

Awareness of postural orthostatic tachycardia syndrome is required in adolescent syncope

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Abstract

We investigated head-up tilt test (HUTT) results across age-groups in syncope/presyncope patients to establish pediatric postural orthostatic tachycardia syndrome (POTS) characteristics. We retrospectively reviewed syncope patients' medical records. Adolescents were defined as 10 to 19 years old, adults as 20 to 59 years old, and older individuals as ≥ 60 years old. From HUTT results, we determined POTS prevalence and differences among the age-groups. We included 147 adolescents, 269 adults, and 123 older patients. Seventy (13.0%) patients (61.4% females; median age: 20 [17–25] years) were diagnosed with POTS. The syndrome was more prevalent among adolescents (33 [22.4%]) than adults (37 [13.8%]), and was absent among older individuals. Affected adolescents had significantly lower resting diastolic blood pressure (DBP) and heart rate (HR), and converted to maximum HR more rapidly than adolescents without the syndrome during the passive phase. Adolescents with POTS demonstrated several unique characteristics compared to adults with and adolescents without this syndrome. POTS may be underrecognized among syncope and presyncope patients, among which 22.4% of adolescents were diagnosed with the syndrome. POTS should be considered when evaluating syncope patients.

Abbreviations: BP = blood pressure, DBP = diastolic blood pressure, HR = heart rate, HUTT = head-up tilt test, OH = orthostatic hypotension, POTS = postural orthostatic tachycardia syndrome, SBP = systolic blood pressure, VVS = vasovagal syncope.

Keywords: head, postural orthostatic tachycardia syndrome, up tilt test

1. Introduction

Syncope is a symptom that presents with abrupt, transient, complete loss of consciousness, an inability to maintain postural tone, and shows rapid, spontaneous recovery.^[1] Initial evaluation of patients with syncope or frequent presyncope includes detailed history taking, physical examination, and electrocardiogram (ECG).^[1] Additional evaluation could involve targeted blood testing, autonomic evaluation, and cardiac monitoring.^[1] Moreover, the head-up tilt test (HUTT) is a practical and widely used tool for evaluating patients with syncope and frequent presyncope.

Postural orthostatic tachycardia syndrome (POTS) is a common form of orthostatic intolerance in young people who experience syncope and frequent presyncope.^[2–4] POTS prevalence is approximately 0.2%.^[5–8] Most patients are aged 15 to 25 years, and >75% are women.^[5,7–11] In an upright posture, common symptoms include lightheadedness, palpitations, tremor, generalized weakness, blurred vision, exercise intolerance, and fatigue.^[2,11] POTS patients complain of chronic fatigue and presyncope, which limit daily activities of living, and they report to the emergency room for syncope in severe cases.^[8,11]

POTS often coexists with other clinical diagnoses such as migraine headaches, irritable bowel syndrome, hypermobile Ehlers-Danlos syndrome, chronic fatigue syndrome, mast cell activation disorder, and autoimmune diseases.^[12–14] Previous study reported that approximately 40% of POTS patients suffered from migraine headaches, 20%–30% from hypermobile Ehlers-Danlos syndrome, and 15% from autoimmune disease.^[15–17] Identifying POTS can be clue to diagnose co-morbidities and screening these diseases should be performed.

POTS is characterized by a sustained heart rate (HR) increase of ≥ 30 beats/min within 10 minutes of standing or during the HUTT, in the absence of orthostatic hypotension (OH). For individuals aged 12 to 19 years, the HR increment is at least 40 beats/min.^[2,9] These phenomena are clearly identified through the HUTT with HR and blood pressure (BP) monitoring.

Recently, awareness of the syndrome has increased, while POTS prevalence per se may also have increased.^[3] However, few studies have compared adolescents with POTS with those without POTS, or with adults with POTS. Here, we investigated the prevalence and characteristics of adolescent POTS and compared these with adult POTS. We also investigated the

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All data generated or analyzed during this study are included in this published article.

