Prognostic Value of Biomarkers in Children and Adolescents With Orthostatic Intolerance

Huijuan Yan¹, Shuo Wang², Hong Cai¹, Juan Zhang¹, Ping Liu¹, Yuwen Wang¹, Runmei Zou¹ and Cheng Wang¹*

¹ Department of Pediatric Cardiovasology, Children’s Medical Center, The Second Xiangya Hospital, Central South University, Changsha, China, ² Department of Neonatology; Xiangya Hospital, Central South University, Changsha, China

Orthostatic intolerance (OI) refers to a series of symptoms that occur during upright standing, which can be relieved when returned to the supine position. OI is a common cause of syncope in children and adolescents. In recent years, more and more studies have been carried out to assess the prognosis of OI by using biomarkers, among which, flow-mediated vasodilation, left ventricular ejection fraction and fractional shortening, hemodynamic change during head-up tilt test, detection of 24-h urinary sodium excretion, body mass index, midregional pro-adrenergocin, and erythrocytic H₂S producing rate are relatively stable, inexpensive, and easy to obtain. With the help of biomarkers, individualized treatment can be carried out to improve the long-term prognosis of children and adolescents with OI. This article reviews the prognostic value of biomarkers in children and adolescents with OI.

Keywords: biomarkers, prognosis, children, adolescents, orthostatic intolerance

INTRODUCTION

Orthostatic intolerance (OI) is a series of symptoms during upright standing that can be relieved when returned to the supine position, such as lightheadedness, headache, fatigue, visual difficulties, pallor, palpitations, nausea, and sweating (1). OI is a clinical syndrome of autonomic regulation disorders. Head-up tilt test (HUTT) is an important method for diagnosing OI. OI is mainly divided into several hemodynamic types, including vasovagal syncope (VVS), postural tachycardia syndrome (POTS), orthostatic hypotension (OH), and orthostatic hypertension (OHT). VVS and POTS, the main forms of pediatric OI, are underlying causes of neurally mediated syncope (NMS), which is defined as syncope due to autonomic nerve dysfunction (2, 3). Hu et al. (4) reported that the incidence of syncope in children and adolescents aged 2~18 years in Changsha was 17.37%, with significant gender differences in different age groups. Bayram et al. (5) and Li et al. (6) reported that 30~50% of children experienced at least one episode of syncope during the adolescent period, most of whom were females and VVS accounted for 60~80% of all pediatric syncope. Acute OI, such as VVS, usually manifests as syncope, which is a transient loss of consciousness (TLOC) and body balance disorder due to transient cerebral ischemia, characterized by a rapid onset, short duration, and spontaneous recovery (7). Two main groups of TLOC are "TLOC due to head trauma" and “non-traumatic TLOC,” and the diagnosis of VVS should exclude other causes of non-traumatic TLOC such as epileptic seizures and psychogenic pseudosyncope (7, 8). Chronic OI is defined as OI that presents for at least 3 months, an example is POTS (9). The symptoms of POTS in adolescents usually appear in early puberty, after the age of 9 years old, and are more common in
females than males (10, 11). Compared with VVS, syncope occurs less frequently in POTS, but most adolescent patients experience fatigue and some form of chronic pain (12). Its pathophysiology is heterogeneous, and the course may vary from patient to patient (13, 14), while comorbidity types and treatment measures can affect short- and long-term outcomes (15). Clinical symptoms of OI may fade or be relieved by the end of the process of the physical changes of puberty, or may accompany patients for a lifetime (16, 17), but it is not associated with significant mortality (18–20).

Abnormal Bezold–Jarish reflex, high level of catecholamine, and dysfunction of the autonomic nervous system, etc., may play important roles in the pathophysiology of VVS (6). Hypovolemia, peripheral vascular dysfunction, hyperadrenergic stimulation, and abnormality of the autonomic nervous function were thought to be involved in the pathogenesis of POTS (21). The current treatments for OI mainly include non-pharmacological therapy (health education, autonomic nervous function exercise, and increasing the intake of water and salt), pharmacological therapy (midodrine hydrochloride and metoprolol) and pacemaker therapy (3). The majority of patients respond to a combination of physical methods as well as pharmacotherapy (22), and can anticipate a full and complete recovery (23, 24). Although OI is a functional cardiovascular disease with self-limitation and favorable prognosis (25, 26), the occurrence of symptoms can seriously affect the physical and mental health, learning ability, and quality of life of children (27, 28), so it is of great necessity to find simple indicators to describe the prognosis of OI. Biomarkers can be used for qualitative or quantitative testing to reflect the changes in disease conditions and assess the efficacy. They provide an objective basis for guiding clinical judgment on the prognosis of VVS and POTS in children and adolescents, which is of great clinical value. Current biomarkers for evaluating the prognosis of OI mainly include flow-mediated vasodilation (FMD) (29), left ventricular ejection fraction (LVEF) and fractional shortening (LVFS) (30), 24-h urinary sodium excretion (31), body mass index (BMI) (32), mid-regional fragment of pro-adrenomedullin (MR-proADM) (33), erythrocytic hydrogen sulfide (H₂S) producing rate (34), heart rate (HR), etc. Since there are few studies on biomarkers for other types of OI such as OH and OHT, we have not yet retrieved the relevant literature that meets the requirements. This article provides a review of the prognostic value of biomarkers, predictors of treatment efficacy, and recurrence, for OI, especially for VVS and POTS.

Biomarkers in Prognostic Assessment of Pediatric Vasovagal Syncope

Predictors of Therapeutic Efficacy in the Management of Pediatric Vasovagal Syncope

