



# Acceleration index predicts efficacy of orthostatic training on postural orthostatic tachycardia syndrome in children

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## Abstract

The objective of this study was to examine the utility of the acceleration index observed in an electrocardiogram (ECG) for the prediction of the effectiveness of orthostatic training in pediatric patients diagnosed with postural orthostatic tachycardia syndrome (POTS). This investigation focused on children diagnosed with POTS and undergoing orthostatic training at the Department of Pediatrics of Peking University First Hospital from January 2012 to October 2022. Specifically, patients hospitalized from January 2012 to December 2019 were included in the training set (54 cases), while those hospitalized from January 2020 to October 2022 were included in the external validation set (37 cases). All children received a 3-month orthostatic training, and the baseline symptom score (SS) was calculated in agreement with the pretreatment orthostatic intolerance symptom frequency. Additionally, we determined post-treatment SS during follow-up via telephone after the 3-month treatment. Children with a decrease in post-treatment SS by  $\geq 50\%$  of the baseline were considered as responders; otherwise, they were considered as non-responders. Demographic data (age, sex, and body mass index), hemodynamic parameters (supine blood pressure, time to achieve a positive standing test, maximum increase in heart rate during the standing test, maximal heart rate reached during the standing test, and blood pressure at the point of maximal heart rate during the standing test), and electrocardiographic parameters (RR interval in the supine position, shortest RR interval in the upright position, and acceleration index) were collected from all the children prior to treatment. Univariate and multivariate regression analysis were conducted to investigate factors associated with the efficacy of orthostatic training. The predictive value of these indicators for the therapeutic effectiveness of orthostatic training in children with POTS was evaluated using receiver operating characteristic (ROC) analysis, and the indicators were validated using the validation set. Among the 54 children in the training set, 28 responded to orthostatic training, and 26 were nonresponsive. Compared with the non-responders, the responders demonstrated a significant reduction in acceleration index ( $P < 0.01$ ). The ROC curve for the predictive value of the acceleration index exhibited an area under the curve = 0.81 (95% confidence interval: 0.685–0.926). With the acceleration index threshold  $< 27.93\%$ , the sensitivity and specificity in the prediction of orthostatic training efficacy among children with POTS were 85.7% and 69.2%, respectively. The external validation results demonstrated that using acceleration

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index < 27.93% as the threshold, the sensitivity, specificity, and accuracy of predicting orthostatic training efficacy among children with POTS were 89.5%, 77.8%, and 83.8%, respectively.

**Conclusions:** Electrocardiographic acceleration index can be used to predict the effectiveness of orthostatic training in treating children with POTS.

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#### What is Known:

- Postural orthostatic tachycardia syndrome (POTS) is a chronic orthostatic intolerance involving multiple mechanisms. Autonomic dysfunction is one of the main mechanisms of POTS in children and could be treated with orthostatic training.
- In order to improve the efficacy of orthostatic training in children with POTS, it is particularly important to identify the patients with autonomic dysfunction as the main mechanism before the treatment.

#### What is New:

- We found acceleration index of the electrocardiogram (ECG) can be used as a satisfactory index to predict the efficacy of orthostatic training in the treatment of POTS in children.
  - Using the acceleration index to predict the efficacy of orthostatic training on POTS in children is easy to be popularized in hospitals at all levels because it is non-invasive, convenient, and not expensive.
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**Keywords** Dysautonomia · Adolescent · Pediatric · Electrocardiogram acceleration index · Orthostatic training

#### Abbreviations

AUC	Area under curve
BMI	Body mass index
CI	Confidence interval
ECG	Electrocardiogram
HUTT	Head-up tilt test
OR	Odds ratio
ORS	Oral rehydration salts
POTS	Postural orthostatic tachycardia syndrome
ROC	Receiver operating characteristics
SS	Symptom score

#### Introduction

Postural orthostatic tachycardia syndrome (POTS) is a chronic syndrome characterized by orthostatic intolerance and significant tachycardia in an upright position, with patients often experiencing symptoms, such as dizziness, palpitations, chest tightness, and gastrointestinal symptoms, after standing for a long time or changing from a sitting to a standing position, which significantly affects their quality of life [1–3]. The reported prevalence of POTS in children is approximately 6.8% [4]. Currently, the main treatment options for children with POTS include orthostatic training, fluid loading, oral rehydration salts,  $\beta$ -adrenoceptor blockers,  $\alpha$ -adrenoceptor agonists, fludrocortisone, pyridostigmine, and ivabradine. However, observational studies showed unsatisfactory outcomes in children with POTS who received unselective treatment [5]. Therefore, there is an urgent need to further improve the therapeutic efficacy for children with POTS.