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Key Notes

- Postural orthostatic tachycardia syndrome is more prevalent among adolescents than adults, and is absent among older individuals.
- Adolescent postural orthostatic tachycardia syndrome has distinguishing features, with significantly lower resting diastolic blood pressure and heart rate, and more rapid conversion to maximum heart rate than adolescents without the syndrome during the passive phase of the head-up tilttest.
- Postural orthostatic tachycardia syndrome should be considered when evaluating syncope patients.

characteristics of adolescents with POTS as compared with adolescents without the syndrome.

2. Methods

We retrospectively reviewed the medical records of patients who visited Chung-Ang University Hospital, Seoul, Korea, and underwent the HUTT to evaluate syncope and frequent presyncope between January 2016 and December 2019. The data obtained included age, sex, height, body weight, body mass index, laboratory outcomes, comorbidities, and records of BP and HR during the HUTT. Patients diagnosed with obvious causes of syncope or presyncope, such as arrhythmia, structural heart disease, epilepsy, cerebrovascular disease, thyroid disease, anemia, or medication were excluded. We analyzed the positive HUTT results and compared differences between the 3 age-groups. The adolescent group was defined as 10 to 19-years-old, the adult group as 20 to 59-years-old, and the older individual group as ≥ 60 -years-old. We also compared POTS characteristics among these 3 groups. Additionally, we compared HUTT results of adolescents with POTS with adolescents without the syndrome.

2.1. The Newcastle protocol for the HUTT

Patients underwent the HUTT using the Newcastle protocol.^[18–21] When patient experiences syncope associated with hypotension, with or without bradycardia during the test, the test is considered as positive. OH is defined by the steady decrease in systolic BP ≥ 20 mm Hg or diastolic \geq BP 10 mm Hg within 3 minutes of upright posture. Vasovagal syncope (VVS) occurs after 3 minutes of standing from supine.

2.2. Statistical analysis

Data are described as number (percentage), median (interquartile range) or mean \pm standard deviation. Pairwise deletion was used for missing values. Categorical values were compared using the Chi-square test. Analysis of variance, and the Kruskal–Wallis test were used to test differences among groups. *t*-Tests and Mann–Whitney *U* tests were used for POTS subgroup analysis. *P* values $< .05$ were considered statistically significant. Data were analyzed using SPSS software (Version 26.0, IBM Corp., Armonk, NY).

2.3. Ethical statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted after obtaining approval from the Institutional Review Board of Chung-Ang University Hospital

(IRB no. 2107-047-19377) and the need to obtain informed consent was waived due to the retrospective nature of the study.

3. Results

During the study period, 746 syncope/presyncope patients were tested with the HUTT. Seventy-one cases were excluded: 31 with arrhythmia (atrial fibrillation, sick sinus syndrome, high-degree atrioventricular (AV) block, AV node reentry tachycardia, symptomatic ventricular premature contraction, Wolff–Parkinson–White syndrome, atrial flutter, atrial bradycardia, and Brugada syndrome); 2 with structural heart disease (hypertrophic cardiomyopathy); 8 with epilepsy; 3 with vertebralbasilar insufficiency; 20 with medication associated syncope (medication for hypertension and benign prostatic hyperplasia); 4 with anemia; and 3 with hyperthyroidism. Overall, 136 cases (20.1%) of 675 tested negative on the HUTT (Fig. 1).

In the remaining 539 HUTT-positive patients, the median age was 31 (19–58) years and the percentage of females was 64.2%. We divided these 539 patients into 3 groups: 147 adolescents, 269 adults, and 123 older individuals. In the adolescents, females comprised 62.6% of the adolescent group, 70.0% of the adult group, and 53.7% of the older group. This proportion was statistically significantly higher in the adolescent and adult group than in the older individuals. Although height, weight, and body mass index showed statistically significant differences among the 3 groups, there were no clinically significant differences in anthropometrics (Table 1).

Resting systolic blood pressure (SBP) and diastolic blood pressure (DBP) were statistically significantly different among the 3 groups and increased with age. Maximum HR during the passive-phase HUTT was also statistically significantly different among the groups and increased with younger age (Table 1).

Based on HUTT results, 70 patients (13.0%) were diagnosed with POTS: 33 adolescents (22.4%), 37 adults (13.8%), and no older individuals. There was a significant difference in POTS prevalence among the 3 groups (Table 1 and Fig. 2). The percentage of VVS tended to be higher with aging. The positive ratio for passive phase HUTT was 33.6% in the adolescent group, 16.6% in the adult group, and 8.9% in the older group. These ratios were statistically significantly different and increased with younger age (Table 1).