Multiple biomarkers have predictive value for the therapeutic efficacy of pediatric VVS. Wu et al. (35) and White et al. (36) found that abnormal regulation of vascular endothelium function may be involved in the occurrence of VVS. Color Doppler ultrasound detection of FMD changes in the brachial artery is a non-invasive examination that can reflect vascular endothelial function in children with VVS. Zhang et al. (37) found a significant increase in FMD in children with VVS compared with healthy children (11.93 ± 4.46 vs. 8.46 ± 2.18 %, p < 0.05). The enhancement of FMD of blood vessels during postural changes in children with VVS may lead to blood stasis in the lower extremities and abdomen, which leads to syncope through the Bezold–Jarisch reflex. Zhang et al. (29) found that FMD in children with VVS after treatment of midodrine hydrochloride (MD) was significantly lower than that before treatment (11.07 ± 3.11 vs. 7.64 ± 1.81%, p < 0.001), and FMD in patients with good therapeutic efficacy was significantly higher than that with poor therapeutic efficacy (11.93 ± 2.83 vs. 7.80 ± 1.63%, p < 0.01). For a FMD of 8.85% as cutting value to predict efficacy of MD for treating VVS, the ROC curve showed that the area under the curve (AUC) was 0.895, the sensitivity and specificity of which were 90.0 and 80.0%. FMD could be a predictor of the efficacy of MD for treating children with VVS. The status of high catecholamine is one of the pathogenesis of VVS (38), and a certain dose of catecholamine such as dobutamine can increase LVEF and LVFS in humans with normal cardiac function (39, 40). Therefore, LVEF and LVFS may reflect the level of plasma catecholamine to an extent. Song et al. (30) followed up 30 children with VVS after metoprolol treatment, the LVEF and LVFS in the reactive group were significantly higher than those in the non-reactive group (LVEF: 72.8 ± 2.8 vs. 65.5 ± 4.6%, p = 0.001; LVFS: 41.1 ± 1.9 vs. 35.8 ± 3.6%, p = 0.002). To predict the efficacy of metoprolol intervention for 6 months, when the AUC was 0.906, with LVEF of 70.5% as a cutoff value, its sensitivity and specificity were 81.3 and 88.9%, respectively; when the AUC was 0.903, with LVFS of 37.5% as a cutoff value, its sensitivity and specificity were 93.8 and 66.7%, respectively. This study showed that children with VVS who had relatively high levels of LVEF and LVFS might achieve ideal therapeutic efficacy with β-blocker therapy. LVEF and LVFS, which are measured by echocardiography, are relatively stable, reliable, and safe. The increase in the level of catecholamine in the body can also be characterized by an excessive increase in HR. Zhang et al. (41) investigated the value of HR changes during HUTT and predictive value thereof in evaluating the efficacy of metoprolol therapy in children with VVS. It was found that the HR before positive response to HUTT was significantly higher in the effective treatment group than that of the ineffective treatment group (123 ± 15 vs. 96 ± 17 beats/min, p < 0.01), HR increment before positive response to HUTT showed significant difference among groups (42 ± 16 vs. 18 ± 13 beats/min, p < 0.01). Compared with that of the baseline value, if an increase of 30 beats/min in HR before positive response to HUTT was taken as a cutoff value, with respect to predicting the metoprolol efficacy in the treatment of VVS, the sensitivity was 81.0%, and the specificity was 80.0%. It may be more effective to choose β-blockers for those with a significant HR increase before positive response to HUTT. The QT interval dispersion (QTd) reflects the difference of electrical activity of cardiomyocytes in different parts of the ventricle, which is closely related to the autonomic
nervous function in children. Meanwhile, autonomic dysfunction
is one of the pathogenesis of VVS. Liu et al. (42) followed
up 27 children with cardioinhibitory vasovagal syncope (VVS-
CI). They found that QTd of the non-responsive group after
intervention (non-drug intervention or oral rehydration salts)
was longer than that of the responsive group (37 ± 4 vs. 29 ±
5 ms, p < 0.001). The AUC was 0.906. Taking QTd of 34.50 ms
as the cutoff value, the sensitivity of predicting response to VVS-CI
intervention was 90.0% and the specificity was 82.4% (Table 1).
QTd of electrocardiogram has a good estimation value in the
prognosis of VVS-CI in children and adolescents, but further
research is needed to select specific therapy. In summary, LVEF
has the largest AUC (0.906). Therefore, LVEF was chosen as a
predictor of the efficacy of β-blocker therapy on VVS in children
with priority.

**Risk Factors of Recurrence of Pediatric Vasovagal Syncope**

Some biological indicators are valuable for the recurrence prediction of VVS. Hemoglobin concentration (HGB) can be
used to estimate blood volume in the clinic. Kabul et al. (43)
reported a close correlation between platelet count (PLT) and
autonomic nerve. Song et al. (44) reported the blood routine
parameters of 63 children with VVS and found that baseline
HGB (HR = 1.055, 95% CI: 1.007–1.105), mean corpuscular
hemoglobin (MCH) (HR = 0.612, 95% CI: 0.423–0.884), and
PLT (HR = 1.015, 95% CI: 1.006–1.024) might be the influencing factors of the syncopal recurrence of VVS in children. The risk
of future syncope events increased by 5.5 and 1.5% for each
additional unit of HGB and PLT, and decreased by 38.8% for each
additional unit of MCH. Ye and Ma (45) also reported the blood routine results in 82 children with VVS, and found that HGB,
PLT, and MCH were higher in the recurrence group than those
in the non-recurrence group (HGB: 135.91 ± 16.33 vs. 117.22 ±
15.74 g/L, p < 0.05; PLT: 259.95 ± 47.32 × 10^9/L vs. 228.75 ±
55.33 × 10^9/L, p < 0.05; MCH: 29.71 ± 3.52 vs. 22.10 ± 2.11
pg, p < 0.05). Increasing HGB, PLT, and MCH might be the
risk factors of recurrence in children with VVS. Children in both
studies were treated with basic treatment (including predisposing
causes avoiding, standing training, autonomic nervous function
exercise, and oral rehydration salts). Both studies demonstrated
the relationship between HGB, PLT, and syncope recurrence, but
the contrary results of MCH. As the sample size of the study
is small, a multi-center large sample study is needed to increase the
conviction and reliability of the results.

In recent years, the research on the indicators for predicting the recurrence of VVS has been continuously updated.
Chronotropic competence refers to the function that the HR
increases appropriately with the increase in the metabolic
needs of the body under the action of various physiological
and pathological factors (46). Zhang et al. (47) reported that
the chronotropic competence was an important indicator of
cardiac autonomic nervous function in children with VVS. They
analyzed 28 children with VVS, of which four children with
cardioinhibitory type had chronotropic incompetence (CI), while
the incidence of CI in children with vasodepressor type was only
33.3%. VVS children with CI responded poorly to treatment
(including health education, oral rehydration salt, metoprolol, or
midodrine), and the recurrence rate of syncope was significantly
higher than that of children without CI (52.9 vs. 10.0%, p < 0.05).
This study suggests that CI may be a significant predictor for poor
prognosis in children with VVS.