Autonomic dysfunction is the main mechanism of POTS in children, and orthostatic training is a nonpharmacological

therapy for pediatric POTS, which is believed to improve autonomic function [6–9]. Prior research has indicated that corrected QT interval dispersion may serve as a marker of autonomic function and could potentially predict efficacy. Lu et al. demonstrated that pretreatment-corrected QT dispersion aided in forecasting the outcome of autonomic exercise in children with POTS [10]. Nonetheless, numerous factors may impact QT dispersion, given that its specificity was only 60%. Therefore, identifying more sensitive and specific indicators for predicting the effectiveness of orthostatic training continues to be a challenge in treating children with POTS. The acceleration index in an electrocardiogram (ECG) reflects the immediate alteration of the heart rate when the patient changes from a supine to an upright position [11, 12]. Several studies found that the acceleration index was positively correlated to sympathetic activity [13–15]. However, whether the acceleration index can be used as a marker for predicting the effectiveness of orthostatic training on pediatric POTS treatment remains unclear.

This study explores whether the acceleration index is applicable as a predictive factor for the orthostatic training efficacy in children with POTS, thereby helping us to make a relatively accurate judgment of the main pathogenesis of the patient before treatment and to provide evidence for individualized treatment of POTS in children.

#### Materials and methods

##### Patients

Children with a confirmed diagnosis of POTS and those who received orthostatic training in the Department of Pediatrics of Peking University First Hospital between January

2012 and October 2022 were enrolled in this retrospective study. Specifically, children hospitalized from January 2012 to December 2019 and those from January 2020 to October 2022 were included in the training and validation sets, respectively. This study was conducted in accordance with the Declaration of Helsinki's principles and approved by the Ethics Committee of Peking University First Hospital (2022 [496]).

The diagnostic criteria for POTS [16, 17] consist of the following: (1) presence of symptoms exacerbated by predisposing factors like prolonged standing; (2) symptoms of orthostatic intolerance, including headache, dizziness, blurred vision, fatigue, palpitations, chest tightness, exercise intolerance, hand tremors, or syncope, typically experienced in an upright position; (3) a positive response suggestive of POTS during head-up tilt test (HUTT); and (4) exclusion of cardiovascular, neurological, and endocrine and metabolic disorders that could lead to symptoms of orthostatic intolerance.

The criteria for diagnosing POTS during a HUTT [18] include the following: (1) there is a sustained increase in heart rate of  $\geq 40$  beats per minute (bpm) and/or attainment of a maximal heart rate within 10 min after tilting during HUTT, meeting the specified thresholds of  $\geq 130$  bpm for children aged 6–12 years and  $\geq 125$  bpm for those aged 12–18 years; and (2) a decrease in systolic blood pressure by  $< 20$  mmHg (1 mmHg = 0.133 kPa) and a decrease in diastolic blood pressure by  $< 10$  mmHg within 10 min after tilting during HUTT.

The inclusion criteria for the participants were as follows: (1) children who were hospitalized at the Peking University First Hospital between January 2012 and October 2022 with a confirmed diagnosis of POTS; (2) those at the age range of 5–18 years; (3) those receiving standardized assessments, including the record of the complete medical history, physical and neurological examinations, 12-lead ECG, HUTT, and standing tests; and (4) those treated with health education and orthostatic training for at least 3 months.

The exclusion criteria for the participants were as follows: (1) children with cardiovascular disease, cerebrovascular disease, endocrine diseases such as hyperthyroidism and Addison's disease, hypovitaminosis D, or iron deficiency; (2) those with non-sinus rhythm; (3) those with incomplete baseline medical records; and (4) those, in addition to orthostatic training, were receiving pharmacological therapy, such as metoprolol, midodrine, or oral rehydration salts.

## Data collection

The data of all children were obtained from the Medical Records Management Digital System (Kaihua, Beijing, China). The study encompassed demographic data (age, sex, and body mass index [BMI]), hemodynamic parameters

(supine blood pressure, maximal increase in heart rate during the standing test, maximal heart rate reached during the standing test, and blood pressure at the point of maximal heart rate during the standing test), and electrocardiographic parameters (the period between the two adjacent R waves (RR interval) in the supine position, the shortest RR interval in the upright position, and acceleration index).

