

Increased Endogenous Sulfur Dioxide Involved in the Pathogenesis of Postural Tachycardia Syndrome in Children: A Case-Control Study

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Abstract

Background: The pathogenesis of postural tachycardia syndrome (POTS) remains unclear. This study aimed to explore the changes and significance of sulfur dioxide (SO₂) in patients with POTS.

Methods: The study included 31 children with POTS and 27 healthy children from Peking University First Hospital between December 2013 and October 2015. A detailed medical history, physical examination results, and demographic characteristics were collected. Hemodynamics was recorded and the plasma SO₂ was determined.

Results: The plasma SO₂ was significantly higher in POTS children compared to healthy children (64.0 ± 20.8 μmol/L vs. 27.2 ± 9.6 μmol/L, respectively, *P* < 0.05). The symptom scores in POTS were positively correlated with plasma SO₂ levels (*r* = 0.398, *P* < 0.05). In all the study participants, the maximum heart rate (HR) was positively correlated with plasma levels of SO₂ (*r* = 0.679, *P* < 0.01). The change in systolic blood pressure from the supine to upright (ΔSBP) in POTS group was smaller than that in the control group (*P* < 0.05). The ΔSBP was negatively correlated with baseline plasma SO₂ levels in all participants (*r* = -0.28, *P* < 0.05). In the control group, ΔSBP was positively correlated with the plasma levels of SO₂ (*r* = 0.487, *P* < 0.01). The change in HR from the supine to upright in POTS was obvious compared to that of the control group. The area under curve was 0.967 (95% confidence interval: 0.928–1.000), and the cutoff value of plasma SO₂ level >38.17 μmol/L yielded a sensitivity of 90.3% and a specificity of 92.6% for predicting the diagnosis of POTS.

Conclusions: Increased endogenous SO₂ levels might be involved in the pathogenesis of POTS.

Key words: Blood Pressure; Children; Pathogenesis; Postural Tachycardia Syndrome; Sulfur Dioxide

INTRODUCTION

Postural tachycardia syndrome (POTS) patients show symptoms of orthostatic intolerance with increasing heart rate (HR) when the body moves from supine to an upright position or after standing for a long period.^[1] Our group reported that POTS was present in 6.9% of children.^[2] The pathogenesis of POTS, however, is unclear. Previous studies have shown that decreases in blood volume, endothelial dysfunction, increased adrenergic response, small fiber neuropathy, autonomic nervous system imbalance, and muscle pump dysfunction may be involved in its pathogenesis.^[3] Regardless, the current vascular mechanisms underlying POTS remain unclear.

Sulfur dioxide (SO₂), a gaseous molecule, has recently been found to have physiological and pathophysiological properties in the cardiovascular system and has attracted a great attention in the recent years.^[4-8] It was shown that

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endogenous and exogenous SO₂ have vasodilatory effects.^[5-8] Zhao *et al.*^[9] found spontaneous blood pressure decrease in hypertensive rats when SO₂ donor was applied, which suggested that SO₂ played an important role in the regulation of vascular function. However, changes in plasma SO₂ levels in children with POTS and their significance have not yet been analyzed. The present study was designed to explore the plasma SO₂ content in POTS children and its relationship with hemodynamic parameters in addition to symptom scoring, thus revealing its possible involvement of SO₂ in the pathogenesis of POTS.

METHODS

Selection and description of participants

The study included 31 POTS children (11 boys and 20 girls) from Peking University First Hospital between December 2013 and October 2015. The mean age range of patients was 12.3 ± 2.3 years. The POTS group had substantial symptoms, such as vertigo, dizziness, headaches, palpitations, chest tightness, changes in complexion, fatigue, blurred vision, and early morning discomfort. The supine position could effectively relieve symptoms, and all patients had a positive head-up test and no other cardiovascular diseases.^[10-12] The controls included 27 children (11 boys and 16 girls) with a mean age of 12.0 ± 0.8 years. They were healthy children without syncope, chest tightness, headache, or other symptoms of orthostatic intolerance, as demonstrated by a normal medical history, physical examination, and laboratory findings. All controls had a negative head-up test and no other cardiovascular diseases. All participants had no recent infection history and no consumption of caffeine, fat, or Vitamin C.