We compared the characteristics of adolescent and adult POTS patients. The median age was 20 (17–25) years (Table 2). The percentage of females overall was 61.4%. The proportion of females in the adolescent group tended to be lower than in the adult group. Resting DBP and HR were statistically significantly lower in the adolescent group (Table 2). Among the 70 POTS patients, 18 patients experienced syncope in the passive-phase HUTT, but there were no statistically significant differences between groups (Table 2).

We also compared the HUTT results of 33 POTS and 124 non-POTS adolescent patients. The percentage of females was higher in the group with VVS than in the negative group. Resting SBP and DBP were similar between groups. Resting HR was statistically significantly lower, and maximum HR in the passive phase was higher in the POTS than in VVS and negative groups (Table 3 and Fig. 3).

4. Discussion

In this study, 70 of 539 patients were diagnosed with POTS. In the adolescent group, POTS was more prevalent than in the adult group, and POTS was absent among the older group. Among those diagnosed with POTS, almost two-thirds were female. Affected adolescents had significantly lower resting diastolic BP and HR, and converted to maximum HR more rapidly than adolescents without the syndrome during the passive phase.

The HUTT places patients in an upright posture, which causes venous pooling in the lower abdomen, buttocks, and legs within

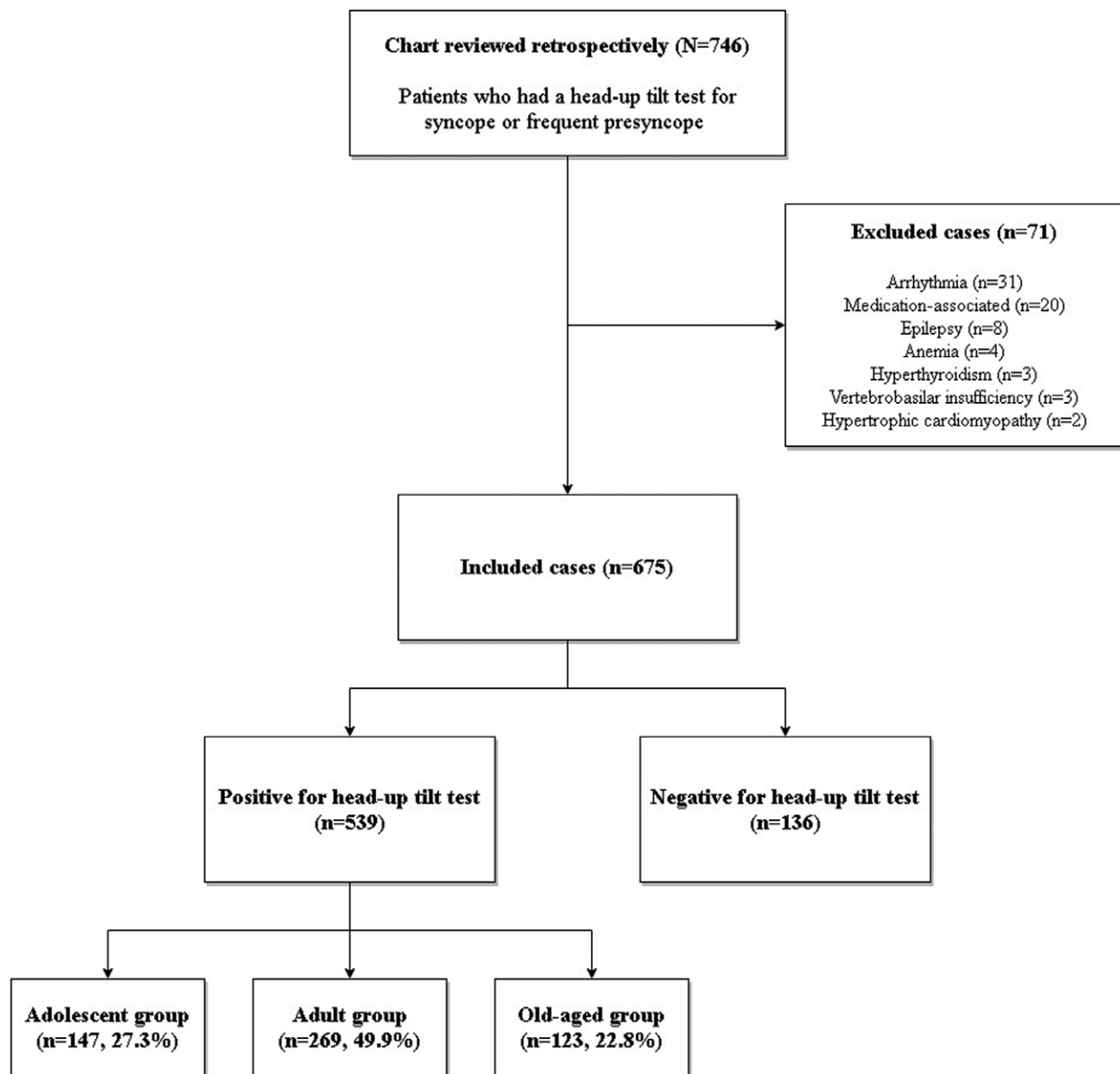


Figure 1. Flow chart of patient selection.

the first 30 seconds.^[3,22] There is a secondary fluid shift from the vasculature to the interstitium, resulting in insufficient cardiac venous return.^[4,23] Arterial baroreceptor responds to reduced stroke volume and pulsatile pressure, producing compensatory vagal withdrawal and sympathetic activation to increase HR, cardiac contractility, and peripheral vascular resistance to maintain BP and tissue perfusion.^[3,4] However, when compensatory mechanisms are absent or incomplete, this test induces hypotension, decreased cerebral blood flow, and syncope. By monitoring HR and BP, we can evaluate the effects of bradycardia and hypotension during fainting. Therefore, it can be performed on patients clinically suspected of having OH, VVS, and POTS.