## Symptom score

Symptom score (SS) was assessed in all the children. First, children were asked individually about the frequencies of occurrence of the respective 10 main orthostatic intolerance symptoms, including headache, syncope, dizziness, palpitations, chest tightness, sweating, hand tremors, blurred vision or amaurosis, gastrointestinal symptoms, and difficulty of concentrating. Then, each symptom was scored according to the frequencies of occurrence as follows (Supplemental Table 1): 0 point represented absence of symptoms; 1 point stood for symptoms once a month; 2 points for symptoms 2–4 times monthly; 3 points for symptoms 2–7 times weekly; and 4 points for symptoms more than once daily. The scores of all 10 orthostatic intolerance symptoms were determined and recorded, respectively. Finally, the SS for each child was calculated by adding up the scores of the 10 symptoms recorded above [19–21]. Using the calculation method above, we assessed the pre-treatment and the post-treatment SS for each child.

## HUTT

### Basic HUTT procedures [22–25]

The participants discontinued any diet, including the consumption of tea and coffee, and medications that affect autonomic function for over five half-lives before this trial. The participants were requested to fast and avoid liquids for at least 4 h before the test. The test was performed between 8:00 am and 11:00 am. The test room environment was quiet, warm, and relatively dim. The tiltable table (SHUT-100A, Standley, Jiangsu) was employed for HUTT, and ECG and heart rate were continuously monitored with the multi-lead ECG monitor (GE, NY, USA). The changes in blood pressure were recorded using a noninvasive continuous blood pressure monitor Finapres Medical system-FMS (Finometer-PRO, FMS company, Amsterdam, Netherlands). Initially, the participants quietly lay for a 10–30 min period in the supine position, and blood pressure and basic ECG were continuously monitored. When stable heart rate, blood pressure, and ECG were achieved, the participants were tilted at 60°, and these three variables were constantly recorded until a positive reaction occurred or 45 min of the test was completed.

## Twelve-lead ECG examination

ECGs were recorded using an electrocardiography machine (FX-7402, Fukuda, Japan). All subjects underwent standard 12-lead surface electrocardiography in both supine and upright positions. The procedure was conducted in a quiet and temperature-controlled dedicated room. Participants were instructed to maintain quiet breathing throughout the examination. The ECG during the supine and upright positions was recorded on thermal paper under the following recording conditions: voltage, 1 mV/cm; paper speed, 25 mm/s. A good quality ECG should include complete lead marks, paper speed, and voltage marks, and the 12-lead ECG pattern should have a stable baseline and clear waveforms.

## Acceleration index measurement

Standing testing was conducted on all the participants for acceleration index calculation.

Standing test procedure [22]: The participants were exposed to a quiet, dimly lit environment at a suitable temperature. The participants were requested to rest for a 10–20 min period in the supine position. After the stabilization of the heart rate, the supine heart rate and blood pressure were simultaneously recorded. Then, the participants were advised to stand for another 10 min without support. The ECG, heart rate, and blood pressure were monitored with the Dash 2000 monitor (General Electric Company, NY, USA) during the resting and 10-min standing period. The participant's complaints of discomfort were recorded throughout the test. When the participant was intolerant to the test, it was terminated at once, and the participant was assisted to return to the supine position.

Calculation of acceleration index [26]: Eligible ECGs were digitized using a scanner. The digitized ECG patterns were magnified threefold on a high-resolution (3840 × 2160) computer screen, and ECG parameters were measured by a trained researcher using Image-Pro Plus version 6.0.0.260 image analysis software. The average RR interval within the first 15 s before the change in body position and the minimal RR interval within 15 s following the body position change were measured by the same researcher in both the training and validation sets. Standard ECG RR intervals were measured in lead II, with each RR interval measured three times and averaged. The acceleration index was calculated according to previous studies [11, 12] using the formula: acceleration index =  $[(A - B)/A] \times 100\%$ , where  $A$  represented the average RR interval within 15 s before the change in position, and  $B$  represented the minimal RR interval within 15 s following the change in position.

