Heart Rate and Heart Rate Difference Predicted the Efficacy of Metoprolol on Postural Tachycardia Syndrome in Children and Adolescents

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Objective To evaluate the ability of heart rate (HR) and HR difference during head-up tilt test (HUTT) and to predict clinical improvement related to metoprolol treatment in children and adolescents with postural tachycardia syndrome (POTS).

Study design This was a retrospective cohort study. A total of 53 subjects (27 male, aged 6-12 years old, mean age 11.79 ± 1.50 years old) with POTS treated with metoprolol were involved from July 2012 to September 2019. In total, 52 subjects who underwent health examination during the same period were matched as the control group. Subjects in both groups underwent HUTT. The HR distance between 5 minutes and 0 minutes (HR difference 5) and between 10 minutes and 0 minutes (HR difference 10) during HUTT was calculated.

Results The POTS group was significantly greater than the control group in HR 5, HR 10, HR difference 5, and HR difference 10 ($P < .01$). There was no statistical difference in HR 0 between the 2 groups ($P > .05$). In total, 53 subjects with POTS were followed up for 96.0 (IQR, 40.5, 134.5) days during treatment with metoprolol. HUTT results demonstrated that 58.49% of subjects with POTS had a response and symptom scores were reduced after intervention. HR and HR difference were useful in predicting the efficacy of metoprolol on POTS. When HR 5, HR 10, HR difference 5, and HR difference 10, respectively, were ≥110, 112, 34, and 37 beats/min, the sensitivity and specificity were 82.50% and 69.23%, 84.62% and 69.70%, 85.29% and 89.47%, and 97.56% and 64.86%, respectively.

Conclusions HR and HR difference are helpful to predict the efficacy of metoprolol on POTS in children and adolescents. *(J Pediatr 2020;224:110-4)*.

Postural tachycardia syndrome (POTS) is a disease secondary to autonomic dysfunction. In children and adolescents, presyncope and syncope are its most common manifestations.[1] It is estimated to affect between 0.1% and 1% of the US population.[2,3] This is a heterogeneous clinical syndrome that is characterized by sustained and excessive sinus tachycardia upon standing, in the absence of orthostatic hypotension and with chronic symptoms of orthostatic intolerance. Although POTS is a functional cardiovascular disease with self-limited and good prognosis,[4,5] patients' physical and mental health, learning, and life quality are severely affected because of recurrent symptoms.[6,7]

It has been reported that some biomarkers are useful in predicting the prognosis of POTS. Hydrogen sulfide yield in red blood cells,[8] flow-mediated vasodilation of the brachial artery,[9] systolic blood pressure decreased or diastolic blood pressure changed from supine to orthostatic position,[10] body mass index,[11] baroreflex sensitivity,[12] sodium urine level at 24 hours,[13] plasma midregional fragment of pro-adrenomedullin,[14] postural plasma norepinephrine levels,[15] plasma C-type natriuretic peptide (CNP),[16] salivary cortisol levels,[17] heart rate variability,[18] and correction of QT-interval dispersion of electrocardiogram (ECG) index[19] have predictive values for the efficacy of treatment in POTS.

The standing test or head-up tilt test (HUTT) is also an important auxiliary method for the diagnosis of POTS. Lin et al reported that the change of heart rate (HR) during the HUTT was useful in predicting the response to oral rehydration salt in children with POTS; the HR difference between the orthostatic and supine position and the maximum HR within 10 minutes after being upright in patients who had a response to intervention were significantly greater than those who had no responses to intervention ($P < .01$).[20] The sensitivity and specificity for effective treatment were 72% and 70%, respectively, when HR difference between the orthostatic and recumbent position was >41 beats/min. The sensitivity and specificity of effective treatment were 48% and 78%, respectively, when in the orthostatic position within 10-minute maximal HR was >123 beats/min. Whether HR and HR difference of

AUC	Area under the curve
CNP	C-type natriuretic peptide
ECG	Electrocardiogram
HR	Heart rate
HUTT	Head-up tilt test
POTS	Postural tachycardia syndrome

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HUTT can be used as indicators to predict the efficacy of metoprolol on POTS in children and adolescents has not been reported. We explored the predictive value of HR and HR difference on the efficacy of metoprolol in children and adolescents with POTS.

Methods

The study population consisted of those subjects who underwent HUTT and were diagnosed with POTS with follow-up at The Second Xiangya Hospital, Central South University between July 2012 and September 2019. The subjects were matched to conditions who underwent a health examination in the outpatient clinic of the Child Care Specialty of the same hospital during the same period.

