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Clinical and prognostic significance of detecting postural orthostatic sinus tachycardia in young patients

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Postural orthostatic sinus tachycardia (POST) is characterized by pronounced tachycardia upon transitioning from a supine to an upright position, without orthostatic hypotension, accompanied by various symptoms such as palpitations, dizziness, headache, fatigue, weakness, reduced exercise tolerance, blurred or "foggy" vision, anxiety, shortness of breath, and others. However, the detection rate and prognostic significance of POST in medical university students during a prospective study have not been fully investigated. Furthermore, data on the clinical value of using screening tests for its detection are lacking.

Aim. To determine the feasibility of using screening testing for detecting POST in medical university students and to evaluate its clinical and prognostic significance in a prospective study.

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Material and methods. Over the period from 2007 to 2012, 5,560 medical university students aged 20-26 years were examined. Various orthostatic symptoms at rest and/or during the transition from supine to upright position were observed in 534 (9.6%) patients. When these symptoms were identified, screening testing was performed, including measurement of heart rate and blood pressure (BP) in the supine position, followed by measurements in the orthostatic position, with subsequent verification using a tilt-table test. Cardiac and extracardiac causes of POST were excluded. Patients with POST were advised to modify their lifestyle, and, if ineffective, to receive beta-blockers and/or a selective inhibitor of If-channels (ivabradine). The follow-up period after inclusion in the study was 12–14 years.

Results. POST was identified in 2.8% of medical university students aged 20-26 years, predominantly in women (83%). The sensitivity, specificity, and accuracy of POST diagnosis based on screening testing results with subsequent verification using the tilt-table test were 79.35%, 90.05%, and 85.26%, respectively. Following lifestyle modification and/or treatment with beta-blockers or ivabradine, all patients with POST showed significant clinical improvement both at the start of treatment and during subsequent follow-up: orthostatic symptoms resolved. On repeated examinations, including during tilt-table testing, POST was no longer registered. During prospective follow-up, 36.13% of patients with POST developed hypertension (HTN), 23.87% were found to have mitral valve prolapse (MVP), and 38.06% registered ventricular extrasystole. The development of HTN was highly correlated with a family history of arterial hypertension (odds ratio (OR) = 5.02) and increased BP in the orthostatic position (OR = 3.05), while MVP was correlated with retrograde atrial activation immediately following ventricular extrasystole (OR = 12.4).

Conclusion. POST was identified in 2.8% of medical university students aged 20–6 years, predominantly in females. The sensitivity, specificity, and accuracy of POST diagnosis based on screening test results were 79.35%, 90.05%, and 85.26%, respectively. The occurrence of POST with elevated BP during orthostatic testing are predictors for the development of HTN, MVP, and ventricular extrasystole.

Keywords: postural orthostatic sinus tachycardia, clinical and prognostic significance, screening testing, manifesting symptoms, principles of therapeutic treatment.

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Introduction

Postural orthostatic sinus tachycardia (POST) is a relatively common disorder, and its diagnosis has increased significantly in recent years [1]. However, the causes and mechanisms of its development remain insufficiently understood [2]. POST has been described following viral infections (including coronavirus), surgical procedures, pregnancy, irritable bowel syndrome, and other diseases and/or conditions [1, 2]. In addition to the main clinical manifestations—pronounced tachycardia upon transitioning from a supine to an upright position without orthostatic hypotension—various symptoms may be present, such as palpitations, dizziness, headache, fatigue, weakness, reduced exercise tolerance, blurred or "foggy" vision, anxiety, shortness of breath, and others [1, 2]. In most patients with POST, nonpharmacological and pharmacological measures are chosen empirically, based on the presenting symptoms [3]. POST is most frequently observed in young adult women, who are typically either in education or at the beginning of their careers [1, 2, 4].

However, the frequency of detection and the prognostic value of POST in medical university students in a prospective study have not been fully investigated. Moreover, data on the clinical utility of screening testing for this syndrome are lacking.

Aim—to determine the feasibility of using screening testing to detect POST in medical university students and to evaluate its clinical and prognostic significance in a prospective study.