Before the commencement of the study, the repeatability and stability of the measurement method were evaluated. In the repeatability test, electrocardiographic parameters were

measured independently by two researchers, including those who later conducted the actual data measurements, in 15 children. Subsequently, the results obtained by these two researchers were compared for consistency. In the stability test, the same researcher repeated measurements of the ECG parameters in 15 children every week and compared the results of both measurements.

## Treatment and follow-up

All participants received orthostatic training following the diagnosis of POTS. The protocol for orthostatic training was as follows: the child stood approximately 15–20 cm from the wall, with their back leaning against the wall for 3 to 5 min each time. The duration of each training session was gradually increased up to 30 min based on the child's tolerance level. If symptoms of orthostatic intolerance occurred during training, it was immediately discontinued. Orthostatic training sessions were repeated once to thrice daily for a total of 3 months. Additionally, health education was provided to the children, including guidance on ensuring adequate sleep, avoiding triggers, and preparing for emergency measures in the event of orthostatic intolerance symptoms.

SS was calculated based on the frequency of orthostatic intolerance symptoms [19–21]. The frequency of symptoms before orthostatic training was recorded as the baseline SS. Children with POTS were followed up through telephone communication. Trained researchers conducted the follow-up, assessing treatment compliance and symptom frequency to calculate the post-treatment SS. Participants were classified as responders if their SS decreased by at least 50% compared to baseline; otherwise, they were classified as non-responders [22].

## Statistical analysis

This study utilized Microsoft Excel (Microsoft, Redmond, WA, USA) for entering patient information and SPSS version 26.0 (IBM, New York, USA) for statistical analysis. The graphs were plotted using the GraphPad Prism version 9.5.0 software (GraphPad Software, San Diego, USA). The repeatability and stability of ECG measurements were assessed using paired sample  $t$ -tests or paired sample nonparametric tests.

## Univariate analysis

Normally distributed data were presented as mean  $\pm$  standard deviation, and the Student's  $t$ -test was used for comparison. Non-normally distributed data were represented as median and quartiles, and the Mann–Whitney U test was conducted for comparison. The enumeration data were represented

as frequency and percentage (%), with the  $\chi^2$  test used for comparison.

## Multivariate analysis

The significant factors obtained from the univariate regression analysis in responders compared with non-responders and the demographic characteristics indicators in the training set were subjected to binary logistic regression analysis to determine the odds ratios (ORs) and 95% confidence intervals (CIs). The predictive value of the acceleration index for orthostatic training treatment efficacy in children with POTS was assessed through receiver operating characteristic (ROC) analysis, followed by determining the area under the curve (AUC) values. Consistent with the maximum Youden index, the acceleration index threshold with preferable sensitivity and specificity in predicting orthostatic training effectiveness on children with POTS from the training set was determined.

## External validation

According to the acceleration index threshold obtained from the training set, we classified participants from the validation set as responders or non-responders to determine the sensitivity, specificity, and accuracy of the acceleration index in predicting the efficacy of orthostatic training treatment in the validation set.

## Results

### Patient's basic features

All POTS patients in this study met the diagnostic standard that there was a sustained increase in heart rate of  $\geq 40$  beats

per min (bpm) within 10 min after tilting during HUTT. A total of 60 cases were included in the training set, of which 6 (10.0%) were lost to follow-up. Of the remaining 54 cases (28 males and 26 females, aged 6–17 years), 28 (51.9%) and 26 (48.1%) were responders and non-responders to orthostatic training, respectively.

A total of 39 cases were included in the validation set, of which 2 were lost to follow-up with a rate of 5.1%, and finally, 37 cases were included in the study. Of these (14 males and 23 females, aged 8–16 years), 19 (51.4%) and 18 (48.6%) were responders and non-responders, respectively. The flow chart of the inclusion procedure for this study is shown in Fig. 1.