POTS diagnostic criteria for children and adolescents were as follows[1]: In children and adolescents, there are predisposing factors such as persistent standing or sequence standing from the lying or squatting position to the upright position, nervousness or fear, or a hot environment. Symptoms included dizziness, headache, nausea, blurred vision, chest tightness, palpitations, hand shaking and cold sweat, and even syncope after orthostatic position. HR within 10 minutes of HUTT was increased by ≥40 beats/minute compared with supine position or maximum HR reached standard (6-12 years old ≥130 beats/minute, 12-18 years old ≥125 beats/minute), and no significant decrease in blood pressure (decreased systolic blood pressure <20 mm Hg, diastolic blood pressure <10 mm Hg).

Other medical conditions were evaluated by detailed medical history, physical examination, blood biochemistry (fasting blood glucose, myocardial enzymes), ECG, 24-hour Holter ECG, radiographic chest examination, echocardiogram, electroencephalogram, and computed tomography/magnetic resonance imaging of the head. Subjects with syncope or presyncope caused by organic cardiocerebral vascular disease, psychogenic disease and other system diseases were excluded.

This study complied with medical ethics standards and was approved by the Medical Ethics Committee of The Second Xiangya Hospital, Central South University, Ethical Audit No. Study 012 (2014). Subjects stopped all drugs that affect autonomic function for more than 5 half-lives before the examination and discontinued diets that may affect autonomic function.[1] Fasting was maintained at least 4 hours before the test. The test environment was quiet and dim with optimal temperature. The guardians of subjects signed a written informed consent form. All subjects underwent HUTT from 8:00 a.m. to 11:00 a.m. Subjects urinated before the test and rested in the supine position for 10 minutes. The tilting device was a SHUT-100 tilt test monitoring software system from Beijing Standley Technology Co, Ltd (Beijing, China). Subjects were instructed to lie on an inclined diagnostic bed with ankle and knee bands fixed to avoid flexion. The subjects lay quietly for 10 minutes, and the baseline HR, blood pressure, and ECG were recorded. Within 15 seconds, the patients were converted to 60° with head upwards and feet secured. The HR, blood pressure, and ECG were continuously monitored and recorded until the test was terminated after a positive reaction, and the diagnostic bed was restored in horizontal position within 10 seconds.

The instantaneous HR of HUTT at baseline state, 5 minutes, and 10 minutes was defined as HR 0, HR 5, and HR 10, respectively. HR difference (HR difference 5, HR difference 10) is the difference between instantaneous HR at HUTT (5 minutes and 10 minutes) and the baseline HR.

Symptom scoring was applied to evaluate the effect of metoprolol on the treatment of POTS. The score was calculated according to the occurrence frequency of clinical symptoms of subjects with POTS at the time of diagnosis and follow-up; symptom score at the time of diagnosis was recorded as baseline score, and symptom score at the time of follow-up was recorded as the end score. The score included the following clinical symptoms: syncope, dizziness, chest tightness, nausea, palpitation, headache, blurred vision, hand shaking, and cold sweat. The score calculation standard was as follows: 0, no symptoms; 1, symptoms less than once on average per month; 2, 2-4 times on average per month; 3, 2-7 times on average per week; and 4, more than once on average per day. All the scores were the sum of each symptom-based score. After children and adolescents were diagnosed with POTS, baseline symptom scores were recorded, and scores were recorded again at follow-up according to the symptom score system.[12]

For subjects with POTS, based on nonpharmacologic therapy (health education, upright training, increased water and salt intake), oral metoprolol (1 mg/kg•d) was added for 3 months.

In total, 53 subjects with POTS were completely followed up. The follow-up time was up to December 2019. During the follow-up, the medical history was evaluated, and HUTT was re-examined. The treatment effect was evaluated re-examining HUTT for 10 minutes. If the HR was increased by <40 beats/min or the maximum HR did not reach the standard of the corresponding age group of POTS, the participant was considered as having a response to the treatment.

SPSS 22.0 statistical software (IBM Corp, Armonk, New York) was used for all data analyses. The data were presented as mean ± SD and median and quartile [25 percent, 75 percent], and the t test was used for comparison between groups. Count data were compared between groups using the χ^2 test. The receiver operating characteristic curve was used to evaluate the sensitivity and specificity of predictive indicators (HR and HR difference) to judge the predictive efficacy. The area under the curve (AUC) was used to express the predictive ability of predictive indicators. When the Youden index (the sum of sensitivity and specificity and then minus 1) is the largest, the sensitivity and specificity are the best. This node is selected as the boundary value of the prediction index. $P < .05$ was considered significant statistically.