In our study, patient age ranged from 11 to 45 years, with a median age of 20 (17–25) years. Thieben et al^[11] reported a mean age of 30.2 ± 10.3 years among 152 POTS patients. Moon et al^[24] reported a mean age of 31.1 ± 1.3 years among 107 POTS patients in Korea. Atik et al^[25] reported on 474 adolescents with syncope, in 27.2% of patients in whom POTS was diagnosed. Hamrefors et al^[26] reported 236 young adults (age: 18–40 years) with syncope, with POTS accounting for 30.5%. Previous studies^[4,11,26] also found no POTS in an older group,

probably due to the aging process and pathophysiology of orthostatic intolerance.

The percentage of females in our POTS population was 61.4%. However, Thieben et al^[11] reported a stronger female predominance (4:1). Staples et al^[27] reported that females comprised 79% of POTS patients in a single tertiary care center. Boris et al^[28,29] reported that, in pediatric POTS, female patients outnumbered males 3.45:1. In previous studies,^[27,28] about 90% to 95% of the study population were Caucasian, in contrast to our Asian patient population. Moon et al^[24] reported quality of life in POTS patients in Korea and their percentage of females was 62.6%. Li et al^[30] reported on POTS in Chinese children and found that 53.0% were female. Thus, the results of our study are consistent with studies based on the Asian population. The percentage of females among POTS patients could vary by race, but further studies investigating sex differences in POTS between Caucasians and Asians are needed.

Resting SBP and DBP increased with aging in our population.^[31,32] Maximum HR decreased with aging, as explained by Ebert et al^[33] Among our 70 POTS patients, resting DBP and HR were lower in the adolescent group. Moreover, resting HR

Table 1
Characteristics of 539 patients in the three groups.

