


# Post-Concussive Orthostatic Tachycardia is Distinct from Postural Orthostatic Tachycardia Syndrome (POTS) in Children and Adolescents

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## Abstract

**Background:** Orthostatic tachycardia (OT) affects some patients after concussion/mild traumatic brain injury (mTBI). In this study, we sought to identify the factors associated with increased risk for OT in patients with mTBI. **Methods:** We conducted a retrospective review of 268 patients (8-25 years) with mTBI/concussion to determine the prevalence of OT, defined as orthostatic heart rate change  $\geq 40$  bpm for those  $\leq 19$  years of age and  $\geq 30$  bpm on active standing test for those  $> 19$  years of age. **Results:** Among the study population, 7% ( $n = 19$ ) exhibited post-concussive OT. The only significant difference between OT and non-OT groups was that history of prior concussion was more prevalent in the OT group. **Conclusion:** A substantial subset (7%) of concussion clinic patients exhibit OT. While POTS literature describes female and adolescent predominance, post-concussive OT had similar prevalence across age and gender groups in this study, suggesting that it may be distinct from POTS.

## Keywords

concussion, traumatic brain injury, adolescents, children, rehabilitation

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## Background

Autonomic dysfunction after moderate and severe traumatic brain injury (TBI) has been well described, with reports of worse long-term neurological outcomes in affected patients, compared to those without post-traumatic autonomic dysfunction.<sup>1-3</sup> Emerging evidence suggests that autonomic dysfunction also occurs after mild traumatic brain injury (mTBI)/concussion (henceforth the term *concussion* will be used to refer to both mTBI/concussion).<sup>4</sup> The mechanisms underlying autonomic dysfunction after TBI are poorly understood, but may involve vulnerability to traumatic injury in brain regions responsible for autonomic function, such as the hypothalamus, limbic cortex, and midbrain nuclei.<sup>5</sup> Previous studies have investigated autonomic dysfunction after concussion as manifested by changes in heart rate variability (HRV), cerebral perfusion, pupillary dynamics, ocular pressure, and arterial pulsatility.<sup>4,6-8</sup> Post-concussive orthostatic tachycardia (OT) is a form of post-concussive autonomic dysfunction that has not yet been extensively studied.

OT is one of several autonomic disorders that can precipitate orthostatic intolerance (OI). These autonomic disorders are characterized by symptoms elicited by transitioning from the supine to upright position and relieved by returning to a

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recumbent position. Typical symptoms may include lightheadedness, fatigue, headache, weakness, exercise intolerance, cognitive dysfunction, anxiety, and depression; these symptoms are usually accompanied by physical signs, especially tachycardia and/or hypotension.<sup>9,10</sup> Most literature on OT focuses on patients with postural orthostatic tachycardia syndrome (POTS). POTS is a chronic condition defined by a sustained increase in heart rate (HR) of  $\geq 30$  beats per minute (bpm) in patients over 19 years of age or  $\geq 40$  bpm in patients 19 years of age and under, in the absence of orthostatic hypotension, upon transition from supine to standing or upon upright tilt on head-up tilt test (HUT).<sup>9,11</sup> The most common presenting symptoms of POTS are dizziness, headache, and fatigue, but other common features include brain fog, insomnia, exercise intolerance, and anxiety.<sup>12-14</sup>

There is considerable overlap between POTS symptoms and post-concussion symptoms, such as headache, fatigue, brain fog, disturbance in mood, and anxiety.<sup>15,16</sup> Moreover, concussion was found to be the second most common trigger preceding POTS onset in a group of 708 patients at a pediatric autonomic disorders clinic, second only to infection among the triggers assessed.<sup>12</sup> Li and colleagues reported similar findings in their earlier study of 150 patients presenting to a pediatrics department with symptoms of OI.<sup>17</sup>

Given the relative paucity of information on differentiating OT from POTS, the present study describes the prevalence, demographics, injury characteristics, and clinical history associated with OT in a large cohort of children and adolescents presenting to a specialized, multidisciplinary concussion clinic. We then examined the relationship between OT and other post-concussive symptoms. We hypothesized that patients with post-concussive OT would have clinical characteristics consistent with those seen in POTS patients without concussion: higher prevalence in females, in adolescents, and in patients with greater time between injury and presentation.<sup>18</sup> We also hypothesized that patients with post-concussive OT have similar symptoms to non-concussed POTS patients, namely: dizziness, headache, fatigue, drowsiness, and anxiety/nervousness. Importantly, the goal of our study was not to describe POTS secondary to concussion, but rather to describe orthostatic tachycardia as one form of post-concussive autonomic dysfunction.

## Methods

### Participants

We completed a retrospective review of consecutive patients who presented to the UCLA Steve Tisch BrainSPORT Clinic and the UCLA Easton Clinic for Brain Health between May 2016 and October 2019 and consented to participate in the BrainSPORT Clinic Registry. Patients were included if they met the following criteria: (1) mTBI or concussion diagnosis (including complicated mTBI – those with mTBI rated as Glasgow Coma Scale [GCS] 13-15 with intracranial abnormalities on standard neuroimaging); (2) 8 to 25 years of age at presentation; (3) information in the medical record on orthostatic vital signs and a complete concussion symptom checklist – either the Sport Concussion Assessment Tool - 5th Edition (SCAT-5) Graded Symptom Checklist (GSC) or the age-appropriate version of the

Post-concussion Symptom Inventory (PCSI). Patients were excluded if they had a pre-existing POTS diagnosis and/or a diagnosis of moderate-severe TBI, as defined by GCS  $< 14$ .<sup>19</sup> Information regarding patients' demographics, injury characteristics, past medical history (including current medications), family history, symptom checklists, and orthostatic vital sign measurements were extracted from the electronic medical record. Ethical approval was obtained from the UCLA Institutional Review Board as part of a larger study, "Acute Monitoring and Long-Term Outcome Following Traumatic Brain Injury or Concussion" (IRB #11-001760). Written informed consent was obtained from the patients or their legal authorized representatives for anonymized patient information to be published in this article.