### Repeatability and stability of ECG measurement

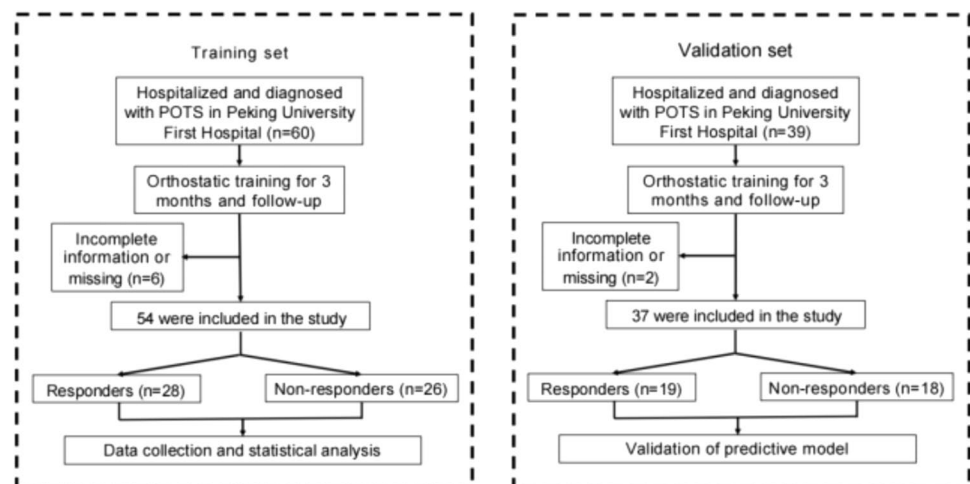
In the repeatability test, mean RR intervals within 15 s before position change (A) and minimal RR interval within 15 s following body position change (B) were not significantly different between the two values of each of the parameters measured by the two independent researchers ( $P > 0.05$ ) (Table 1), indicating the reproducibility of the method.

In the stability test, no significant difference in A and B between the two values measured at an interval of 1 week by the same researcher was observed ( $P > 0.05$ ) (Table 1), indicating the stability of the method.

### Univariate analysis

All patients underwent standing tests in our study. A total of 13 variables were included for univariate regression analysis, comprising demographic characteristics (sex, age, BMI, and pretreatment SS), hemodynamic parameters (supine systolic blood pressure, supine diastolic blood pressure, maximal increase in heart rate during

**Fig. 1** Flow chart for enrollment of children with POTS. POTS, postural orthostatic tachycardia syndrome



**Table 1** Repeatability and stability of ECG acceleration index measurement

Patient number	Repeatability test				Stability test			
	A (ms)		B (ms)		A (ms)		B (ms)	
	Tester 1	Tester 2	Tester 1	Tester 2	1st	2nd	1st	2nd
Patient 1	629	629	478	478	629	631	478	487
Patient 2	733	733	580	580	733	733	580	580
Patient 3	923	938	592	588	923	938	592	596
Patient 4	888	882	572	577	888	896	572	582
Patient 5	706	706	489	489	706	698	489	493
Patient 6	938	923	661	652	938	938	661	661
Patient 7	652	645	547	551	652	652	547	547
Patient 8	561	556	500	500	561	566	500	500
Patient 9	909	909	577	567	909	909	577	581
Patient 10	698	682	565	550	698	706	565	575
Patient 11	571	561	419	419	571	566	419	423
Patient 12	845	857	609	609	845	870	609	600
Patient 13	659	659	564	564	659	659	564	564
Patient 14	682	682	586	581	682	690	586	582
Patient 15	1017	1000	902	898	1017	1017	902	907
<i>t/Z</i> value	1.373		-1.620		-1.832		-1.758	
<i>P</i> value	0.191		0.105		0.088		0.079	

A, the mean duration of the RR interval within 15 s before changing position; B, the shortest RR interval within 15 s after changing position

the standing test, maximal heart rate reached during the standing test, systolic blood pressure at the point of maximal heart rate during the standing test and diastolic blood pressure at the point of maximal heart rate during the standing test), and electrocardiographic parameters (RR interval in the supine position, shortest RR interval in the upright position, and acceleration index). Compared with the non-responders in the training set, responders demonstrated a significant reduction in acceleration index ( $P < 0.01$ ). No statistically significant differences were observed for the other variables in both groups ( $P > 0.05$ , Tables 2 and 3).

## Multivariate analysis

The acceleration index was subjected to multivariate regression. This study also conducted binary logistic regression analysis to explore factors related to therapeutic efficacy, baseline acceleration index, and demographic characteristics (sex, age, and BMI), which were included as independent variables, probably affecting the autonomic function of the children (Table 4). The results showed that the baseline acceleration index was an independent factor related to orthostatic training efficacy among children with POTS. The AUC of ROC curve for baseline acceleration index in the prediction of orthostatic training effectiveness in children with POTS was 0.81 (95% CI: 0.685–0.926) (Fig. 2). Considering a cutoff value of  $< 27.93\%$  according to the

**Table 2** Comparison of characteristics between responders and non-responders to orthostatic training in children with POTS in the training set