Ethical approval

Guardians of all children were informed of the study purpose and research methods, and informed consent was obtained from all individual participants included in the study. The study was approved by the First Hospital of Peking University Ethics Committee in Beijing. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the *Helsinki declaration* of 1975, as revised in 2000.

Technical information

Head-up tilt test

Head-up tilt test was applied to diagnose POTS. First, children were kept quietly in the supine position on the tilt table (HUT-821, Beijing Juchi, China) for 10 min, and their HR, blood pressure, and electrocardiograph were recorded by a Dash 2000 Multi-lead Physiological Monitor (General Electric, New York, USA). Then, the tilt table was tilted to 60° angle, and the HR, blood pressure, and an electrocardiograph were monitored until the occurrence of a positive response or the completion of the test (with a process of 45 min). During the test, if the HR increased by ≥40 beats or the maximum HR of ≥130 times/min (6–12 years) or ≥125 beats/min (13–18 years) was accompanied by two of the following symptoms

such as dizziness or vertigo, headache, fatigue, blurred vision, morning discomfort, palpation, chest tightness, and paleness, the positive of POTS could be diagnosed.^[11,12]

Symptom score calculation

To avoid the influence of different operators, all the symptoms were assessed by one operator. The symptom scores included the following ten symptoms: distraction, nausea, palpitations, headache, tremor, syncope, dizziness or vertigo, lightheadedness, sweating, and blurred vision, and the final score was calculated by summing the scores of separate symptoms. Zero point was given if the symptom did not occur; 1 point was given if the symptom occurred once per month; 2 points were given if the symptom occurred 2–4 times/month; 3 points were given if the symptom occurred 2–7 times/week; and 4 points were given if the symptom occurred more than once per day.^[13-15]

Plasma sulfur dioxide measurement

SO₂ concentrations were determined as follows.^[8] When children were kept in the supine position, blood was obtained and placed in an anticoagulant tube and was then centrifuged at 2000 rpm for 20 min. Then, aprotinin (Kangjia Hongyuan, China) at a ratio of 1:100 was added to the supernatant. The supernatant was stored in a refrigerator at -20°C. For high-performance liquid chromatography analysis of SO₂, 100 μl of plasma, 70 μl of sodium borohydride (Sigma Company, USA), and 10 μl of mBrB (Sigma Company, USA) were added to a tube, which were then incubated at 42°C for 7 min. Then, 50 μl of a perchloric acid mixture was added before the plasma was centrifuged at 12,400 rpm for 10 min. The two mobile phases used for analysis consisted of methanol (JT Baker Company, USA): acetic acid (Guoyao Company, China): water at a volume ratio of 5:0.25:94.75, potential of hydrogen 3.4, and pure methanol. All detection procedures were performed at an excitation wavelength of 390 nm and absorption wavelength of 479 nm. The human subjects' samples were collected from December 2013 to October 2015. We had access to information that could identify individual participants during or after data collection.

Statistical analysis

Data were analyzed using SPSS 20.0 (SPSS, Chicago, IL, USA). The homogeneity of variance was analyzed by the Kolmogorov–Smirnov *Z*-test. Differences between the two groups were compared using a *t*-test. The sex ratio was analyzed using the Chi-square test. Correlations were analyzed using the Pearson's correlation. A value of *P* < 0.05 was considered statistically significant. The predictive value of plasma SO₂ was determined using a receiver operating characteristic curve. If the confidence interval (*CI*) for AUC had a value of *P* < 0.05, the indicator was considered to have predictive value.

RESULTS

Demographic data, hemodynamics, and plasma sulfur dioxide

The maximum HR was faster and the baseline plasma SO₂ level was higher in the POTS group than that in the control

group ($P < 0.05$). No significant differences in age, weight, and systolic and diastolic blood pressures during the supine posture and the standing posture were found between the POTS group and the control group ($P > 0.05$) [Table 1].