	Total N = 539	Adolescent n = 147 (27.3%)	Adult n = 269 (49.9%)	Older n = 123 (22.8%)	P value
Female (N, %)	346 (64.2)	92 (62.6)	188 (70.0)	66 (53.7)	<.01
Median age (years)	31 (19–58)	15 (13–18)	34 (24–49)	67 (63–74)	<.001
Height (cm)	164.4 ± 8.6	166.5 ± 9.7	164.8 ± 8	161.7 ± 8.2	<.001
Weight (kg)	59.6 ± 12.4	55.6 ± 13.2	60.7 ± 12.6	62.1 ± 9.8	<.001
BMI (kg/m ²)	22.2 ± 3.6	20.4 ± 3.6	22.2 ± 3.6	23.8 ± 3.0	<.001
Resting SBP (mm Hg)	114 ± 13.6	110.6 ± 10.4	112.1 ± 12.2	121.9 ± 16.4	<.001
Resting DBP (mm Hg)	71.7 ± 9.7	67.3 ± 7.2	72.2 ± 9.9	75.8 ± 9.9	<.001
Resting HR (bpm)	70.0 ± 12.3	70.7 ± 11.7	70.2 ± 12.7	68.7 ± 11.9	.46
Maximum HR (bpm)†	94.4 ± 19.4	106.4 ± 15.8	93.4 ± 18.9	82.1 ± 15.3	<.001
Positive for passive phase †	103 (19.4)	48 (33.6)	44 (16.6)	11 (8.9)	<.001
Termination time (min) †	16 ± 7.3	15.4 ± 7.5	16.4 ± 6.5	17.4 ± 9.2	.66
OH (N, %)	31 (5.8)	10 (6.8)	11 (4.1)	10 (8.1)	.23
VVS (N, %)	430 (81.3)	104 (70.7)	221 (82.2)	113 (91.9)	.30
POTS (N, %)	70 (13.0)	33 (22.4)	37 (13.8)	0 (0)	<.001

Results are described as N (%), median (interquartile range) or mean ± standard deviation.

BMI = body mass index, DBP = diastolic blood pressure, HR = heart rate, OH = orthostatic hypotension, POTS = postural orthostatic tachycardia syndrome, SBP = systolic blood pressure, VVS = vasovagal syncope.

† Data are collected and analyzed at the passive phase of the head-up tilt test.

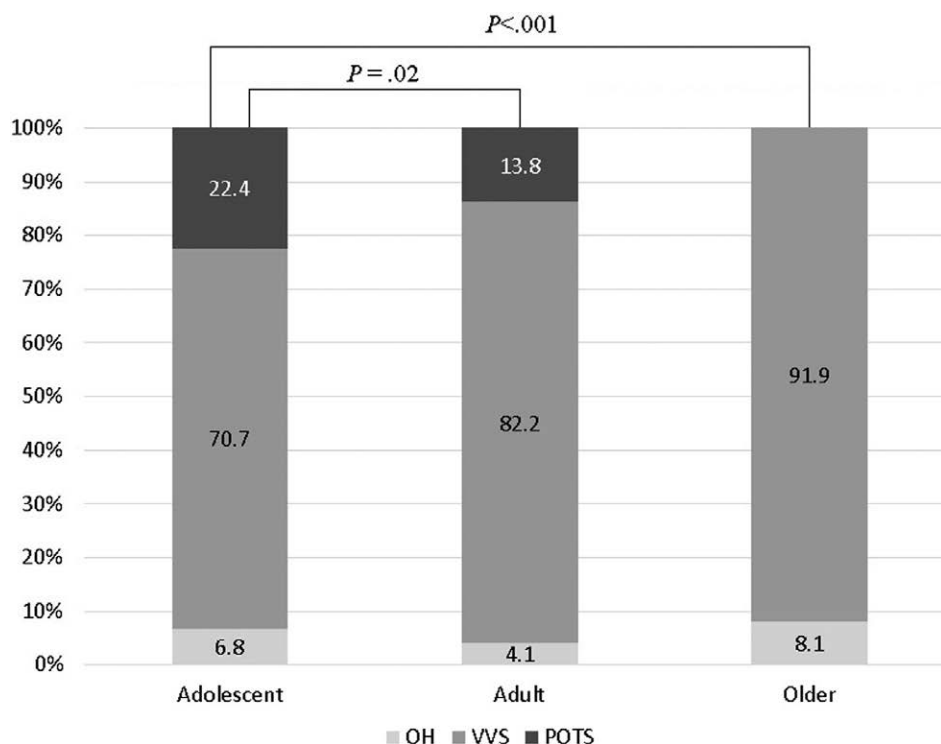


Figure 2. Comparison of HUTT results by age-group. HUTT = head-up tilt test.

was lower and maximum HR in the passive phase was higher in POTS adolescents than in non-POTS adolescents. These results suggested that pediatric POTS patients tend to have lower peripheral vascular resistance and DBP than adult POTS patients, and have a tendency for HR to rise more easily than pediatric non-POTS patients. To confirm these and elucidate the underlying reason, autonomic function tests will be required.

