Frequency Domain Indices of Heart Rate Variability are Useful for Differentiating Vasovagal Syncope and Postural Tachycardia Syndrome in Children

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Objective To explore the value of frequency domain indices of heart rate variability (HRV) in the differential diagnosis between pediatric vasovagal syncope and postural tachycardia syndrome (POTS).

Study design Eighty-five patients aged 7-16 years with either vasovagal syncope or POTS were enrolled in the experimental group; 18 healthy children served as controls. Holter electrocardiography was used to detect HRV frequency-domain indices in patients with vasovagal syncope, patients with POTS, and control subjects. The differences in HRV indices were compared between the vasovagal syncope and POTS groups. The receiver operating characteristic (ROC) curve was calculated to analyze the predictive value of HRV for the differential diagnosis between vasovagal syncope and POTS in children. In addition, 37 children aged 7-17 years with either vasovagal syncope or POTS were recruited as an external validation group.

Results The daytime ultra-low frequency (dULF), nighttime ULF (nULF), daytime very low frequency (dVLF), and nighttime VLF (nVLF) were higher in the vasovagal syncope group compared with the POTS group ($P < .01$ for dULF, dVLF, and nVLF; $P < .05$ for nULF). The dULF, nULF, dVLF, and nVLF yielded a sensitivity of 73.3%, 71.1%, 68.9%, and 62.2%, respectively, and a specificity of 72.5%, 62.5%, 60.0%, and 60.0%, respectively, to differentiate vasovagal syncope from POTS. The external validation with clinical diagnostic standard showed that a dULF cutoff value of 36.2 ms^2 for differentiating POTS from vasovagal syncope yielded a sensitivity of 71.4%, a specificity of 75.0%, and an accuracy of 73.0%.

Conclusion dULF may be a useful measure for the differential diagnosis between vasovagal syncope and POTS in adolescents. *(J Pediatr 2019;207:59-63).*

Orthostatic intolerance refers to a series of symptoms that result when a patient assumes a standing position, including dizziness, headache, blurred vision, chest tightness, palpitations, nausea, hand tremors, inattention, and fainting. These symptoms present primarily in school-age children and adolescents, seriously affecting daily life and learning quality and increasing the risk of accidental injury due to syncope.[1,2] Vasovagal syncope and postural tachycardia syndrome (POTS) are common underlying diseases in children with orthostatic intolerance.[3] Because vasovagal syncope and POTS differ in treatment strategies and methods, it is important to accurately distinguish between the 2 disorders.[4,5] Although the clinical manifestations of vasovagal syncope and POTS can be similar, POTS presents with chronic and day-to-day symptoms and even syncope in some cases, making a clinical differential diagnosis between vasovagal syncope and POTS difficult. At present, the identification of vasovagal syncope and POTS is based mainly on clinical manifestations and positive changes in the head-up tilt test (HUTT),[6,7] in which the hemodynamic changes sometimes overlap. Furthermore, HUTT is performed only in large hospitals in China and is associated with certain risks.[8] Therefore, identifying a method for differentiating between vasovagal syncope and POTS in clinical practice would be useful.

In a previous study, Zhang et al found that plasma hydrogen sulfide is an effective indicator for vasovagal syncope and POTS, with sensitivity of 90% and specificity of 80%.[9] However, hydrogen sulfide is not stable in plasma, which limits its clinical use. Li et al found that serum iron was a more stable biomarker that differentiated vasovagal syncope from POTS with a sensitivity of 92.5% and specificity of 64.7%.[10] However, plasma iron determination requires venipuncture. Therefore, other noninvasive, stable, easy to use, and repeatable indicators for the differential diagnosis between vasovagal syncope and POTS should be evaluated.

