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Acceleration Index Predicts Efficacy of Orthostatic Training on Vasovagal Syncope in Children

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Objective To explore the value of the acceleration index as a predictor of therapeutic response to orthostatic training in children with vasovagal syncope (VVS).

Study design Thirty-three children with VVS were recruited and treated with orthostatic training. The therapeutic response of each patient was evaluated after 3 months of treatment. A Pearson correlation was calculated between the acceleration index and the severity of VVS. The value of the acceleration index in predicting the therapeutic response to orthostatic training was assessed by analysis of the receiver operating characteristic curve.

Results Among the 33 children with VVS, 20 were found to be responders and the remaining were nonresponders. The mean acceleration index was significantly lower in responders compared with nonresponders (21.10 ± 6.61 vs 31.36 ± 9.00; $P = .001$) and it was negatively correlated with positive response time in the head-up tilt test, with systolic blood pressure and with diastolic blood pressure at positive response time in the head-up tilt test ($P < .05$). The receiver operating characteristic curve for the predictive value of the acceleration index showed that the area under the curve was 0.827 (95% CI, 0.676-0.978; $P = .002$), and a cutoff value of the acceleration index of 26.77 yielded a sensitivity of 85.0% and a specificity of 69.2%.

Conclusions The acceleration index may be useful for predicting the efficacy of orthostatic training on VVS in children. *(J Pediatr 2019;207:54-8).*

Syncope is common in children, accounting for 1%-2% of pediatric emergency department visits. It is precisely defined as a transient loss of consciousness due to global cerebral hypoperfusion, accompanied by loss of muscular tension and failure to maintain an active position.[1,2] An estimated 60%-70% of cases of syncope in children are vasovagal syncope (VVS).[3,4] Recurrent syncope tends to overstress children and their parents by impacting their quality of life and even causing unpredictable injuries from falling.[5] Therefore, effective treatment for children with VVS is extremely important. Numerous factors, including autonomic nervous dysfunction, vasomotor dysfunction, abnormal Bezold-Jarisch reflex, and genetic factors, are considered potential mechanisms for VVS.[6-9] As a result, orthostatic training to improve autonomic nervous function has been considered an important treatment option for pediatric patients with VVS.[10-12] The differing predominant underlying mechanisms of VVS in children limit the efficacy of general orthostatic training for all cases, however.[13,14] To increase the efficacy of orthostatic training for children with VVS, the ability to identify in advance those patients with VVS who show evidence of autonomic nervous dysfunction as the possible predominant mechanism is important, because those patients are more likely to be responsive to orthostatic training.

The acceleration index reflects the immediate variation of a patient's heart rate on a change from the supine to the upright position.[15] A positive correlation between the acceleration index and plasma epinephrine levels within the first minute after standing was observed by Sundkvist et al,[16] which led the authors to suggest that the acceleration index might represent sympathetic activity. Other studies have supported this conclusion.[17,18] Therefore, in the present study, we attempted to examine whether the acceleration index could effectively predict the efficacy of orthostatic training in children with VVS.

Methods

Thirty-three children with VVS (17 males and 16 females) were recruited in this case-control study. The patients presented at the Department of Pediatrics at

AUC	Area under the receiver operating characteristic curve
BRS	Baroreflex sensitivity
HUTT	Head-up tilt test
ROC	Receiver operating characteristic
VVS	Vasovagal syncope

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Peking University First Hospital complaining of syncope between July 2016 and February 2018. The average patient age was 10.5 ± 2.7 years. A detailed history, physical examination, and medical tests to exclude the possibility of cardiogenic syncope, neurologic diseases, and metabolic diseases were obtained for each patient. VVS was diagnosed using the head-up tilt test (HUTT).[19] Criteria for VVS in children include (1) syncopal attack in older children; (2) the presence of predisposing factors, such as persistent standing, rapid position changes, stifling environment, and depression; (3) positive HUTT; and (4) the exclusion of other diseases that could produce syncope.[19] This study was approved by the Ethics Committee of Peking University First Hospital, and written informed consent was obtained from a parent/guardian of each enrolled patient.