### Measurement of Orthostatic Vital Signs

Measuring orthostatic vital signs on intake is standard of care for all patients presenting to the BrainSPORT clinic and is performed with a modified active standing test (AST). In our modified AST, a trained medical assistant takes the patient's blood pressure and pulse via digital sphygmomanometer and pulse oximeter, respectively, at three set intervals: (1) after lying supine for 2 minutes; (2) after sitting upright for 2 minutes; and (3) after standing unsupported for 2 minutes.

### Definition of OT

In accordance with the 2015 Heart Rhythm Society Expert Consensus Statement on POTS, we defined OT as an elevation in heart rate of  $\geq 40$  bpm for patients  $\leq 19$  years and  $\geq 30$  bpm for patients  $> 19$  years of age, when transitioning between the supine and standing positions, in the absence of orthostatic hypotension.<sup>11</sup> This definition is based on normative data for heart rate response to HUT in pediatric patients.<sup>20</sup> While this consensus statement only defines OT for patients  $\geq 12$  years of age due to the absence of studies in children  $< 12$  years of age, we chose to include younger patients in our study in order to reflect the entirety of our clinic population and to characterize positional heart rate change in younger patients. We recognize that our findings in these patients must be carefully considered given the limited evidence and understanding of OT in this age group. In all analyses, we treated OT as a dichotomous categorical variable. We also performed a secondary analysis excluding patients  $< 12$  years of age at presentation. We defined orthostatic hypotension as a drop in systolic blood pressure  $\geq 20$  mm Hg between supine and standing positions and, likewise, treated orthostatic hypotension as a dichotomous variable.<sup>9</sup> Patients with orthostatic hypotension were included in our sample.

Previous research has found that a significant proportion of adolescents with symptoms of OI after concussion have an elevation in HR of 30-39 bpm on HUT or AST, which does not meet the diagnostic OT cutoff for their age group of  $\geq 40$  bpm.<sup>21,22</sup> Given those findings, we performed a secondary analysis using an HR cutoff of  $\geq 30$  bpm for OT in all patients.

### Definition of Concussion and Assessment of Symptoms

Concussion was diagnosed in accordance with the consensus definition from the fifth International Conference on Concussion in Sport held in Berlin in 2016.<sup>15</sup> Therein, concussion is defined as a "traumatic brain injury induced by biomechanical forces," either from a direct blow to the head or neck, or to elsewhere on the body with an impulsive force transmitted to the head, which results in the rapid onset of transient neurological impairment and a range of clinical signs and symptoms that follow a typical course. Patients were included in this study if they were deemed by the clinician to have a concussion based on mechanism of injury,

presence and timing of typical post-concussion symptoms, and recovery trajectory consistent with concussion.

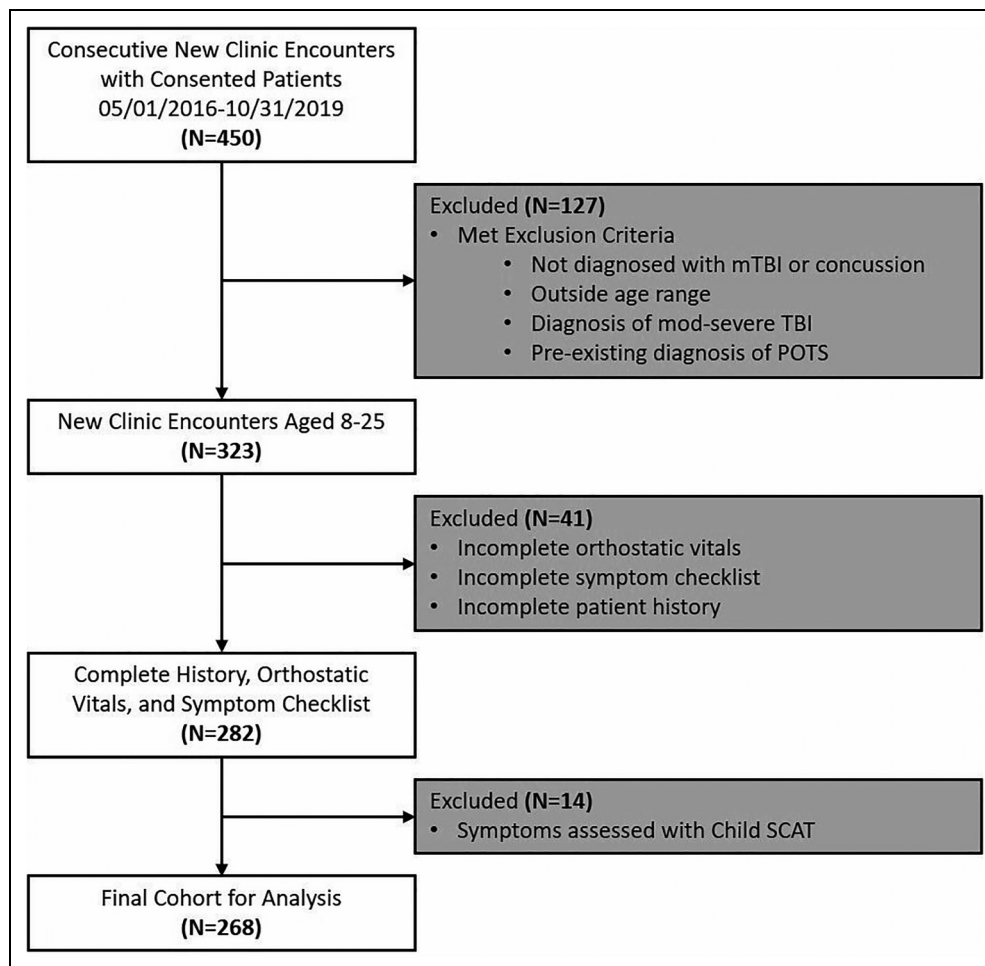
Concussion symptoms in this cohort were assessed with one of three commonly used symptom checklists: the GSC from the SCAT-5, the PCSI 13–18 Year Old Version (PCSI 13–18), or the PCSI 8–12 Year Old Version (PCSI 8–12).<sup>23–26</sup> The use of different symptom checklists was due in part to the age ranges of the participants and in part to changes in the standard of care at the BrainSPORT clinic over the study period. One additional checklist – the Child SCAT-3 – was used to assess some patients 8–12 years of age who otherwise met our inclusion criteria. Because the Child SCAT-3 differs significantly from the other three checklists and could not be adapted as easily for pooled analysis of common symptoms, patients whose symptoms were assessed with the Child SCAT-3 were eliminated from the final cohort (Figure 1).