**BIOMARKERS IN PROGNOSTIC ASSESSMENT OF PEDIATRIC POSTURAL TACHYCARDIA SYNDROME**

**Predictors of Non-pharmacological Therapy in Postural Tachycardia Syndrome**

Physical therapy and sleep-promoting therapy are important
parts of non-pharmacological therapy in children with POTS. Lu
et al. (48) explored whether electrocardiography (ECG) variables
could be used to predict responses to physical treatment in
children with POTS. The results showed that 40 children with
POTS had prolonged baseline QTd and HR-corrected QTd
(QTcd) compared with healthy children, and a longer baseline
QTd for responders to physical treatment (69.2 ± 31.2 vs. 43.5
± 25.9 ms, p < 0.05). When the AUC was 0.730, using 43 ms as a
cutoff of QTcd, yielded a sensitivity of 90.0% and a specificity of
60.0%. Physical treatment is a safe and inexpensive approach and
frequently used in the clinic, so QTcd has great clinical practical
value. Circulating catecholamine excess is considered as one of
the pathogenesis of POTS. The levels of the catecholamines
have been found to correlate with cortisol levels (49). Follenius
et al. (50) found that insufficient sleep or sleep disruption is
associated with significant increases in plasma cortisol levels.
Salivary cortisol concentrations have been used to predict the
efficiency of sleep-promoting treatment in children with POTS
since salivary cortisol levels reflect serum cortisol levels (51). Lin
et al. (52) found that cortisol concentrations in children with
POTS (40 cases) were significantly higher at all time points than
those in the control group (p < 0.05 for all) and significantly
higher in responders than in non-responders (4.83 ± 0.73 vs.
4.05 ± 0.79 ng/ml, p = 0.003). With the AUC of 0.758, salivary
cortisol >4.1 ng/ml at awakening yielded 83.3% sensitivity and
68.7% specificity in predicting therapeutic efficacy of
sleep-promoting treatment in POTS (Table 2). Salivary cortisol
determination helps to prevent and manage sleep problems,
which is of great significance to promote the physical and mental
health of children with POTS. Therefore, QTcd and salivary
cortisol can be used as predictors of non-drug treatment in
POTS children.

Hypovolemia has been reported to be associated with the
onset of POTS (21). The sodium content of the body determines
the volume of extracellular fluid, including plasma. Taking oral
rehydration salts (ORS) is an effective way to increase the
intake of water and salt, and multiple biological indicators have
predictive value for the efficacy of ORS. Zhang et al. (31) explored
whether 24-h urinary sodium excretion served as an indicator
of the efficacy of ORS in children with POTS (30 cases). The
results showed that 24-h urine sodium excretion of patients with
POTS was lower than controls (117.09 ± 58.63 vs. 193.88 ±

Fmotiers in Pediatrics | www.frontiersin.org 3 November 2021 | Volume 9 | Article 752123
91.12 mmol/24 h, p = 0.022). Symptom severity was negatively correlated with 24-h urinary sodium excretion (r = −0.754; p < 0.001). The AUC was 0.879. Taking the 24-h urine sodium concentration of 124 mmol/24 h as the cutoff value, the sensitivity and specificity of predicting the efficacy of POTS in children were 76.9 and 93.0%. The 24-h urine sodium excretion is a useful indicator because it can identify salt-deficient individuals and predict which ones will benefit most from increased salt intake. In addition, Li et al. (32) found that BMI in the POTS group (54 cases) was significantly lower than that in the control group (18.22 ± 3.23 vs. 20.62 ± 3.05 kg/m², p < 0.01), and the BMI in responders to ORS was significantly lower than that of non-responders (16.32 ± 2.28 vs. 20.43 ± 2.74 kg/m², p < 0.01). When the BMI was 18.02 kg/m², the AUC was 0.923, and it had high sensitivity (92.0%) and high specificity (82.8%) for predicting the efficacy of ORS treatment for POTS (32). A study by Stewart et al. suggested that BMI was associated with blood volume (61). BMI is a stable and inexpensive predictor and can be measured readily in the outpatient setting. Lu et al. (53) reported that in 35 children with POTS, ORS as an intervention, the baseline mean corpuscular hemoglobin concentration (MCHC) values of responders was higher than that of non-responders (351.1 ± 9.0 vs. 341.5 ± 12.2 g/L, p < 0.05). The AUC was 0.73. The use of a cutoff value for MCHC of 347.5 g/L yielded a sensitivity of 68.8% and a specificity of 63.2% in predicting the effect of ORS for treating POTS. A study by Lin et al. showed that low red blood cell volume played an important role in POTS (62), which was associated with hypovolemic state. The MCHC may

### TABLE 1 | Predictors of therapeutic efficacy of pediatric VVS.

| References       | Interventions | Biomarkers | Cutoff values | AUC  | Sensitivity (%) | Specificity (%) |
|------------------|---------------|------------|---------------|------|----------------|-----------------|
| Zhang et al. (29) | MD            | FMD        | >8.85%        | 0.895| 90.0           | 80.0            |
| Song et al. (33)  | Metoprolol    | LVEF       | ≥70.5%        | 0.906| 81.3           | 88.9            |
| Zhang et al. (41) | Metoprolol    | LVFS       | ≥37.5%        | 0.903| 93.8           | 66.7            |

MD, Midodrine hydrochloride; FMD, Flow-mediated vasodilation; LVEF, Left ventricular ejection fraction; LVFS, Left ventricular short axis shortening; HR, Heart rate; QTcd, HR-corrected QT interval dispersion; BMI, Body mass index; MCHC, Mean corpuscular hemoglobin concentration; TR, Triangular index; SDNN index, Standard deviation index of all sinus intervals; HR5, Instantaneous HR of HUTT at 5 min; HR10, Instantaneous HR of HUTT at 10 min; HRD5, Difference between instantaneous HR at HUTT 5 min and the baseline HR; HRD10, Difference between instantaneous HR at HUTT 10 min and the baseline HR.

