

## Research Paper

# Orthostatic Tachycardia in Children With and Without Persisting Post-concussion Symptoms Following Mild Traumatic Brain Injury: A Prospective Controlled Study



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## ABSTRACT

**Background:** Twenty five percent of children who sustain a mild traumatic brain injury (mTBI) or concussion experience persisting post-concussion symptoms (PPCS). The symptoms of PPCS significantly overlap with postural orthostatic tachycardia syndrome (POTS). We aimed to review the literature and investigate the prevalence of POTS in children and adolescents recovering from mTBI.

**Methods:** This single centre controlled cross-sectional cohort study recruited children (aged 8–18 years inclusive) diagnosed with mTBI in the emergency department. At 4–6 weeks postinjury, children completed the Active Stand Test. The primary outcome was change in heart rate alongside clinical symptoms consistent with POTS.

**Results:** A total of 113 participants (64 PPCS, 24 mTBI with no clinical symptoms [asymptomatic], and 25 healthy controls) of similar age (mean 13.9 years) and sex ( $n = 55$  [48.7%] male) underwent orthostatic testing. There were no significant group differences in heart rate or blood pressure at baseline, or within 10 minutes of standing. Three (4.8%) symptomatic participants satisfied POTS diagnostic criteria, compared to zero asymptomatic and one (4.2%) control participant.

**Conclusions:** Using the Active Stand Test, a small proportion of children with PPCS satisfied clinical POTS criteria. Although it should be considered in the differential diagnosis, POTS is not common nor over-represented in PPCS.

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## Introduction

Mild traumatic brain injury (mTBI) is common amongst youth, occurring in one in five children before the age of sixteen.<sup>1</sup> Following injury, patients commonly experience somatic, cognitive, affective and sleep-related symptoms which can persist for several months.<sup>2</sup> In 25% of children, symptoms last longer than 4 weeks,<sup>2,3</sup> described as persisting post-concussion symptoms (PPCS).<sup>1,2</sup> Risk factors for PPCS in children and adolescence include female sex, older age, previous concussion where symptoms have

lasted longer than 7 days, migraine, and premorbid psychosocial factors.<sup>3,4</sup> PPCS can be described by several phenotypes with varying predominant symptoms. These phenotypes include migraine-like post-traumatic headache, cervico-vestibular, cognitive, and affective symptoms, as well as symptoms of autonomic dysfunction including postural orthostatic tachycardia syndrome (POTS).<sup>5–7</sup>

POTS is a type of sympathetic dysfunction characterized by dizziness or light-headedness that occurs on standing and often presents in adolescence.<sup>8</sup> Often seen in Ehlers-Danlos syndrome,<sup>9</sup> it can also be precipitated by noncranial trauma, surgery or viral illness<sup>10,11</sup> and is most common in Caucasian adolescent females.<sup>11</sup> Some studies have suggested a relationship between traumatic brain injury (TBI)/concussion and onset of POTS,<sup>2</sup> where injury to cortical and subcortical regions of the brain may result in autonomic nervous system dysregulation, leading to orthostatic symptoms seen in POTS.<sup>12,13</sup> Although its pathophysiology is not completely understood, POTS results in pooling of blood in the

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legs, increased heart rate (HR), and decreased cerebral perfusion,<sup>14</sup> resulting in orthostatic intolerance (OI). Furthermore, autonomic dysregulation may cause reductions in cerebral blood flow, resulting in difficulty to complete exercise at maximum intensity.<sup>15</sup> Symptoms of POTS are highly variable and systemic, affecting cardiovascular, gastrointestinal, and neurological systems.<sup>11</sup> The most common of these symptoms are dizziness, light-headedness, palpitations, presyncope, and syncope,<sup>9,11,16</sup> which are commonly seen in PPCS.<sup>2</sup>