Table I. Heart rate and heart rate difference comparison between POTS group and control group

Characteristics	Control	POTS	t/X^2	*P* value
n	52	53		
Male/female	26/26	27/26	0.009	.923
Age, y	11.48 ± 2.00	11.79 ± 1.50	0.906	.367
HR 0	79.87 ± 12.23	78.87 ± 17.35	0.340	.735
HR 5	96.98 ± 13.33	115.51 ± 17.21	6.160	.000
HR 10	98.98 ± 14.98	118.08 ± 18.84	5.741	.000
HR difference 5	17.31 ± 8.25	37.08 ± 8.91	11.794	.000
HR difference 10	19.90 ± 10.04	40.19 ± 11.28	9.639	.000

HR values are beats/minute, mean ± SD.

Results

In the group with POTS, there were 53 subjects aged 8-14 years old, 27 male and 26 female, with an average age of 11.79 ± 1.50 years. The control group had 52 subjects aged 6-16 years old, 26 male and 26 female, with an average age of 11.48 ± 2.00 years. There was no significant difference in age and sex between the group with POTS and the control group (Table I). HR 5, HR 10, HR difference 5, and HR difference 10 were significantly greater in the group with POTS than in those in the control group ($P < .01$), and HR 0 was not statistically different between the 2 groups (Table I).

In total, 53 subjects were followed up for an average of 96 (40.5, 134.5) days. All subjects with POTS showed improvement on symptoms of syncope, dizziness, palpitations nausea, blurred vision, hand shaking, cold sweat, and headache after treatment. The symptom score at follow-up was lower than that at first visit ($P = .000$) (Table II). A total of 58.49% (31 subjects) of children and adolescents with POTS had a response after intervention, and HUTT results did not support the diagnostic standard.

The AUC at HR 5 was 0.794, (SE 0.043), 95% CI (0.710-0.879). When HR 5 was ≥110 beats/minute, the sensitivity of predicting the effect of metoprolol on POTS was 82.50% and the specificity was 69.23%. The AUC at HR 10 was 0.802 (SE 0.043), 95% CI (0.717-0.887). When HR10 was ≥112 beats/minute, the sensitivity to predict the effect of metoprolol on POTS was 84.62%, and the specificity was 69.70% (Figure 1).

The AUC at HR difference 5 was 0.905 (SE 0.046), 95% CI (0.815-0.994). When HR difference 5 was ≥34 beats/minute, the sensitivity of predicting the effect of metoprolol on POTS was 85.29%, and the specificity was 89.47%. The AUC at HR difference 10 was 0.901 (SE 0.033), 95% CI (0.836-0.966). When HR difference 10 was ≥37 beats/minute, the sensitivity to predict the effect of metoprolol on POTS was 97.56%, and the specificity was 64.86% (Figure 2).

Table II. Comparison of symptom scores of POTS in children and adolescents

Times	n	Symptom score
First visit	53	2.68 ± 0.85
The end of follow-up	53	1.02 ± 0.31
t		13.366
P value		.000

Discussion

The beta blocker metoprolol can slow down HR and improve symptoms by inhibiting sympathetic nerve activity, reducing the activation of cardiac baroreceptors, and blocking the high level of catecholamines in blood circulation. Recent studies provide objective evidence that metoprolol has a good intervention efficacy on POTS. Lin et al reported that CNP had predictive value in the treatment efficacy of metoprolol on POTS in children with the plasma CNP critical value ≥32.55 pg/mL, the sensitivity and specificity of which were 95.8% and 70%.[16] Zhang et al reported that positional plasma noradrenalin level predicted the response to POTS treatment.[15] They found that once orthostatic plasma noradrenalin reached a level of ≥3.59 pg/mL, it predicted the efficacy of metoprolol on POTS symptoms with a sensitivity of 76.9% and specificity of 91.7%. Lin et al found that salivary cortisol levels predicted the response to treatment with sleep promotion and found that the cortisol concentration in patients with POTS was significantly greater than in the control group (all $P < .05$).[17] Salivary cortisol concentration during arousal in responders was significantly greater than that of nonresponders ($P = .003$). When salivary cortisol was ≥4.1 ng/mL at awakening, the sensitivity and specificity of the predicted response to sleep promotion methods were 83.3% and 68.7%, respectively. Our study found that the HUTT became negative in 31 subjects (58.49%) after a median follow-up of 96 days, suggesting that metoprolol had a good efficacy on children and adolescents with POTS. The mechanism by which HR and HR difference predict the therapeutic response of beta blockers to POTS may be related to metoprolol inhibiting the activation of adrenergic receptors in the brainstem and reducing the increase in HR mediated by parasympathetic nerve activity of the heart.[21,22] Wang et al reported that HR variability could predict the response of children with POTS to metoprolol treatment and found that the combination of baseline trigonometric index ≤33.7 and SD index of all sinus intervals ≤79.0 milliseconds also could predict response to metoprolol treatment.[18] Lu et al found that when correction of QT-interval dispersion was ≤43.0 milliseconds, the sensitivity and specificity of predicting the good efficacy of the physical method on POTS were 90% and 60%, respectively.[19] Our study found that HR index of HR 5, HR 10, HR difference 5, and HR difference 10 had good prediction for the efficacy of metoprolol on POTS. When HR 5 was ≥110 beats/min, the sensitivity was 82.50% and the specificity was 69.23%. When HR 10 was ≥112 beats/minute, the sensitivity was 84.62% and the specificity was 69.70%. When HR difference 5 was ≥34 beats/minute, the sensitivity was 85.29% and the specificity was 89.47%. When HR difference 10 was ≥37 beats/minute, the sensitivity was 97.56% and the specificity was 64.86%.