The receiver operating characteristic curve of plasma sulfur dioxide for predicting the diagnosis of postural tachycardia syndrome

The AUC was 96.7% (95% CI, 0.928–1.000), indicating that it yielded a high predictive value for using a plasma SO_2 cutoff value of 38.17 $\mu\text{mol/L}$ to support the diagnosis of POTS. The sensitivity was 90.3% and the specificity was 92.6% [Figure 1].

Correlation between symptom scores and plasma sulfur dioxide levels

The symptom scores were positively correlated with plasma SO_2 levels in the POTS group ($n = 31$, $r = 0.398$, $P < 0.05$) [Figure 2a].

Correlation between the maximum heart rate and plasma sulfur dioxide levels in children

In all the study participants, the maximum HR was positively correlated with plasma SO_2 level ($n = 58$, $r = 0.679$, $P < 0.01$) [Figure 2b].

Change in systolic blood pressure from a supine to an upright position in the postural tachycardia syndrome group and controls

The upright systolic blood pressure (SBP) was significantly increased relative to the supine SBP in controls. However, the upright SBP exhibited a decreasing trend compared to the supine SBP in the POTS group. The SBP change from a supine to an upright position (ΔSBP) significantly differed between the two groups ($P < 0.01$) [Figure 3a].

Correlation between the change in systolic blood pressure from supine to an upright position and baseline plasma sulfur dioxide levels in participants

The ΔSBP was positively correlated with baseline plasma SO_2 levels in all participants ($n = 58$, $r = -0.28$, $P < 0.05$) [Figure 3b]. The ΔSBP was positively correlated with baseline plasma SO_2 levels in the control group ($n = 27$, $r = 0.487$, $P < 0.01$) [Figure 3c]. The SBP had no correlation with baseline plasma SO_2 levels in the POTS group ($n = 31$, $P > 0.05$).

DISCUSSION

Currently, the pathogenesis of POTS is not fully understood, although abnormal diastolic function and endothelial function in POTS children were proposed and confirmed. In 1940, MacLean and Allen first reported the presence of hypovolemia in children with POTS, and further studies revealed an increased venous capacity in the lower extremities of children with POTS attributable to the local anatomy and functional abnormality of the lower limbs.^[16,17] The decrease in 24-h urinary sodium excretion might be related to changes in circulation volume in POTS children.^[18,19]

Table 1: Demographic characteristics, hemodynamics, and plasma SO_2

Items	Control ($n = 27$)	POTS ($n = 31$)	t/χ^2	P
Gender (male/female)	11/16	11/20	0.169	>0.05
Age (years)	12.0 \pm 0.8	12.3 \pm 2.3	0.702	>0.05
Height (cm)	145.3 \pm 10.4	157.9 \pm 15.8	3.551	<0.01
Weight (kg)	42.4 \pm 7.32	48.8 \pm 15.4	1.973	>0.05
Supine SBP (mmHg)	107.1 \pm 10.0	109.2 \pm 15.8	0.618	>0.05
Supine DBP (mmHg)	67.3 \pm 7.9	65.7 \pm 11.6	-0.597	>0.05
Supine HR (bpm)	83.9 \pm 7.3	76.8 \pm 10.0	-3.052	<0.01
HR _{max} (bpm)	104.2 \pm 7.1	124.2 \pm 10.3	8.473	<0.01
Upright SBP (mmHg)	112.1 \pm 10.0	106.2 \pm 15.6	-1.679	>0.05
Upright DBP (mmHg)	73.0 \pm 8.4	71.0 \pm 11.1	-0.789	>0.05
Basal plasma SO_2 ($\mu\text{mol/L}$)	27.2 \pm 9.6	64.0 \pm 20.8	8.439	<0.01

All data were shown as mean \pm SD or n . POTS: Postural tachycardia syndrome; SBP: Systolic pressure; DBP: Diastolic blood pressure; HR: Heart rate; HR_{max}: Maximum heart rate; SO_2 : Sulfur dioxide.