The GSC, PCSI 13–18, and PCSI 8–12 are similar with respect to symptoms assessed, symptom domain representation, and wording. To prepare symptom data for pooled analysis, two major differences were accommodated. Firstly, on the GSC and PCSI 13–18, patients score their symptoms on a 7-point (0–6) Likert scale, whereas, on the PCSI 8–12, patients score their symptoms on a 3-point (0–2) Likert scale. To compare symptoms across our entire clinic cohort, we scaled individual

symptom scores on the PCSI 8–12 by a factor of three. For instance, a score of 1 on the 0–2 Likert scale was multiplied by 3, yielding a score of 3 for the purposes of comparison. Secondly, the GSC, PCSI 13–18, and PCSI 8–12 assess a total of 22, 21, and 17 symptoms, respectively. To account for differences between checklists in the number of symptoms assessed, we compared patients only on the set of 17 symptoms which are common and comparably worded across all three checklists (Supplementary Figure S1). For analysis, values for individual symptoms, the total number of common symptoms reported, and total common symptom severity were treated as continuous variables.

## Medications

Certain medications may affect orthostatic vital sign measurements and OI symptoms.<sup>27,28</sup> Therefore, we noted seven classes of such medications: (1) tricyclic antidepressants (ie, amitriptyline is commonly prescribed for post-traumatic headache); (2) beta-blockers (ie, propranolol, also prescribed for post-traumatic headache); (3) serotonin-norepinephrine reuptake inhibitors (SNRIs) (ie, duloxetine, prescribed for post-traumatic headache, pain, and/or mood



**Figure 1.** Patient Selection – This consort diagram delineates how patients were selected for this study. All patients presented to the UCLA Steve Tisch BrainSPORT Clinic and consented to be part of the clinic registry. Patients were included if they had a concussion/mTBI diagnosis, were in the specified age range (8–25 years old) at presentation, and had both orthostatic vital signs and a complete symptom checklist. Patients were excluded if they had pre-existing POTS diagnosis or diagnosis of moderate-severe TBI.

disturbance); (4) alpha-agonists (ie, clonidine, prescribed for anxiety); (5) alpha-antagonists (ie, prazosin, prescribed for nightmares secondary to post-traumatic stress disorder); (6) stimulants (ie, amphetamine/dextroamphetamine for attention deficit hyperactivity disorder); and (7) other, which included cyproheptadine (prescribed for headache prevention because of its antihistaminergic, anticholinergic, and anti-serotonergic effects). We collected information on current medication use from the medical record, identifying whether patients had a prescription for one or more medications in the above classes at the time of their visit. The presence or absence of a prescription medication in each of the seven classes above was treated as a dichotomous variable. Patients who were prescribed the above medications were included in the primary analysis. To address the potential confounding effects of these medications on our results, we performed a secondary analysis excluding patients who were using medications known to potentially affect OT presentation at the time of the study.

### Statistical Analysis

Demographics, injury history, medical history, and symptom data are described with means and standard deviations or medians and interquartile ranges, as appropriate. Characteristics of patients with and without OT – including our hypothesis-driven variables of interest (ie, sex prevalence, dizziness, headache, fatigue, drowsiness, and anxiety) – were compared using either Pearson's Chi-squared or Fisher's exact test for categorical variables and either two-tailed t-test or Mann–Whitney test for continuous data. The Shapiro–Wilk test was used to assess the normality of continuous variables. Odds ratios, Cohen's *d*, or rank-biserial correlation *r* were used as appropriate to assess effect sizes for categorical and continuous variables, respectively. Age was dichotomized corresponding to the approximate onset of puberty (13 years), and time to presentation was dichotomized to the clinical definition of persistent post-concussion symptoms (PPCS, defined as symptoms persistent at 3 months).<sup>29</sup>

Four post-hoc analyses were performed. We performed the descriptive analysis above on OT patients stratified by sex to identify sex differences among patients presenting with OT. We repeated the analysis on the overall cohort using an HR cutoff of  $\geq 30$  bpm for all patients, given findings in the literature previously discussed. Next, we repeated the analysis after excluding patients <12 years of age. Finally, we repeated the analysis after excluding patients that were taking medications that may have contributed to OT. Tables corresponding to these analyses can be found in the Supplemental materials.

In all analyses, a *P*-value <.05 was considered significant. Effect sizes are reported to guide the interpretation of statistical results, but we did not correct for multiple comparisons. Analyses were performed using R version 4.0.0 in R Studio.<sup>30–33</sup>

## Results

### Overall Cohort

Of 450 consecutive, new patients presenting to our clinic and consenting to participate in our registry, 268 patients met all inclusion criteria (Figure 1). In the overall cohort, 51% (136/268) of patients were female, and the median age was 16 [IQR 14–18] years. Median time to presentation was 46.5 [18–104] days post-injury. Descriptive statistics for the overall cohort can be found in Tables 1, 2, and 3.

### OT versus Non-OT Groups

In the overall cohort, 7% (19/268) of patients were found to have OT. Seven of 268 (2.6%) patients were found to have orthostatic hypotension. No patient had both OT and orthostatic hypotension. For the purposes of this analysis, the seven patients with orthostatic hypotension in the absence of OT were counted among the 249 patients in the non-OT group.