AUC	Area under the curve	nULF	Nighttime ultra-low frequency
dULF	Daytime ultra-low frequency	nVLF	Nighttime very low frequency
dVLF	Daytime very low frequency	POTS	Postural tachycardia syndrome
HR	Heart rate	ROC	Receiver operating characteristic
HRV	Heart rate variability	ULF	Ultra-low frequency
HUTT	Head-up tilt test	VLF	Very low frequency

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Previous studies have shown that heart rate variability (HRV) is an indicator that reflects the autonomic nervous system activity in the Bezold-Jarisch reflex response,[11] which is involved in the pathogenesis of vasovagal syncope.[12,13] The aim of the present study was to investigate the value of HRV in differentiating between vasovagal syncope and POTS by targeting the frequency domain indices.

Methods

Patients with a diagnosis of vasovagal syncope (22 males and 23 females; median age, 12.0 years; range 10.0-13.5 years) were recruited for the vasovagal syncope group. They were admitted to the Department of Pediatrics, Peking University First Hospital between 2015 and 2018. Forty patients (13 males and 27 females; mean age, 12.0 ± 2.3 years) with a diagnosis of POTS were recruited for the POTS group. A total of 18 healthy children (9 males and 9 females, mean age, 11.1 ± 2.7 years) were recruited as a healthy control group based on history, physical examination, and laboratory findings. In addition, 21 patients with vasovagal syncope and 16 with POTS (mean age, 11.5 ± 2.4) who were admitted to our hospital in 2018 were included as an external validation group for comparisons of HRV-based diagnoses and clinical criteria-based diagnoses. The enrolled children and their parents were informed of the purpose of the study and agreed to provide relevant research information. This study was approved by the Ethics Committee of the First Hospital of Peking University in Beijing.

Before the head-up tilt test (HUTT) all drugs affecting autonomic function were stopped for at least 5 half-lives, and participants fasted for at least 4 hours. A multilead electrocardiography monitor (Dash 2000; General Electric, New York, New York) was used in a quiet room. The child was placed supine on the tilt table (HUT-821; Beijing Juchi, Beijing, China) to record basal heart rate, blood pressure, and orthostatic intolerance symptoms for approximately 10 minutes. The bed was tilted to 60°, and heart rate, blood pressure, and orthostatic intolerance symptoms were continuously monitored until a positive response occurred or the 45-minute examination reached completion. Drugs, such as nitroglycerin, were not used during the HUTT.[14,15]

The criteria for the diagnosis of vasovagal syncope were (1) older age; (2) presence of predisposing factors, such as persistent standing and rapid changes in position from supine to upright; (3) syncope or presyncope determined clinically; (4) drop in blood pressure on the HUTT (systolic blood pressure ≤80 mmHg or diastolic blood pressure ≤50 mmHg or mean blood pressure drop ≥25%); heart rate (HR) decline of <75 bpm for children aged 4-6 years, <65 bpm for those aged 7-8 years and <60 bpm for those aged 8 years; and (5) absence of other diseases that can cause syncope, such as cardiac syncope and cerebrovascular diseases.[16,17]

The criteria for the diagnosis of POTS were (1) older age; (2) symptoms on rapid position change from supine or sitting to standing or prolonged standing; (3) orthostatic intolerance symptoms, such as dizziness, headache, fatigue, blurred vision, chest tightness, palpitations, hand tremors, and even syncope; (4) HR increase of >40 bpm or a maximum of ≥130 bpm in children aged 6-12 years or ≥125 bpm in those aged 13-18 years during the first 10 minutes of the standing test or the HUTT; and (5) absence of other diseases that can cause syncope, such as cardiac syncope and cerebrovascular diseases.[18,19]

