Salivary Cortisol Levels Predict Therapeutic Response to a Sleep-Promoting Method in Children with Postural Tachycardia Syndrome

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Objective To determine the value of salivary cortisol concentrations in predicting the efficacy of sleep-promoting treatment in children with postural tachycardia syndrome (POTS).

Study design This prospective study involved 40 children with POTS and 20 healthy children (controls). POTS was diagnosed using the head-up or head-up tilt test. Patients with POTS received a sleep-promoting treatment: >8 hours of sleep every night and a midday nap in an appropriate environment; no drinking water or exercising before bedtime; and urination before bedtime. The Pittsburgh Sleep Quality Index was used to evaluate sleep quality, and symptom scores were used to assess POTS severity. Salivary samples were collected upon awakening, 30 minutes after awakening, at 12:00 p.m., 4:00 p.m., and 8:00 p.m., and at bedtime before treatment. Enzyme-linked immunosorbent assay was used to measure salivary cortisol concentrations.

Results Cortisol concentrations were significantly higher in patients with POTS than in the controls at all time points ($P < .05$ for all). PSQI scores were significantly higher in patients with POTS (7.2 ± 3.0) than in the controls (1.35 ± 1.39; $t = -10.370$, $P < .001$). Salivary cortisol concentrations at awakening were significantly higher in responders than in nonresponders (4.83 ± 0.73 vs 4.05 ± 0.79 ng/mL, $t = -3.197$, $P = .003$). The area under the receiver operating characteristic curve was 75.8%, (95% CI 59.3%-92%). Cut-off at-awakening salivary cortisol concentrations of >4.1 ng/mL yielded 83.3% sensitivity and 68.7% specificity in predicting therapeutic efficacy.

Conclusions At-awakening salivary cortisol concentrations may predict the efficacy of sleep-promoting treatment in patients with POTS *(J Pediatr 2017;■■:■■-■■)*.

Postural tachycardia syndrome (POTS) is a subtype of orthostatic intolerance. Children and adolescents with POTS show an increase in heart rate of ≥40 beats·minute^{-1} or a maximum heart rate of >120 beats·minute^{-1} during the head-up test or head-up tilt test.[1] Orthostatic symptoms include dizziness or vertigo, chest tightness, headache, palpitations, pallor, blurred vision, fatigue, and syncope. These symptoms last for more than 1 month. Some children with POTS have severe clinical symptoms that impact their daily life. POTS is a multisystemic condition with heterogeneous clinical features and pathophysiology that can be disabling. Therefore, timely and effective treatment or prevention of the condition is important. The risk of POTS has been shown to be almost 6 times greater in those who sleep for <8 hours/day than in those who sleep for >8 hours/day.[2] However, the specific nature of the sleep problems in patients with POTS is not fully understood.

Follenius et al found that increased cortisol levels were not concomitant with a specific sleep stage but generally accompanied prolonged waking periods.[3] This implies that cortisol-releasing mechanisms may be involved in sleep regulation. In healthy subjects, increased cortisol accompanies waking periods and stage-N1 sleep, whereas slow-wave sleep is associated with declining plasma cortisol levels. Therefore, decreased slow-wave sleep increases cortisol levels, which might induce syndromes similar to POTS. Song et al reported that sleep deprivation could significantly increase serum cortisol level and affect mental health in service men.[4] Therefore, we speculated that cortisol may reflect sleep quality. We sought to determine if the cortisol rhythm differed between patients with POTS and healthy children, and if this rhythm predicted the efficacy of sleep-promoting treatments in children with POTS.

Methods

A total of 60 subjects, including 40 children with POTS and 20 healthy children, were recruited from the outpatient and inpatient pediatric departments of Shaanxi Provincial People's Hospital and Children's hospital of Zhejiang University School of Medicine, China. The children with POTS had the following manifestations: dizziness or vertigo, chest tightness, headache, palpitations, paleness, blurred vision,

POTS	Postural tachycardia syndrome
PSQI	Pittsburgh Sleep Quality Index
ROC	Receiver operating characteristic

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fatigue, or syncope. They underwent a thorough history taking, physical examination, and laboratory investigations, including electrocardiography, electroencephalography, blood glucose and blood biochemistry tests, and cranial computed tomography or magnetic resonance imaging to exclude cardiac, neurologic, metabolic, and psychogenic causes. The 20 healthy children had normal findings on medical history, physical examination, electrocardiography, electroencephalogram, head-up test, and head-up tilt test. All children were informed about the purposes of the research and agreed to participate. Written informed consent was obtained from the parents or guardians of all the study subjects. The study was approved by the ethics committees of Shaanxi Provincial People's Hospital and Children's Hospital, Zhejiang University School of Medicine.