### TABLE 2 | Predictors of therapeutic efficacy of pediatric POTS.

| References       | Interventions | Biomarkers | Cutoff values | AUC  | Sensitivity (%) | Specificity (%) |
|------------------|---------------|------------|---------------|------|----------------|-----------------|
| Lu et al. (48)   | Physical treatment | QTcd       | ≥43 ms        | 0.730| 90.0           | 60.0            |
| Lin et al. (52)  | Promoting sleep | Salivary cortisol | >4.1 ng/ml | 0.758| 83.3           | 68.7            |
| Zhang et al. (31) | ORS           | 24-h urinary sodium | <124 mmol/24h | 0.879| 76.9           | 93.0            |
| Li et al. (32)   | ORS           | BMI       | ≤18.02 kg/m²  | 0.923| 92.0           | 82.8            |
| Lu et al. (53)   | ORS           | MCHC     | >347.5 g/L    | 0.730| 88.8           | 63.2            |
| Lin et al. (54)  | ORS           | HRD       | ≥41 beats/min | 0.780| 84.0           | 56.0            |
| Li et al. (55)   | ORS           | BRSc     | ≥17.01 ms/mmHg| 0.855| 85.7           | 87.5            |
| Zhang et al. (33) | MD            | MR-proADM | >61.5 pg/ml   | 0.879| 100.0          | 71.6            |
| Yang et al. (34) | MD            | Erythrocytic H₂S producing rate | ≥27.1 nmol/min/10³ RBC | 0.813| 78.9           | 77.8            |
| Liao et al. (56) | MD            | FMD       | ≥9.85%        | 0.803| 74.4           | 80.0            |
| Zhang et al. (57) | Metoprolol    | Norepinephrine | >3.59 pg/ml | 0.785| 76.9           | 91.7            |
| Lin et al. (58)  | Metoprolol    | CNP      | >32.55 pg/ml  | 0.821| 95.8           | 70.0            |
| Wang et al. (59) | Metoprolol    | TR index | TR ≤33.7      | 0.807| 85.3           | 81.8            |
| Wang et al. (60) | Metoprolol    | SDNN index | SDNN ≤79.0 ms | 0.820|                |                 |

ORS, Oral rehydration salts; MD, Midodrine hydrochloride; HR, Heart rate; QTcd, HR-corrected QT interval dispersion; BMI, Body mass index; MCHC, Mean corpuscular hemoglobin concentration; TR, Triangular index; SDNN index, Standard deviation index of all sinus intervals; HR5, Instantaneous HR of HUTT at 5 min; HR10, Instantaneous HR of HUTT at 10 min; HRD5, Difference between instantaneous HR at HUTT 5 min and the baseline HR; HRD10, Difference between instantaneous HR at HUTT 10 min and the baseline HR.
reflect the characteristics of the red blood cells and, thus, predict the effectiveness of ORS therapy. Lin et al. (54) reported the change in HR during the HUTT of 54 children with POTS, which showed that compared with the non-responding group, the HR change during HUTT was greater in the responding group before treatment (46 ± 10 vs. 37 ± 9 beats/min, p = 0.001), and the upright maximum HR (HRmax) in 10 min was also higher in the responding group (122 ± 12 vs. 113 ± 10 beats/min, p = 0.010). ORS for children with POTS would be predicted to be effective when the HR difference (HRD) between orthostatic and supine position was 41 beats/min and the HRmax in upright for 10 min was 123 beats/min before treatment, its orthostatic and supine position was 41 beats/min and the HRmax predicted to be effective when the HR difference (HRD) between.

The MR-proADM is relatively stable and can reflect levels of adrenomedullin (ADM), which is related to vasodilation (64, 65). Peripheral vascular dysfunction is an important pathophysiological mechanism of POTS (21). Zhang et al. (33) found that plasma levels of MR-proADM in children with POTS (57 cases) were significantly higher than that in the control group [75.0 (62.5–96.0) vs. 58.5 (50.3–69.0) pg/ml, p < 0.01], and was higher in the effective group of MD treatment than that in the ineffective group [24.7 ± 9.9 vs. 13.5 ± 6.6 mmHg, p < 0.01]. The AUC was 0.855. A cutoff value of BRS of 17.01 ms/mmHg yielded the predictive sensitivity of 85.7% and specificity of 87.5%. Detection of BRS could well predict the disease outcome of POTS, and it was convenient, inexpensive, and non-invasive in the prediction. In summary, 24-h urine sodium excretion, BMI, MCHC, HR and HRD, and BRS can all be used as predictors of efficacy. BMI has the largest AUC (0.923), so it was recommended as a predictor of the efficacy of ORS treatment for POTS children with hypovolemia with priority.

### Predictors of Pharmacological Therapy in Postural Tachycardia Syndrome

The MR-proADM, erythrocytic H2S producing rate, and FMD can help to predict the efficacy of MD on POTS (33, 34, 56). The MR-proADM is relatively stable and can reflect levels of adrenomedullin (ADM), which is related to vasodilation (64, 65). Peripheral vascular dysfunction is an important pathophysiological mechanism of POTS (21). Zhang et al. (33) found that plasma levels of MR-proADM in children with POTS (57 cases) were significantly higher than that in the control group [75.0 (62.5–96.0) vs. 58.5 (50.3–69.0) pg/ml, p < 0.01], and was higher in the effective group of MD treatment than that in the ineffective group [24.7 ± 9.9 vs. 13.5 ± 6.6 mmHg, p < 0.01]. The AUC was 0.855. A cutoff value of BRS of 17.01 ms/mmHg yielded the predictive sensitivity of 85.7% and specificity of 87.5%. Detection of BRS could well predict the disease outcome of POTS, and it was convenient, inexpensive, and non-invasive in the prediction. In summary, 24-h urine sodium excretion, BMI, MCHC, HR and HRD, and BRS can all be used as predictors of efficacy. BMI has the largest AUC (0.923), so it was recommended as a predictor of the efficacy of ORS treatment for POTS children with hypovolemia with priority.

Erythrocytic H2S-producing rate may play a role in abnormal vasodilation in children with POTS. Yang et al. (34) explored the role of erythrocytic H2S-producing rate in predicting the therapeutic efficacy of MD in children with POTS (28 cases). H2S production from erythrocytes was significantly higher in the POTS group than that in the control group (p < 0.01), and it was also significantly higher in responders to MD than non-responders (39.2 ± 17.5 vs. 23.3 ± 12.5 nmol/min/10^8 RBC, p < 0.05). The AUC was 0.813. Using erythrocytic H2S producing rate of 27.1 nmol/min/10^8 RBC as a cutoff value, the sensitivity and specificity for predicting efficacy were 78.9 and 77.8%, respectively. As a biomarker, erythrocytic H2S-producing rate is relatively stable, inexpensive, and simple to test. FMD and abnormal endothelial function may also play important roles in the development of POTS (67). Liao et al. (56) found that FMD values in children with POTS (108 cases) were significantly higher than those in controls (11 ± 3 vs. 6 ± 2%, p < 0.001), and that FMD values of MD responders were significantly higher than those in MD non-responders (11 ± 3 vs. 8 ± 2%, p < 0.05). The AUC was 0.803, and FMD of 9.85% had a high sensitivity (74.4%) and specificity (80.0%) for a 3-month therapy (Table 2). In general, MR-proADM has the largest AUC (0.879). It is suggested that MR-proADM should be chosen as a predictor of the efficacy of MD treatment for POTS children with vascular dysfunction with priority.