A 24-hour dynamic electrocardiogram was continuously recorded with a Mortara dynamic electrocardiograph recording analyzer (Mortara Instrument, Milwaukee, Wisconsin). Artifacts were removed through human-machine dialog. The HRV frequency domain index analysis was performed with H-Scribe software (Mortara Instrument). The measures were as follows: ultra-low frequency (ULF; 0-0.003 Hz), VLF (very low frequency; 0.003-0.04 Hz), low frequency (LF; 0.04-0.15 Hz), high frequency (HF; 0.15-0.40 Hz), total power (TP; variance of all normal-to-normal (NN) intervals, ≤0.4 Hz), and the ratio of LF to HF (LF/HF).[20] All time domain indicators in this study were based on the total 24-hour recording, and data analysis of the frequency domain indicators was performed every 5 minutes. Manually, 06:00-21:59 was defined as daytime, 22:00-05:59 was defined as nighttime, and the frequency domain index values of the day and night were obtained. Subjects were prohibited from drinking coffee, tea, or alcohol and taking drugs that could affect autonomic function on the day before the test and on the test day. Participants were also asked to refrain from strenuous exercise and emotional excitement.

SPSS 23.0 (IBM, Armonk, New York) was used for statistical analyses. Data normality was assessed using the Shapiro-Wilk test. Data that conformed to the normal distribution were expressed as mean ± SD. Data that were not normally distributed were expressed as median (IQR). One-way ANOVA analysis or the Kruskall-Wallis H test was used for comparison among multiple groups, and the Bonferroni test was used for comparisons between 2 groups. Categorical data are represented by case number, and the χ^2 test was used for comparisons among groups. The ROC curve was used to evaluate the sensitivity and specificity of the indicators to predict the effect. The area under the curve (AUC) indicates the predictive ability of the prediction indicators. An AUC of 0.5-0.7 represents a low predictive power, an AUC of 0.7-0.9 represents moderate predictive power, and an AUC >0.9 represents the best predictive power. For the validation of daytime ULF (dULF) values, an additional 37 patients were analyzed for external validation. Statistical significance was set at $P < .05$.

Results

There were no statistically significant differences in sex, age, height, weight, or body mass index between the POTS group and the vasovagal syncope group ($P > .05$) (**Table I**).

The dULF, daytime VLF (dVLF), nighttime VLF (nVLF), daytime LF (dLF), and daytime TP (dTP) values were higher in the vasovagal syncope group compared with the healthy control group ($P < .01$ for dULF, dVLF, and nVLF; $P < .05$ for dLF and dTP). However, there was no significant difference in the HRV frequency domain index between the POTS group and the healthy control group ($P > .05$) (**Table I**). The dULF,

Table I. Comparison of the demographic characteristics and frequency domain indices among the vasovagal syncope, POTS, and control groups

Groups	POTS	Vasovagal syncope	Control	F/χ^2	*P* value
Patients, n	40	45	18		
Males/females, n	13/27	22/23	9/9	2.835	.242
Age, y	12.0 ± 2.3	12.0 (10.0-13.5)	11.1 ± 2.7	3.172	.205
Height, cm	160.0 (147.5-165.0)	156.2 ± 12.0	152.7 ± 12.0	0.825	.662
Weight, kg	44.8 (37.0-55.0)	46.7 ± 10.7	44.4 ± 11.4	1.126	.569
BMI, kg/m^2	17.9 (16.4-20.1)	18.9 ± 2.7	18.8 ± 2.9	0.932	.628
dLF, ms^2	613.6 (447.9-776.1)	744.2 ± 267.1*	511.1 ± 248.1	9.816	.007
nLF, ms^2	720.5 ± 312.2	663.7 (498.2-958.7)	495.4 (380.9-1005.8)	1.512	.47
dHF, ms^2	328.6 (177.9-486.3)	327.2 (207.5-495.0)	262.2 (115.6-470.9)	3.314	.191
nHF, ms^2	907.2 (478.8-1750.0)	730.8 (541.9-1394.9)	615.8 (385.2-1256.9)	1.169	.557
dTP, ms^2	1543.9 (1069.6-1929.0)	1839.2 ± 621.3†	1296.4 ± 636.9	9.827	.007
nTP, ms^2	2174.0 (1560.8-3357.0)	2058.4 (1644.0-3270.0)	2199.0 ± 1325.5	2.346	.31
dLF/HF, ms^2	3.0 (2.3-3.8)	3.2 ± 1.0	3.7 ± 1.6	2.057	.357
nLF/HF, ms^2	0.96 (0.7-1.7)	1.0 (0.7-1.6)	1.1 (1.0-1.5)	1.836	.339