Before the head-up test, the children were instructed to stop taking any drugs that might affect autonomic function. The test was performed in a quiet room at a suitable temperature. Heart rate and blood pressure were continuously monitored during the test with a Dash 2000 Multi-Lead Physiological Monitor (General Electric, New York, New York). The children were required to lie down for at least 10 minutes and were then asked to stand up for 10 minutes. The test was discontinued if a positive response appeared within 10 minutes of standing. If the changes in the heart rate and blood pressure were within the normal range during the head-up test, the head-up tilt test was performed on the following day.

All children fasted at least 4 hours before the head-up tilt test and instructed to not use any drugs that might affect autonomic function. The children lay on the tilt table (HUT-821; Beijing Juchi, Beijing, China), and their heart rate and blood pressure were continuously monitored with a Dash 2000 Multi-Lead Physiological Monitor (General Electric). Once the heart rate had stabilized, the table was tilted to a 60° angle, and the heart rate and blood pressure were monitored until either a positive response appeared or the test was complete (at the end of 45 minutes). A positive response consisted of an increase in heart rate of ≥40 beats·minute^{-1} or a maximum heart rate of >120 beats·minute^{-1} accompanied with any 2 of the following symptoms: dizziness or vertigo, chest tightness, headache, palpitations, pallor, blurred vision, fatigue, or syncope during tilting. POTS was diagnosed if a positive response was obtained.[5]

The diagnostic criteria for POTS are (1) normal heart rate in the supine position; (2) more than 2 clinical symptoms on standing, such as dizziness or vertigo, lightheadedness, headache, fatigue, pallor, blurred vision, chest tightness, palpitations, hand tremors, and syncope; (3) increment in heart rate ≥40 beats·minute^{-1} or maximum heart rate >120 beats·minute^{-1} after standing during the head-up test or head-up tilt test, with at least 2 of the above symptoms; (4) symptoms relieved or diminished by recumbence and symptoms persisting for ≥1 month; and (5) exclusion of other cardiovascular, neurologic, or metabolic diseases.[6]

Sleep quality was measured prior to the head-up and head-up tilt tests. The Pittsburgh Sleep Quality Index (PSQI), standardized for this population and language, was used to evaluate sleep quality. The PSQI is an 18-item, self-reported questionnaire used to evaluate habitual sleep quality. The 18 individual items generate 7 "component" scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medications, and daytime dysfunction. Each of these 7 scores is weighted equally on a scale from 0 to 3, with 0 indicating no difficulty and 3 indicating severe difficulty. The global score ranges from 0 to 21, with high scores indicating poor sleep quality; scores >5 suggest clinically significant sleep complaints.[7]

All patients were treated with the following sleep-promoting methods: (1) more than 8 hours of sleep every night, from 10:00 p.m. to 6:30 a.m. or 7:00 a.m.; (2) 40 minutes to 1 hour of a midday nap after lunch; (3) no exercise before bedtime; (4) choose one of the following measures to help fall asleep: quiet music, reading, yoga, and a hot bath; (5) an appropriate environment/temperature; (6) little or no water 1 hour before bedtime; and (7) urination before bedtime.

All patients were evaluated using symptom scores and the head-up test or head-up tilt test before the treatment. Symptoms were also scores during outpatient follow-up visits after 3 months of the sleep-promoting treatment. The 10 main clinical symptoms of POTS are syncope, dizziness, lightheadedness, nausea, heart palpitations, headaches, hand tremors, sweating, blurred vision, and inattention. Symptom scores were assigned as follows: no POTS symptoms, 0 points; 1 symptom once a month, 1 point; 1 symptom 2-4 times per month, 2 points; 1 symptom 2-7 times per week, 3 points; and 1 symptom at least once per day, 4 points. Symptom scoring was repeated to evaluate the overall severity of the disease. Patients were considered as responders if their symptom scores decreased by 2 or more points after treatment; they were considered nonresponders if their symptom scores decreased by <2 points.[8]

Saliva samples were collected from each participant before the treatment. The salivary sample–collection protocol was explained to each study participant, and they were shown the correct use of the Salivette saliva-collection device (Sarsted, Leicester, United Kingdom). Participants were told not to eat, drink, smoke, brush their teeth, or use mouthwash in the 30 minutes before salivary collection and not to drink alcohol on the day of sample collection. Salivary specimens were collected when the children awakened, 30 minutes after awakening, at 12:00 p.m., 4:00 p.m., 8:00 p.m., and at bedtime. These time points were expected to span the peak and nadir of cortisol release during waking hours.[9] No saliva stimulants were used to encourage salivation. Salivettes were placed into the mouth, on top of the tongue for 2 minutes per sampling time point. After collection, the saliva samples were immediately refrigerated and stored at -80°C until being assayed. Enzyme-linked immunosorbent assays were used to measure salivary cortisol concentrations.

Statistical Analyses

The data were analyzed with the SPSS v 13.0 software (SPSS Inc, Chicago, Illinois). Categorical data were expressed as number of cases, and continuous data were expressed as mean ± SD. The χ^2 test and *t* test were used to analyze between-

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