Material and methods

During the period from 2007 to 2012, a total of 5,560 medical university students aged 20–26 years (mean 22.7 ± 0.1 years) were examined. During a screening

questionnaire, which included collection of complaints, medical history, etc., it was found that 534 (9.6%) patients experienced palpitations, chest pain or discomfort, dizziness, blurred vision, dyspnoea, headache, fatigue, and "trembling" in the body or limbs at rest and/or upon transitioning from supine to upright position; these symptoms diminished or resolved completely in the supine position or at rest. After an indepth clinical, laboratory, and instrumental examination, which included 1 to 3 day Holter electrocardiogram (ECG) monitoring, and assessment of central and intracardiac haemodynamics using a Hitachi EUB 5500 echocardiograph according to standard methods [4], 356 (66.67%) of the 534 patients were enrolled in the study. Inclusion criteria: sinus rhythm, absence of structural heart disease, left ventricular ejection fraction ⩾ 55%, and informed consent from the patient to participate in the study and receive treatment. Exclusion criteria: presence of cardiac and extracardiac diseases such as hypertension (HT), mitral valve prolapse (MVP), cardiomyopathies, thyrotoxicosis, phaeochromocytoma, epilepsy, anaemia, frequent supraventricular and ventricular extrasystoles (⩾ 100 per day), or other factors such as anxiety disorders, hyperventilation, fever, pain of various localisation, acute and chronic infections, dehydration, venous insufficiency of the lower extremities, irritable bowel syndrome, chronic fatigue, neurological pathology, alcohol abuse, coffee consumption, intake of cardioactive drugs, etc. [3–5].

In all patients included in the study, when one or more of the above symptoms were detected, screening testing was performed. This involved measuring heart rate (HR) and blood pressure (BP) after 20–30 minutes of rest in the supine position, then in the upright position and/or with headup tilt for 10–20 minutes, followed by repeated recordings of these haemodynamic parameters in the supine position. HR was determined by pulse palpation and/or using a pulse oximeter, and BP was measured using a domestic automatic sphygmomanometer that recorded pulse rate and pressure parameters every 3–4 minutes after the first measurement. Screening testing was conducted 3–4 times a week, always in the morning immediately after waking up, in the evening, and several times during the day.

In all patients with positive screening questionnaire results, 1 to 3 day Holter ECG and BP monitoring ("Kardiotekhnika04AD3(M)", INCART Ltd., Cardiology Research Institute, Ministry of Health of Russia, St. Petersburg) were performed, and a tilttable test according to the Westminster protocol was carried out [4]. The tilt test was conducted between 8:00 and 11:00 a.m. in a quiet environment, on an empty stomach, at a comfortable room temperature of 20–23 °C and humidity of 30–50%. Intake of any medications and smoking were prohibited. In the first stage, the patient remained supine for 20 minutes; in the second stage, they were tilted to a 60° upright position for up to 40 minutes; and in the third stage, they returned to the supine position for another 20 minutes. POST was diagnosed both during screening testing and during the tilt test when an increase in HR of ⩾ 30 beats/min compared with baseline was noted, with the HR reaching 120 beats/min or more, accompanied by a decrease in systolic and diastolic BP of no more than 20 mmHg and 10 mmHg, respectively, or by an increase in BP [3–7]. Throughout all stages of the tilt test, ECG was continuously recorded, and heart rate variability (HRV) parameters were calculated with automatic exclusion of extrasystoles using an electrocardiograph "PolispektrVR" (Neirosoft Ltd., Ivanovo), along with systolic and diastolic BP. For HRV assessment, 5 minute ECG fragments were used, recorded during the last 5 minutes in the supine position before tilting, then during the last 5 minutes of orthostasis, and at the end of the subsequent return to the supine position (last 5 minutes). HRV analysis included quantitative and spectral parameters: SDNN—standard deviation of normal RR intervals (ms), VLF—very lowfrequency component (0–0.04 Hz, ms^2), reflecting neurohumoralmetabolic regulatory pathways; LF—lowfrequency component (0.04–0.15 Hz, ms^2), reflecting sympathetic activity; HF—highfrequency component (0.15–0.4 Hz, ms^2), reflecting parasympathetic activity; and the LF/HF ratio (in units) [5, 8, 9].

All patients were advised to modify their lifestyle, including aerobic physical exercise for 20–40 minutes a day, 3–5 times a week. In cases of POST with BP reduction during the tilt test, compression garments, countermanoeuvres, and increased water intake (e.g., up to 2–3 litres per day, especially after waking up) were recommended. If these measures were ineffective, or if BP increased upon standing, subtherapeutic doses of betablockers (metoprolol tartrate 6.25–12.5 mg, bisoprolol fumarate 1.25–2.5 mg) and/or the selective Ifchannel inhibitor ivabradine hydro-

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chloride 1.25–2.5 mg were used, in accordance with the guidelines in force at the time of the study [1–3, 4]. It should be noted that none of the nonpharmacological or pharmacological methods recommended for treating POST, including at the time of writing this article, have been confirmed by large randomised clinical trials [1–3, 5].