Patients were instructed to avoid taking any medication that could influence autonomic nervous system activity for at least 5 times the half-life of the relevant drugs and to fast for 4 hours before the HUTT. The testing environment was quiet and dimly lit, with a suitable room temperature. Electrocardiography, heart rate, and blood pressure were continuously monitored using the Finometer PRO monitoring system (Finapres Medical Systems, Enschede, The Netherlands). Patients were positioned on a tilt table (HUT-821; Beijing Juchi, Beijing, China) at a 60° tilt after 10 minutes of rest and maintained in this position for 45 minutes. If a positive response was observed, then the test was terminated. Resuscitation facilities were prepared before the test.[19] Positive signs of HUTT are as follows: (1) significant hypotension (ie, systolic blood pressure ≤80 mmHg, diastolic blood pressure ≤ 50 mmHg, or a ≥25% decrease in mean blood pressure), (2) bradycardia (ie, heart rate <75 bpm in children aged 4-6 year, <65 bpm in those aged 6-8 years, and <60 bpm in those aged >8 years), (3) sinus arrest, or (4) second-degree or greater atrioventricular block and asystole persisting for >3 seconds.[19]

In the protocol for immediate heart rate alteration from supine position to standing, medications that could influence autonomic nervous system activity were also avoided by patients for at least 5 times the half-life of the relevant drug before the test. The test was conducted at a suitable temperature and in a quiet environment. Electrocardiograms were continuously monitored using the HUT-821 (Beijing Juchi). Patients were positioned on a tilt table at 90° passively after a 10-minute rest and maintained in the upright position for 6 minutes. The acceleration index was calculated as follows:

acceleration index = [(A - B)/A] × 100,

where A is the mean duration (in milliseconds) of the beat-to-beat interval (RR interval) during the 15 seconds before changing positions and B is the first shortest RR interval after changing positions.[20,21]

All patients were treated with orthostatic training twice a day for 3 months after being diagnosed with VVS. In the orthostatic training program, the patient was instructed to stand against a wall for a gradually increasing duration of between 3 minutes and 30 minutes, depending on his or her orthostatic tolerance, with the feet 15 cm away from the wall and leaning with the upper back against the wall without moving.[10,22-24]

Follow-up was carried out in the outpatient setting or via telephone after 3 months of orthostatic training. Questionnaires were used to evaluate compliance, as well as the occurrence and frequency of syncope. Patients with no syncopal events from the beginning of treatment were considered "responders," and those with 1 or more syncopal events were considered "nonresponders."

Data analysis was performed using SPSS version 21.0 (IBM, Armonk, New York). Data were expressed as mean ± SD, and the Shapiro-Wilk test was applied to evaluate the normality of the distribution of continuous data before statistical analysis. The independent Student *t* test was used to compare continuous variables with normal distribution between the 2 groups. The χ^2 test was performed to compare differences in the proportion of categorical variables between the 2 groups. The Pearson correlation test was used to examine the correlation between normal distribution indices. A receiver operating characteristic (ROC) curve was used to evaluate the predictive value of the acceleration index in assessing the therapeutic effect of orthostatic training, and the area under the ROC curve (AUC) was calculated to evaluate the predictive value of the acceleration index. The acceleration index was confirmed as a reliable predictor if the 95% CI of the AUC did not contain 0.5 or $P < .05$. An AUC of 0.5-0.7 was considered to indicate low predictive value; 0.7-0.9, moderate predictive value; and >0.9, high predictive value. $P < .05$ was considered statistically significant.

Results

Among the 33 study patients, 22 showed a vasoinhibitory response, 10 had a mixed inhibitory response, and 1 had a cardioinhibitory response during the HUTT. According to the follow-up results, 20 patients (60.6%) were classified as responders, and the remaining 13 (39.4%) were nonresponders.

No significant differences were found between responders and nonresponders in terms of sex ratio, age, weight, height, supine blood pressure, hemodynamic patterns of VVS, positive response time in the HUTT, or heart rate and blood pressure at the positive response time in the HUTT ($P > .05$) (**Tables I** and **II**). However, the mean acceleration index was significantly lower in responders compared with nonresponders (21.10 ± 6.61 vs 31.36 ± 9.00; $P = .001$) (**Table III**).

In all patients, the acceleration index was negatively correlated with positive response time in the HUTT ($r = -0.360$; 95% CI, -0.626 to -0.019; $P = .040$). In addition, the acceleration index was negatively correlated with systolic blood pressure ($r = -0.355$; 95% CI, -0.622 to -0.013; $P = .043$) and diastolic blood pressure ($r = -0.379$; 95% CI, -0.639 to -0.041; $P = .030$) at a positive response time in the HUTT (**Figure**, A-C).