Our passive-phase HUTT results were consistent with those of Sheldon et al,^[34] who insisted that younger patients were more likely to faint during passive tilt testing. The positive ratio for passive phase HUTT was higher with younger age: 33.6% in adolescents, 16.6% in adults, and 8.9% in the older group, respectively. These results suggest that younger patients are more vulnerable to orthostatic stress. Ebert et al^[33] found that there was a decreased hemodynamic response to postural stress,

causing lower body negative pressure in older patients, because they have less peripheral sequestration than younger patients. Consequently, more movement of thoracic blood in younger patients might cause stimulation of baroreceptors, increasing VVS triggers.^[34]

In the adolescent group, 7 patients were diagnosed with epilepsy among 9 excluded patients. In adult group, 28 patients were diagnosed with an arrhythmia and 20 patients were medication-associated syncope. Therefore, electroencephalogram, ECG, and 24-h Holter monitoring should be conducted if patients in this age-group present with syncope. Moreover, the medication they are taking should be thoroughly investigated.

POTS is an under-recognized disease but recently has gained more attention. It represents various symptoms of orthostatic intolerance and patients often report to hospital for syncope

Table 2
Characteristics of adolescent and adult postural orthostatic tachycardia syndrome patients.

	Total N = 70	Adolescent n = 33 (47.1%)	Adult n = 37 (52.9%)	P value
Female (N, %)	43 (61.4)	17 (51.5)	26 (70.3)	.11
Age (years)	20 (17–25)	17 (13–18.5)	25 (22–29.5)	<.001
Height (cm)	167.8 ± 8.7	170.2 ± 9.2	165.5 ± 7.7	.03
Weight (kg)	59.6 ± 12.9	59 ± 12.8	60.2 ± 13.1	.63
BMI (kg/m ²)	21.4 ± 3.6	20.7 ± 3.2	22 ± 3.8	.09
Resting SBP (mm Hg)	112 ± 11.2	112.1 ± 12.8	112 ± 9.7	.99
Resting DBP (mm Hg)	69.8 ± 8.4	67 ± 7.7	72.3 ± 8.4	<.01
Resting HR (bpm)	72.6 ± 14.1	66.5 ± 10.5	78 ± 14.7	<.001
Maximum HR (bpm) †	121.6 ± 14.8	121.1 ± 13	122.2 ± 16.5	.86
Positive for passive phase †	18 (25.7)	11 (33.3)	7 (18.9)	.17
Termination time (min) †	19.8 ± 5.2	20 ± 5.3	19.4 ± 5.4	.73

Results are described as N (%), median (interquartile range) or mean ± standard deviation.
 BMI = body mass index, DBP = diastolic blood pressure, HR = heart rate, SBP = systolic blood pressure.
 † Data are collected and analyzed at the passive phase of the head-up tilt test.

Table 3
Comparison of adolescent postural orthostatic tachycardia syndrome (POTS) and age-matched non-POTS patients.

	Total N = 157	POTS n = 33	VVS n = 104	Negative n = 20	P value
Female (N, %)	95 (60.5)	17 (51.5)	70 (67.3)	8 (40)	.04
Median age (years)	15 (13–18)	17 (13–18.5)	15 (13–17)	16 (13–17)	.07
Height (cm)	166.2 ± 9.5	170.2 ± 9.2	164.9 ± 8.5	163.6 ± 12.8	.02
Weight (kg)	55.7 ± 12.4	59 ± 12.8	54.5 ± 11.6	56.8 ± 15.1	.24
BMI (kg/m ²)	20.5 ± 3.3	20.7 ± 3.2	20.4 ± 3.3	20.7 ± 3.3	.78
Resting SBP (mm Hg)	111 ± 10.2	112.1 ± 12.8	110.4 ± 9.3	112.1 ± 10.1	.62
Resting DBP (mm Hg)	67.4 ± 7.2	67 ± 7.7	67.6 ± 7	66.4 ± 7.7	.56
Resting HR (bpm)	71.5 ± 12	66.5 ± 10.5	72.2 ± 11.9	75.7 ± 12.7	.01
Maximum HR (bpm) †	106.1 ± 15	121.1 ± 13	101.9 ± 13	103.2 ± 13	<.001
Positive for passive phase †	38 (27.7)	11 (33.3)	27 (26.0)	-	.41
Termination time (min) †	17.8 ± 6.5	20 ± 5.3	16.9 ± 6.8	-	.18

