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EVALUATION OF HEART RATE VARIABILITY IN CHILDREN PRESENTING WITH SYNCOPE

SENKOP İLE BAŞVURAN ÇOCUKLARDA KALP HIZI DEĞİŞKENLİĞİNİN DEĞERLENDİRİLMESİ

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ABSTRACT

Objective: This study evaluated the diagnostic value of heart rate variability (HRV) parameters obtained from 24-hour Holter monitoring in pediatric patients with vasovagal syncope (VVS) and compared them to a control group. The study also analyzed time-domain and frequency-domain HRV parameters to explore the autonomic mechanisms underlying VVS and the diagnostic potential of HRV.

Methods: This retrospective study was conducted at Giresun Women's and Children's Health Training and Research Hospital. The study included 41 pediatric patients with syncope and 36 healthy controls who underwent 24-hour Holter electrocardiography (ECG) monitoring for suspected arrhythmia; however, no arrhythmia was found. Comprehensive cardiac, neurological, and demographic evaluations were performed for all participants. HRV parameters were analyzed from 24-hour Holter recordings, and group comparisons were performed using the Mann–Whitney U test. Spearman correlation and Receiver Operating Characteristic analyses were also conducted.

Results: Time-domain HRV parameters were significantly lower in the syncope group compared to those in the control group ($p < 0.05$). No significant differences were observed in frequency-domain parameters. The standard deviation of normal-to-normal RR intervals (SDNN) demonstrated the highest diagnostic accuracy, with a cut-off value of <163 ms (Area Under the Curve: 0.753, sensitivity: 72.2%, specificity: 75.6%).

Conclusion: HRV parameters obtained from 24-hour Holter monitoring provide valuable insights into autonomic imbalance in pediatric VVS. SDNN emerged as a strong diagnostic marker in this regard. Further studies with larger, more homogeneous populations are needed to establish normative HRV values and refine diagnostic criteria in pediatric populations.

Keywords: 24-hour Holter monitoring, autonomic imbalance, heart rate variability, vasovagal syncope

ÖZ

Amaç: Bu çalışmada, pediatrik vazovagal senkop (VVS) hastalarında 24 saatlik Holter monitörizasyonu ile elde edilen kalp hızı değişkenliği (HRV) parametrelerinin tanısal değerinin değerlendirilmesi ve kontrol grubu ile karşılaştırılması amaçlanmıştır. Zaman alanı ve frekans alanı HRV parametreleri incelenerek VVS'nin altta yatan otonom mekanizmaları ve HRV'nin tanısal potansiyeli araştırılmıştır.

Yöntem: Retrospektif tasarlanan bu çalışma, Giresun Kadın Doğum ve Çocuk Hastalıkları Eğitim ve Araştırma Hastanesi'nde gerçekleştirildi. Çalışmaya, senkop şikayeti ile başvuran 41 çocuk hasta ve aritmi şüphesi nedeniyle 24 saatlik Holter elektrokardiyografi (EKG) monitorizasyonu yapılan ancak herhangi bir aritmiye rastlanmayan 36 sağlıklı kontrol dahil edildi. Tüm hastalar kapsamlı kardiyak, nörolojik ve demografik değerlendirmelere tabi tutuldu. HRV parametreleri 24 saatlik Holter EKG kayıtlarından analiz edildi ve gruplar arası farklar Mann-Whitney U testi ile değerlendirildi. Ayrıca, Spearman korelasyon ve Alıcı Çalışma Karakteristiği (ROC) analizi yapıldı.

Bulgular: Zaman alanı HRV parametreleri, senkop grubunda kontrol grubuna göre anlamlı olarak düşük bulundu ($p<0,05$). Frekans alanı parametreleri açısından gruplar arasında anlamlı fark tespit edilmedi. Ardışık normal sinüs kalp atımları arasındaki sürenin standart sapmasının (SDNN) 163 ms altındaki değerler, vasovagal senkopu öngörmede en yüksek tanısal doğruluğu gösterdi (Eğrinin Altındaki Alan (AUC): 0,753, duyarlılık: %72,2, özgüllük: %75,6).

Sonuç: Yirmidört saatlik Holter monitörizasyonu ile elde edilen HRV parametreleri, pediatrik VVS hastalarında otonom disfonksiyonu değerlendirmede etkili bilgiler sağlayabilir. SDNN, güçlü bir tanısal belirteç olarak öne çıkmaktadır. Normatif HRV değerlerinin oluşturulması için daha geniş ve homojen popülasyonlarla yapılacak çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: 24 saat Holter monitörizasyonu, kalp hızı değişkenliği, otonomik dengesizlik, vazovagal senkop.

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Introduction

Syncope is a temporary and self-limiting loss of consciousness caused by decreased cerebral blood flow and marked by rapid onset, brief duration, and spontaneous recovery.[1,2] Syncope is a frequent clinical concern in children and adolescents, with approximately 15% having at least one episode by the end of childhood adolescence.[3,4] Vasovagal syncope (VVS) is the most common cause, typically triggered by long periods of standing, emotional stress, or environmental factors.[1] VVS is linked to autonomic imbalance, which may involve parasympathetic overactivity, sympathetic inhibition, or a combination of both, thereby resulting in hypotension and bradycardia.[1,5] While typically harmless, recurrent VVS considerably influences quality of life and impacts physical, psychological, and psychosocial activities.[6,7]

Heart rate variability (HRV) is defined as the variation in time between successive heartbeats.[8] Measuring this variability provides a non-invasive assessment of autonomic nervous system (ANS) activity. It indicates the balance between sympathetic and parasympathetic heart rate regulation and assesses autonomic balance, blood pressure, gas exchange, vascular tone, and functions such as gut activity and facial muscle movement regulation.[9,10] ANS activity enables us to better adjust to difficult environmental and psychological factors. Conversely, disruption of this system and the resulting decrease in HRV, a marker of autonomic imbalance, have been associated with negative effects on a range of cardiovascular and non-cardiovascular conditions in both adults and children.[9,11,12] Moreover, HRV has been used for various clinical conditions, including respiratory distress syndrome, significant patent ductus arteriosus, congenital heart defects, neonatal sepsis, necrotizing enterocolitis, anxiety disorders, obstructive sleep apnea, depression and neurological issues injuries.[13-21] But a higher HRV is not always positive; it can indicate a higher mortality risk, particularly in older adults, likely due to conduction issues and abnormalities.[22] Therefore, many studies have been conducted to establish optimal HRV norm values; however, studies on children in this field remain limited.[9,23,24] An ideal HRV is a sign of a robust, adaptable ANS capable of effective self-regulation.