In the ROC curve of the acceleration index for predicting the therapeutic effect of orthostatic training, the AUC was

Table I. Baseline characteristics of responders and nonresponders

Characteristics	Characteristics						
	Sex, male/ female, n	Age, y, mean ± SD	Weight, kg, mean ± SD	Height, cm, mean ± SD	Supine SBP, mmHg, mean ± SD	Supine DBP, mmHg, mean ± SD	Patterns of VVS, VI/MI + cardioinhibitory response, n
Responders (n = 20)	9/11	10.1 ± 2.9	39.6 ± 15.2	146.6 ± 16.8	111 ± 10	70 ± 7	14/6
Nonresponders (n = 13)	8/5	11.1 ± 2.4	43.6 ± 11.3	150.5 ± 15.4	113 ± 13	65 ± 10	8/5
χ^2/*t* value*	0.863	−1.054	−0.819	−0.673	−0.519	1.682	—†
P value	.353	.300	.419	.506	.607	.103	.714

DBP, diastolic blood pressure; *MI*, mixed inhibitory response; *SBP*, systolic blood pressure; *VI*, vasoinhibitory response.
*The χ^2 test was used in comparisons of sex ratio and patterns of VVS, whereas the Student *t* test was applied to comparisons of other items.
†Fisher exact test.

calculated as 0.827 (95% CI, 0.676-0.978; *P* = .002). Using an acceleration index of 26.77 as the cutoff value, the sensitivity was 85.0%, the specificity was 69.2%, and the positive predictive value was 78.8% (**Figure**, D).

Discussion

Previous studies have reported varying effectiveness of the unselected use of orthostatic training. In one study, only 57% of patients with VVS showed improvement in symptoms after orthostatic training.[13] In the present study, we found a significantly lower mean acceleration index in responders compared with nonresponders (21.10 ± 6.61 vs 31.36 ± 9.00; *P* = .001), and noted that an acceleration index cutoff of 26.77 yielded a sensitivity of 85.0% and a specificity of 69.2% for predicting the effectiveness of orthostatic training in children with VVS.

The mechanisms underlying the better therapeutic efficacy of orthostatic training in patients with a lower acceleration index are not fully understood, in part because of the complexity of the mechanisms for VVS. The acceleration index reflects sympathetic activity. Normally, orthostatic stress evokes compensatory vasoconstriction via an increase in sympathetic nerve traffic to maintain normal blood pressure and cerebral perfusion. Withdrawal of sympathetic activity with the resulting predominant parasympathetic activity can result in the failure of this compensatory mechanism, leading to decreased blood pressure and possibly syncope during tilt testing.[25,26] The therapeutic efficacy of orthostatic training is thought to be the result of augmenting sympathetic activity and reducing vascular compliance, which increases peripheral vascular resistance and reduces blood accumulation in the lower part of the body.[10,11,27]

Therefore, indices to identify relatively low sympathetic activity may be useful for selecting patients for orthostatic training. Chun et al identified baroreflex sensitivity (BRS) in the supine position before treatment as predictive of the efficacy of orthostatic training.[28] In their study, the mean BRS was lower in nonresponders compared with responders (7.99 ± 5.84 ms/mmHg vs 18.17 ± 10.09 ms/mmHg; *P* = .008), and a BRS cutoff of 8.945 ms/mmHg yielded a sensitivity of 86.5% and a specificity of 80.0% for predicting effectiveness.[28] However, specific equipment for continuous heart rate and blood pressure monitoring is needed for calculating BRS, and this equipment is not widely available in the clinic setting, which limits the clinical application of this index. The measurement of acceleration index has distinct advantages over BRS, including ease and rapidity of performance and lower cost.[29] In the present study, the hemodynamic patterns of VVS did not differ between responders and nonresponders, suggesting no significant impact of hemodynamic patterns on the results.

In conclusion, the acceleration index is a promising indicator for predicting the therapeutic efficacy of orthostatic

Table II. Positive response characteristics of responders and nonresponders in the HUTT

Characteristics	Characteristics			
	Positive response time in HUTT, min, mean ± SD	HR at positive response time in HUTT, bpm, mean ± SD	SBP at positive response time in HUTT, mmHg, mean ± SD	DBP at positive response time in HUTT, mmHg, mean ± SD
Responders (n = 20)	18.2 ± 13.3	94 ± 34	73 ± 12	43 ± 9
Nonresponders (n = 13)	19.7 ± 15.8	90 ± 35	68 ± 9	43 ± 10
t value	−0.018	0.358	1.215	0.010
P value	.985	.723	.234	.992

HR, heart rate.