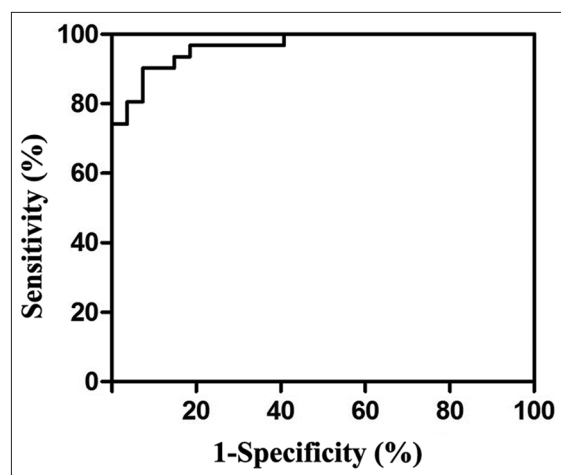


Figure 1: The ROC curve of the plasma SO_2 level for the diagnosis of POTS. The longitudinal axis represents the sensitivity in the diagnosis of POTS. The transverse axis represents the false-positive rate (1-specificity) of the diagnosis. The area under the curve was 96.7% (95% confidence interval: 0.928–1.000; $P < 0.01$). ROC: Receiver operating characteristic; SO_2 : Sulfur dioxide; POTS: Postural tachycardia syndrome.

Although significant progress has been made in the study of the pathogenesis of POTS concerning the cause of abnormal vasodilation and vascular endothelial dysfunction, uncertainty still remains, which requires further study.

In the recent years, an endogenous SO_2 pathway was discovered in the cardiovascular system,^[20] and SO_2 could cause vasodilation and regulate endothelial cell function.^[5-7] Our team observed that an SO_2 donor, sodium sulfite/sodium bisulfite, could lead to a significant decrease in blood pressure,^[8] and the application of an SO_2 donor resulted in a significant relaxation of the aortic rings.^[21] Therefore, to explore the possible mechanisms responsible for the development of POTS, in this present study, we first showed that the plasma concentration of SO_2 in POTS group ($64.0 \pm 20.8 \mu\text{mol/L}$) was significantly higher than

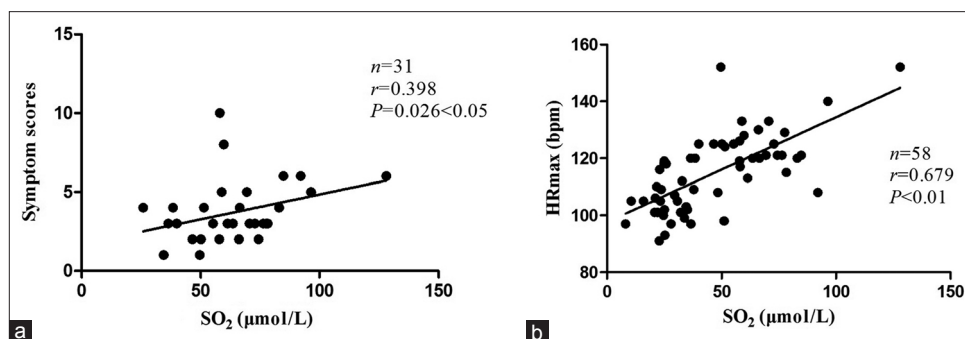


Figure 2: Correlation analysis between symptom scores and plasma SO_2 levels and between maximum HR and plasma SO_2 levels in patients. (a) Correlation analysis between symptom scores and plasma SO_2 levels in children with POTS. Symptom scores and plasma SO_2 levels were positively correlated in the POTS group ($n = 31$, $r = 0.398$, $P < 0.05$). (b) Correlation analysis of the maximum HR and plasma SO_2 levels. In all the study participants, the maximum HR was positively correlated with the plasma SO_2 level ($n = 58$, $r = 0.679$, $P < 0.01$). SO_2 : Sulfur dioxide; POTS: Postural tachycardia syndrome; HR: Heart rate.