The followup period after enrolment was 12–14 years. Patients selfmonitored HR and BP in the supine and upright positions daily. All examinations, including assessment of patient status and ECG recording, were performed once a month; Holter ECG and BP monitoring were performed at least once every 3–6 months; and the tilt test was performed once a year (with the patient's informed consent).

The study was conducted in accordance with Good Clinical Practice standards and the principles of the Declaration of Helsinki.

Ethical approval. The study was approved by the Ethics Committees of the I.I. Mechnikov St. Petersburg State Medical Academy of Roszdrav (Protocol No. 12, dated 30 December 2010). (In 2012, the I.I. Mechnikov St. Petersburg State Medical Academy was merged with MAPO and renamed the I.I. Mechnikov NorthWestern State Medical University of the Ministry of Health of Russia).

Statistical analysis

For statistical processing of the obtained data, the normality of the distribution of quantitative variables was assessed using the Kolmogorov–Smirnov and Gaussian tests. Mean values and standard deviations (M ± SD), Student's ttest, and x^2-test were used. A pvalue < 0.05 was considered statistically significant. Linear pairwise and rank (Pearson) correlation were used, and the association between quantitative and qualitative binary variables was assessed using logistic regression with calculation of odds ratios (OR).

Results

Screening testing data showed that when HR was determined by pulse palpation and/or pulse oximeter, and BP measured with a domestic sphygmomanometer in the supine position, followed by assessment of these parameters in the upright position, POST was diagnosed in 152 (42.70%) of the 356 enrolled patients, with reproduction of orthostatic tachycardia symptoms at least 2–3 times per week over 3–6 months. Upon tilttable testing and Holter ECG and BP monitoring, POST was confirmed in 123 (80.92%) of the 152 patients with positive screening results, and was identified in 32 (15.69%) of the 204 patients with negative screening results; no patient developed presyncope or syncope. The sensitivity, specificity, and diagnostic accuracy of POST detection by screening testing were 79.35%, 90.05%, and 85.26%, respectively.

All patients were divided into two groups. The main (I) group consisted of 155 (43.54%) of the 356 patients with confirmed POST by tilt test and Holter monitoring, with a mean age of 22.4 ± 1.6 years. The remaining patients formed the control (II) group, with a mean age of 23.1 ± 1.9 years (p > 0.05). Women predominated in both groups. In group II, there were significantly more 6thyear students and those consuming more than 5 g/day of table salt, and significantly fewer 4th and 5thyear students and those with a family history of hypertension (HT) compared with group I (Table 1). No statistically significant differences were found for the other studied parameters.

It should be noted that 4th and 5th year students take 6 and 5 exams, and 4 and 5 differentiated credit

Table 1. **Characteristics of patients in Groups I and II at enrolment**

Parameter	Group I, n = 155	Group II, n = 201
Men	26 (16.77 %)	32 (15.92%)
Woman	129 (83.23%)	169 (84.08%)
4th year students	88 (56.77%)	67 (33.34%)*
5th year students	41 (26.45%)	11 (5.47%)*
6th year students	26 (16.77%)	123(61.19%)*
Body mass index ⩽ 18,5 kg/m^2	12 (7.74%)	16 (7.96%)
Body mass index ⩾ 25 kg/m^2	23 (14.84%)	35 (17.41%)
Family history of hypertension†	143 (92.26%)	64 (31.84%)*
Family history of cardiovascular diseases, including coronary heart disease†	73 (47.10%)	77 (38.30%)
Joint hypermobility	67 (43.23%)	89 (44.28%)
Salt intake > 5 g/day	16 (10.32%)	89 (44.28%)*
Smoking	56 (36.13%)	82 (40.80%)
Excessive psychoemotional stress	86 (55.48%)	94 (46.77%)
Physical inactivity	58 (37.42%)	66 (32.84%)
Palpitations and/or cardiac "irregularities"	127 (81.94%)	176 (87.56%)
Discomfort and/or stabbing pain in the left chest	68 (43.87%)	93 (46.27%)
Dizziness	59 (38.06%)	76 (37.81%)
Increased fatigue	83 (53.55%)	114 (56.72%)
"Trembling" in the body or lower extremities	18 (11.61%)	26 (12.94%)

Note. †—development of diseases at a young age in parents or in the family;
*—significant difference compared with Group I (p < 0.05).

tests (equivalent in importance to exams), respectively, while in the 6th year there is mainly only one—the final state exam. The average grade point during the training period in groups I and II was 3.4 ± 0.4 and 4.6 ± 0.5, respectively ($p < 0.05$).

