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ORIGINAL ARTICLE

Clinical characteristics and hemodynamic responses to head-up tilt test in children and adolescents with unexplained sighing

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Abstract

Objective Sighing is a common symptom in children and adolescents. In this study, we explored the clinical characteristics and hemodynamic responses to head-up tilt test (HUTT) in children and adolescents with unexplained sighing.

Methods One hundred ninety-two children and adolescents complaining of unexplained sighing were enrolled as study group after excluding chest wall, lung, heart diseases, and psychogenic disorders. Sixty-nine healthy individuals were enrolled as control group. All the subjects underwent HUTT.

Results Nitroglycerin-stimulated HUTT positive rate was higher in the study group than the control group (24.0% vs 10.1%, $P = 0.014$). In total, 32.3% of patients with sighing had positive responses to HUTT, which was higher than that of healthy individuals (32.3% vs 15.9%, $P = 0.009$). Among 62 cases with positive responses to HUTT in the study group, 48 cases were vasoinhibitory type vasovagal syncope (VVS), 5 cases were mixed type VVS, 3 cases were cardioinhibitory type VVS, 5 cases were postural tachycardia syndrome, and one case was orthostatic hypertension. Sighing patients with positive responses to HUTT had female dominance (54.8% vs39.2%, $P = 0.045$), older mean age (9.6 ± 2.8 vs 8.1 ± 2.7 years old, $P = 0.001$), higher basic systolic blood pressure (104.8 ± 10.4 vs 101.1 ± 9.9 mmHg, $P = 0.019$), and higher diastolic blood pressure (66.0 ± 7.5 vs 62.9 ± 9.2 mmHg, $P = 0.021$) compared with those of negative responses.

Conclusions Nearly one-third of children and adolescents with unexplained sighing had positive responses to HUTT, demonstrating that sighing was related to dysfunction of the autonomic nervous system. Elder female patients with higher systolic and diastolic blood pressure were more likely to have positive responses to HUTT.

Keywords Sighing · Head-up tilt test · Orthostatic intolerance · Children · Adolescents

Introduction

A sigh is a long and deep breath that is deemed to be an expression of stress, sadness, and exhaustion of relief [1]. Sighing starts from the fetus as the sigh-like breathing movement and continues throughout life [2]. Sighing is generally unnoticed and occurs spontaneously every several minutes. Sighing can prevent alveoli from collapsing and help to fill them with air due to a heavy breath, restoring lung resistance and compliance. However, excessive sighing is a pathological condition called sighing dyspnea, also known as hyperventilation syndrome [3]. Sighing dyspnea is commonly seen in anxiety disorders, including panic disorder, phobias, and post-traumatic stress disorder [4]. Symptoms including sighing, chest tightness, and dyspnea are also associated with asthma or poor asthma control [5].

Sighing is produced in a brainstem region containing a cluster of several thousand neurons called the preBötzinger complex (preBötC). A small subset of these neurons express receptors of bombesin neuropeptide family, and receive bombesin peptidergic signals from other breathing control neurons, together forming the central control neural circuit of sighing [2]. Peripherally, sighing is regulated by two kinds of receptors: mechanoreceptors and chemoreceptors. The pulmonary mechanoreceptors sense the change in lung volume and transmural pressure and transmit the signals of alveolar collapse to the brain by the vagal nerve [6]. These data demonstrate that sighing is regulated by the autonomic nervous system.

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Sighing is frequent in children and adolescents. Most of these children and adolescents have normal chest X-ray, electrocardiogram, and pulmonary function, but complains of recurrently spontaneous sighing. These patients and their families are profoundly troubled and visit doctors frequently, contributing to patients and physician costs and frustration. To define the causes of sighing is of great importance in clinical practice. Head-up tilt test (HUTT), like Valsalva maneuver, deep breathing, and handgrip tests, is an important tool applied to assess the function of autonomic nervous system [7, 8]. Herein, HUTT was utilized to depict the hemodynamic type of unexplained sighing in children and adolescents.

Methods

Study population

The medical history of patients who complained of recurrent sighing and visited Syncope Ward, Children's Medical Center, The Second Xiangya Hospital, Central South University between June 2007 and September 2018, was retrospectively reviewed. Chest wall, lung, and heart diseases were excluded after an evaluation consisting of history, physical examination, baseline laboratory testing, 12-lead electrocardiogram (ECG), echocardiogram, chest X-ray, pulmonary function, and exhaled nitric oxide. Psychogenic disorders were excluded via a clinical assessment by an experienced psychologist. Eventually, 192 cases of patients (107 males, aged from 4 to 15 years old) were recruited as study group. Sixty-nine cases (45 males, aged from 4 to 14 years old) of age- and gender-matched healthy volunteers were enrolled as control group. Subjects of the two groups did not have a history of syncope before. All the subjects underwent HUTT.