In cases of syncope, lower HRV frequently indicates an autonomic imbalance, particularly in VVS, where there is excessive parasympathetic activity or diminished sympathetic response is predominant.[11,25] By analyzing time-domain and frequency-domain parameters, HRV provides valuable insights into the pathophysiological mechanisms underlying syncopal episodes, thereby making it an essential non-invasive tool in clinical investigations.[9,23] Despite its potential, only a limited number of pediatric studies have investigated HRV in VVS, thus leaving a gap in understanding baseline HRV values and their diagnostic utility in this population.[26]

This study aims to evaluate the predictive value of HRV parameters obtained from 24-hour Holter monitoring, which is regarded as more reliable and comprehensive than short-term HRV measurements, in distinguishing pediatric patients with VVS from healthy controls. By investigating both time-domain and frequency-domain HRV metrics, the study seeks to clarify the autonomic mechanisms underlying VVS and explore the potential of HRV as a diagnostic tool. These findings could help refine diagnostic criteria and enhance clinical management strategies for pediatric syncope.

Methods

The study was approved by the ethics committee of Giresun University (April 2023 / Decision No: 2) and were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments.

Study Population

This retrospective cross-sectional study was conducted between June 2022 and December 2024, with 92 patients aged 6–12 years who presented with acute loss of consciousness at the Pediatric Neurology and Pediatric Cardiology outpatient clinics of Giresun Women's and Children's Health Training and Research Hospital. The study focused exclusively on pediatric patients diagnosed with VVS. It was conducted according to the principles outlined in the Canadian Cardiovascular Society and Canadian Pediatric Cardiology Association Position Statement on the Approach to Syncope in the Pediatric Patient.[27] VVS is a syncopal syndrome usually triggered by standing for over 30 seconds or encountering pain, emotional stress. It presents symptoms such as warmth, sweating, pallor, and nausea; is linked to hypotension and relative bradycardia when present; and is characterized by post-event fatigue.

The control group consisted of patients who underwent 24-hour Holter monitoring for ventricular extrasystoles rather than palpitations, thus ensuring a more appropriate comparison with the patient group. Additionally, the patients were divided into two age groups: those aged 6–12 years were classified as the preadolescent group, and those aged 12–18 years were classified as the adolescent group.

Syncope Group Inclusion Criteria

- At least three syncopal episodes within the last year
- No serious cardiac finding (including ECG, 24-hour Holter monitoring, and echocardiography (may be accompanied by mild symptoms that do not require treatment or follow-up)
- Normal neurological evaluations (including EEG)
- No other identifiable etiology for syncope (anemia, psychological disease)
- No medication used for acute and chronic diseases

Control Group Inclusion Criteria

- No syncope history within the last year

- No cardiac, neurological, or psychological symptoms (may be accompanied by mild symptoms that do not require treatment or follow-up)
- No medication used for acute and chronic diseases
- No arrhythmia on Holter monitoring.

Patient Selection

Patients presenting to the pediatric cardiology clinic with acute loss of consciousness and a preliminary diagnosis of cardiac syncope were initially evaluated with a detailed medical history and physical examination. Patients diagnosed with typical VVS during this evaluation were discharged with recommendations for lifestyle modifications and follow-up. Patients referred with murmurs, palpitations, chest pain, family history of cardiac disease, history of sudden death, prolonged loss of consciousness (>5 minutes), or recurrent syncope underwent further investigations, including electrocardiography (ECG), echocardiography, and 24-hour Holter monitoring.

Among these patients, those diagnosed with VVS formed the study group. Following exclusions for epileptic seizures (n = 6, generalized tonic-clonic), cardiac syncope (n = 2, pulmonary embolism, supraventricular tachycardia), and incomplete Holter data (n = 43), 41 patients diagnosed with VVS were included in the study. The control group included patients referred to the pediatric cardiology clinic due to a murmur but without complaints. Among these patients, those who underwent Holter monitoring because ventricular extrasystoles were detected on their ECG and had no ventricular extrasystoles or any other arrhythmias on Holter recordings were included.

Data Collection

A retrospective review was conducted on the medical records of patients diagnosed with VVS. Demographic data—including gender, age, weight, height, body mass index, socioeconomic status, and educational background—were obtained. Information regarding the pattern, timing, frequency, and duration of syncope, triggering factors, and history of cardiac or neurological diseases was recorded. Clinical findings from physical examinations, blood pressure measurements, ECGs, echocardiograms, and 24-hour Holter monitoring parameters were analyzed. Laboratory results were also collected, including hemoglobin, glucose, sodium, calcium, potassium, thyroid-stimulating hormone, vitamin B12, and vitamin D levels. Moreover, the Modified Calgary score of all patients included in the study was calculated and recorded.[28]

24-Hour ECG Monitoring

All participants underwent 24-hour ECG recordings using a GE Healthcare SEER 1000 Holter monitor (seven channels, California, USA). The Holter device was attached during daily activities, and the recorded data were analyzed using the device's proprietary software and with artifact corrections applied. The HRV parameters analyzed in this study included both time-domain and frequency-domain measures, described below.[11,25,29]