Before the tilt test, patients in group II had a statistically significant increase in the power of all HRV parameters with a significant decrease in LF/HF compared with group I. At the end of the tilt test and after its completion, both groups showed a significant increase in VLF power and LF/HF ratio, and a decrease in LF and HF. In group I, in the upright position, a significant increase in HR and a rise in BP were observed compared with baseline; in all these patients, maximal BP during orthostasis did not exceed 139/89 mmHg. Importantly, in group I at the beginning of the tilt test, BP remained virtually unchanged or slightly decreased (by 5–10 mmHg), and then increased. No significant changes were observed in other parameters (Table 2).

Within 3–6 months of adherence to the recommended therapy, including lifestyle modification and pharmacological agents (betablockers or ivabradine), the clinical condition of patients in both groups significantly improved: symptoms such as palpitations, discomfort in the left chest, dizziness, increased fatigue, etc., resolved. To eliminate palpitations following excessive psychoemotional stress, patients used betablockers or ivabradine. Upon reexamination, including tilttable testing, POST was not diagnosed in any patient of group I.

After graduation, 127 (81.94%) of group I and 179 (89.05%) of group II remained working in the national healthcare system ($p > 0.05$); among them, 64 (50.39%) and 145 (81.01%) respectively were physicians in therapeutic specialties (family medicine, dermatology, cardiology, gastroenterology, neurology, etc.) ($p < 0.05$), while the rest were engaged in diagnostic activities, i.e., laboratory physicians, endoscopists, echocardiographers, ultrasound specialists, etc.

During prospective followup, HT was diagnosed in 56 (36.13%) of group I and in 11 (5.47%) of group II ($p < 0.05$) (Fig. 1); MVP was found in 37 (23.87%) and 6 (2.99%) respectively ($p < 0.05$) (Fig. 2). Ventricular extrasystoles of class II–V according to M. Ryan (1975) [10] were recorded in 59 (38.06%) of group I and in 5 (2.49%) of group II ($p < 0.05$), including those with retrograde atrial activation after premature ventricular complexes. Irritable bowel syndrome was observed in 6 (3.87%) and 7 (3.48%) patients, respectively ($p > 0.05$). The development of HT was highly correlated (OR > 1) with a family history of HT (OR = 5.02) and with increased BP during orthostasis compared with supine baseline (OR = 3.05), while MVP was associated with retrograde atrial activation after premature ventricular complexes (OR = 12.4).

Discussion

Precise epidemiological data on the prevalence of POST are lacking; however, some reports suggest that this syndrome affects 0.1–0.5% of the general population, and in young women it may be found in up to 3% of cases [1–3]. POST is identified across different age groups but is most common in young women, with a femaletomale ratio of approximately 4:1 [1–3].

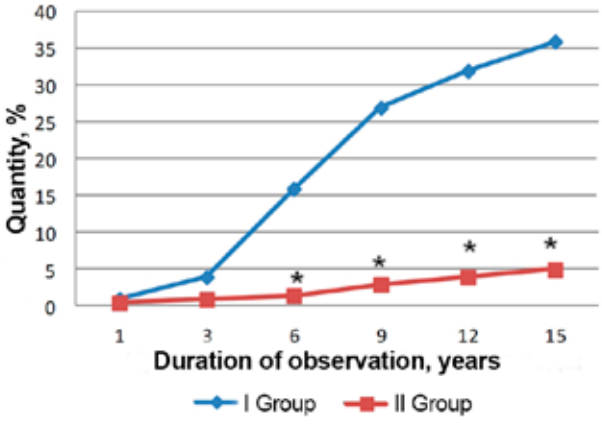

Fig. 1. Kaplan–Meier curves for the development of hypertension (HT) in patients of Groups I and II.
Note. *—significant difference compared with Group I($p < 0.05$).