Results are described as N (%), median (interquartile range) or mean ± standard deviation.
 BMI = body mass index, DBP = diastolic blood pressure, HR = heart rate, negative = negative for HUTT, POTS = postural orthostatic tachycardia syndrome, SBP = systolic blood pressure, VVS = vasovagal syncope.
 † Data are collected and analyzed at the passive phase of the head-up tilt test (HUTT).

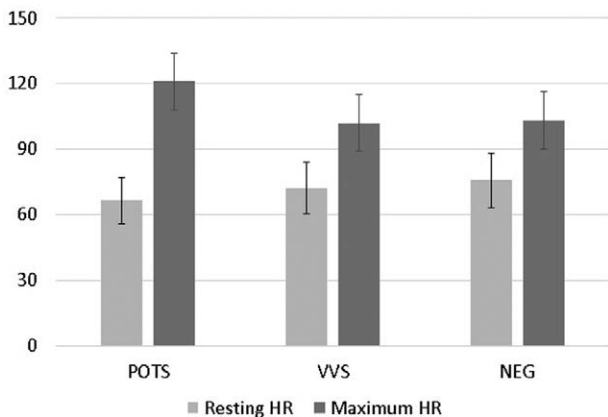


Figure 3. Box plot of age distribution in POTS patients. POTS = postural orthostatic tachycardiac syndrome.

or frequent presyncope. HUTT can be used to evaluate syncope in these patients. Excessive tachycardia observed in the upright posture is suggestive of POTS. In such cases, clinicians should rule out several neurologic, cardiac, hematological, endocrinological, and autoimmune abnormalities, which may mimic POTS.^[11,35,36] For those diagnosed with POTS, measuring

elevated norepinephrine levels when standing, testing autonomic function, and identifying reduced renin and aldosterone levels in patients with hypovolemia will be helpful to classify POTS subtypes.^[8,11,37–41]

Our study had several limitations. As a retrospective study, there was a lack of consistency in medical records, which were not always systematically organized. There was no independent syncope-specific clinic at our hospital, so that some patients may have been insufficiently evaluated, although there could be various causes for syncope. Most patients were examined in neurology and cardiology departments, but syncope may sometimes be related to endocrinology and even rheumatology. Because of under-recognition, POTS was often unintentionally overlooked in our study, even though HUTT was performed. Therefore, future studies with a multidisciplinary approach and an established protocol should be conducted to evaluate POTS in more detail. Furthermore, BP and HR follow-up are needed to determine whether these vital signs change in the POTS group and whether orthostatic intolerance worsens with age. A long-term prospective follow-up study is required to determine whether patients who showed POTS in youth progress to other type of orthostatic intolerance, such as VVS, with age. Moreover, the number of POTS patients in each group was not sufficiently large for detailed statistical analysis. Thus, larger prospective studies are needed in future.

5. Conclusions

POTS is prevalent from adolescence to young adulthood. POTS is an under-recognized disorder among the syncope/presyncope population, and about 22.4% of adolescents were identified as POTS in our study. Adolescent POTS patients have unique characteristics, as compared to adult POTS patients or non-POTS adolescents. Meticulous history taking with an awareness of POTS can prevent missed diagnosis. Consideration of changes in BP, HR, and symptoms in the HUTT would prevent missing POTS diagnoses and avoid unnecessary neurological and cardiovascular evaluation. Accordingly, understanding the index of suspicion for POTS is important in interpreting HUTT results in syncope patients.

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