All time-domain parameters were calculated using the complete 24-hour Holter recordings. Minimum, maximum, and mean heart rates were analyzed to assess HRV over the recording period. The total number of QRS complexes and the total duration of Holter recordings were quantified. Mean and median RR intervals—representing the average and median times between successive R waves, respectively—were measured in milliseconds. The standard deviation of normal-to-normal (SDNN) RR intervals, served as a global marker of HRV. At the same time, the standard deviation of the averages of normal-to-normal (SDANN) RR intervals across all five-minute segments, thereby reflecting longer-term variability. The overall variability of RR intervals was further assessed using the standard deviation of RR (SDRR) intervals. Further, the HRV triangular index (HRV TI) quantified overall variability by dividing the total number of all NN intervals by the peak height of their histogram. Additionally, NN50, representing the count of interval differences greater than 50 milliseconds between successive NN intervals, and pNN50%, the percentage of such intervals, was calculated to assess short-term variability. The root mean square of successive RR interval differences (RMSSD) provided insight into parasympathetic activity. Lastly, the SDNN Index, derived as the mean of the five-minute standard deviations of NN intervals over 24 hours, provided a measure of variability attributed to cycles shorter than five minutes.[9]

Frequency-domain parameters were also analyzed to evaluate the power distribution across different frequency bands[9]:

- High-frequency (HF) power in normalized units: The relative power of the high-frequency band (0.15 Hz–0.4 Hz) in normal units.
- Low-frequency (LF) power in normalized units: The relative power of the low-frequency band (0.04 Hz–0.15 Hz) in normal units.
- The LF/HF ratio, calculated as the ratio of LF power to HF power, is a marker of autonomic balance.
- The Symindex, derived from logarithmic transformation, assesses the ratio of LF power to HF power in normalized units, thus offering another perspective on the balance between sympathetic and parasympathetic contributions to HRV.

Statistical Analysis

This study conducted all statistical analyses using SPSS version 25 (IBM Corp., Armonk, NY, USA). The Shapiro–Wilk test was used to assess the normality of continuous variables. Since the data did not follow a normal distribution, continuous variables were presented as median (minimum–maximum) values, while categorical variables were summarized as numbers and percentages

(n, %). Patients were categorized into two groups: the patient group (individuals experiencing syncope) and the control group (individuals not experiencing syncope). The Mann–Whitney U test was used to compare continuous variables across groups, and categorical variables were assessed using the chi-square test. For variables identified as statistically significant in the Mann–Whitney U test, receiver operating characteristic (ROC) analysis was conducted to determine threshold values for predicting syncope. Further, corresponding ROC curves were generated to visualize the discriminatory ability of these variables. The correlation matrix heatmap was generated to analyze the relationships between statistically significant HRV parameters. The heatmap was created with the assistance of the ChatGPT-4.0 model (OpenAI, San Francisco, USA), which facilitated the visualization of these relationships. The research utilized a 95% confidence interval, thereby guaranteeing strong and dependable statistical results. A significance level of $p < 0.05$ was deemed statistically significant for all tests.

Results

The median age of the study population was 13 years (25th–75th percentile: 11–15 years), and 55.8% of the participants were female. Normal sinus rhythm was observed in 80.5% of patients, while normal echocardiographic findings were noted in 64.9% of them. The median systolic and diastolic blood pressures were 110 mmHg (97.5–116.5) and 61 mmHg (56–68.5) (Table 1).

Table 1. Characteristics of Clinical and Demographic Data in Syncope and Control Groups

Parameters		n (%) Median (25^{th}–75^{th} Percentiles)
Gender	Male	34 (44.2%)
	Female	43 (55.8%)
Age (years)		13 (11–15)
Family History of Cardiac Disease	Yes	14 (18.2%)
	No	63 (81.8%)
Family History of Epilepsy	Yes	12 (15.6%)
	No	65 (84.4%)
Family History of Syncope	Yes	3 (3.9%)
	No	74 (96.1%)
Rhythm	Normal Sinus Rhythm	62 (80.5%)
	Sinus Arrhythmia	9 (11.7%)
	Sinus Bradycardia	4 (5.2%)
	Sinus Tachycardia	2 (2.6%)
Echocardiographic Findings	Normal	50 (64.9%)
	Mitral Insufficiency	18 (23.4%)
	PFO	4 (5.2%)
	Aortic Pathologies	1 (1.3%)
	MVP-MI	1 (1.3%)
	PDA	1 (1.3%)
	Coronary Chamber Fistula	2 (2.6%)
Number of Syncope (episodes)		2 (1–3)
RDW_SD (%)		37 (34.2–39.0)
RDW_CV (%)		13 (12.45–13.60)
Glucose (mg/dL)		78 (70–87)
TSH (µIU/ml)		2.06 (1.6–2.8)
Hemoglobin (g/dL)		13.2 (12.4–13.9)
Vitamin B12 (pg/ml)		345 (262–473)
Vitamin D (nmol/l)		18 (12.3–23.5)
Systolic Blood Pressure (mmHg)		110 (97.5–116.5)
Diastolic Blood Pressure (mmHg)		61 (56–68.5)
Mean Blood Pressure (mmHg)		75.3 (69.8–83.7)
QTc Interval (ms)		405 (391–419)
SF (%)		38 (36–42)
Holter HRV Minimum (ms)		55 (49–59)
Holter HRV Average (ms)		85 (77–89)
Holter HRV Maximum (ms)		143 (133–152)
Holter Duration (hours)		19.7 (18.6–21.1)

Abbreviations: B12: Vitamin B12, BP: Blood Pressure, CV: Coefficient of Variation, HRV: Heart Rate Variability, MI: Mitral Insufficiency, MVP: Mitral Valve Prolapse, PDA: Patent Ductus Arteriosus, PFO: Patent Foramen Ovale, QTc: Corrected QT Interval, RDW: Red Cell Distribution Width, SD: Standard Deviation, SF: Shortening Fraction, TSH: Thyroid-Stimulating Hormone

The median age of participants was 13 years (6–17) in the syncope group and 14 years (9–17) in the control group ($p = 0.095$). The Holter minimum heart rate was 57 bpm (43 bpm–76 bpm) in the syncope group and 51.5 bpm (40 bpm–81 bpm) in the control group ($p = 0.015$). The SDNN and SDANN values were significantly lower in the syncope group, with medians of 139 ms (97 ms–264 ms) and 113 ms (71 ms–237 ms) ($p < 0.001$ for both) (Table 2).