We found no difference in the proportion of sexes between groups (*P* = .24, OR = 0.55). Groups were similar in age and time to presentation. There were no meaningful differences between the OT and non-OT groups in the variables pertaining to demographics, injury characteristics, or medical history, with one exception: 79% (15/19) of patients in the OT group reported history of previous concussion (>1 concussion), compared to 48% (120/149) in the non-OT group (*P* = .02, OR = 3.87). These results are summarized in Tables 1 and 2.

We found little evidence that the POTS symptom profile was more prevalent in OT patients than in non-OT patients (Table 3). Patients with OT reported feeling more drowsiness (*P* = .05, *r* = 0.12). The groups did not differ significantly on any other symptom of interest, including dizziness (*P* = .68, *r* = 0.03), headache (*P* = .51, *r* = 0.04), fatigue (*P* = .42, *r* = 0.05), and nervousness/anxiety (*P* = .5582, *r* = 0.04). Lastly, neither total symptom severity (*P* = .47, *r* = 0.04) nor total number of common symptoms (*P* = .3, *r* = 0.06) was found to differ significantly between groups. These results are summarized in Table 3.

### Secondary Analyses

**Applying HR Cut-off of 30 bpm.** When the descriptive analysis of the overall cohort was repeated using the HR cutoff of 30 bpm for all patients, 20.5% (55/268) of patients were found to have OT. There were no statistically significant differences between OT and non-OT patients in terms of demographics, injury characteristics, medical history, or symptom profile, with the following exceptions: those in the OT group were more likely to have been prescribed a stimulant medication (*P* = .03, OR = 3.60), and, as seen in the primary analysis, those in the OT group reported more drowsiness (*P* = .01, *r* = 0.15). Results from this analysis are summarized in Supplementary Tables S1, S2, and S3.

**Gender prevalence of OT.** The proportion of females was 36.8% in the OT group (7/19) and 51.8% (129/249) in the non-OT group, with no significant difference between groups (*P* = .24). The results of subgroup analyses showed that females with OT were older than males with OT (*P* < .01, *r* = 0.72). In the OT group, no females were <13 years of age, whereas 25% (3/12) of males were <13 years of age. There was no significant age difference between females and males in either the non-OT group, or the overall cohort. With regard to patient history, females with OT were more likely to report pre-existing history of anxiety (*P* < .01) or depression (*P* = .04); no males in the OT group reported history of either condition. With respect

**Table 1.** Overall Cohort Demographics, Orthostatic Vitals, and Injury Characteristics.

	OT Status			P-Value <sup>a</sup>	Effect Size <sup>b</sup>
	Overall (N = 268)	Non-OT Group (N = 249)	OT Group (N = 19)		
<b>Demographics</b>					
Sex (Female)	136 (51%)	129 (51.8%)	7 (36.8%)	.24	OR = 0.55 [95% CI 0.2–1.45]
Age (Years)	16 [IQR 14–18]	16 [IQR 14–18]	16 [IQR 14–19]	.68	r = –0.03 [95% CI –0.15–0.1]
Age <13 years	28 (10%)	25 (10%)	3 (15.8%)	.43	OR = 1.74 [95% CI 0.37–5.76]
<b>Basic Health &amp; Orthostatic Vitals</b>					
Height (m)	1.68 [IQR 1.61–1.75]	1.68 [IQR 1.6–1.76]	1.68 [IQR 1.63–1.73]	.84	r = –0.01 [95% CI –0.13–0.1]
Weight (kg)	61.2 [IQR 52.3–71.6]	61.4 [IQR 52.4–71.7]	60.1 [IQR 48.7–70.7]	.59	r = –0.03 [95% CI –0.16–0.09]
Supine Heart Rate (BPM)	66 [IQR 59–75]	66 [IQR 59–76]	62 [IQR 55–69]	.04*	r = –0.13 [95% CI –0.23–0.01]
Sitting Heart Rate (BPM)	74.1 [SD 14]	73.6 [SD 13.7]	80.6 [SD 16.7]	.09	d = 0.50 [95% CI 0.03–0.97]
Standing Heart Rate (BPM)	86.6 [SD 16.2]	85.2 [SD 15.5]	105.5 [SD 12.6]	<.001*	d = 1.33 [95% CI 0.84–1.81]
Orthostatic Change in Heart Rate (BPM)	18 [IQR 10–27]	17 [IQR 10–25]	43 [IQR 40–44]	<.001*	r = 0.44 [95% CI 0.34–0.52]
Supine Systolic Blood Pressure (mm Hg)	114 [IQR 107–120]	113 [IQR 107–120]	115 [IQR 105–120]	.93	r < 0.01 [95% CI –0.13–0.12]
Sitting Systolic Blood Pressure (mm Hg)	114 [IQR 107–121]	114 [IQR 106–121]	112 [IQR 109–117]	.99	r < 0.01 [95% CI –0.12–0.11]
Standing Systolic Blood Pressure (mm Hg)	112 [IQR 105–120]	112 [IQR 105–120]	114 [IQR 106–119]	.88	r = 0.01 [95% CI –0.1–0.12]
Orthostatic Change in Systolic Blood Pressure (mm Hg)	–2 [IQR –7–4]	–2 [IQR –7–4]	0 [IQR –8.5–4]	.86	r = 0.01 [95% CI –0.11–0.14]
<b>Injury Characteristics</b>					
Time to Presentation (Days)	46.5 [IQR 18–104]	46 [IQR 18–103]	54 [14–100.5]	.74	r = 0.02 [95% CI –0.1–0.14]
Time to Presentation ≥3 Months	77 (29%)	71 (28.5%)	6 (31.6%)	.79	OR = 1.17 [95% CI 0.39–3.13]
<b>Concussion Mechanism</b>					
Sport/Recreation	178 (66%)	166 (66.7%)	12 (63.2%)	.74	NA
Struck	31 (12%)	29 (11.6%)	2 (10.5%)		
Motor Vehicle Accident	28 (10%)	24 (9.6%)	4 (21.1%)		
Fall (Non-Sport)	23 (9%)	22 (8.8%)	1 (5.3%)		
Assault	4 (1%)	4 (1.6%)	0		
Other	3 (1%)	3 (1.2%)	0		
Unknown	1 (<1%)	1 (<1%)	0		
Intracranial Injury or Skull Fracture	13 (5%)	11 (4.4%)	2 (10.5%)	.32	OR = 0.37 [95% CI 0.09–2.78]
Anterograde Amnesia	43 (16%)	40 (16.1%)	3 (15.8%)	1	OR = 0.99 [95% CI 0.31–4.66]
Retrograde Amnesia	65 (24%)	59 (23.7%)	6 (31.6%)	.71	OR = 0.46 [95% CI 0.24–2.03]
Loss of Consciousness	42 (16%)	40 (16.1%)	2 (10.5%)	.27	OR = 1.32 [95% CI 0.34–9.5]
Seizure	7 (3%)	5 (2%)	2 (10.5%)	.052	OR = 0.16 [95% CI 0.03–1.37]