Factors	Groups		<i>t/Z/χ</i> <sup>2</sup> value	<i>P</i> value
	Responders	Non-responders		
Number ( <i>n</i> (%))	28 (51.9%)	26 (48.1%)	–	–
Gender (M/F)	15/13	13/13	–0.216	0.803
Age (yrs)	13.00 (11.75, 14.00)	12.00 (10.25, 14.00)	0.987	0.328
BMI (kg/m <sup>2</sup> )	20.6 ± 4.0	20.6 ± 4.0	–0.013	0.990
Systolic blood pressure (mmHg)	113.9 ± 12.0	113.0 ± 12.6	0.266	0.791
Diastolic blood pressure (mmHg)	65.5 ± 8.8	66.7 ± 10.1	–0.476	0.636
Symptom score (points)	6.5 (3.8, 10.0)	5.0 (3.0, 8.0)	1.281	0.204

POTS postural orthostatic tachycardia syndrome, BMI body mass index

**Table 3** Comparison of hemodynamic and electrocardiographic parameters between responders and non-responders to orthostatic training in children with POTS in the training set

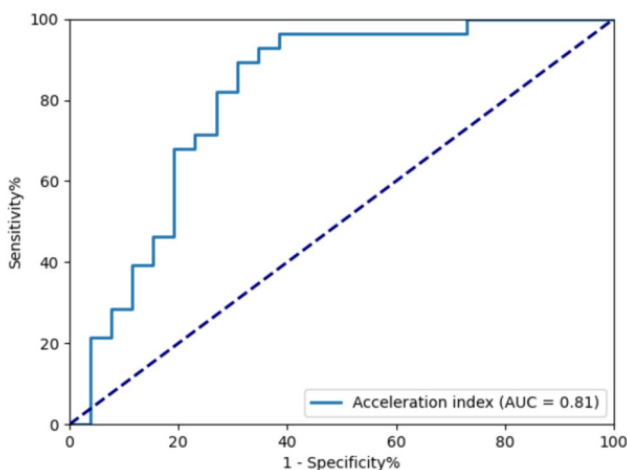
Factors	Groups		t/Z value	P value
	Responders	Non-responders		
Maximum heart rate difference in standing test (bpm)	46.1 ± 8.8	44.9 ± 9.0	0.486	0.629
Maximum heart rate in standing test (bpm)	116.2 ± 15.1	119.0 ± 11.3	−0.792	0.432
Systolic blood pressure at maximum heart rate in standing test (mmHg)	112.7 ± 13.8	111.9 ± 13.8	0.225	0.823
Diastolic blood pressure at maximum heart rate in standing test (mmHg)	72.0 ± 9.5	70.0 ± 9.0	0.793	0.432
RR interval in supine position (ms)	778.11 ± 171.45	815.15 ± 144.90	−0.860	0.394
The shortest RR interval in upright position (ms)	625.92 ± 121.81	567.42 ± 80.04	1.741	0.088
Electrocardiographic acceleration index (%)	20.02 ± 7.42	29.18 ± 11.35	−3.478	<0.01

POTS postural orthostatic tachycardia syndrome

**Table 4** Binary logistic regression model for predicting effectiveness of orthostatic training in children with POTS in training set

Factors	B	S.E	Wald	P value	OR	95%CI for OR
Electrocardiographic acceleration index	−0.124	0.042	−2.979	<0.01	0.883	0.805–0.949
Sex	−0.299	0.638	−0.469	0.639	0.741	0.204–2.572
Age	0.194	0.134	1.459	0.144	1.215	0.948–1.615
BMI	0.016	0.094	0.165	0.869	1.016	0.845–1.226
Constant	0.637	2.018	0.315	0.752	1.892	–

POTS postural orthostatic tachycardia syndrome, SE standard error, OR odds ratio, CI confidence interval, BMI body mass index, kg/m<sup>2</sup>



**Fig. 2** ROC curve of ECG acceleration index in training set to predict the efficacy of orthostatic training in children with POTS. The X-axis represents 1-specificity for prediction of the efficacy of orthostatic training treatment, and the Y-axis represents sensitivity for prediction of the efficacy of orthostatic training treatment. The 45-degree reference line of this figure indicates equal sensitivity and specificity. The blue curve represents the ROC curve for the predictive value of ECG acceleration index for the efficacy of orthostatic training treatment, with an area under the curve of 0.81 and a 95% confidence interval of 0.685–0.926. POTS, postural orthostatic tachycardia syndrome

maximum Youden index, the sensitivity and specificity in the prediction of orthostatic training effectiveness were 85.7% and 69.2%, respectively.