Table 2. Comparative Analysis of Clinical, Hemodynamic, and Heart Rate Variability Parameters Between the Pediatric Syncope and Control Groups

Parameters (Unit)		Syncope Group (N = 41) Median (Min–Max), n (%)	Control Group (N = 36) Median (Min–Max), n (%)	p
Age (years)		13 (6–17)	14 (9–17)	0.095[a]
Number of Syncope (episodes)		2 (1–6)	0 (0)	<0.001[a]
RDW SD (%)		35.6 (31.6–45.3)	38.5 (29–47.9)	0.001[a]
RDW CV (%)		12.6 (10.6–15.6)	13.4 (12.4–15.6)	<0.001[a]
Glucose (mg/dL)		76 (68–95)	75 (69–99)	0.234
Hemoglobin (g/dL)		13.2 (10–16.6)	13.1 (11.2–16.9)	0.890[a]
TSH (µIU/mL)		1.9 (0.6–4.8)	2.12 (0.64–6.1)	0.253[a]
Vitamin B12 (pg/ml)		342 (158–828)	370 (136–2630)	0.862[a]
Vitamin D (nmol/l)		16 (3.8–42)	19 (7.4–47.2)	0.279[a]
Systolic Blood Pressure (mmHg)		109 (80–134)	110 (85–138)	0.845[a]
Diastolic Blood Pressure (mmHg)		61 (54–82)	64 (57–86)	0.552[a]
Mean Blood Pressure (mmHg)		78 (72–91)	80 (70–94)	0.564[a]
Baseline Heart Rate (bpm)		80 (53–114)	80 (56–121)	0.732[a]
QTc Interval (ms)		410 (379–465)	396 (383–426)	0.038[a]
Shortening Fraction (SF) (%)		38 (31–49)	37 (32–48)	0.849[a]
Time Domain Parameters				
Holter Minimum Heart Rate (bpm)		57 (43–76)	51.5 (40–81)	0.015[a]
Holter Mean Heart Rate (bpm)		86 (73–107)	82.5 (60–105)	0.179[a]
Holter Maximum Heart Rate (bpm)		143 (122–168)	147 (101–178)	0.588[a]
Mean RR Interval (ms)		730 (575–998)	760 (588–1034)	0.147[a]
SDNN (ms)		139 (97–264)	182 (65–289)	<0.001[a]
SDANN (ms)		113 (71–237)	148.5 (43–265)	<0.001[a]
Median RR Interval (ms)		716 (556–996)	740 (556–1004)	0.526[a]
HRV TI		30 (18–50)	39 (18–52)	0.001[a]
SDRR (ms)		34 (20–139)	42.5 (20–73)	0.028[a]
PNN50 (%)		22 (1–54)	31 (6–69)	0.008[a]
RMSSD (ms)		57 (28–272)	67 (32–327)	0.038[a]
SDNNI (ms)		54 (28–149)	67 (30–198)	0.009[a]
NN50		22.119 (6.022–65.361)	29.565 (4.116–73.469)	0.011[a]
Frequency Domain Parameters				
LF (nu)		69.9 (27.9–89.4)	69.8 (14.8–91.8)	0.475[a]
HF (nu)		23.1 (7.5–68.3)	22 (7.7–65.6)	0.806[a]
LF/HF Ratio		2.8 (0.4–12.0)	3.42 (0.27–11.83)	0.775[a]
Symindex		0.99 (–0.9–2.48)	1.23 (–1.27–2.47)	0.581[a]
Gender	**Female**	23 (56.1%)	20 (55.6%)	1.000[b]
	Male	18 (43.9%)	16 (44.4%)	
Modified Calgary Score		3.5 (–1–6)	Not applicable	-

Table 2 notes: [a] Mann–Whitney U test, [b] Pearson Chi-square test

Abbreviations: bpm: Beats Per Minute, CV: Coefficient of Variation, HF: High Frequency, HRV: Heart Rate Variability, LF: Low Frequency, NN50: Number of Normal-to-Normal Intervals >50 ms, nu: Normalized Units, PNN50: Percentage of NN50, QTc: Corrected QT Interval, RDW: Red Cell Distribution Width, RMSSD: Root Mean Square of Successive Differences, SDANN: Standard Deviation of the Average of NN Intervals, SDNN: Standard Deviation of NN Intervals, SDNNI: Standard Deviation of Successive Differences of NN Intervals, SDRR: Standard Deviation of R-R Intervals, SF: Shortening Fraction, TSH: Thyroid-Stimulating Hormone.

Significant differences were observed in HRV parameters between preadolescent and adolescent patients in the syncope group. Adolescents had higher SDNN (p = 0.001), SDANN (p = 0.007), and HRV triangular index (p = 0.038) values. The mean RR interval (p = 0.009) and median RR interval (p = 0.012) were also higher in the adolescent group. In the frequency domain, the LF component was higher in adolescents (p = 0.039). The mean heart rate in the 24-hour Holter ambulatory was lower in adolescents than preadolescents, but this difference was not statistically significant (p = 0.064). (Table 3)

Adolescents had significantly higher SDNN and SDANN values than preadolescents in the control group (p < 0.05). The mean RR interval was significantly longer in the adolescent group, while the mean heart rate in the 24-hour Holter ambulatory was significantly lower (p < 0.05). In the frequency domain, the LF component, LF/HF ratio, and Symindex were significantly higher in adolescents, while the HF component was lower (p < 0.05). (Table 4)

The diagnostic performance of parameters was evaluated using ROC analysis. Among the parameters, SDNN demonstrated the highest diagnostic accuracy, with an area under the curve (AUC) of 0.753 (95% CI: 0.642–0.864), a cut-off value of <163 ms, sensitivity of 72.2%, and specificity of 75.6% (p < 0.001). (Table 5 and Figure 1)

The Spearman correlation coefficients revealed a significant positive correlation between SDNN Index (ms) and RMSSD (ms) (r = 0.92, p < 0.001). Additionally, the SDNN Index (ms) correlated strongly with PNN50 (%) (r = 0.90, p < 0.001) (Figure 2).