\*Denotes statistical significance ( $P < .05$ ). Uncorrected P-values are reported.

<sup>a</sup>P-values resulting from two-tailed Mann–Whitney U-test or independent samples t-test for continuous variables and Chi-squared test or Fisher's exact test for categorical variables.

<sup>b</sup>r, Cohen's d, or odds ratio (OR) is presented in accordance with the statistical test performed. ORs were not estimated for injury characteristic variables with more than two levels.

to history of anxiety, a similar pattern is observed in patients without OT (females 33.6% [43/128], males 22.3% [27/121],  $P = .07$ , OR = 1.74 [95% CI 0.99–3.08]) and in the overall

cohort (females 34.8% [47/135], males 20.3% [27/133],  $P = 0.01$ , OR = 2.03 [95% CI 1.2–3.63]). With respect to history of depression, a slight female predominance was observed,

**Table 2.** Medical History & Current Medications in the Study Population.

	OT Status			P-Value <sup>a</sup>	Effect Size
	Overall (N = 268)	Non-OT Group (N = 249)	OT Group (N = 19)		
<i>Patient History</i>					
Previous Concussion (>1)	135 (50%)	120 (48%)	15 (79%)	.02*	OR = 3.87 [95% CI 1.35–14.3]
Headache	91 (34%)	83 (33%)	8 (42%)	.46	OR = 1.43 [95% CI 0.53–3.72]
Anxiety	74 (28%)	70 (28%)	4 (21%)	.6	OR = 0.69 [95% CI 0.19–2.02]
Depression	47 (18%)	44 (18%)	3 (16%)	1	OR = 0.9 [95% CI 0.19–2.9]
Attention Deficit Hyperactivity Disorder (ADHD)	33 (12%)	30 (12%)	3 (16%)	.71	OR = 1.41 [95% CI 0.3–4.60]
Learning Disability	36 (13%)	32 (13%)	4 (21%)	.30	OR = 1.83 [95% CI 0.48–5.5]
Sleep Disorder	51 (19%)	49 (20%)	2 (11%)	.54	OR = 0.52 [95% CI 0.07–1.95]
<i>Family History</i>					
Headache or Migraine	118 (44%)	110 (44%)	8 (42%)	.82	OR = 0.88 [95% CI 0.33–2.29]
ADHD or Learning Disability	55 (21%)	49 (20%)	6 (32%)	.25	OR = 1.85 [95% CI 0.61–4.99]
Psychiatric Disorder	92 (34%)	85 (34%)	7 (37%)	1	OR = 1.09 [95% CI 0.39–2.86]
<i>Prescription Medications</i>					
α-Agonist	2 (1%)	2 (1%)	0	1	NA
α-Antagonist	0	0	0	1	NA
β-Blocker	3 (1%)	2 (1%)	1 (5%)	.2	OR = 7.16 [95% CI 0.22–92.5]
Serotonin-Norepinephrine Reuptake Inhibitor	0	0	0	1	NA
Stimulant	13 (5%)	11 (4%)	2 (11%)	.23	OR = 2.67 [95% CI 0.36–11.2]
Tricyclic Antidepressant	11 (4%)	10 (4%)	1 (5%)	.56	OR = 1.48 [95% CI 0.06–8.6]
Other	0	0	0	1	NA

\*Denotes statistical significance ( $P < .05$ ). Uncorrected P-values are reported.

<sup>a</sup>P-values resulting from Chi-squared or Fisher's exact tests.

but this difference was not significant among patients without OT or in the overall cohort. There were no significant differences between females and males with OT in the remaining variables pertaining to demographics, injury characteristics, medical history, or symptoms. Given the small number of patients in the OT group, results must be interpreted cautiously. These results are summarized in Supplementary Tables S4, S5, and S6.

**OT versus non-OT Groups:  $\geq 12$  years of age.** When we excluded patients <12 years of age from analysis, the remaining cohort included 240 patients (54% [130/242] female, median age 16 years [IQR 15–19]); OT was present in 6.7% (16/240). There were no statistically significant differences between the OT and non-OT groups in terms of demographics, medical history, injury characteristics, or symptoms, except for the presence of post-traumatic seizure, reported in 2.2% (5/224) of patients in the non-OT group and in 12.5% (2/16) of patients in the OT group ( $P = .04$ , OR = 6.63). See Supplementary Tables 7, 8, and 9.

**OT versus non-OT Groups: patients without use of selected medications.** When we excluded patients that had been prescribed an alpha-agonist, alpha-antagonist, beta blocker, SNRI, tricyclic antidepressant, stimulant, and/or cyproheptadine, the remaining cohort included 242 patients (50.4% [122/242] female, median age 16 years [IQR 14–18.75]); OT

was present in 6.6% (15/227). There were no statistically significant differences between the OT and non-OT groups in terms of demographics, medical history, injury characteristics, or symptoms, with two exceptions. As observed in patients  $\geq 12$  years of age, the OT group reported a higher incidence of post-traumatic seizure (OT group 13.3% [2/15], non-OT group 2.2% [5/227],  $P = .04$ , OR = 7.26). In line with the pattern observed across other analyses, those in the OT group were more likely to report history of previous concussion (OT group 80% [12/15], non-OT group 47.1% [107/227],  $P = .02$ , OR = 4.27). See Supplementary Tables 10, 11, and 12.