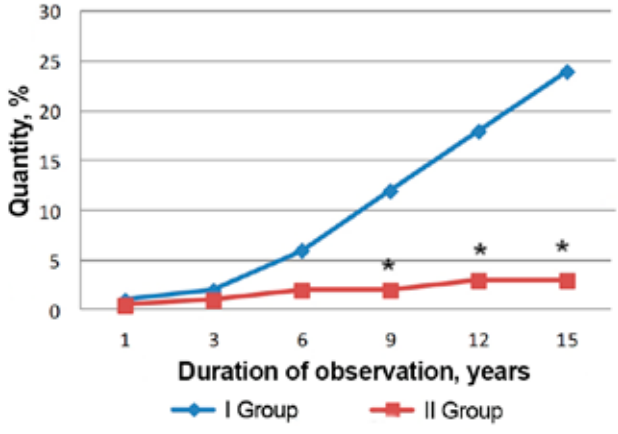

Fig. 2. Kaplan–Meier curves for the development of mitral valve prolapse (MVP) in patients of Groups I and II.
Note. *—significant difference compared with Group I ($p < 0.05$).

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Table 2. **Comparative characteristics of HR, BP and HRV parameters during the tilttable test in Groups I and II**

Parameter \ Groups	Group I, n = 155			Group II, n = 201		
	А	Б	В	А	Б	В
HR, beats/min	65±5	129±12†	68±6	69±5	73±7*	71±4
Systolic BP, mm Hg	109±6	125±5†	109±6	110±7	112±9	111±5
Diastolic BP, mm Hg	71±5	84±4†	69±4	72±5	74±4	71±5
SDNN, ms	27±7	29±6	28±6	42±6	49±7	41±6
VLF, ms^2	724±117	1975±147†	833±124†	1424±127*	2034±149*†	1556±159*
LF, ms^2	365±64	293±68†	389±69†	456±55*	369±52*†	463±58*
HF, msc^2	115±46	67±39†	127±48†	428±51*	286±46*†	412±54*
LF/HF, units	3.14±0.59	4.37±0.67†	3.06±0.61†	1.06±0.34*	1.37±0,46*†	1.12±0.43*

Note. А—parameters in the supine position before the tilttable test; В—at the end of the tilttable test; С—after the tilttable test while the patient was in the horizontal position.
*—significant difference compared with Group I; †—significant difference compared with baseline data ($p < 0.05$).

Similar data were obtained in the present study.

The clinical and pathogenic mechanisms of POST development are not well understood. This syndrome has been reported in patients with various conditions, including rheumatoid arthritis, hyperthyroidism, fibromyalgia, diabetes mellitus, amyloidosis, sarcoidosis, systemic lupus erythematosus, oncological diseases, epilepsy, and others [1–3]. The main proposed mechanisms include neuropathic, hyperadrenergic, and hypovolaemic [1–3]; however, the appearance of symptoms such as dizziness, headache, palpitations, sweating, etc., upon standing does not necessarily indicate a specific underlying mechanism [1, 2]. Likely, all mechanisms are interrelated, and the development of POST is determined by the predominant interplay among them [1–3, 10, 11].

In the present study, based on clinical, laboratory, and instrumental examination, the most probable diseases and conditions that could be a cause of POST were excluded.

According to screening testing, POST was diagnosed in 42.7% of all enrolled patients, with reproduction of orthostatic tachycardia symptoms at least 2–3 times a week over 3–6 months, which complied with the guidelines in force at the time of the study (2006) [4]. It should be noted that the same criteria are used in the latest international guidelines [2, 3]. The sensitivity, specificity, and diagnostic accuracy of POST detection by screening testing were 79.35%, 90.05%, and 85.26%, respectively.

Low power of all HRV parameters with a significant increase in the LF/HF ratio in patients with POST indicates a rigid rhythm with sympathetic predominance [5, 6]. Lower VLF power compared with patients without POST suggests a high risk of developing orthostatic tachycardia, possibly due to increased venous volume in the major veins of the lower extremities with normal venous valve function [3, 6]. The significant decrease in LF and HF power and the increase in LF/HF ratio during tilt testing reflect enhanced sympathoadrenal components of autonomic regulation, while the significant increase in VLF power indirectly indicates baroreceptor activation [3, 6], accompanied by vasoconstriction, increased HR, and elevated BP—with these changes being more pronounced in POST patients. Therefore, in the patients included in this study, the hyperadrenergic mechanism is likely the main driver of POST induction.