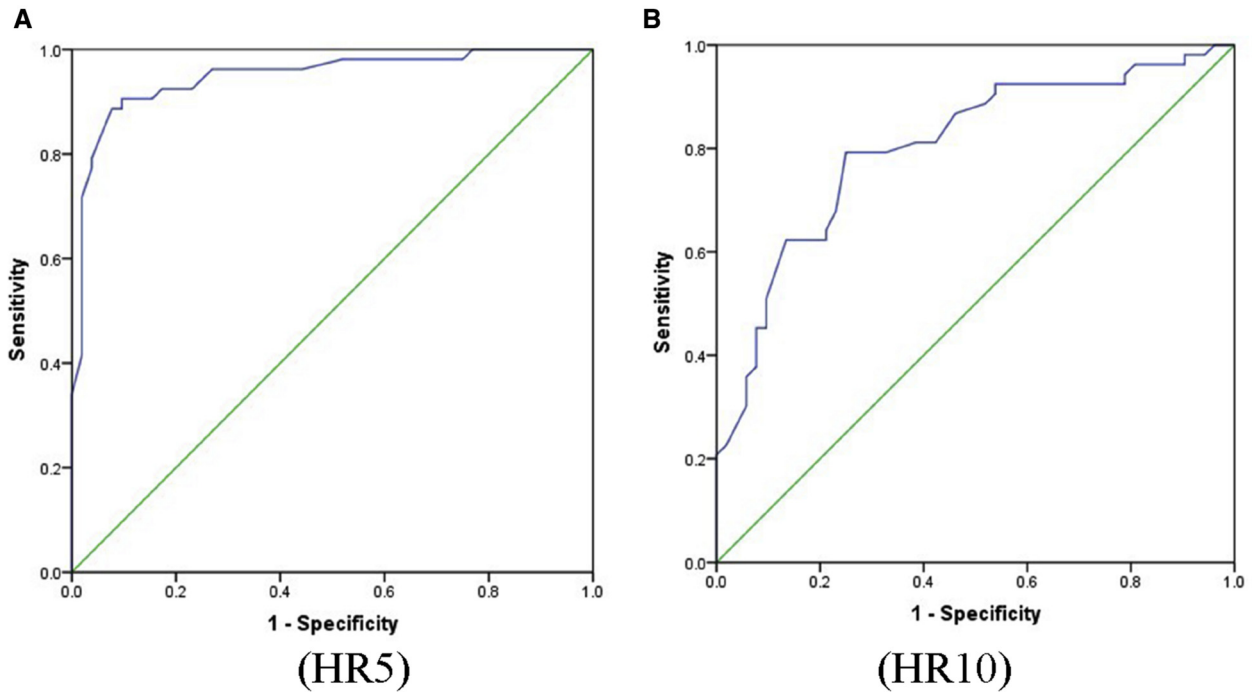

Figure 1. The receiver operating characteristic curve of HR predicting the efficacy of metoprolol on POTS in children and adolescents. **A,** (HR 5): The instantaneous HR of HUTT at 5 minutes. **B,** (HR 10): The instantaneous HR of HUTT at 10 minutes. The y-axis represents sensitivity, and the x-axis represents the false-positive rate (1 – specificity). The 45° *straight line* stands for the reference line indicating the sensitivity, and the false-positive rate is equal.