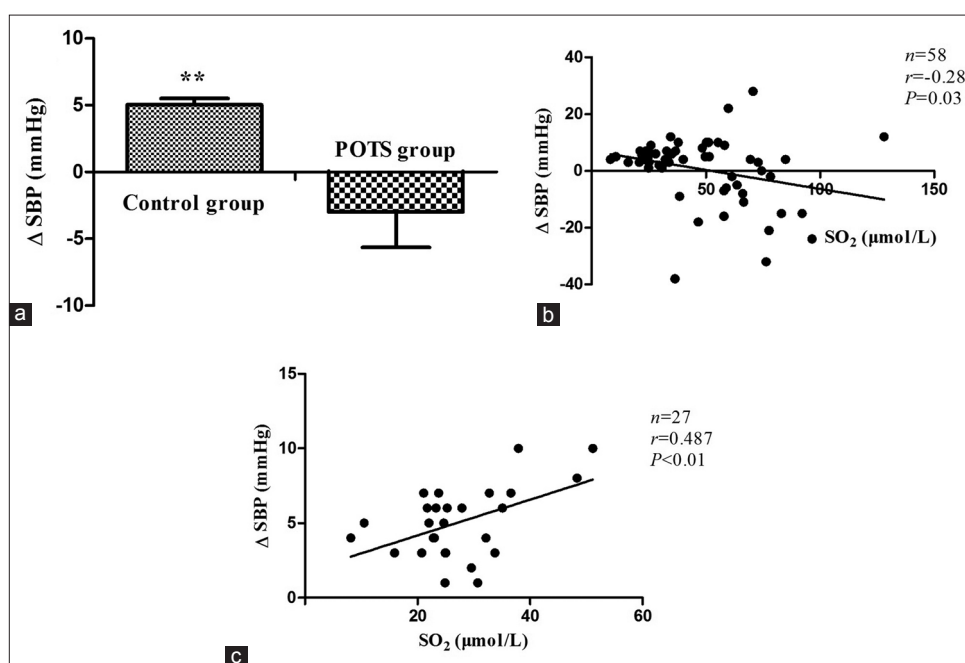


Figure 3: Blood pressure and plasma SO_2 analysis. (a) Comparison of the ΔSBP between the POTS and control groups. The difference in the ΔSBP between the two groups was statistically significant ($P < 0.01$). (b) The correlation between ΔSBP and plasma SO_2 in all participants ($n = 58$, $r = -0.28$, $P < 0.05$). (c) Correlation analysis of ΔSBP and plasma SO_2 levels in the control group ($n = 27$, $r = 0.487$, $P < 0.01$). SO_2 : Sulfur dioxide; POTS: Postural tachycardia syndrome; ΔSBP : Systolic blood pressure from the supine to upright.

that of the control group ($27.2 \pm 9.6 \mu\text{mol/L}$) [Table 1]. More interestingly, there was a significant decrease in blood pressure when patients changed their posture from supine to upright as compared with the controls. Hence, the possible reason for this increase in HR is likely associated with the decrease of blood pressure from the supine to upright position in POTS since patients with POTS need to have an excessively increased HR to compensate for the possibly reduced cardiac output caused by the decreased blood pressure. Therefore, the increased plasma SO_2 may be responsible for the decrease in blood pressure in POTS children, which was likely involved in the pathogenesis of POTS. Furthermore, our findings that the plasma SO_2 level was positively correlated with the maximum HR during upright posture and the symptom scores of the patients

further confirmed our abovementioned hypothesis that endogenous SO_2 was involved in the pathogenesis of POTS.

