. Furthermore, the threshold value of the HRRi-1 that can be used for prediction of cardioinhibitory syncope development was determined to be 41 with 75% precision and 72% specificity. If normal values of the HRRi in the normal healthy population are known, exercise test protocols are standardised, and patients are selected carefully, the sensitivity and specificity of the HRRi for differentiation and diagnosis of neurogenic syncope can be increased. The value of HRRi-1 in our control group is consistent with previous studies. Danieli et al. [22] compared the HRRi of athletes with a healthy population, and they found that endurance-trained athletes had higher HRRi than the healthy population (52 ± 11 vs. 33 ± 9 , $p < 0.001$). Both endurance training athletes and cardioinhibitory syncope patients have higher HRRi. However, resting heart rates, myocardial thickness, cardiac volumes, and chamber size are different in training athletes [23]. Therefore, HRR will be valuable for the diagnosis of cardioinhibitory syncope if the patients are selected from those with recurrent unexplained syncope and those without being exercise-trained population.

In line with the information above, both in HUTT and EST, initially sympathetic activity increases and parasympathetic activity decreases, and then parasympathetic activity predominates, especially in the first minute of the recovery period, and determines the heart rate recovery index. The parasympathetic system is quantitatively evaluated in the EST with the HRRi, while it can be evaluated quantitatively in HUTT with the decrease in blood pressure and heart rate. Based on the current study, it is thought that those patients who had rapid and extreme bradycardia during the EST might also be vulnerable to extreme bradycardia and pauses rather than hypotension in HUTT.

Limitations of the study

In this study, the reproducibility of the threshold value of the HRRi for cardioinhibitory syncope should be tested by further studies. Because of the lack of a gold-standard test in the diagnosis of neurogenic syncope, the only test to compare the sensitivity and specificity of the HRRi is HUTT, which has different sensitivity and specificity. Therefore, it is possible that false positive or false negative results were obtained in the case of differentiation of the syncope types. Even though the control group was selected from among healthy individuals who did not have syncope, it is possible that potential syncope candidates could be mistakenly included in the control group because HUTT was not performed. Furthermore, prospective studies with larger numbers of patients are needed to test the reproducibility, the sensitivity, and the specificity of our findings in order to improve diagnostic evaluation.

Although HUTT and EST are characterised by the same head-up position of the patient, they are not the same because of different muscle involvement. The HRRi is computed after combined physical and gravitational stresses in EST, whereas HUTT deals only with the influence of gravity.

CONCLUSIONS

Patients with cardioinhibitory syncope have a deep and rapid decline in heart rate both in the recovery period of EST and during HUTT. The HRRi that is obtained after the EST has a predictive feature for the distinction of cardioinhibitory syncope.

Conflict of interest: none declared

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