HUTT protocol

HUTT consisted of two stages: unstimulated HUTT and sublingual nitroglycerin-stimulated HUTT. The protocol had been conducted according to the previous study [9]. HUTT was subject to approval by the Ethics Committee of The Second Xiangya Hospital, Central South University. Informed consent was issued by all the subjects directly or their guardians. The subjects were asked to lay still for 10 min, and then, basic heart rate (HR), blood pressure (BP), and ECG were recorded. Subjects were tilted at 60° head upward. HR, BP, and ECG were recorded continuously until either 45-min duration or development of syncope or intolerable near syncope symptoms. If syncope occurred, patients were rapidly put in the supine position. If subjects did not develop syncope or presyncope, they underwent nitroglycerin-stimulated HUTT. Tilted posture was maintained, subjects were sublingually medicated with nitroglycerin, and then, HR, BP, and ECG were recorded until for 20 min or syncope or presyncope occurred.

Positive responses to HUTT included vasovagal syncope (VVS), postural tachycardia syndrome (POTS), and orthostatic hypertension (OHT) in the study [10]. VVS was defined as the development of syncope or presyncope accompanied by hypotension (systolic BP ≤ 80 mmHg in children, and/or diastolic BP ≤ 50 mmHg, or over 25% decrease in mean blood pressure), bradycardia (< 75 bpm in children between 4 and 6 years old, < 65 bpm in children between 6 and 8 years old, < 60 bpm in children above 8 years old), or cardiac arrest > 3 s. VVS was further classified into three responses: vasoinhibitory type (significant reduction in BP but insignificant change in HR), cardioinhibitory type (significant reduction in HR but insignificant change in BP), and mixed type (significant reduction both in BP and HR). POTS was defined as dizziness, chest distress, headache, palpitation, and pallor with one of the following within 10 min of HUTT: an increase in HR ≥ 40 bpm in children and adolescents or by a maximum HR > 130 bpm in children between 6 and 12 years old and > 125 bpm in adolescents between 12 and 18 years old. OHT was defined as (within 3 min of HUTT) orthostatic intolerance symptoms and an increase in systolic BP ≥ 20 mmHg, and/or diastolic BP increments ≥ 25 mmHg in children between 6 and 12 years old, ≥ 20 mmHg in adolescents between 12 and 18 years old, or upright BP ≥ 130/90 mmHg in children between 6 and 12 years old and ≥ 140/90 mmHg in adolescents between 12 and 18 years old without an obvious change in HR.

Statistical analysis

Statistical analysis was performed by SPSS 17.0 (IBM Corp, Armonk, New York). Data were described as mean ± SD for continuous variables following normal distribution and analyzed by Student *t* tests. Continuous variables for data not following normal distribution were expressed as the median with inter quartile range (IQR) and analyzed using the Mann-Whitney *U* test. Dichotomized variables were expressed by percent prevalence and compared using χ^2 tests or Fisher exact tests. P value < 0.05 was considered statistically significant.

Results

Clinical characteristics of healthy individuals and sighing patients

As shown in Table 1, there are no statically significant differences in age, gender, BMI between healthy individuals, and sighing patients (all $P > 0.05$).

Table 1 Clinical characteristics of control and study group (mean ± SD)

Groups	*n*	Males (*n*, %)	Females (*n*, %)	Age (years)	BMI (kg/m^2)
Control group	69	45(65.2)	24(34.8)	9.4 ± 2.7	16.9 ± 2.7
Study group	192	107(55.7)	85(44.3)	8.7 ± 2.8	16.8 ± 2.9
t/x^2 value		1.879*		1.961	0.071
P value		0.170		0.053	0.943

*Referred to x^2 value. *BMI* body mass index

Hemodynamic responses to HUTT in the control and study group

In the study group, 48 cases are vasoinhibitory type VVS (7 cases had positive responses to unstimulated HUTT, and 41 cases had positive responses to nitroglycerin-stimulated HUTT), 3 cases are cardioinhibitory type VVS, 5 cases are mixed type VVS, 5 cases are POTS, and one case is OHT (Fig. 1). In the control group, 9 cases are vasoinhibitory type VVS (2 cases were positive to unstimulated HUTT, and 7 cases were positive to nitroglycerin-stimulated HUTT), and 2 cases are POTS (Fig. 1). During the unstimulated stage, the positive rate was not significant between the two groups, whereas nitroglycerin-stimulated HUTT positive rate in the study group was higher than that of the control group (24.0% vs 10.1%, $P = 0.014$). In total, 32.3% of patients with sighing had positive responses to HUTT, which was higher than that of healthy individuals (32.3% vs 15.9%, $P = 0.009$) (Table 2).