## Discussion

Few studies have examined POTS and/or OT in patients presenting after concussion. In this study, we sought to determine the prevalence of OT post-concussion and to describe the clinical features of this group of patients. In previous work, Heyer and colleagues' exploratory study of post-concussion autonomic dysfunction in 34 adolescents presenting to a pediatric headache clinic between 3 weeks and 6 months post-injury showed that 41.2% had OT (defined as HR change  $>30$  bpm or HR  $>120$  bpm when upright), and 29.4% had isolated syncope on HUT.<sup>34</sup> Those with OT reported more lightheadedness and higher overall post-concussive symptom burden on the PCSI.<sup>34</sup> More recently, Kokorelis and colleagues examined OI among children and adolescents presenting to a

**Table 3.** Common Symptoms in the Study Population.

	OT Status			P-Value <sup>a</sup>	Effect Size
	Overall (N = 268)	Non-OT Group (N = 249)	OT Group (N = 19)		
<i>Overall</i>					
Total Common Symptom Severity	24 [IQR 9–42.3]	24 [IQR 9–42]	31 [IQR 11.5–47.5]	.47	r = 0.04 [95% CI –0.1–0.17]
Total Number of Common Symptoms	10 [IQR 5–13]	9 [IQR 5–13]	11 [IQR 6–14.5]	.3	r = 0.06 [95% CI –0.07–0.19]
<i>Physical Symptoms</i>					
Impaired Balance	1.2 [SD 1.7]	1.1 [SD 1.7]	1.4 [SD 1.9]	.6	r = 0.03 [95% CI –0.1–0.16]
Blurred Vision	1.1 [SD 1.7]	1.1 [SD 1.7]	1.1 [SD 1.7]	1	r < 0.01 [95% CI –0.11–0.13]
Dizziness	1.5 [SD 1.8]	1.5 [SD 1.8]	1.6 [SD 1.8]	.68	r = 0.03 [95% CI –0.1–0.14]
Headache	2.6 [SD 1.9]	2.6 [SD 1.9]	2.3 [SD 2.1]	.51	r = –0.04 [95% CI –0.16–0.08]
Nausea	1.1 [SD 1.6]	1.1 [SD 1.6]	1.4 [SD 1.7]	.29	r = 0.06 [95% CI –0.05–0.19]
Sensitivity to Light	1.9 [SD 1.8]	1.9 [SD 1.8]	1.8 [SD 2]	.9	r = –0.01 [95% CI –0.13–0.11]
Sensitivity to Noise	1.5 [SD 1.8]	1.5 [SD 1.8]	1.2 [SD 1.3]	.78	r = –0.02 [95% CI –0.11–0.08]
<i>Cognitive Symptoms</i>					
Confusion	1.4 [SD 1.8]	1.3 [SD 1.8]	1.6 [SD 1.7]	.43	r = 0.05 [95% CI –0.07–0.16]
Difficulty Concentrating	2.6 [SD 1.9]	2.6 [SD 1.9]	2.4 [SD 2]	.83	r = –0.01 [95% CI –0.14–0.1]
Difficulty Remembering	2.0 [SD 2.0]	2 [SD 2]	2.1 [SD 2.1]	.91	r = 0.01 [95% CI –0.11–0.14]
Feeling Slow	1.9 [SD 1.9]	1.9 [SD 1.9]	1.9 [SD 2]	.79	r = –0.02 [95% CI –0.13–0.1]
Mental Fog	1.7 [SD 1.9]	1.7 [SD 1.9]	1.9 [SD 2.1]	.78	r = 0.02 [95% CI –0.11–0.15]
<i>Symptoms Related to Sleep &amp; Fatigue</i>					
Drowsiness	1.8 [SD 1.8]	1.7 [SD 1.8]	2.7 [SD 2.1]	.05* <sup>b</sup>	r = 0.12 [95% CI –0.01–0.24]
Fatigue	2.4 [SD 2.0]	2.4 [SD 2]	2.7 [SD 2.1]	.42	r = 0.05 [95% CI –0.08–0.17]
<i>Emotional Symptoms</i>					
Irritability	1.8 [SD 1.8]	1.8 [SD 1.8]	1.8 [SD 1.7]	.91	r = 0.01 [95% CI –0.1–0.13]
Nervousness or Anxiety	1.6 [SD 1.9]	1.6 [SD 1.9]	1.9 [SD 2.1]	.55	r = 0.04 [95% CI –0.09–0.17]
Sadness	1.3 [SD 1.8]	1.3 [SD 1.9]	1.3 [SD 1.5]	.71	r = 0.02 [95% CI –0.09–0.14]

\*Denotes statistical significance ( $P < .05$ ). Uncorrected P-values are reported.

<sup>a</sup>P-values resulting from Mann–Whitney U-tests.

<sup>b</sup>p = .048.

N.B.: For each individual symptom, the most common response is 0, hence the choice to present the mean [SD] in place of the median or mode. Please note, however, that the distributions of these variables are non-normal.

multidisciplinary concussion clinic.<sup>21</sup> Of 114 patients in their study, 72% (82/114) reported OI symptoms on a screening questionnaire developed by the authors. Of those reporting OI symptoms, 29% (24/82) met criteria for either OT (defined as HR change >40 bpm or HR >120 bpm on standing) or neurally mediated hypotension (defined as a decrease  $\geq 25$  mmHg in systolic blood pressure after 3 minutes of standing from supine on AST). An additional 35 patients with positive symptom screens did not meet criteria for OT or orthostatic hypotension, but did exhibit an orthostatic HR increase between 30–39 bpm – below the 40 bpm threshold for patients under 19 years, but above the 30 bpm threshold for older patients. The present study is the largest to date to examine the prevalence and clinical characteristics of post-concussive OT in children and young adults.