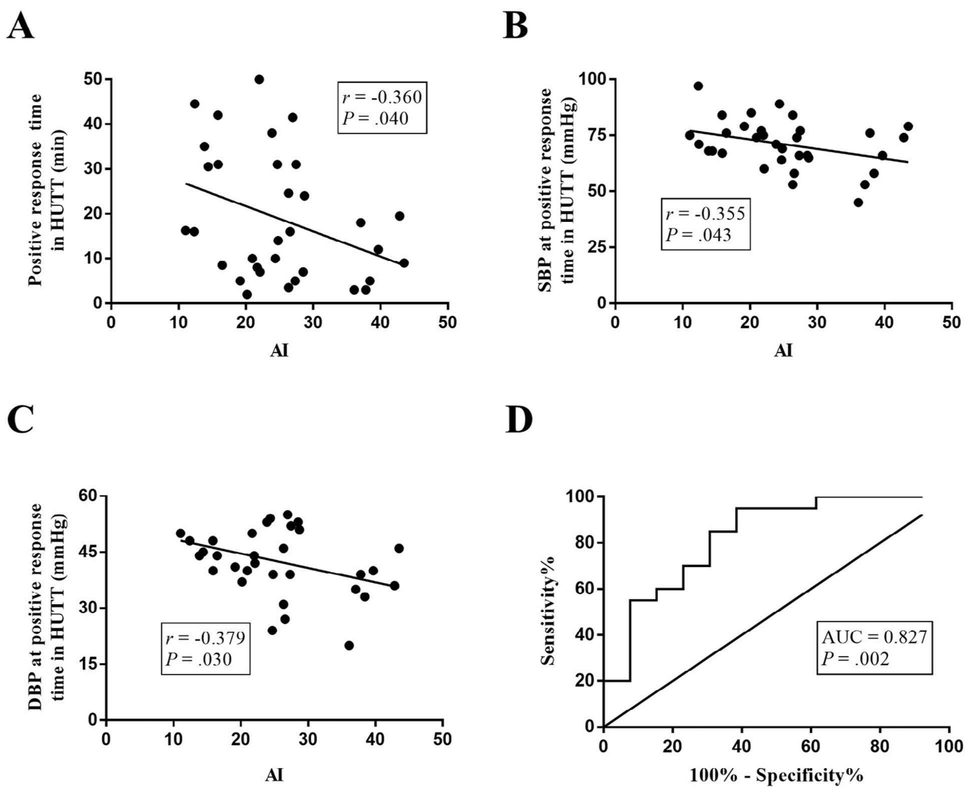

Figure. Correlations among the acceleration index, the severity of vasovagal syncope, and the ROC curve of various cutoff values of the acceleration index for predicting the therapeutic effect of orthostatic training in children with VVS. Correlations between the acceleration index and **A**, positive response time in HUTT; **B**, systolic blood pressure; and **C**, diastolic blood pressure at positive response time in HUTT are shown. **D**, the AUC is 0.827 (95% CI, 0.676-0.978; *P* = .002). *AI*, acceleration index; *DBP*, diastolic blood pressure; *SBP*, systolic blood pressure.

training in children with VVS. An acceleration index <26.77 predicts a better therapeutic response. The major limitation of this study is the relatively small sample size. Large-scale multicenter investigations are needed to study the predictive value of the acceleration index in the prognosis of patients with VVS after intervention with pharmacologic therapy. ■

Table III. Immediate heart rate alteration on change from supine to upright position

Characteristics	Alteration		
	A, ms, mean ± SD	B, ms, mean ± SD	Acceleration index, mean ± SD
Responders (n = 20)	711.67 ± 95.63	560.35 ± 82.08	21.10 ± 6.61
Nonresponders (n = 13)	826.86 ± 138.58	557.60 ± 46.93	31.36 ± 9.00
t value	−2.831	0.109	−3.774
P value	.008	.914	.001

A, mean duration of the RR interval during the 15 seconds before changing positions.
B, the first shortest RR interval after changing positions.

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