Metoprolol is a commonly used drug for POTS treatment in children, and recent studies have found that a variety of biomarkers can be used to predict the efficacy of metoprolol. They are of great importance for the individual therapy of POTS in hyperadrenergic children and adolescents. Increases in orthostatic plasma norepinephrine are the core of the biochemical changes of hyperadrenergic children with POTS (21). Zhang et al. (57) reported that the symptom severity in children with POTS (25 cases) was positively correlated with their orthostatic plasma norepinephrine level (r = 0.599; p < 0.001), and orthostatic plasma norepinephrine level in the response group to metoprolol was significantly higher than that in the non-response group (5.10 ± 2.69 vs. 2.93 ± 1.79 pg/ml, p = 0.028). The AUC was 0.785. Once orthostatic plasma norepinephrine level was ≥3.59 pg/ml, it predicted the efficacy of metoprolol on POTS with a sensitivity of 76.9% and specificity of 91.7%. In addition, Takekoshi et al. (68) and Springer et al. (69) separately found that plasma C-type natriuretic peptide (CNP) played a role in increasing the secretion of plasma catecholamine and accelerating the HR. The increased plasma level of catecholamine was suggested to be involved in the pathogenesis of POTS. Lin et al. (58) reported significantly higher plasma CNP levels in children with POTS (34 cases) than in healthy children (51.9 ± 31.4 vs. 25.1 ± 19.1 pg/ml, p < 0.001). They also found that plasma CNP in responders to metoprolol was significantly higher than that in non-responders (59.1 ± 33.5 vs. 34.8 ± 16.7 pg/ml, p = 0.037) before treatment. The AUC was 0.821. When the plasma CNP was >32.55 pg/ml, the sensitivity and specificity for predicting the efficacy of metoprolol were 95.8 and 70.0%, respectively. As a biomarker, plasma CNP cannot only predict the efficacy but also reflect the severity of the pathophysiology of
children with POTS. Heart rate variability (HRV) is an important reference indicator of autonomic regulation and is also used in the efficacy prediction of metoprolol in children with POTS. Wang et al. (59) found that baseline triangular (TR) index and standard deviation index of all sinus intervals (SDNN index) were significantly lower in responders than in non-responders to metoprolol (TR: 27.3 ± 6.10 vs. 35.7 ± 7.2, p < 0.01; SDNN: 63.2 ± 12.8 vs. 84.5 ± 18.3 ms, p < 0.01) in 45 children with POTS. The AUC for TR index and SDNN index was 0.807 and 0.820, respectively. Combined baseline TR index ≤33.7 and SDNN index ≤79.0 ms as cutoff values, the sensitivity and specificity to predict efficacy of metoprolol were 85.3 and 81.8%, respectively. HRV indicators may be non-invasive and easy-to-use predictors. Wang et al. (60) found that HR and HRD during HUTT could predict the efficacy of metoprolol in children and adolescents with POTS. The results showed that HR5, HR10 (instantaneous HR of HUTT at 5 and 10 min, respectively), HRD5 and HRD10 (the difference between instantaneous HR at HUTT 5 and 10 min, and the baseline HR, respectively) were significantly higher in the group with POTS than those in the control group (p < 0.01). The AUC at HR5, HR10, HRD5, and HRD10 was 0.794, 0.802, 0.905, and 0.901, respectively. They found when HR5, HR10, HRD5, HRD10 ≥110, 112, 34, 37 beats/min, respectively, the sensitivity and specificity to predict response to metoprolol were 82.5 and 69.2%, 84.6 and 69.7%, 85.3 and 89.5%, 97.6 and 64.9%, respectively (Table 2). The indicator is relatively simple and easy to obtain, but it is susceptible to changes in mood. Therefore, the HUTT procedures should be strictly followed to ensure the accuracy of the data collection. In summary, orthostatic plasma norepinephrine, plasma CNP, TR index and SDNN index, and HR and HRD can all be used as predictors of efficacy. HRD5 has the largest AUC (0.905), therefore it is recommended that HRD5 should be selected as a predictor of the efficacy of metoprolol treatment for hyperadrenergic children with POTS with priority.

Certainly, the research on the indicators that predict the therapeutic efficacy in the management of pediatric POTS is also constantly being updated. Wang et al. (70) reported changes in rate-pressure product (RPP) in children with POTS (53 cases). The results showed that when RPP at HUTT 5 min (RPP5) was 11,548.5 bpm·mmHg, the AUC was 0.669, the sensitivity and specificity to predict the response after POTS intervention (including health education, upright training, ORS, and metoprolol) were 81.8 and 61.7%, respectively. When RPP at HUTT 10 min (RPP10) was 10,988.0 bpm·mmHg, the AUC was 0.769, the sensitivity and specificity were 77.8 and 86.2%, respectively. Liu et al. (71) followed up 57 children with POTS for median of 55 days and found that the reactive group had a longer QTd after intervention (including health education, exercise of autonomic nervous function, ORS, and metoprolol) than the non-responsive group (35 ± 6 vs. 25 ± 5 ms, p < 0.001). The AUC was 0.91. Using QTd of 30 ms as a cutoff value, the sensitivity to predict response to POTS intervention is 82.9%, and the specificity is 81.8%. RPP and QTd have prognostic value for POTS, but whether they had prognostic value for specific pharmacological therapy should be further evaluated.

**CONCLUSION**

OI is a clinical syndrome of autonomic regulation disorders. VVS and POTS are more common in school-age children and often occur in early adolescence. Most of the current studies have reported a good overall prognosis for OI, independent of significant mortality. There has been more research on the prognosis of OI in recent years, especially for VVS and POTS, and the predictive value of biomarkers has been gradually popularized in clinical practice. FMD, LVEF and LVFS, BMI, 24-h urinary sodium excretion, MR-proADM, and erythrocyte H2S producing rate are relatively stable, non-invasive, and easy to implement biomarkers. Plasma norepinephrine is unstable in blood circulation and the method of detecting CNP has relatively complex operating procedure. The 24-h HRV is affected by physical activity during the day, and hemodynamic change during HUTT is susceptible to emotional effects. However, there is a lack of large, multi-center, and long-term follow-up studies, and the longest follow-up period is about 5.4 years, so the evaluation value of some indicators needs to be further confirmed. If patients have high compliance, early lifestyle change and physical intervention can achieve ideal treatment effects. At the same time, with the help of biomarkers, suitable drugs can be selected for different patients, and even individualized treatment can be realized, which can improve the long-term prognosis of children and adolescents with OI and avoid the occurrence of poor outcomes and even death.