### External validation

For external validation, children with electrocardiographic acceleration index < 27.93% and ≥ 27.93% in the validation set were predicted to respond and not respond to orthostatic training, respectively. Compared with the actual follow-up results, the sensitivity, specificity, and accuracy of the acceleration index were 89.5%, 77.8%, and 83.8%, respectively, for predicting orthostatic training efficacy (Table 5).

### Discussion

We found that, compared with non-responders, children with POTS who responded well to orthostatic training demonstrated remarkably decreased electrocardiographic acceleration index. Thus, the acceleration index could be used as a predictor for orthostatic training effectiveness in children with POTS. When the acceleration index < 27.93% was used

**Table 5** Results of external validation of electrocardiographic acceleration index in predicting the efficacy of orthostatic training in children with POTS

Electrocardiographic acceleration index-predicted efficacy outcome	Clinical standard-based follow-up efficacy outcome, <i>n</i>		Total
	Responders	Non-responders	
Responders	17	4	21
Non-responders	2	14	16
Total	19	18	37

The sensitivity, specificity, and accuracy of ECG acceleration index in predicting the efficacy of orthostatic training were 89.5%, 77.8%, and 83.8%, respectively

*POTS* postural tachycardia syndrome

as a threshold condition, the sensitivity and specificity in the prediction of orthostatic training effectiveness were 85.7% and 69.2%, respectively. External validation showed that electrocardiographic acceleration index predicted orthostatic training effectiveness in children with POTS, and its sensitivity, specificity, and accuracy were 89.5%, 77.8%, and 83.8%, respectively.

The current study revealed that orthostatic training was more effective in children with POTS who had lower electrocardiographic acceleration index. This finding aligns with a previous study by Tao et al., which demonstrated that children with vasovagal syncope (another form of orthostatic intolerance) and decreased mean acceleration index responded more favorably to orthostatic training [26]. Ector et al. [27] showed that patients with autonomic dysfunction experienced clinical improvement solely through orthostatic training, without requiring medical intervention. They concluded that repeated orthostatic stress exposure may treat the cardiovascular reflex impairment, which can be adjusted and restored with long-term orthostatic training treatment. Abe et al. revealed that orthostatic self-training once or twice a day could prevent neurally mediated syncope during 1–11 months of follow-up [28, 29].

Electrocardiographic acceleration index reflects the immediate change in heart rate as the patient switches from the supine to an upright position, which reflects sympathetic activity according to the previous studies [30]. Sundkvist et al. noted a positive correlation between electrocardiographic acceleration index and plasma epinephrine content during the initial 1 min post-standing ( $r=0.59$ ,  $P<0.05$ ) [13]. Additionally, several studies have indicated that patients with diabetes and autonomic neuropathy who exhibit lower electrocardiographic acceleration index also display reduced adrenergic responses [31, 32]. Another previous study showed a reduction in maximum heart rate

during HUTT and a significant rise in systemic vascular resistance after 6 weeks of orthostatic training [6]. Consequently, according to these studies and the results in our study, we hypothesized that individuals with POTS, showing relatively lower acceleration index, might experience inadequate orthostatic sympathetic activation, and, thus, might derive greater benefits from orthostatic training. Although it is known that a considerable portion of patients with POTS demonstrate increased sympathetic nervous system tone (known as hyperadrenergic POTS), however, another subtype with partial peripheral sympathetic denervation (known as neuropathic POTS) also has been reported [33]. Under normal conditions, postural stress induces compensatory vasoconstriction through sympathetic activation triggered by baroreceptors to maintain normal orthostatic blood pressure and cerebral perfusion. However, the compensatory physiological regulation mechanism in the patients with neuropathic POTS is damaged, and the venous return is continuously insufficient; thus, the heart rate in standing position abnormally increases, and orthostatic intolerance occurs [34]. Therefore, the therapeutic effect of upright training therapy may be the result of improving impaired sympathetic activity and reducing the sensitivity of cardiopulmonary receptors, so it could increase peripheral vascular resistance [6, 7, 22]. We speculated that POTS patients with lower acceleration index would obtain more benefits from orthostatic training since those patients might have a damaged sympathetic system-controlled vasoconstrictor reserve [35]. However, whether children with lower acceleration index are the “neuropathic POTS” subtype should be identified in further studies. And the specific mechanisms by which orthostatic training improves the symptoms of POTS should be clarified in the future.

