Total Peripheral Vascular Resistance, Cardiac Output, and Plasma C-Type Natriuretic Peptide Level in Children with Postural Tachycardia Syndrome

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Objective To investigate the total peripheral vascular resistance (TPVR), cardiac output (CO), and plasma C-type natriuretic peptide (CNP) levels in children with postural tachycardia syndrome (POTS) during supine, upright, and return to supine.

Study design Twenty-nine children with POTS, aged 12 ± 3 years, were recruited, and 32 healthy children, aged 11 ± 2 years, served as controls. Heart rate (HR), blood pressure, TPVR, and CO were continuously monitored with Finapres Medical System, and plasma CNP levels were detected with Sandwich immunoluminescence assay.

Results In children with POTS, upright TPVR and CO were significantly lower than those in supine position, and they rose again when they returned to supine position. However, in healthy control patients, both TPVR and CO did not change during supine, upright, and supine again positions. Also, in the supine position, there was no significant difference in TPVR and CO between POTS children and control subjects ($P > .05$). When upright, however, TPVR and CO in children with POTS were significantly lower than those of controls. Plasma CNP levels were significantly greater in children with POTS than that of controls (32.8 ± 9.7 vs 24.2 ± 8.4 [pg/mL], $P < .01$), and symptom scores and ΔHR positively correlated with plasma CNP levels in children with POTS (symptom scores: $r = 0.490$, $P < .01$; ΔHR: $r = 0.508$, $P < .001$), but CO negatively correlated with plasma CNP levels ($r = -0.446$, $P < .01$).

Conclusion Reduced TPVR and CO associated with the elevated plasma CNP might be involved in the pathogenesis of POTS. *(J Pediatr 2015;166:1385-9)*.

Postural tachycardia syndrome (POTS) is a subtype of orthostatic intolerance, with excessive increase in heart rate (HR) and orthostatic intolerance, including dizziness, headache, palpitation, fatigue, chest tightness, and nausea, associated with long-term standing or position changes from supine to upright.[1-3] Previous findings suggest that the pathogenesis of POTS mainly involves central hypovolemia, autonomic nervous system dysfunction, vascular endothelial dysfunction, and muscle pump dysfunction.[4-10] Up to now, however, the mechanisms responsible for POTS have not been fully understood. Whether there are any change in total peripheral vascular resistance (TPVR) and cardiac output (CO) during upright position in children with POTS remains unidentified.

TPVR refers to the total blood flow resistance of the circulatory system, which reflects the role of vascular obstruction of blood flow, mainly associated with the magnitude of peripheral vascular compliance. The possible change in TPVR in children with POTS has not been understood. The factors regulating peripheral vessel tone, include nitric oxide (NO), endothelin-1, prostaglandins, local metabolites such as ATP, anaerobic metabolism of lactic acid, as well as local neuritis factor substance P.[11] Human atrial natriuretic peptide, brain natriuretic peptide, and adrenomedullin are vasorelaxant agents with diuretic function.[12-16] Belonging to the family of natriuretic peptide, C-type natriuretic peptide (CNP) has a high expression in the vascular endothelium, and a relatively high homology with atrial natriuretic peptide and brain natriuretic peptide.

CO is defined as the blood flow from left ventricle or right ventricle to systemic or pulmonary circulation per minute. Within a certain range, CO elevates as HR increases, and appropriate HR produces maximum CO. In children with POTS, the HR increases when they are standing upright. The change in CO with children with POTS has not been understood fully. Therefore, in the present study, TPVR and CO were investigated in children with POTS during orthostatic posture for a better understanding of the mechanisms for POTS in children.

BP	Blood pressure
CNP	C-type natriuretic peptide
CO	Cardiac output
HR	Heart rate
NO	Nitric oxide
POTS	Postural tachycardia syndrome
TPVR	Total peripheral vascular resistance

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Methods

Twenty-nine children with POTS presenting with orthostatic intolerance symptoms and who were admitted in the department of Pediatrics in Peking University First Hospital between December 2013 and June 2014 were enrolled in the present study and were defined as the POTS group. All patients were diagnosed with POTS by the upright test. Fourteen were boys and 15 were girls, with a mean age range of 12 ± 3 years. Thirty-two healthy children were recruited as control group based on the normal findings in history, physical examination, and the upright test; 17 were boys and 15 were girls, with a mean age range of 11 ± 2 years. The study was approved by Ethics Committee of Peking University First Hospital, and all parents of children had signed the informed consent.