**SUMMARY**

For VVS, FMD of 8.85% taken as a cutoff value can be considered as a predictor of the efficacy of MD treatment. LVEF of 70.5% and LVFS of 37.5%, and an increase of 30 beats/min in HR before positive response in HUTT taken as cutoff values can be considered as predictors of the efficacy of metoprolol treatment, respectively. According to the largest AUC (0.906), LVEF was recommended as a predictor of the efficacy of β-blocker therapy on VVS children with priority.

For POTS, when selecting non-pharmacological therapy, QTd of 43 ms as a cutoff value can be considered as a predictor of the efficacy of physical treatment. Salivary cortisol of 4.1 ng/ml at awakening as a cutoff value can be considered as a predictor of the efficacy of sleep-promoting treatment. A 24-h urine sodium of 124 mmol/24 h, BMI of 18.02 kg/m², MCH of 347.5 g/L, and HRD between orthostatic and supine position of 41 beats/min combined with HRmax in upright 10 min of 123 beats/min as cutoff values can be considered as predictors of the efficacy of ORS treatment, respectively. For pharmacological therapy, MR-proADM of 61.5 pg/ml, erythrocytic H2S of 27.1 nmol/min/10⁸RBC, and FMD of 9.85% as cutoff values can be considered as predictors of the efficacy of MD treatment, respectively. Orthostatic norepinephrine of 3.59 pg/ml, plasma CNP of 32.55 pg/ml, and TR index of 33.7 combined with SDNN index of 79.0 ms, and HR5, HR10, HRD5, HRD10 of 110, 112, 34, 37 beats/min, respectively, as cutoff values can be considered as predictors of the efficacy of metoprolol treatment, respectively. According to the largest AUC...
document. All authors have read and approved the final manuscript and assume full responsibility for its contents.

**FUNDING**

This work was supported by grants from the Hunan Province Clinical Medical Technology Innovation Guidance Project in China (2020SK53405, 2020SK53406).

**AUTHOR CONTRIBUTIONS**

HY conceptualized, prepared, wrote the manuscript, and made the tables. SW, HC, JZ, PL, YW, and RZ participated in providing documentation. RZ and CW reviewed, edited, and revised the manuscript. All authors have read and approved the final manuscript and assume full responsibility for its contents.