BMI, body mass index.
Data are mean ± SD or median (IQR) unless indicated otherwise.
*$P < .05$ vs control.
†$P < .01$ vs control.

nULF, dVLF, and nVLF were markedly higher in the vasovagal syncope group compared with the POTS group ($P < .01$ for dULF, nULF, and dVLF; $P < .05$ for nVLF). There was no significant difference in other HRV frequency domain indicators between vasovagal syncope group and POTS group ($P > .05$) (**Figure 1**).

The ROC curve was plotted to assess the value of dULF, nULF, dVLF, and nULF for the differential diagnosis between vasovagal syncope and POTS. The 95% CI obtained does not include 0.5, suggesting that it has predictive value for a differential diagnosis (**Figure 2**). The ROC curve for dULF as the indicator between vasovagal syncope and POTS showed an AUC

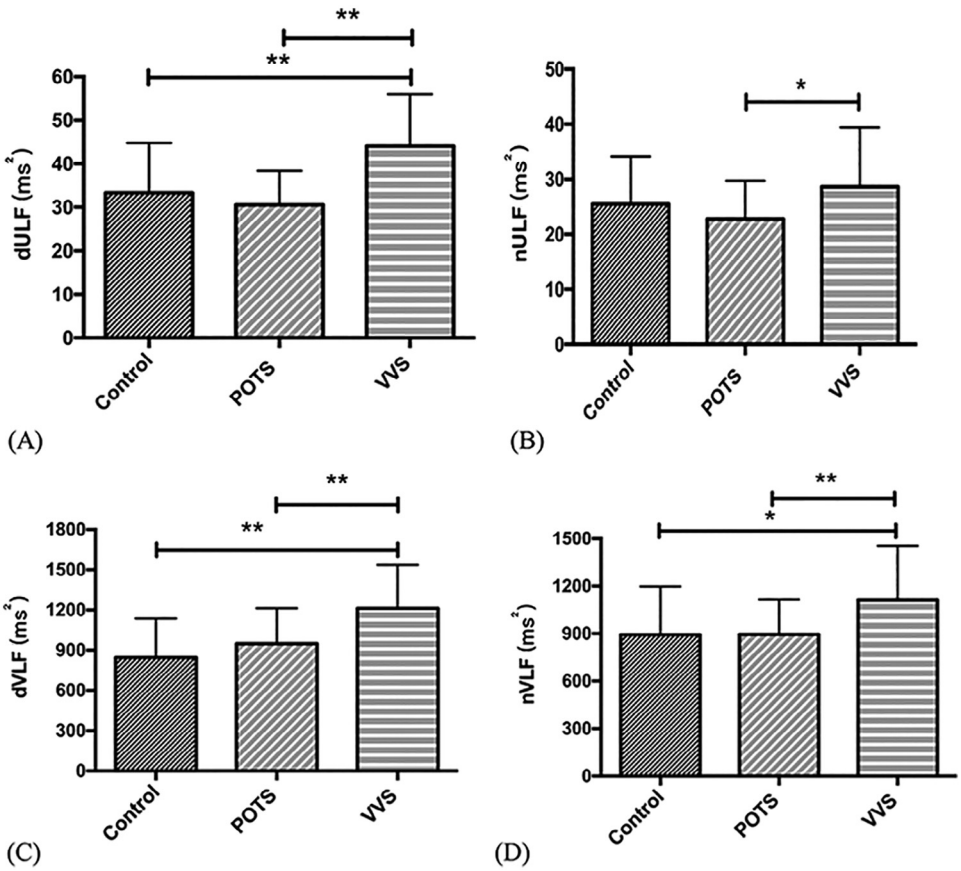

Figure 1. Comparison of **A,** dULF, **B,** nULF, **C,** dVLF and **D,** nVLF values in the POTS, vasovagal syncope, and control groups. *$P < .05$; **$P < .01$.