In recent years, an increase in systolic BP of ⩾ 20 mmHg upon standing has been termed "excessive orthostatic pressor response to standing," whereas the term "orthostatic hypertension" is used when systolic BP in the upright position reaches ⩾ 140 mmHg compared with supine baseline [7]. Diagnostic criteria for defining pathological "orthostatic arterial hypertension" in POST patients have not been established [1–3]. Notably, the term "pathological orthostatic arterial hypertension" is absent from clinical guidelines for the diagnosis and treatment of hypertension in adults [8]. On the other hand, according to the ARIC (Atherosclerosis Risk in Communities) study, identifying "orthostatic hypertension" in patients without cardiovascular pathology—defined as an increase in systolic BP ⩾ 20 mmHg and/or diastolic BP ⩾ 10 mmHg upon standing, or an upright systolic BP ⩾ 140 mmHg—is associated with a high risk of developing various cardiovascular diseases [9].

According to the results of the present study, all patients with POST exhibited an increase in diastolic BP of > 10 mmHg upon standing. These patients will be the subject of further followup.

In patients with joint hypermobility, POST with a hypotensive BP response to standing is frequently observed, but usually without orthostatic hypotension. However, in the present study, joint hypermobility syndrome was recorded with similar frequency (slightly over 40%) both in patients with POST and in those without tachycardia upon standing. The absence of BP reduction and orthostatic hypotension in hypermobile patients, despite having similar clinical symptoms to those with POST, may possibly be due to excessive dietary salt intake.

Within six months after starting the recommended therapy, including lifestyle modification and the use of betablockers and/or ivabradine, and during subsequent followup, the clinical condition of all POST patients significantly improved. Symptoms such as palpitations, left chest discomfort, dizziness, increased fatigue, etc., resolved, indirectly supporting a possible hyperadrenergic mechanism of orthostatic tachycardia. Later, during prospective followup, when periodic palpitations or cardiac irregularities occurred, e.g., after excessive psychoemotional stress, patients used betablockers and/or ivabradine to alleviate these symptoms. At repeated examinations, including tilttable testing, POST was not detected in any patient.

POST may have indirectly influenced the choice of specialty after medical school graduation. Among those who remained in the national healthcare system, about 50% and 80% of those with and without POST, respectively, were physicians in therapeutic disciplines. The impact of POST on specialty choice will be a subject of further investigation.

It is currently known that the contribution of hereditary predisposition to the development of HT, especially when hypertension is detected in parents or close relatives at a young age (< 55 years), ranges from 50 to 60% (possibly more). This is likely due to excessive sympathicotonic influence, manifested in the present study by increased HR and BP during orthostasis in POST patients, as well as by the effects of peptides produced in the medulla oblongata (vasoactive intestinal peptide, somatostatin, enkephalins, neurotensin, substance P, etc.) [10, 11]. Because depressor mechanisms that cause arteriolar dilation remain intact, HT manifests at a later stage [10, 11].

The source of ventricular ectopy in the region of the mitral and/or tricuspid annulus may be the papillary muscles or the left ventricular outflow tract. In patients without structural heart disease, there is a high risk of developing arrhythmogenic nonmyxomatous MVP, which appears to be due to thinning and/or elongation of chordae, and to a lesser extent, superficial fibrosis of the mitral valve leaflets [12–15]. Retrograde atrial activation after premature ventricular ectopy may induce MVP formation due to dyssynchrony (dysfunction) between papillary muscles and ventricular myocardium [12, 13, 16].

Thus, the development of POST with a concomitant increase in BP during orthostasis compared with supine baseline, in the absence of cardiac and extracardiac causes, can be considered a predictor of future cardiovascular diseases, such as HT, MVP, and ventricular arrhythmias.

Conclusion

POST was identified in 2.8% of medical university students aged 20–26 years, predominantly in women (83%), with a femaletomale ratio of 5:1. For initial diagnosis of POST, all patients presenting with orthostatic symptoms should undergo screening testing, including measurement of HR and BP in the supine position, followed by upright position and/or headup tilt. Based on screening test results, the sensitivity, specificity, and accuracy of POST detection were 79.35%, 90.05%, and 85.26%, respectively. A significant increase in HR and BP parameters during orthostasis was observed predominantly in POST patients, indirectly suggesting a possible hyperadrenergic mechanism of orthostatic tachycardia. In these patients, the main approach to managing orthostatic symptoms, in addition to lifestyle modification, is the use of betablockers and/or ivabradine. During prospective followup, HT was diagnosed in 36.13% of patients with POST, MVP in 23.87%, and ventricular extrasystoles in 38.06%. The development of HT was highly correlated (OR > 1) with a family history of HT (OR = 5.02), with increased BP in the upright position (OR = 3.05), while MVP was associated with retrograde atrial activation after premature ventricular complexes (OR = 12.4).

Conflict of interest: none declared.

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