There are several methods used to diagnose POTS. The gold standard method employs the Head Up Tilt (HUT) test.<sup>17,18</sup> In the HUT, patients lie securely on a tilt table in the supine position for at least 5 min and are then tilted upright to an angle of 60–70°, during which HR and blood pressure (BP) are monitored. The HUT, however, is limited by its cost, availability, need for specialized equipment, and long testing time. In addition, the HUT is often poorly tolerated and associated with discomfort and stress.<sup>19</sup> Therefore, tests which can be performed at the bedside may be a more practical alternative. One such alternative is the Active Stand Test (AST).<sup>20,21</sup> The AST measures the 'skeletal muscle pump' physiological response, where the body compresses and releases pressure on the veins of the lower limbs, forcing blood to return to the heart.<sup>20,21</sup> Here, participants must lie down for 10 minutes to ensure cardiovascular stabilization, followed by standing as quickly as possible during inspiration.<sup>20</sup> HR and BP are measured immediately before and at several timepoints after participants stand upright. Recent evidence indicates that the AST may provide a more accurate diagnosis of POTS compared to the HUT.<sup>21</sup> While both tests show similar sensitivity (87% for AST and 93% for HUT), the AST demonstrates a higher specificity (67% for AST vs 40% for HUT)<sup>21</sup>; although these values may vary depending on diagnostic criteria used.<sup>22–24</sup>

Generally, the diagnostic criteria for POTS in adulthood include an increase in average HR  $\geq 30$  bpm or maximum HR  $\geq 120$  bpm within 10 minutes of standing without a significant decrease in systolic BP  $>20$  mmHg<sup>25</sup>, alongside clinical orthostatic symptoms such as light headedness, dizziness, fatigue or weakness, headache, and blurred or dimmed vision, which must improve on recumbency.<sup>14,21,23</sup> However, the temporal relationship and duration of these symptoms are not well defined, where some studies specify observation of orthostatic symptoms during the provoking test, but others state that symptoms must be chronic (i.e., lasting more than 3 months) but not necessarily observed during the test.<sup>16,26</sup>

Alternative diagnostic criteria are required for children due to differences in autonomic responses arising from ongoing nervous system development. Children have relatively immature cardiovascular systems, characterized by a smaller stroke volume, thinner vessel walls, larger vessel diameters, and incomplete nervous system regulation,<sup>27</sup> which results in relatively high levels of sympathetic input,<sup>23</sup> and therefore higher basal HRs and greater orthostatic HR variation.<sup>16,23,28,29</sup> In children, change in HR when moving from supine to upright positions is greater than in adults, with normal 95 percentile ranges from approximately 35–50 bpm.<sup>23,30,31</sup> These differences must be taken into account for an accurate diagnosis of POTS in children, although the literature is varied (Table 1). General consensus on the suggested criteria for POTS diagnosis in children is a HR increase  $\geq 40$  bpm or absolute HR  $\geq 130$  bpm for children aged  $\leq 12$  years ( $\geq 120$  bpm in children aged 13–18 years) within the first 10 minutes of testing, without a drop  $\geq 20$  mmHg in systolic BP or  $\geq 10$  mmHg in diastolic BP.<sup>23,41,42</sup>

Correctly diagnosing POTS in the context of PPCS following mTBI has important treatment implications. Previous research has suggested distinct prognoses for children with POTS or PPCS who display signs of syncope or presyncope (e.g., light-headedness)<sup>16</sup>;

however, further research is needed to understand the distinction between OI as a persisting symptom following pediatric mTBI, and POTS.<sup>16</sup> In this study, we aimed to investigate the prevalence of POTS in children and adolescents recovering from mTBI using the AST. We hypothesized that, following mTBI, a proportion of children diagnosed with PPCS would satisfy criteria for POTS and that this would be overrepresented in symptomatic children compared to children who had clinically recovered following mTBI (asymptomatic) and healthy children.