As for the mechanisms for SO_2 vasorelaxation, people found that the vasodilatory effects of SO_2 were blocked by nicardipine, a calcium channel blocker, and glyburide, a K_{ATP} channel blocker,^[22-25] which suggests an involvement of calcium channels and K_{ATP} channel in vasorelaxation. The vasodilatory mechanism of SO_2 depends on its concentration. If the concentration of SO_2 is $>500 \mu\text{mol/l}$, the vasodilatory effects are independent of the endothelial system but related to K_{ATP} channels and the inhibition of L-type calcium channels.^[22-24] In contrast, if the concentration of SO_2 is $<450 \mu\text{mol/L}$, the vasorelaxant mechanism depends on the big-conductance calcium-activated K^+ (BKCa) and cyclic guanosine monophosphate.^[24] SO_2 induced the K_{ATP} and BKCa

channel activation via upregulating the expressions of Kir6.1, Kir6.2, SUR2B, and BKCa channel subunits α and β 1 in rat aortic rings, while SO₂ inhibited the L-type calcium channel by downregulating the Cav1.2 and Cav1.3 expressions.^[25]

A significant difference in body height is observed in POTS children, which would result in a different body mass index in children with POTS. Previous studies have shown that children with POTS might have a lower body mass index than the control group,^[26] although the body mass index had no correlation with the plasma content of SO₂ in children with POTS ($P = 0.471$) in the present study.

The current study has several limitations. The findings showed that endogenous SO₂ was involved in the pathogenesis of POTS. However, the study could not show a causal relationship between SO₂ and the pathogenesis of POTS. Air pollution is prevalent, and SO₂ exposure could affect the overall health of the population. Previous studies have found that a 10- μ g/m³ increase in SO₂ was associated with emergency treatments with odds ratios of 1.026 (95% CI: 1.019–1.033) for circulatory diseases and 1.037 (95% CI: 1.020–1.055) for coronary heart disease.^[27] However, the effect of SO₂ in the air on POTS requires further study. Cohort studies for both controls and patients from rural areas and studies of POTS according to ethnicity would be useful for future investigations. In addition, in future studies, a large sample size with long-term follow-up is needed to clarify the role of SO₂ in the pathogenesis of POTS, especially regarding the vascular mechanisms for functional cardiovascular diseases.

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Conflicts of interest

There are no conflicts of interest.

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内源性二氧化硫含量升高可能与儿童体位性心动过速综合征的发病机制相关

摘要

目的: 体位性心动过速综合征 (postural tachycardia syndrome, POTS) 的发病机制尚不明确, 此研究的目的是为了探索血浆二氧化硫 (sulfur dioxide, SO₂) 含量在POTS患儿中的变化及意义。

方法: 本研究共有31例POTS患儿和27例健康对照组儿童。31例POTS患儿均为于2013年12月到2015年10月期间在北京大学第一医院儿科以直立不耐受症状就诊的患儿。病史询问, 体格检查, 人口学特征及血流动力学参数等信息数据进行了收集。同时测定了POTS患儿和健康对照组儿童血浆SO₂含量。

结果: POTS患儿血浆SO₂含量明显高于对照组 ($64.0 \pm 20.8 \mu\text{mol/l}$ vs. $27.2 \pm 9.6 \mu\text{mol/l}$, $P < 0.05$); POTS患儿血浆SO₂含量与症状评分呈正相关 ($n = 31$, $r = 0.398$, $P < 0.05$); 血浆SO₂含量与最大心率呈正相关 ($n = 58$, $r = 0.679$, $P < 0.01$); POTS组的平卧位到直立位的血压变化值 (Δ (平卧)) 明显低于对照组 ($P < 0.05$); POTS组和对照组的 Δ 和对照与血浆SO₂含量呈负相关 ($n = 58$, $r = -0.28$, $P < 0.05$); 对照组的 Δ 和对照组的与血浆SO₂含量呈正相关 ($n = 27$, $r = 0.487$, $P < 0.01$); POTS组的平卧位到直立位的心率变化值 (Δ (平)) 明显高于对照组; 采用ROC曲线分析血浆SO₂含量诊断POTS的价值, 曲线下面积为0.967, 置信区间为 (95% CI 0.928–1.000), 以血浆SO₂含量38.17 $\mu\text{mol/l}$ 为界值, 敏感度为90.3%, 特异度为 92.6%。

结论: 内源性SO₂含量升高可能与POTS的发病机制有关。