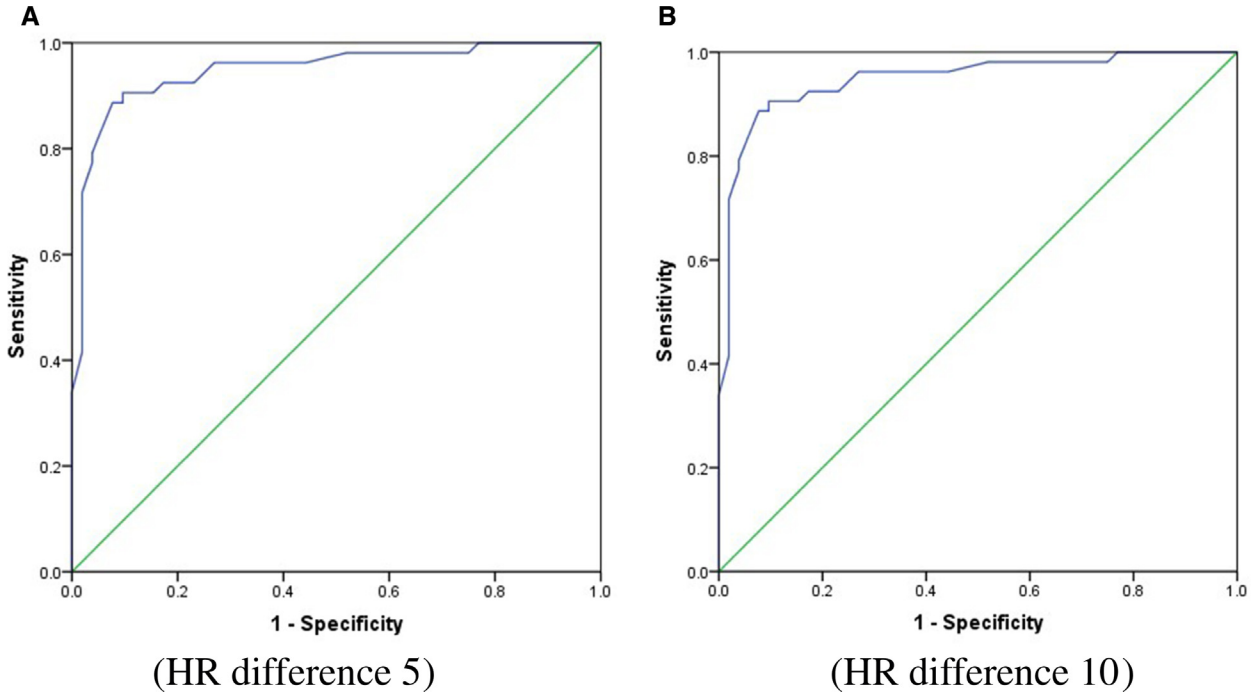

Figure 2. The receiver operating characteristic curve of HR difference to predict the efficacy of metoprolol on POTS in children and adolescents. **A,** (HR difference 5): The difference between instantaneous HR at HUTT 5 minutes and the baseline HR. **B,** (HR difference 10): The difference between instantaneous HR at HUTT 10 minutes and the baseline HR. The y-axis represents sensitivity, and the x-axis represents the false-positive rate (1 – specificity). The 45° *straight line* stands for the reference line indicating the sensitivity, and the false-positive rate is equal.

These results are consistent with the conclusion of Lin et al.[20] They reported that the change of the HR during HUTT was useful in predicting the response to oral rehydration salts. However, it has been reported that some indicators of ECG are valuable for the diagnosis of POTS but not for the prognosis. Wang et al reported 100 cases of children and adolescents with POTS (mean age 11.0 ± 2.40 years), on the supine and orthostatic ECG, when HR difference was ≥15 beats/minute, or T-wave amplitude differences in lead V_5 ≥0.15 mV, lead V_4 and lead V_6 ≥0.10 mV, or a combination of diagnostic sensitivity and specificity on POTS were 35.0% and 88.7%, respectively.[23] However, T-wave amplitude differences did not help to evaluate the prognosis of POTS in children and adolescents.

We found that HR and HR difference are helpful to predict the efficacy of metoprolol on POTS in children and adolescents. The index is relatively simple and easy to obtain. Although the detection of HR and HR difference is simple, the measurement of HR is susceptible to emotional changes. Therefore, HUTT procedures should be strictly followed to ensure the accuracy of data acquisition. ■

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