## Materials and Methods

### Design

This study was conducted in the context of a prospective controlled cohort study of children aged between 8 and 18 years (inclusive) with mTBI diagnosed in the emergency department of the Alberta Children's Hospital, involving children who were recruited as part of the PLAYGAME Trial,<sup>43</sup> a randomized controlled trial investigating the efficacy of melatonin as a treatment for PPCS. The current study includes only baseline data and participants were not on any trial medication. Ethical approval was obtained from the University of Calgary (REB13-0372) and University of Queensland (2017001523) Ethical Review Boards, standards of Good Clinical Practice standards were observed, and the Consolidated Standards of Reporting Trials guidelines were followed including registration at [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT01874847). All children gave written assent, and a parent/caregiver gave written consent for study participation.

### Participants

Children and adolescents with mTBI were screened for eligibility in the emergency department into the study and permission to contact families at 4–6 weeks postinjury was obtained. Mild TBI was defined as an impact to the head or body with a Glasgow Coma Score  $> 13$ , resulting in at least one of the following: an observed loss of consciousness  $<30$  minutes or at least one acute symptom suggesting neurological dysfunction attributable to the injury.<sup>1</sup> Concussion was considered as part of the mTBI spectrum.<sup>44</sup> Exclusion criteria included assault, suspected child abuse, alcohol or drug use at the time of injury, significant past medical or psychiatric history (e.g., inflammatory bowel disease, rheumatological disease, depression or anxiety under the care of a psychiatrist or psychologist; however, attention deficit hyperactivity disorder or headache disorders were not excluded), marked language barrier, a previous mTBI within the last 3 months, failure to recover from a previous mTBI (as determined by the family at screening and confirmed during the clinical assessment), and the use of medications that could affect sleep or BP (e.g., melatonin, amitriptyline, benzodiazepine, steroids, selective serotonin uptake inhibitors etc.). Participants with hypertension at baseline (defined as BP above the 99th percentile) or a positive pregnancy test were excluded.<sup>45</sup>

Details of the study process is shown in Fig 1. Recovery trajectory at 4 to 6 weeks postinjury was determined using the Postconcussion Symptom Inventory (PCSI). The PCSI is a validated age-appropriate, standardized questionnaire that consists of 26 symptom scores with four domains (physical, cognitive, emotional, and sleep/fatigue) and provides an overall rating of concussive symptoms.<sup>2,37</sup> Preinjury PCSI scores were retrospectively obtained at the initial visit (baseline). Children were considered to be symptomatic (i.e., show persisting post-concussion symptoms [PPCSs]) if they reported a two-point increase in two or more symptoms (nonsleep related), or a ten-point

**TABLE 1.**

The Various Physiological Diagnostic Criteria for Orthostatic Intolerance and Postural Orthostatic Tachycardia Syndrome in Pediatric Studies