**REFERENCES**

1. Stewart JM. Orthostatic intolerance in pediatrics. J Pediatr. (2002) 140:404–11. doi: 10.1067/mpd.2002.122727
2. Shen WK, Sheldon RS, Benditt DG, Cohen MI, Forman DE, Goldberger ZD, et al. 2017 ACC/AHA/HRS guideline for the evaluation and management of patients with syncope: a report of the american college of cardiology/american heart association task force on clinical practice guidelines and the heart rhythm society. Circulation. (2017) 136:e60–122. doi: 10.1161/CIR.0000000000000537
3. Wang C, Li Y, Liao Y, Tian H, Huang M, Dong X, et al. Chinese Pediatric Cardiology Society (CPCS) guideline for diagnosis and treatment of syncope in children and adolescents. Sci Bull. (2018) 63:1558–64. doi: 10.1016/j.scib.2018.09.019
4. He E, Liu X, Chen Q, Wang C. Investigation on the incidence of syncope in children and adolescents aged 2-18 years in Changsha. Front Pediatr. (2021) 9:638394. doi: 10.3389/fped.2021.638394
5. Bayram AK, Pamuko C, Per H. Current approaches to the clinical assessment of syncope in pediatric population. Childs Nerv Syst. (2016) 32:427–36. doi: 10.1007/s00381-015-2988-8
6. Li H, Gao L, Yuan Y. Advance in the understanding of vasovagal syncope in children and adolescents. World J Pediatr. (2021) 17:58–62. doi: 10.1007/s42759-020-00367-z
7. Brignole M, Maya A, de Lange FJ, Deharo JC, Elliott PM, Fasciulli A, et al. 2018 ESC guidelines for the diagnosis and management of syncope. Eur Heart J. (2018) 39:1883–948. doi: 10.36593/JP.2018.0161
8. Kenny RA, Brignole M, Dan GA, Deharo JC, van Dijk JG, Doherty C, et al. Syncope unit: rationale and requirement – the european heart rhythm association position statement endorsed by the heart rhythm society. Europace. (2015) 17:1325–40. doi: 10.1093/europace/eu5115
9. Stewart JM, Boris JR, Chelimsky G, Fischer PR, Fortunato JE, Grubb BP, et al. Pediatric disorders of orthostatic intolerance. Pediatrics. (2018) 141:e20171673. doi: 10.1542/peds.2017-1673
10. Johnson NJ, Mack KJ, Kuntz NL, Brands CK, Porter CJ, Fischer PR. Postural orthostatic tachycardia syndrome: a clinical review. Pediatr Neurol. (2010) 42:77–85. doi: 10.1016/j.pediatrneurol.2009.07.002
11. Boris JR, Bernadzikowski T. Demographics of a large paediatric postural orthostatic tachycardia syndrome program. Cardiol Young. (2018) 28:668–74. doi: 10.1017/S1047951117002888
12. Kritzberger CJ, Antiel RM, Wallace DP, Zacharias JD, Brands CK, Fischer PR, et al. Functional disability in adolescents with orthostatic intolerance and chronic pain. J Child Neurol. (2011) 26:593–8. doi: 10.1177/0887899410390366
13. Brewster JA, Garland EM, Biaggioni I, Black BK, Ling JF, Shubao CA, et al. Diurnal variability in orthostatic tachycardia: implications for the postural tachycardia syndrome. Clin Sci. (2012) 122:25–31. doi: 10.1042/CS20110077
14. Heyer GL, Fedak EM, LeGros AL. Symptoms predictive of postural tachycardia syndrome (POTS) in the adolescent headache patient. Headache. (2013) 53:947–53. doi: 10.1111/head.12103
15. Reilly CC, Floyd SV, Lee K, Warwick G, James S, Gall N, et al. Breathlessness and dysfunctions breathing in patients with postural orthostatic tachycardia syndrome (POTS): the impact of a physiotherapy intervention. Auton Neurosci. (2020) 223:102601. doi: 10.1016/j.autneu.2020.102601
16. Kizilbash SJ, Ahrens SP, Bruce BK, Chelimsky G, Driscoll SW, Harbeck-Weber C, et al. Adolescent fatigue, POTS, and recovery: a guide for clinicians. Curr Probl Pediatr Adolesc Health Care. (2014) 44:108–33. doi: 10.1067/cppeds.2013.12.01
17. Serletis A, Rose S, Sheldon AG, Sheldon RS. Vasovagal syncope in medical students and their first-degree relatives. Eur Heart J. (2006) 27:1965–70. doi: 10.1093/eurheartj/ehl147
18. Sheldon RS, Grubb BN, Olhansky B, Shen WK, Calkins H, Brignole M, et al. Heart rhythm society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. Heart Rhythm. (2015) 12:e41–63. doi: 10.1016/j.hrthm.2015.03.029
19. Soliati M, Cassaza G, Dipaola F, Rusconi AM, Cernuschi G, Barbic E, et al. Syndrome recurrence and mortality: a systematic review. Europace. (2015) 17:390–8. doi: 10.1093/europace/euu327
20. Soteriades ES, Evans JC, Larson MG, Chen MH, Chen L, Benjamin EJ, et al. Incidence and prognosis of syncope. N Engl J Med. (2002) 347:878–85. doi: 10.1056/NEJMoa021407
21. Liao Y, Du J. Pathophysiology and individualized management of vasovagal syncope and postural tachycardia syndrome in children and adolescents: an update. Neurosci Bull. (2020) 36:667–81. doi: 10.1007/s12264-020-00497-4
22. Agarwal AK, Garg R, Ritch A, Sarkar P. Postural orthostatic tachycardia syndrome. Postgrad Med J. (2007) 83:478–80. doi: 10.1136/pgmj.2006.050546
23. Kimpinski K, Figuerola JJ, Singer W, Sletten DM, Iodice V, Sandroni P, et al. A prospective, 1-year follow-up study of postural tachycardia syndrome. Mayo Clin Proc. (2012) 87:476–52. doi: 10.1016/j.mayocp.2012.02.020
24. Bhatia R, Kizilbash SJ, Ahrens SP, Killian JM, Kimmes SA, Kneobel EE, et al. Outcomes of adolescent-onset postural orthostatic tachycardia syndrome. J Pediatr. (2016) 173:143–53. doi: 10.1016/j.jpeds.2016.02.035
25. Pessoa SA, Lemos A, Freitas J, Maciel MJ. Long-term follow-up of patients with postural tachycardia syndrome. Clin Auton Res. (2012) 22:151–3. doi: 10.1007/s10286-011-0155-1
26. Novak P. Autonomic disorders. Am J Med. (2019) 137:420–36. doi: 10.1016/j.amjmed.2018.09.027
27. Chen L, Li X, Todd O, Wang C, Jin H, Du J. A clinical manifestation-based prediction of haemodynamic patterns of orthostatic intolerance in children: a multi-centre study. Cardiol Young. (2014) 24:469–53. doi: 10.1017/S1047951113000929
28. Andersen JB, Czosek RJ, Knilians TK, Marino BS. The effect of paediatric syncope on health-related quality of life. Cardiol Young. (2012) 22:583–8. doi: 10.1017/S1047951112000133
29. Zhang F, Liao Y, Li X, Chen L, Jin H, Du J. The predictive value of flow-mediated vasodilation on therapeutic efficacy of midorine hydrochloride for vasovagal syncope in children. Chin J Prac Pediatr. (2012) 27:102–5. CNRLSUN/ZSEK.2012-02-089
30. Song J, Li H, Wang Y, Liu P, Li X, Tang C, et al. Left ventricular ejection fraction and fractional shortening are useful for the prediction of the therapeutic response to metoprolol in children with vasovagal syncope. Pediatr Cardiol. (2018) 39:1366–72. doi: 10.1007/s00246-018-1904-x
31. Zhang Q, Liao Y, Tang C, Du J, Jin H. Twenty-four-hour urinary sodium excretion and postural orthostatic tachycardia syndrome. J Pediatr. (2012) 161:281–4. doi: 10.1016/j.jpeds.2012.01.054
32. Li H, Wang Y, Liu P, Chen Y, Feng X, Tang C, et al. Body mass index (BMI) is associated with the therapeutic response to oral rehydration solution
in children with postural tachycardia syndrome. Pediatr Cardiol. (2016) 37:1313–8. doi: 10.1007/s00246-016-1436-1

33. Zhang F, Li X, Ochs T, Chen L, Liao Y, Tang C, et al. Midregional pro-adrenomedullin as a predictor for therapeutic response to midodrine hydrochloride in children with postural orthostatic tachycardia syndrome. J Am Coll Cardiol. (2012) 60:313–20. doi: 10.1016/j.jacc.2012.04.025

34. Yang J, Zhao J, Du S, Liu D, Fu C, Li X, et al. Postural orthostatic tachycardia syndrome with increased erythrocytic hydrogen sulfide and response to midodrine hydrochloride. J Pediatr. (2013) 163:1169–73.e2. doi: 10.1016/j.jpeds.2013.03.039

35. Wu L, Ding Y, Xu X, Zhou J, Yuan J, Tong L, et al. Changes of plasma endothelin, EDRE and heart rate variability during the table tilt test in patients with vasovagal syncope. Chin J Cardiol. (1998) 26:53–5. doi: 10.3760/j.issn.0253-3758.1998.06.015

36. White M, Cernack P, Courtmamache M, Stewart D, Talajic M, Mikes E, et al. Impaired endothelin-1 release in tilt-induced syncope. Am J Cardiol. (1998) 81:460–4. doi: 10.1016/s0002-9149(97)00393-7

37. Zhang Q, Du J, Li Y, Ai Y. Endothelial function in children with vasovagal syncope via color Doppler flow imaging. Chin J Pract Pediatr. (2005) 13:482–4. doi: 10.3986/j.issn.1005-2224.2005.08.013

38. Grubb BP. Pathophysiology and differential diagnosis of neurocardiogenic syncope. Am J Cardiol. (1999) 84:3–9. doi: 10.1016/s0002-9149(99)00691-8

39. Edner M, Brodin LL, Al-Khalili F, Svane B, StAhle A, et al. Changes in systolic and diastolic function indexes throughout dobutamine stress echocardiography in healthy volunteers and patients with ischemic heart disease. Echocardiography. (1998) 15:625–34. doi: 10.1111/j.1540-8175.1998.tb00660.x