Table 3. Comparison of HRV Parameters Between Preadolescents and Adolescents in the Syncope Group.

Parameters (Unit)		Preadolescent Group (N = 20) Median (25th–75th Percentiles) or n (%)	Adolescent Group (N = 21) Median (25th–75th Percentiles) or n (%)	p
Gender	Female	10 (50%)	13 (61.9%)	0.536[b]
	Male	10 (50%)	8 (38.1%)	
Age (years)		10 (7.25–11)	15 (14–16)	<0.001[a]
Time Domain Parameters				
Holter Mean Heart Rate (bpm)		88 (79–96)	85 (79–87)	0.064[a]
Mean RR Interval (ms)		704 (640–765)	766 (724–811)	0.009[a]
SDNN (ms)		123.5 (110.0–136.5)	157 (141–191)	0.001[a]
SDANN (ms)		99 (86.3–117.5)	133 (103.5–155.5)	0.007[a]
Median RR Interval (ms)		688 (620–768)	756 (712–804)	0.012[a]
HRV TI		27 (23–33)	32 (27–37)	0.038[a]
SDRR (ms)		43 (32.5–58.3)	46 (36.5–64.5)	0.523[a]
PNN50 (%)		16 (10.5–27.8)	25 (16.5–32)	0.215[a]
RMSSD (ms)		54,5 (40–74.3)	60 (48–78.5)	0.489[a]
SDNNI (ms)		50.5 (40.3–68)	64 (45–86.5)	0.106[a]
NN50		19730 (11573–28597)	22975 (15779–31340)	0.335[a]
Frequency Domain Parameters				
LF (nu)		61.54 (44.93– 72.30)	72.15 (57.95–79.50)	0.039[a]
HF (nu)		25.52 (18.84–45.58)	20.41 (14.63–29.33)	0.137[a]
LF/HF Ratio		2.50 (1.03–3.83)	3.38 (2.06–5.57)	0.130[a]
Symindex		0.91 (0.03–1.34)	1.19 (0.65–1.57)	0.241[a]

Table 3 notes: [a] Mann–Whitney U test, [b] Pearson Chi-square test

Abbreviations: bpm: Beats Per Minute, HF: High Frequency, HRV: Heart Rate Variability, LF: Low Frequency, LF/HF Ratio: Ratio of Low Frequency to High Frequency, NN50: Number of Normal-to-Normal Intervals >50 ms, nu: Normalized Units, PNN50: Percentage of NN50, RMSSD: Root Mean Square of Successive Differences, SDANN: Standard Deviation of the Average of NN Intervals, SDNN: Standard Deviation of NN Intervals, SDNNI: Standard Deviation of Successive Differences of NN Intervals, SDRR: Standard Deviation of R-R Intervals.

Table 4. Comparison of HRV Parameters Between Preadolescents and Adolescents in the Control Group.

Parameters (Unit)		Preadolescent Group (N = 14) Median (25th–75th Percentiles) or n (%)	Adolescent Group (N=22) Median (25th–75th Percentiles) or n (%)	p
Gender	Female	7 (50%)	13 (59.1%)	0.734[b]
	Male	7 (50%)	9 (40.9%)	
Age (years)		12 (10.8–12)	15 (14–16.3)	<0.001[a]
Time Domain Parameters				
Holter Mean Heart Rate (bpm)		90 (74–98.3)	82 (72–86)	0.041[a]
Mean RR Interval (ms)		697.5 (632–833)	772 (716–856)	0.038[a]
SDNN (ms)		157 (123-190)	197 (167.5–227.3)	0.025[a]
SDANN (ms)		131 (104.8–148.3)	166 (141.3–207.3)	0.011[a]
Median RR Interval (ms)		676 (636–836)	752 (690–838)	0.061[a]
HRV TI		32.5 (28–41.8)	40 (33.8–47)	0.071[a]
SDRR (ms)		62 (40.3–91.3)	47.5 (38.5–72.8)	0.160[a]
PNN50 (%)		31.5 (12.5–43.3)	31 (20.5–32.3)	0.962[a]
RMSSD (ms)		79.5 (49–109.5)	64 (51.5–91.3)	0.689[a]
SDNNI (ms)		75.5 (51–103.8)	67 (55.8–98.5)	0.885[a]
NN50		30897 (17538–40830)	27711 (20854–34718)	0.450[a]
Frequency Domain Parameters				
LF (nu)		51.88 (47.58–71.79)	78.40 (61.45–81.63)	0.012[a]
HF (nu)		35.9 (22.47–43.74)	17.59 (14.16–29.40)	0.017[a]
LF/HF Ratio		1.40 (1.10–3.58)	4.39 (2.08–5.73)	0.021[a]
Symindex		0.33 (0.10–1.22)	1.48 (0.73–1.75)	0.021[a]

Table 4 notes: [a] Mann–Whitney U test, [b] Pearson Chi-square test

Abbreviations: bpm: Beats Per Minute, HF: High Frequency, HRV: Heart Rate Variability, LF: Low Frequency, LF/HF Ratio: Ratio of Low Frequency to High Frequency, NN50: Number of Normal-to-Normal Intervals >50 ms, nu: Normalized Units, PNN50: Percentage of NN50, RMSSD: Root Mean Square of Successive Differences, SDANN: Standard Deviation of the Average of NN Intervals, SDNN: Standard Deviation of NN Intervals, SDNNI: Standard Deviation of Successive Differences of NN Intervals, SDRR: Standard Deviation of R-R Intervals.