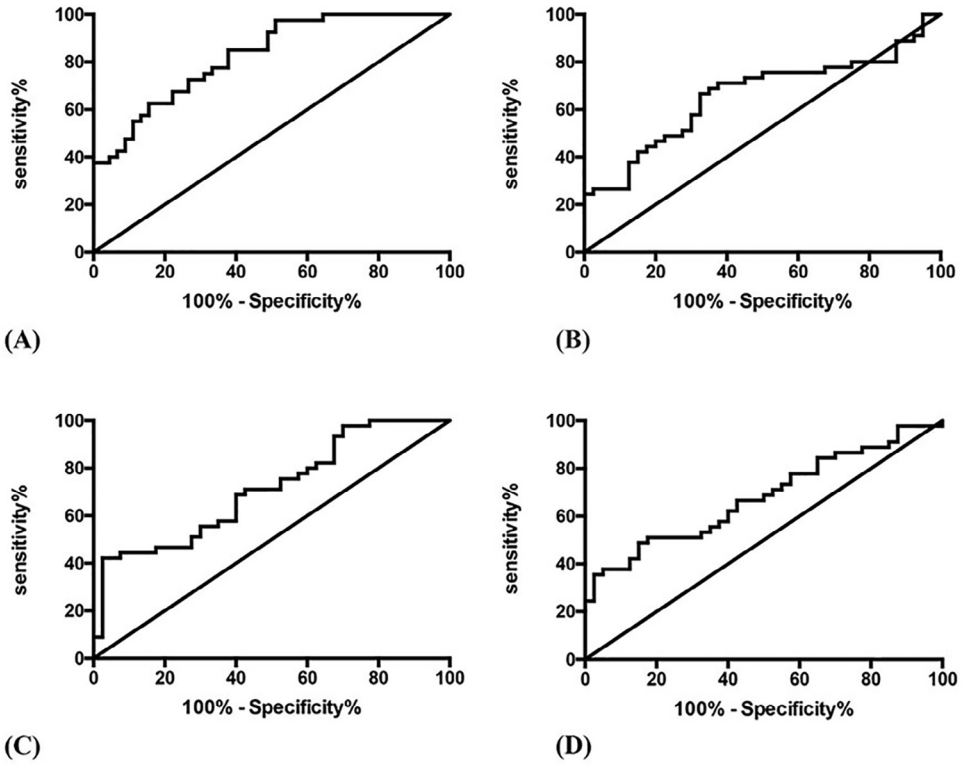

Figure 2. dULF, nULF, dVLF, and nVLF values as indicators in the differential diagnosis vasovagal syncope and POTS as predicted by the ROC curve (n = 85). **A,** For dULF, the AUC value was 0.826 (95% CI, 0.742-0.910), and the cutoff value of 36.2 ms^2 for differential diagnosis yielded a sensitivity of 73.3% and a specificity of 72.5%. **B,** For nULF, the AUC value was 0.659 (95% CI, 0.541-0.777), and the nULF cutoff value of 23.1 ms^2 for differential diagnosis yielded a sensitivity of 71.1% and a specificity of 62.5%. **C,** For dVLF, the AUC value was 0.712 (95% CI, 0.604-0.821), and the dVLF cutoff value of 1004.7 ms^2 for differential diagnosis yielded a sensitivity of 68.9% and a specificity of 60%. **D,** For nVLF, the AUC value was 0.681 (95% CI, 0.568-0.793), and the nVLF cutoff value of 944.5 ms^2 for differential diagnosis yielded a sensitivity of 62.2% and a specificity of 60.0%.