Because orthostatic vitals are standard of care in our clinic, this is also the first study to describe OT prevalence in all patients presenting to a specialty clinic for concussion, as prior studies have only looked at patients exhibiting OI symptoms.<sup>21,34</sup> Overall, our findings strengthen the case that a significant proportion of patients who present to a concussion clinic exhibit some form of OI. Our finding that 7% of patients

exhibited OT on a modified AST is notable. When using the 30 bpm HR cut-off for OT, a much higher prevalence was observed. This is consistent with Kokorelis and colleagues' finding that a substantial subset of patients reporting OI symptoms exhibit a sub-threshold HR increase of 30–39 bpm. Combining patients exhibiting OT (N = 19) and orthostatic hypotension (N = 7) in our sample, the prevalence of OI on modified AST would be 9.7%. Kokorelis and colleagues reported a 29% prevalence of OI on AST (25.6% with isolated OT and 3.7% with orthostatic hypotension or both orthostatic hypotension and OT). In their study, however, only patients with symptoms of OI underwent the AST.<sup>21</sup> Additionally, they performed a standard AST with a 10-minute standing condition, whereas our modified AST with a 2-minute standing condition may have significantly underestimated the overall prevalence of OT.<sup>35</sup> Abbreviated protocols are more practical in the setting of a clinic that does not specialize in OI, and AST and HUT protocols with 2-minute, 3-minute, and 5-minute challenge conditions have been used to diagnose POTS in the literature, especially prior to 2015.<sup>9,36-39</sup> While Roma and colleagues found that a 10-minute standing condition

was significantly more sensitive than 2 minutes, there is still some disagreement in the literature regarding the superiority of the longer challenge condition.<sup>35</sup> Kirbiš and colleagues, for example, reported comparable diagnostic results at 3-minutes and 9-minutes with both AST and HUT protocols and that both methods obtained similar results overall.<sup>39</sup> The field as a whole has yet to resolve significant issues regarding the comparability of HUT and AST, the reproducibility of both diagnostic methods, and the influence of conditions extraneous to the test parameters (eg, hydration status, time of day, degree of deconditioning) on the measured values.<sup>40,41</sup>

POTS pathophysiology is heterogeneous, and mechanisms may include sympathetic hyperactivity, sympathetic hypoactivity, hypovolemia, and deconditioning.<sup>42</sup> Typical POTS populations consistently exhibit female and adolescent preponderance.<sup>9,12,18</sup> In contrast, a similar prevalence of OT across sexes and age groups was observed in this study of pediatric patients with concussion, as reported previously.<sup>21</sup> This finding suggests that the pathophysiology of post-concussive OT may differ from that of POTS. In addition, POTS by definition is a chronic condition. While our study did not evaluate post-concussive OT over time, previous literature suggests that post-concussive OT may resolve in tandem with the resolution of other post-concussive symptoms.<sup>34</sup>

Physical deconditioning may contribute to post-concussive OT, as it is common after concussion and known to contribute to OI. Heyer and colleagues found that 75% of patients who initially had an abnormal HUT after concussion subsequently had resolution of these abnormalities as their other post-concussive symptoms resolved and they returned to activity.<sup>34</sup> This suggests that as the deconditioned state was corrected, the underlying mechanism for their OT resolved. Notably, the study included only 34 patients. Kokorelis and colleagues similarly found that patients with OI reported a significant decrease in physical activity after vs. before injury, which at the very least suggests that the patients in their study were deconditioned while they were symptomatic. These studies provide evidence that deconditioning may contribute to post-concussive OT. If deconditioning were the predominant underlying mechanism, however, we would have expected to see a greater prevalence of post-concussive OT among those presenting to clinic further from the time of injury, per our hypothesis. In our analysis, OT prevalence did not vary significantly by time to presentation. Possible explanations for this discrepancy are that time from injury does not always correlate with continued inactivity and that patients may physiologically adapt to the deconditioned state over time. In any case, the role of deconditioning and its relationship to other underlying mechanisms of post-concussive OT remains unclear and warrants further study.

As previously mentioned, the pathophysiological mechanisms underlying OT are complex and may be affected by medication use. Beta-blockers reduce sympathetic input into the sinus node, thereby lowering heart rate and potentially masking or treating underlying OT.<sup>42</sup> Clonidine, an alpha-agonist, reduces central hyperadrenergic activity, which may also alleviate OI symptoms.<sup>42</sup> On the other hand, both

stimulants and SNRIs have sympathomimetic effects, which may cause or exacerbate tachycardia.<sup>18</sup> To account for potential medication effects, we noted whether patients were previously prescribed any medications which might affect their orthostatic vital signs or OI symptoms (Table 2).

In our primary analysis, we did not find any differences between the OT and non-OT groups with respect to these medications. In a secondary analysis performed after excluding patients who were prescribed the selected medications (Supplementary Tables 10–12), increased frequency of post-traumatic seizure was observed in the OT group; however, this finding must be interpreted with caution, given the small number of patients with post-traumatic seizure and the wide confidence interval associated with the OR. Notably, in our secondary analysis applying an HR cut-off of 30 bpm for all patients, we found that patients with OT were more likely to have been prescribed a stimulant (Supplementary Table 2). While it is possible that stimulant use may have contributed to post-concussive OT in some patients, there were relatively few patients who were prescribed stimulants in either group, making it difficult to detect a true effect secondary to medication use. The other medications that we assessed did not appear to have a significant effect on OT in our study population. The interpretation of all results with respect to medications should be tempered by the fact that we were unable to gather data on medication adherence from the medical records.

Our results did not support the hypothesis that those with post-concussive OT have a specific symptom profile. The only point of differentiation between the OT and non-OT groups was a marked elevation of drowsiness severity in study participants with OT. However, the small magnitude and effect size associated with that finding suggest that this is likely not a clinically meaningful difference.