Table 5. Diagnostic Performance of Heart Rate Variability Parameters in Identifying Pediatric Syncope

Test Result Variable (Unit)	Area	Cut-Off	95% CI	Sensitivity (%)	Specificity (%)	p-value
SDNN (ms)	0.753	<163	0.642–0.864	72.2	75.6	<0.001
SDANN (ms)	0.752	<133.5	0.643–0.862	69.4	70.7	<0.001
HRV TI	0.719	<33.5	0.603–0.834	66.7	68.3	0.001
SDRR (ms)	0.645	<38.5	0.519–0.772	66.7	63.4	0.029
PNN50 (%)	0.675	<27.5	0.554–0.796	66.7	68.3	0.008
SDDNI (ms)	0.672	<64.5	0.550–0.794	61.1	63.4	0.01
RMSSD (ms)	0.638	<61	0.514–0.762	61.1	58.5	0.038
NN50	0.668	<26005	0.545–0.791	63.9	63.4	0.011

Abbreviations: CI: Confidence Interval, HRV TI: Heart Rate Variability Triangular Index, NN50: Number of Normal-to-Normal Intervals >50 ms, PNN50: Percentage of NN50, RMSSD: Root Mean Square of Successive Differences, SDANN: Standard Deviation of the Average of NN Intervals, SDDN: Standard Deviation of NN Intervals, SDRR: Standard Deviation of R-R Intervals, SDNNI: Standard Deviation of Successive Differences of NN Intervals.

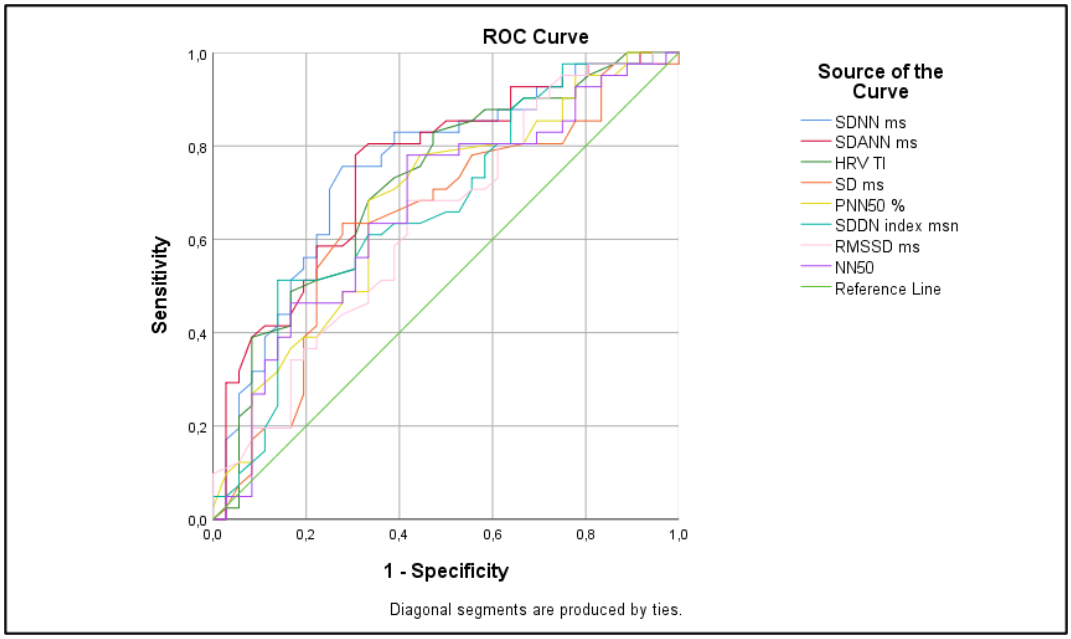

Figure 1. The ROC curve of heart rate variability parameters for predicting vasovagal syncope. (See Table 3). ROC: Receiver operating characteristic.

Discussion

Our study compared pediatric patients with syncope to an asymptomatic control group with ventricular extrasystoles, and we observed that only time-domain HRV parameters—including SDNN, SDANN, pNN50%, RMSSD, SDNN Index, and NN50—were significantly reduced in the syncope group during 24-hour Holter monitoring. These findings are consistent with previous studies that demonstrated decreased HRV in children with syncope. A unique aspect of our study is that it is the first to include HRV-TI and Symindex as HRV parameters in pediatric patients with syncope. While a significant difference was identified in HRV-TI values between the syncope and control groups, no significant difference was observed in Symindex.

Syncope constitutes a significant proportion of hospital admissions in the pediatric population and is a source of considerable anxiety for both children and their families. Thus, it is crucial to eliminate the most concerning etiologies, such as neurological and cardiac causes. The high prevalence of syncope in the community has led to the development of cost-effective approaches, with guidelines published for adult and pediatric populations. According to the guideline, obtaining a detailed medical history and performing a thorough physical examination are essential initial steps, followed by using the Modified Calgary Syncope Score when appropriate.[27,28] Routine investigations—such as ECG, echocardiography, exercise testing, and 24-hour Holter monitoring—are not universally recommended.[27] However, additional cardiological evaluations are advised in cases in which specific red flags are present, including the detection of murmurs suggestive of structural heart disease, syncope triggered by exercise or sound, the absence of prodromal symptoms before the event, a family history of sudden cardiac death or heart disease, or a prolonged recovery period following syncope.[27] The tilt test, commonly used

in adults to differentiate syncope etiologies, has limited utility in children due to challenges in interpretation and its inability to reliably exclude other causes. Consequently, this test is not routinely recommended for pediatric populations.[27,30,31] In our hospital, the absence of tilt testing capabilities prevented its use in our patient cohort. Instead, the diagnosis of VVS was established using the Modified Calgary Syncope Score.[27] This was supplemented by comprehensive cardiological and neurological evaluations and appropriate diagnostic testing to exclude any underlying organic pathology that could explain the syncope episodes.