Clinical data comparison between sighing patients with positive and negative responses to HUTT

In the study group, patients with positive response to HUTT had female dominance (54.8% vs 39.2%, $P = 0.042$), older mean age (9.6 ± 2.8 vs 8.1 ± 2.7 years old, $P = 0.001$), higher basic systolic BP (104.8 ± 10.4 vs 101.1 ± 9.9 mmHg, $P = 0.019$), and higher diastolic BP (66.0 ± 7.5 vs 62.9 ± 9.2 mmHg, $P = 0.021$) compared with those of negative response. There are no significant differences in BMI, history duration, and basic heart rate between patients with positive and negative HUTT responses (Table 3).

Discussion

In the present study, HUTT is used to depict the hemodynamic responses in children and adolescents with unexplained sighing for the first time. We found that nearly one-third of patients with unexplained sighing had positive responses to HUTT. Patients with positive HUTT response had female dominance, older mean age, higher basic systolic BP, and higher diastolic BP compared with those of negative response.

Sighing is associated with stressful events and negative emotions, which was reckoned as a physiological and psychological phenomenon. Pulmonary function examination demonstrated that a part of children and adolescents with sighing had airway hyperresponsiveness and airway obstruction [11]. Besides, parts of children with sighing were considered to have psychogenic and functional breathing disorders, which were linked to attention deficit hyperactivity disorder, tic disorders, and specific phobia [12]. HUTT is a safe and efficacious tool used to measure autonomic nerve function and diagnose hemodynamic responses of orthostatic intolerance, such as palpitation, headaches, lightheadedness, and visual disturbances [13, 14]. In our study, more than 30% of children and adolescents with unexplained sighing had positive responses to HUTT. For children and adolescents, the autonomic nervous system is immature and vulnerable to adverse

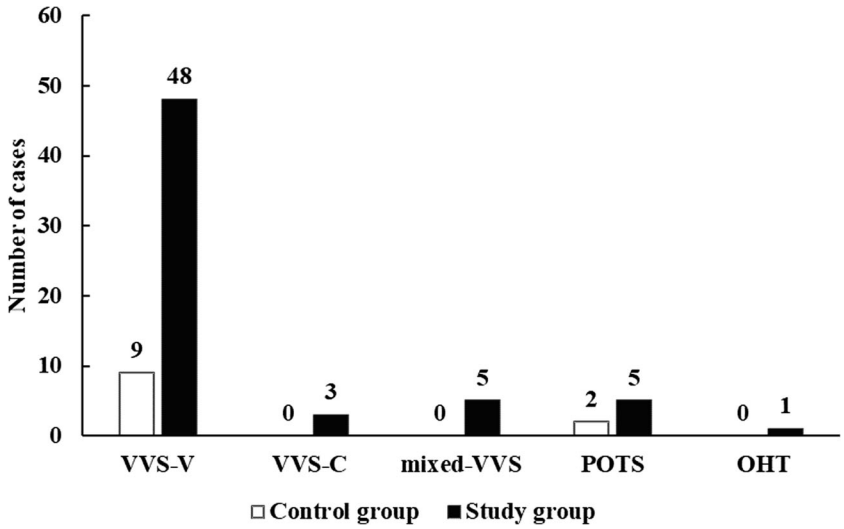

Fig. 1 Hemodynamic type of positive responses to HUTT; VVS-V: vasoinhibitory type vasovagal syncope; VVS-C: cardioinhibitory type vasovagal syncope; mixed-VVS: mixed type vasovagal syncope; POTS: postural tachycardia syndrome; OHT: orthostatic hypertension

Table 2 The positive rate of HUTT in the control and study group (*n*,%)

Groups	Unstimulated HUTT	Nitroglycerin-stimulated HUTT	Total
Control group ($n = 69$)	4 (5.8)	7 (10.1)	11 (15.9)
Study group ($n = 192$)	16 (8.3)	46 (24.0)	62 (32.3)
x^2	0.461	5.985	6.735
P	0.497	0.014	0.009

environmental and physiologic stimuli [15]. When sustained exposure to mental stress or other factors, the body's metabolism declines, resulting in reduced heart rate, superficial breath, and increased functional residual capacity. Hypoxia stimulates afferent neural streams from the baroreceptors, which activates the respiratory center, to induce the onset of sighing. Through a deep breath, oxygen content in the alveoli increases, and then, symptoms of hypoxia are relieved [16]. Based on these data from the past evidence, it is considered that sighing is associated with dysfunction of the autonomic nervous system.