The diagnostic criteria of POTS include the following: (1) mostly older children; (2) presence of symptoms of orthostatic intolerance such as dizziness, headache, amaurosis, palpitations, nausea, blurred vision, or even syncope; (3) fulfilled the diagnostic criteria of upright test: in an upright position for 10 minutes, the increased HR ≥40 beats/min or maximum HR ≥120 beats/min; and (4) other diseases such as cerebrovascular diseases, metabolic diseases, and organic heart diseases were excluded.[17-20]

All children were required to discontinue drugs that affect the autonomic nervous system before the test. In a fasting state, dim light, suitable temperature and quiet environment, children were in the supine position for 10 minutes, and their HR, blood pressure (BP), TPVR, and CO were displayed and recorded using the Finapres Medical System-FMS (FinometerPRO, FMS Company, Amsterdam, Netherlands). Then, children were asked to stand for another 10 minutes and their HR, BP, TPVR, and CO were monitored and recorded or until the occurrence of a positive response. When children were kept standing for 10 minutes or the positive response appeared, they were asked to return to the supine position, and their HR, BP, TPVR, and CO were monitored and recorded with the Finapres Medical System-FMS.

The Finapres Medical System-FMS with a finger sensor was used for continuously monitoring and collecting hemodynamic data generated beat-by-beat. HR, BP, TPVR, and CO were measured using a model flow method.[21-23] With a finger cuff, arterial BP was obtained continuously and noninvasively by using the Finapres Medical System-FMS and BeatScope software (Smart Medical, Gloucestershire, United Kingdom) with the volume-clamp technique maintaining the diameter of the artery under an inflated finger cuff at a set point, thereby determining with time changes in arterial pressure. Diodes were located in the finger cuff, on either side of the finger, to detect changes in artery diameter and change the inflation of the cuff to keep the diameter at the set point. The cuff is inflated or deflated via an air bladder connected to an air hose and pump. The software, using a mathematical model, generates an aortic pulse waveform from the finger arterial pressure wave. This computation takes into account changes in the pulse pressure and waveform shape as the pressure pulse is transmitted down the brachial arteries to the finger arteries. With the Finapres finger cuff, together with BeatScope software, left ventricular stroke volume was calculated and HR, CO, and TPVR were calculated. Variables such as age, sex, body height, and weight also were included in the computation for each individual subject.[21-23] The measured index was derived from the mean of 3-6 cardiac cycles.

When the supine HR and BP of POTS group and control group were steady at 8 a.m., 3 mL of blood were collected from children in POTS group and control group in a fasting quiet state. Girls were not studied during their menstrual period. Blood was stored in test tubes containing EDTA and then was centrifuged at 2000 rpm for 20 min at 4°C. The supernatant was collected, aprotinin was added at 1:100, and the mixture was later frozen at −20°C in the refrigerator. Plasma CNP content was measured with a Sandwich Immunoassay Chemiluminescence (Phoenix Pharmaceuticals, Burlingame, California), and a polyclonal rabbit antibody kit was consumed.

Symptom scoring was primarily based on orthostatic intolerance symptoms, including syncope, dizziness, headache, lightheadedness, nausea, and palpitations. Each score of POTS symptoms was recorded according to the frequency of orthostatic intolerance symptoms. If orthostatic intolerance symptoms never occurred, the symptom score was recognized as zero; if they occurred once per month, it was defined as a score of one; if they occurred 2-4 times per month, it was defined as a score of 2; if they occurred 4-7 times per week, it was defined as a score of 3; and if they occur more than once a day, it was defined as a score of 4. A final score with the sum of all the scores was calculated.[24]

SPSS 16.0 software (IBM, Armonk, New York) was used for data analysis. Measurement data are presented as mean ± SD. The independent-sample t test was used for comparison of CNP content and CO between the groups. Repeated measures ANOVA was used in the comparison of TPVR and CO in the POTS group during supine, upright and repeat supine positions. Pearson correlation analysis was used for correlation analysis, and χ^2 test was used for comparison of rate. $P < .05$ was considered statistically significant.

Results

There were no significant differences in sex ratio, age, body height, weight, supine systolic BP, diastolic BP, and mean BP ($P > .05$) between the 2 groups. Compared with the control group, however, ΔHR in POTS group was significantly increased ($P < .01$; **Table**).

In children with POTS, upright TPVR and CO were significantly lower than those in supine position (TPVR: 1.49 ± 0.35 [mm Hg·min/L] vs 1.78 ± 0.30 [mm Hg·min/L], $P < .01$; CO: 2.08 ± 0.75 [L/min] vs 2.80 ± 1.18 [L/min]), whereas they rose again when children returned to supine from upright (TPVR: 1.83 ± 0.46