The primary pathology of VVS is believed to result from excessive parasympathetic activity, inhibition of the sympathetic system, or a complex interplay between these two systems.[5] The responses of these systems can be triggered and exacerbated by factors such as pain, periods of illness, fasting, prolonged standing, crowded or poorly ventilated environments, and sleep deprivation, ultimately leading to syncope.[5,32] HRV is considered a valuable diagnostic tool for predicting this autonomic imbalance and, due to its non-invasive nature, is easy to implement in clinical practice. Reduced HRV, which reflects autonomic imbalance, has been associated with poor prognosis in various conditions, particularly in adults.[33] Notably, reduced HRV has been correlated with increased mortality rates.[34] Studies in pediatric populations have also demonstrated that decreased HRV is linked to various cardiac and non-cardiac events.[35,36] HRV can be assessed using both time-domain and frequency-domain parameters. Among the time-domain metrics, the most used ones are mean heart rate, RMSSD, and SDNN; in the frequency domain, LF, HF, and the LF/HF ratio are frequently analyzed. Increased SDNN and LF indicate heightened sympathetic activity, whereas elevated RMSSD and HF are more closely associated with enhanced parasympathetic activity. In our study, we also utilized normalized values of LF and HF, which are considered more meaningful than their raw values for assessing autonomic regulation.[1,37] The LF/HF ratio is particularly valuable for determining the balance between sympathetic and parasympathetic nervous system activity.[37]

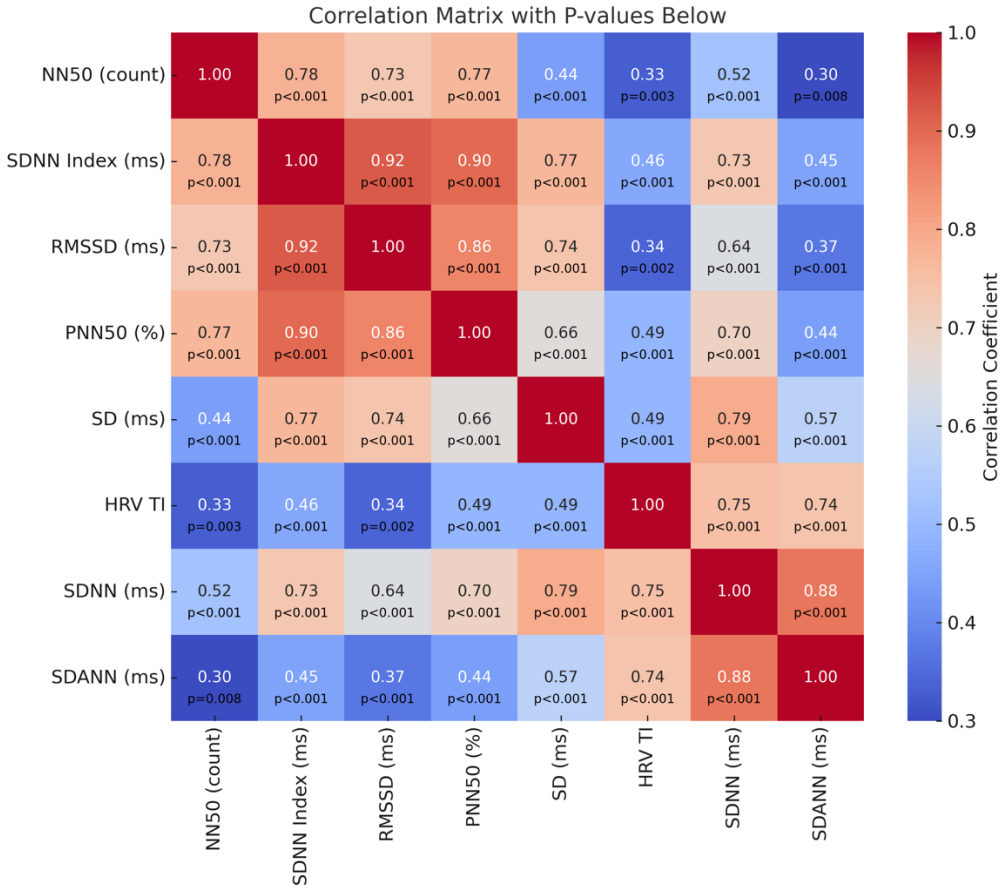

Figure 2. Spearman correlation coefficients matrix map of heart rate variability parameters with p-values. The colors represent the strength and direction of the correlations: red indicates strong positive correlations, blue indicates strong negative correlations, and lighter shades signify weaker relationships.

There is only a limited number of studies focusing on normative HRV values in children. In this context, Gasior et al.[23] conducted a study on healthy children aged 6–13 years and identified heart rate as the most influential factor affecting HRV. They published normative HRV values by categorizing participants based on their heart rates. Using the results of this study to classify our patients, the mean heart rate in the syncope group during Holter monitoring was 86 bpm, which corresponds to the Q3 category (heart rate: >84.3 bpm–92.0 bpm). Within this category, we observed that the time-domain parameter SDNN was increased, while RMSSD and pNN50 (%) were within normal ranges. Additionally, among frequency-domain parameters, an increase in LF (nu) and the LF/HF ratio—alongside a decrease in HF (nu)—was noted. These findings indicate a predominance of sympathetic activity in the syncope group, which contrasts with general literature that suggests parasympathetic dominance in syncope. In the control group, the mean heart rate was 82.5 bpm, which aligns with the Q2 category (heart rate: >77.8 bpm–84.3 bpm) from the same study. When categorized accordingly, it was observed that the control group clustered in a similar manner as the syncope group. The discrepancies between our study and the referenced study may be attributable to differences in methodology, as the referenced study utilized short-term ECG monitoring (five minutes) and was conducted with healthy, non-athletic Caucasian children as participants. Future studies should aim to form age- and physiologically matched cohorts to address these inconsistencies and enable more accurate comparisons. This approach would provide a more robust understanding of normative HRV values in pediatric populations and allow for the better evaluation of autonomic imbalance in conditions such as syncope.

The high prevalence of syncope during adolescence is attributed to the predominant role of vagal tone during this period.[1,38,39] This phenomenon is believed to result from the relatively low blood volume that cannot keep pace with the rapid growth phase in adolescents, thereby leading to increased sympathetic activity.[1] In response, parasympathetic overactivity occurs, culminating in vasovagal syncope.[1] Supporting this information, the study by Sun Hee Shim et al.[1] demonstrated that parasympathetic activity increased when patients were categorized into adolescent and preadolescent groups, while sympathetic activity decreased in the adolescent group. Similarly, our study divided the syncope and control groups into adolescent and preadolescent subgroups. Among adolescents with syncope, significant increases were observed in parameters indicative of heightened sympathetic activity—such as SDNN, LF (nu), and the LF/HF ratio—compared to the preadolescent group. Changes consistent with increased parasympathetic activity were also observed in average heart rate and mean RR intervals. Moreover, significant differences were noted in the adolescent control group in the SDNN, SDANN, LF (nu), and the LF/HF ratio—all of which are associated with sympathetic activity—compared to the preadolescent group. Decreases in parasympathetic parameters were also observed in this group. Based on these findings, our study suggests that sympathetic activity, rather than vagal tone, plays a more dominant role in adolescents, particularly those with syncope.