Nitroglycerin administration expands venous pooling because of peripheral vasodilation, contributing to decreased intraventricular volume, which activates left ventricular mechanoreceptors and parasympathetic nervous system in susceptible individuals [17]. In our results, the positive rate of HUTT both in the control and study group increased after sublingual nitroglycerin administration. Furthermore, children and adolescents with unexplained sighing had a higher positive rate of sublingual nitroglycerin-stimulated HUTT compared with healthy individuals, most of whom were vasoinhibitory type VVS with significant decrease of blood pressure. When nitroglycerin was administrated, these patients presented higher peripheral vasodilation and sharp blood pressure decline, and then, they were more likely to develop positive responses and showed more sign of orthostatic intolerance than healthy individuals. As it was known to us, baroreflex sensitivity was important for maintaining normal blood pressure. Reflex hypotension in response to nitroglycerin suggested that patients with recurrent sighing had autonomic nervous dysfunction, which was associated with abnormal baroreflex sensitivity.

In comparison with clinical data between sighing patients with positive responses and negative responses, we found that the positive HUTT rate was associated with age, gender, and basic BP. Older female children with higher basic systolic BP and diastolic BP tended to present positive responses to HUTT. Males sigh more frequently than females. However, females had higher positive responses to HUTT. In the previous study, females had decreased orthostatic intolerance and a higher incidence of VVS and POTS when compared with males [18]. It suggests that orthostatic intolerance has gender differences, which is related to increases in pubertal hormones such as estrogen, thyroid hormones, growth hormone, insulin, and insulin-like growth factor-1, promoting vasodilatation and decreasing blood volume [19]. In our study, basic systolic BP and diastolic BP in patients with positive HUTT responses were higher compared with those of negative HUTT responses. In a previous study, the circadian rhythm of BP is impaired in patients with neurally mediated syncope, with lower average systolic BP and diastolic BP in daytime and higher average standard deviation-systolic BP at nighttime [20]. Circadian rhythm of BP is associated with function of the autonomic regulatory system. However, whether circadian rhythm of BP is impaired in sighing patients has not been defined in our study. As the present study is a retrospective study, data of ambulatory blood pressure monitoring were not

Table 3 Clinical data comparison between patients with positive and negative HUTT response in the study group

Groups	Males (*n*, %)	Females (*n*, %)	Age (years)	BMI (kg/m^2)	Duration (IQR, months)	Basic HR (bpm)	Basic SBP (mmHg)	Basic DBP (mmHg)
HUTT$^-$ ($n = 130$)	79 (60.8)	51 (39.2)	8.1 ± 2.7	16.8 ± 2.8	2.0 (1.0,9.0)	82.2 ± 12.2	101.1 ± 9.9	62.9 ± 9.2
HUTT$^+$ ($n = 62$)	28 (45.2)	34 (54.8)	9.6 ± 2.8	17.0 ± 2.9	2.0 (1.0,12.0)	81.9 ± 15.3	104.8 ± 10.4	66.0 ± 7.5
$t/x^2/z$	4.145*		− 3.426	− 0.351	0.133**	0.136	− 2.371	− 2.320
P value	0.042		0.001	0.726	0.894	0.892	0.019	0.021

*Referred to x^2 value. **Referred to *z* value. *HUTT* head-up tilt test; *HUTT*$^-$ negative HUTT response; *HUTT*$^+$ positive HUTT response; *IQR* inter quartile range; *BMI* body mass index; *SBP* systolic blood pressure; *DBP* diastolic blood pressure

obtained. Ambulatory blood pressure monitoring should be utilized to depict the circadian rhythm of BP of patients with unexplained sighing in further study.

Furthermore, our work above is preliminary and has some limitations. Though nearly one-third of patients with unexplained sighing had VVS, POTS responses, none of these subjects had a history of syncope before. The positive responses were mainly provoked by nitroglycerin. Nitroglycerin administration increases sensitivity and, however, decreases the specificity. Except for HUTT, other tests such as heart rate variability and measurement of baroreflex sensitivity are needed to assess the integrity of autonomic nervous system. Besides, though these patients with sighing were assessed by an experienced psychologist to exclude psychogenic disorders, it is hard to distinguish psychogenic disorders from dysfunction of the autonomic nervous system, and tests for anxiety or depression are further needed.

In conclusion, about one-third of children and adolescents with unexplained sighing had positive responses to HUTT, demonstrating that sighing was related to dysfunction of the autonomic nervous system. Elder female patients with higher systolic BP and diastolic BP were more likely to have positive responses to HUTT.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This research was approved by the Medical Ethical Committee at The Second Xiangya Hospital, Central South University.

Informed consent statements All included patients or their guardians signed informed consent.

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