of 0.826 (95% CI, 0.742-0.910; $P < .01$), and dULF cutoff value of 36.2 ms^2 yielded a sensitivity of 73.3% and a specificity of 72.5%. The ROC curve for nULF as the indicator between vasovagal syncope and POTS showed an AUC of 0.659 (95% CI, 0.541-0.777; $P = .012 < .05$), and the nULF cutoff value of 23.1 ms^2 yielded a sensitivity of 71.1% and a specificity of 62.5%. The ROC curve for dVLF as the indicator between vasovagal syncope and POTS showed an AUC of 0.712 (95% CI, 0.604-0.821; $P < .01$), and the dVLF cutoff value of 1004.7 ms^2 yielded a sensitivity of 68.9% and a specificity of 60%. The ROC curve of nVLF as the indicator between vasovagal syncope and POTS showed an AUC of 0.681 (95% CI, 0.568-0.793; $P < .01$), and the nVLF cutoff value of 944.5 ms^2 yielded a sensitivity of 62.2% and a specificity of 60%.

For the external validation, the highest dULF value in the foregoing AUC analysis was selected as an indicator in the validation. At a dULF >36.2 ms^2, children with clinical orthostatic intolerance symptoms were diagnosed with vasovagal syncope, and those without orthostatic intolerance symptoms were diagnosed with POTS. On validation with the clinical diagnosis, the sensitivity, specificity, and accuracy of POTS and vasovagal syncope identification by the HRV frequency domain indicators were 71.4%, 75.0%, and 73.0%, respectively (**Table II**).

Discussion

This study showed that the HRV frequency domain indicators were higher in children with vasovagal syncope compared with those with POTS, indicating greater sympathetic nerve excitability of vasovagal syncope in both daytime and nighttime. The use of dULF as the cutoff value to differentiate vasovagal syncope from POTS yielded moderate sensitivity and specificity in this analysis. Using dULF validated by the clinical diagnostic standard showed a sensitivity of 71.4%, specificity of 73.0%, and accuracy of 73.0%.

Table II. Validation of the diagnostic test by dULF (n = 37)

Differential diagnosis between vasovagal syncope and POTS		Clinical standard-based diagnostic outcome, n (%)	
		vasovagal syncope	POTS
HRV-based diagnostic outcome (by dULF cutoff of 36.2 ms^2)	vasovagal syncope	15 (71.4)	4 (25.0)
	POTS	6 (28.6)	12 (75.0)

In this study, HRV, reflective of Bezold-Jarisch reflex abnormalities,[21] was used as an indicator for its noninvasive, quantitative, and reproducibly reflecting autonomic activity. ULF and HF reflect the parasympathetic activity, whereas VLF and LF mainly reflect sympathetic activity.[22-24] Thus, we attempted to analyze the difference in diurnal autonomic function between children with vasovagal syncope and those with POTS, and also to explore the value of the HRV frequency domain index in the differential diagnosis of vasovagal syncope and POTS.

We found higher dULF, nULF, dVLF, and nVLF values in the children with vasovagal syncope compared with those with POTS, indicating greater sympathetic excitability in vasovagal syncope in both the daytime and the nighttime. Our findings indicate that dULF, nULF, dVLF, and nVLF may have value in the differential diagnosis between vasovagal syncope and POTS, and that a dULF cutoff value of 36.2 ms^2 to differentiate vasovagal syncope from POTS yielded relatively favorable sensitivity and specificity, which was also confirmed by external verification.

These results indicate that a dULF cutoff of 36.2 ms^2 can serve as an indicator for the clinical differential diagnosis of vasovagal syncope from POTS in children. Advantages of the dULF as an indicator in the differential diagnosis is that it is noninvasive, easy to perform, and inexpensive.

This study has some limitations, however, including the relatively small number of cases. Future multicenter studies are needed to confirm the useful indicators for the differential diagnosis between vasovagal syncope and POTS in clinics. ■

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