POTS is a complex disorder affecting multiple systems, characterized by persistently elevated heart rate and symptoms of orthostatic intolerance following postural changes, significantly impacting the daily life of patients and their families [32, 36]. Orthostatic training therapy is recommended for children with POTS as it enhances autonomic function and is convenient to implement [37]. However, the pathogenesis of POTS varies among individuals. As mentioned above, orthostatic training may mainly improve impaired sympathetic activity; therefore, unselective use of orthostatic training in all children with POTS may result in limited efficacy. As shown in this study, among the 91 children with a confirmed diagnosis of POTS and who received orthostatic training, the total effective rate was only 51.6%. Thus, if children with POTS characterized by autonomic dysfunction are predicted before treatment and individualized orthostatic training treatment is provided, a significant improvement is noted in the orthostatic training effectiveness in children with POTS [38].



A previous study [10] demonstrated that, compared with normal controls, supine corrected QT dispersion in children with POTS markedly increased, whereas, compared with non-responders, responders to orthostatic training demonstrated increased supine corrected QT dispersion before treatment. When the cutoff value is  $> 43.0$  ms, the sensitivity and specificity of effective treatment with autonomic functional exercise are 90% and 60%, respectively. Therefore, in children with POTS, pretreatment-corrected QT dispersion helps to predict the efficacy of autonomic exercise treatments such as orthostatic training. QT interval dispersion requires measurement of a 12-lead QT interval and corrected QT interval involves a more complex formula for calculation. Although the corrected QT interval dispersion demonstrated high sensitivity, the specificity was only 60%. Lu et al. [10] demonstrated that children treated with orthostatic training also received other methods of autonomic function training such as rubbing the skin of the medial extremities with a dry towel. Therefore, further studies are warranted to enhance the prediction of orthostatic training effectiveness in children with POTS.

This study explored the biomarkers from ECG to predict the effectiveness of orthostatic training in treating POTS in children. Electrocardiographic acceleration index is highly sensitive and specific in the prediction of orthostatic training effectiveness in children with POTS, and the result has been confirmed using a validation set. Meanwhile, the acceleration index can be easily promoted in hospitals at all levels because it is noninvasive, convenient, and inexpensive.

The main limitations of this study include the retrospective study design and the relatively small sample size. Moreover, there was a limitation about the inclusion of patients. The patients were recruited from a single medical center. Prospective, large-sample size multicenter studies should be conducted in the future to further explore the predictive value of electrocardiographic acceleration index for long-term outcomes in children with POTS after orthostatic training. Another limitation is the absence of a healthy control group showing normal acceleration index levels and a control group with orthostatic intolerance but without POTS, such as neurocardiogenic syncope/pre-syncope. Additionally, comorbidities like joint hypermobility and mast cell activation syndrome were not evaluated in all children with POTS in our study. Due to the nature of the retrospective study and the limited number of cases, no subgroup assessment was performed. It would be interesting to explore how the acceleration index changes when some comorbidities are combined in the future. It is also worth noting that the accelerative response of heart rate within the first minute after standing is also seen in initial orthostatic hypotension [39], which is can be seen in children with POTS. It will be interesting to investigate whether there is a difference in

acceleration index between POTS patients with and without initial orthostatic hypotension.

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**Authors' contributions** All authors contributed to the study conception and design. The authors' contributions are as follows: B. X. and Y. G. had primary responsibility for the protocol development, patient enrollment, data collection and verification, and preliminary data analysis and wrote the draft. Q. Z. analyzed the data and revised important content. Y. L., J. D., and H. J. supervised the design and execution of the study, checked the data analysis, contributed to the writing of the manuscript, and had a final approval of the manuscript submitted. All authors read and approved the final manuscript.

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**Data availability** No datasets were generated or analysed during the current study.

## Declarations

**Ethics approval** This study was conducted in accordance with the Declaration of Helsinki's principles. This study has been reviewed and approved by the Ethics Committee of Peking University First Hospital (2022 [496]).

**Consent to participate** Informed consent was obtained from the parents.

**Competing interests** The authors declare no competing interests.

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