In the study by Hosaka et al.,[40] which analyzed 24-hour ambulatory ECG recordings, found no significant differences in mean RR, SDNN, or SDANN values. However, HRV parameters indicative of parasympathetic dominance—such as the SD index, RMSSD, and pNN50—were significantly higher in the neuro-mediated syncope group compared to the control group. Similarly, Kochiadakis et al.[41] reported that baseline HRV indices that reflected parasympathetic dominance were increased in patients with syncope compared to healthy controls. Our study observed significant differences between the syncope and control groups in time-domain parameters, including SDNN, SDANN, HRV-TI, SDRR, pNN50, RMSSD, SDNNI, and NN50. However, no significant differences were noted in frequency-domain parameters. These findings suggest that, as described in the literature, both sympathetic and parasympathetic systems are affected in patients with syncope, thereby indicating autonomic imbalance. In syncope patients, increased sympathetic activity is counterbalanced by increased parasympathetic activity to maintain autonomic equilibrium.

In the study by Sun Hee Shim et al.[1], it was found that SDNN and RMSSD parameters were significantly higher in patients with syncope. Additionally, compared to the control group, normalized LF values and the LF/HF ratio were non-significantly lower and normalized HF values were higher in the syncope group. These findings indicate an increase in parameters suggestive of parasympathetic dominance in patients with syncope. In contrast, our study demonstrated significant differences in parameters that reflect the involvement of both sympathetic and parasympathetic systems in the study group compared to the control group.

Studies that investigate normative HRV values based on 24-hour Holter monitoring in children are limited. Kovalchuk et al.[26] conducted a study involving 56 children with syncope and 41 healthy controls aged 8–17 years, analyzing differences in time- and frequency-domain HRV parameters, such as SDANN, RMSSD, pNN50, LF index, HF index, LF/HF ratio, as well as total power across daytime, nighttime, and 24-hour periods. In the syncope group, compared to the control group, significant reductions were observed in SDANN (during the entire 24-hour period and nighttime), RMSSD (during the entire 24-hour period and daytime), and pNN50 (during daytime). In the frequency-domain analysis, only a significant increase was found in the LF/HF ratio during nighttime. Based on these findings, the authors concluded that pediatric patients with VVS exhibit autonomic imbalance characterized by increased sympathetic activity. In our study, which did not stratify 24-hour Holter monitoring results by time periods, we similarly observed reductions in SDNN, pNN50, and RMSSD values, which are consistent

with the findings of Kovalchuk et al.[26] However, unlike their study, we observed a non-significant increase in LF/HF ratio.

Longin et al.[5] compared the frequency-domain parameters of (HRV) in short-term (five-minute) ECG recordings between children and adolescents aged 5–15 years with neurocardiogenic syncope and their healthy counterparts. In the pediatric group (ages 5–11), significant increases in total power, very low frequency (VLF, 0.01–0.05 Hz), and low-frequency (LF) band values were observed compared to the control group. Significant increases were noted among adolescents in VLF and peak VLF band values. These findings suggest that baseline sympathetic activity is elevated in both children and adolescents with syncope, as shown in the study by Longin et al.[5] However, the study did not include baseline data for parameters indicative of parasympathetic activity, thus making it impossible to conclude parasympathetic regulation. In our research, normalized LF and HF parameters were used, thereby preventing a direct comparison with the results of Longin et al. Nevertheless, the observed changes in our study, which also indicate increased sympathetic activity, align with the findings of Longin et al. and support a similar interpretation regarding the autonomic imbalance in pediatric syncope.

This study has several limitations that warrant consideration. The relatively small sample size and short follow-up period limit the generalizability of the findings, while the exclusion of patients with incomplete Holter data likely affected the homogeneity of the study population. Additionally, the absence of head-up tilt testing, although not routinely recommended in pediatric syncope, restricted our ability to assess autonomic changes during syncope episodes. Further, lack of stratification by syncope subtypes, triggering factors, or symptom severity may have limited identifying specific HRV patterns. Furthermore, intrinsic factors influencing HRV—such as baseline heart rate, physical activity, and respiratory patterns—were not controlled, potentially introducing bias. Future studies with larger, more homogeneous populations and standardized methodologies are needed to establish normative HRV values and refine diagnostic criteria in pediatric syncope.

In conclusion, this study evaluated differences in HRV parameters between pediatric patients with syncope and a control group using 24-hour Holter ECG monitoring. Significant reductions were observed in time-domain parameters—including SDNN, SDANN, HRV-TI, SDRR, pNN50, RMSSD, SDNNI, and NN50in the syncope group compared to controls. At the same time, no meaningful differences were identified in frequency-domain parameters. Notably, the SDNN was the most predictive parameter for identifying syncope in this population. These findings highlight the potential utility of HRV as a diagnostic tool in pediatric syncope. However, the lack of established normative HRV values and limited research in children emphasizes the need for large-scale, multicenter, and prospective studies. Such investigations should aim to standardize HRV measurements, account for confounding factors such as baseline heart rate and physical activity, and further clarify the clinical significance of HRV parameters in pediatric populations.

Compliance with Ethical Standards

The Clinical Research Ethics Committee of Giresun University approved this study on April 4, 2023 (Decision No: 2). Before the study, the parents of all participants provided written informed consent.

Conflict of Interest

The author declares no conflicts of interest.

Author Contribution

Conception and Design of Study: BY, BDD, and ET. Data Acquisition: BY and FCY. Data Analysis: BY and FCY. Drafting Manuscript: BY. Critical Revision of Manuscript: BY, BDD, and ET. Final Approval: BY, BDD, ET, and FCY. Supervision: BY.

Financial Disclosure

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