The absence of a distinct profile of symptoms in post-concussive OT contrasts with Heyer's and colleagues' finding that patients with OT on HUT had higher ratings for lightheadedness and total symptom scores on the PCSI, compared to patients with normal HUT.<sup>34</sup> There are several possible explanations for this discrepancy. In addition to being considerably larger, our sample is also more heterogeneous with respect to time to presentation, injury mechanism, age, and sex, all of which could affect symptom scores. Heyer et al.'s use of HUT to diagnose OT is likely more specific than our modified AST. Our method of scaling and selection of symptoms may have obscured a symptom profile that was present but small in effect size.

The differences between OT and non-OT patients found by Heyer and colleagues could also have been driven by the female predominance of their sample (77% of OT patients). Our findings did not support a distinct symptomatic presentation on the basis of sex, but we did find other differences between sexes within the OT group. Females with OT were more likely to have a history of anxiety and depression than males with OT. Because females in the general population are known to exhibit a higher prevalence of anxiety, we investigated whether these findings were unique to the OT group or



characteristic of our sample.<sup>43-45</sup> With respect to history of anxiety, female predominance was also observed in the non-OT group and in the overall cohort, suggesting that this finding is characteristic of the overall sample. This was not the case with history of depression; therefore, our finding that females in the OT group had a higher prevalence of pre-existing depression may reflect a true association between history of depression and post-concussive OT in females, but it may also be a result of the small number of subjects in the OT group. Based on our analysis, there is little evidence of a clinically meaningful connection between these historical factors and post-concussive OT risk. Our secondary analysis of sex differences showed that males with OT tended to be younger than females with OT. While this may be an effect of sample size, this finding has not been described in prior literature and should be further explored. A growing body of literature supports hormone-mediated sex differences in concussion symptoms and recovery.<sup>46-49</sup> In addition, hormonal effects may mediate sex differences in common post-concussion symptoms such as headaches and anxiety disorders.<sup>50,51</sup> Interestingly, a recent proteomic analysis of patients with POTS found sex-specific biomarker signatures, with higher growth hormone levels in females and lower myoglobin levels in males.<sup>52</sup> A more powerful effect of growth hormone on the manifestation of OT in females, compared with males, could explain why more females presented during or after puberty, while males presented at a younger age.

Our analysis showed that patients in the OT group were significantly more likely than those in the non-OT group to have a history of prior concussion. This finding was replicated after exclusion of patients with current use of selected medications; after exclusion of patients <12 years in age, the trend persisted, but the difference was not significant. More broadly, history of concussion or repetitive head impact may increase risk for autonomic dysfunction. Changes in cerebrovascular reactivity have been linked to head impact burden in competitive boxers, and single seasons of play in a contact sport have been linked to disruptions of cerebrovascular autoregulation, decreased HRV, and alterations of resting-state functional magnetic resonance imaging connectivity within the central autonomic network.<sup>4,53-57</sup> In some of these same datasets, however, history of concussion was not linked with the magnitude or persistence of observed effects, and at least one recent study found minimal changes in cerebrovascular measures over the course of a single season of contact sports.<sup>58,59</sup> This remains an open question and an exciting area of investigation.

There are several important limitations to our study. The present study is retrospective and was conducted on a sample taken from a specialty clinic serving a less acute and more refractory population of concussion patients. Limitations of the data elements that could be captured from chart review prevented analysis of several relevant questions, such as whether post-concussive OT is more common in athletes vs. non-athletes. Given the potential role of deconditioning in the pathophysiology of post-concussive OT, this question should be considered in future studies. In addition, our symptom measures

included multiple symptom checklists, one of which (PCSI 8-12) had to be scaled for comparison. We were careful to compare only symptoms represented on all checklists but recognize that small differences in wording and different scales may have affected subjects' (or their caregivers') interpretations. The modified AST used in this study differs from the more widely used protocol, during which the patient lies supine for 5 minutes and then actively stands for  $\geq 5$  minutes. Use of a modified AST may have affected our results and limits the conclusions that we draw from them. The diagnostic method used to identify OT differed from the standardized approach used to diagnose autonomic disorders in clinical or research settings. Specifically, we measured vital signs supine, sitting for 2 minutes and standing for 2 minutes, which differs from the 10-minute stand test validated for the diagnosis of POTSa.<sup>39</sup> We acknowledge that previous studies have shown that some patients may display a characteristic spike in heart rate after 2-4 minutes of standing, so our short monitoring period and inclusion of the sitting position may have biased our prevalence estimate toward underestimation of the true rate of post-concussive OT in our sample. Finally, without a control group, it is difficult to determine the degree to which concussion explains the observed prevalence of OT. A prospective follow-up study would be strengthened by inclusion of an appropriate control group.

## Conclusions

In this study's large sample of patients, OT was found in 7% of children and young adults presenting for concussion evaluation. Given the absence of a telltale clinical profile for this subpopulation, clinicians may consider screening for OT in all patients presenting for concussion evaluation. Identification of OT in post-concussion patients opens the opportunity for targeted interventions including increasing hydration and salt intake, compression garments, graded exercise programs, pharmacotherapy, and behavioral therapies.<sup>18,60</sup> Furthermore, some medications that are commonly used to treat post-concussion symptoms like migraine (eg, tricyclic antidepressants) may worsen OT, so providers should consider the possibility of post-concussive OT before deciding on a course for management. Similarly, graded exercise protocols, which are commonly prescribed after concussion, may need to be adjusted in patients exhibiting post-concussive OT.<sup>60,61</sup> Although the mechanism, clinical course, and clinical significance are not yet clear, our findings justify further prospective studies of post-concussive OT.

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## Ethical Approval

Ethical approval was obtained from the UCLA Institutional Review Board (IRB #11-001760) as part of a larger study, "Acute Monitoring and Long-term Outcomes Following Traumatic Brain Injury or Concussion."

## Informed Consent

Written informed consent was obtained from the patients or their legal representatives for anonymized patient information to be published in this article.

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## Trial Registration

Not applicable, because this article does not contain any clinical trials.

## Supplemental material

Supplemental material for this article is available online.

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