40. Zeng H, Li W, Li Y, Ma Y, Du J. Evaluation of cardiac beta-adrenergic receptor function in children by dobutamine stress echocardiography. Chin Med J. (1999) 112:623–6. doi: 10.7680/jmip578-1310.1999.06.017

41. Zhang Q, Du J, Zhen J, Li W, Wang Y. Hemodynamic changes during head-up tilt test and predictive value thereof in predicting the efficacy of metoprolol therapy in children with vasovagal syncope. Natl Med J China. (2007) 87:1260–2. doi: 10.7686/jmip576-2491.2007.18.011

42. Liu J, Wang Y, Li F, Lin P, Cai H, Zou R, et al. Diagnostic efficacy and prognostic evaluation value of QT interval dispersion in children and adolescents with cardiovascular syncope. Chin Pediatr Emerg Med. (2021) 28:192–7. doi: 10.1673/cmja.mja16.4912.2021.03.007

43. Kabul HK, Celik M, Yuksel UC, Yalcinkaya E, Gokoglan Y, Bugan B, et al. Increased sympathetic activation in patients with vasovagal syncope is associated with higher mean platelet volume levels. Eur Rev Med Pharmacol Sci. (2014) 18:235–41. doi: 10.1159/000358366

44. Song J, Li H, Li X, Wang Y, Jin H, Du J. Relationship between blood routine test parameters and syncopal recurrence of vasovagal syncope in children. Chin J Pediatr. (2014) (53):1313–8. doi: 10.1007/s00246-016-1436-1

45. Lin J, Zhao H, Shen J, Jiao F. Salivary cortisol levels predict therapeutic response to a sleep-promoting method in children with postural tachycardia syndrome. J Pediatr. (2017) 191:91–5.e1. doi: 10.1016/j.jpeds.2017.08.039

46. Lu W, Yan H, Wu S, Xu W, Jin H, Du J. Hemocytometric measures predict the efficacy of oral rehydration for children with postural tachycardia syndrome. J Pediatr. (2017) 187:220–4. doi: 10.1016/j.jpeds.2017.04.034

47. Lin J, Liu P, Wang Y, Li H, Li X, Zhao J, et al. Evaluation of the changes in heart rate during head-up test predicting the efficacy of oral rehydration salts on postural tachycardia syndrome in children. Chin J Pediatr. (2015) 53:25–9. doi: 10.3760/cma.j.issn.0578-1310.2015.01.005

48. Li H, Liao Y, Wang Y, Liu P, Sun C, Chen Y, et al. Baroreflex sensitivity predicts short-term outcome of postural tachycardia syndrome in children. PLoS ONE. (2016) 11(6):e0167525. doi: 10.1371/journal.pone.0167525

49. Liao Y, Yang J, Zhang F, Chen S, Liu X, Zhang Q, et al. Flow-mediated vasodilation as a predictor of therapeutic response to midodrine hydrochloride in children with postural orthostatic tachycardia syndrome. Am J Cardiol. (2013) 112:816–20. doi: 10.1016/j.amjcard.2013.05.008

50. Zhang Q, Chen X, Li J, Du J. Orthostatic plasma norepinephrine level as a predictor for therapeutic response to metropolol in children with postural tachycardia syndrome. J Transl Med. (2014) 12:249. doi: 10.1186/1479-5876-12-249

51. Lin J, Han Z, Li H, Chen S, Li X, Liu P, et al. Plasma C-type natriuretic peptide as a predictor for therapeutic response to metropolol in children with postural tachycardia syndrome. PLoS One. (2015) 10(12). doi: 10.1371/journal.pone.0129193

52. Wang Y, Zhang C, Chen S, Liu P, Wang Y, Tang C, et al. Heart rate variability predicts therapeutic response to metropolol in children with postural tachycardia syndrome. Front Neurosci. (2019) 13(1214). doi: 10.3389/fnins.2019.01214

53. Wang S, Zou R, Cai H, Wang Y, Ding Y, Tan C, et al. Heart rate and heart rate difference predicted the efficacy of metropolol on postural tachycardia syndrome in children and adolescents. J Pediatr. (2020) 224:110–4. doi: 10.1016/j.jpeds.2020.05.017

54. Stewart JM, Taneja I, Medow MS. Reduced body mass index is associated with increased angiotensin II in young women with postural tachycardia syndrome. Clin Sci. (2007) 113:449–57. doi: 10.1042/CS20070104

55. Lin CJ, Chu YK, Chern CM. RBC volume deficiency in patients with excessive orthostatic decrease in cerebral blood flow velocity. J Chin Med Assoc. (2014) 77:174–8. doi: 10.3399/jcma.2014.01.005

56. Tang C, Li X, Du J. Hydrogen sulfide as a new endogenous gaseous transmitter in the cardiovascular system. Aviat Space Environ Med. (1997) 68:838–43. doi: 10.3389/fnins.2000.000522

57. Kitamura K, Kawagawa K, Kawamoto M, Ichiki Y, Nakamura S, Matsuo H, et al. Adrenomedullin: a novel hypothepsine peptide isolated from human pheochromocytoma. Biochem Biophys Res Commun. (1993) 192:553–60. doi: 10.1006/bbrc.1993.1451

58. Struck J, Tao C, Morgenthaler NG, Bergmann A. Identification of an adrenomedullin precursor fragment in plasma of sepsis patients. Peptides. (2004) 25:1369–72. doi: 10.1016/j.peptides.2004.06.019

59. Springer J, Azer J, Hua R, Robbins C, Adamczyk A, McBoyle S, et al. The natriuretic peptides BNP and CNP increase heart rate and electrical conduction by stimulating ionic currents in the sinoatrial
node and atrial myocardium following activation of guanylyl cyclase-linked natriuretic peptide receptors. *J Mol Cell Cardiol.* (2012) 52:1122–34. doi: 10.1016/j.yjmcc.2012.01.018

70. Wang S, Cai H, Ding Y, Tan C, Yang M, Wang Y, et al. Prognostic value of rate-pressure product in children with postural tachycardia syndrome. *Chin J Appl Clin Pediatr.* (2020) 35:969–73. doi: 10.3760/cma.j.cn101070-20191216-01254

71. Liu J, Wang Y, Li F, Lin P, Cai H, Zou R, et al. Prognostic evaluation value of QT interval dispersion in children and adolescents with postural tachycardia syndrome. *Chin J Pract Pediatr.* (2021) 36:387–91. doi: 10.19538/j.ek2021050616

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Publisher’s Note:** All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

*Copyright © 2021 Yan, Wang, Cai, Zhang, Liu, Wang, Zou and Wang. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.*