| Author(s)                           | n (Population)                 | Mean Age, years (Range) | POTS Test (Duration)  | Time of Outcome | ΔHR                                        | Max HR                                            | Orthostatic Symptoms Definition                                                                                                                                                                                                                                                         |
|-------------------------------------|--------------------------------|-------------------------|-----------------------|-----------------|--------------------------------------------|---------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Zhao et al. 2015 <sup>25</sup>      | 1449 (HC)                      | 12.0 (6–18)             | AST (10 min)          | 3, 6, 9 min     | ≥38                                        | ≥130 bpm if 6–12 years<br>≥125 bpm if 13–18 years | Light-headedness, headache, fatigue, long breath, vertigo, blurred vision, or palpitations observed during the test.                                                                                                                                                                    |
| Singer et al. 2012 <sup>27</sup>    | 106 (HC)<br>654 (OI symptoms)  | 15.0 (8–19)             | HUT (10 min)          | One, 5, 10 min  | ≥40                                        | ≥130 bpm if ≤ 13 years<br>≥120 bpm if ≥ 14 years  | Orthostatic intolerance symptoms such as light-headedness, palpitations, occurring frequently (>50% of the time) when assuming upright position.                                                                                                                                        |
| Boris et al. 2020 <sup>12</sup>     | 708 (POTS diagnosis)           | 15.7 (6–18)             | AST (10 min)          | 3 min           | ≥30                                        | -                                                 | Not specified, noted at any time retrospectively                                                                                                                                                                                                                                        |
| Lin et al. 2014 <sup>32</sup>       | 600 (HC)                       | 11.9 (7–18)             | AST (10 min)          | Within 10 min   | ≥40                                        | >120bpm                                           | At least one of the following symptoms during the 10 minutes standing: dizziness or fainting, chest tightness, headache, palpitations, blurred vision, fatigue; or syncope for at least 3 months                                                                                        |
| Pearson et al. 2022 <sup>33</sup>   | 268 (mTBI/concussion)          | 16 (8–25)               | AST (2 min)           | 2 min           | ≥40 if ≤ 19 years<br>≥30 bpm if > 19 years | >120bpm                                           | None mentioned                                                                                                                                                                                                                                                                          |
| Chan et al. 2022 <sup>34</sup>      | 204 (PANS)                     | 10.7 (7–17)             | HUT or AST (5–10 min) | Within 10 min   | ≥40                                        | ≥130 bpm if ≤ 13 years<br>≥120 bpm if ≥ 14 years  | Light-headedness or palpitations occurring frequently when assuming the upright position                                                                                                                                                                                                |
| Lin et al. 2015 <sup>22</sup>       | 174 (unexplained syncope)      | 11.3 (4–18)             | HUT (up to 45 min)    | Within 45 min   | ≥30                                        | >120bpm                                           | At least one of the following during standing: dizziness or fainting, chest tightness, headache, palpitations, blurred vision, fatigue or syncope                                                                                                                                       |
| Li et al. 2014 <sup>35</sup>        | 131 (POTS diagnosis)           | 11.2 (5–18)             | HUT (10 min)          | Within 10 min   | ≥40                                        | ≥120bpm                                           | Symptoms of orthostatic intolerance including dizziness, weakness, palpitations, pale face, blurred vision, short of breath, syncope, gastrointestinal symptoms, or headache developing on standing or after HUT and resolving with recumbency and should occur repeatedly for ≥1 month |
| Deng et al. 2014 <sup>36</sup>      | 110 (POTS diagnosis)           | 11.9 (6–18)             | HUT (10 min)          | Within 10 min   | ≥30                                        | ≥120bpm                                           | Chronic orthostatic intolerance symptoms, including dizziness, syncope, nausea, palpitations, chest tightness, headache, blurred vision, tremors, cold sweat AND dizziness, vertigo, headache, palpitations, fatigue or blurred vision during HUT                                       |
| Kokorelis et al. 2019 <sup>37</sup> | 82 (PPCS)                      | 15.0 (10–22)            | AST (10 min)          | 10 min          | ≥40                                        | >120 bpm                                          | At least one symptom of orthostatic intolerance.                                                                                                                                                                                                                                        |
| Li et al. 2016 <sup>26</sup>        | 32 (HC)<br>45 (POTS diagnosis) | 12.2 (NA)               | HUT (up to 45 min)    | Within 45 min   | ≥40                                        | ≥120bpm                                           | Dizziness and headache, amaurosis, palpitation, nausea, blurred vision and even syncope in severe cases, with orthostatic intolerance symptoms lasting for at least 3 months AND corresponding with HR changes                                                                          |
| Heyer et al. 2013 <sup>38</sup>     | 70 (OI symptoms)               | 15.3 (11–19)            | HUT (10–45 min)       | Within 10 min   | ≥30                                        | >120bpm                                           | Light-headedness, headache, dimming or blurring of vision, fatigue, diaphoresis, or confusion corresponding with HR changes.                                                                                                                                                            |
| Cai et al. 2021 <sup>39</sup>       | 78 (OI symptoms)               | 12.0 (9–16)             | HUT and AST (10 min)  | Within 10 min   | ≥40                                        | ≥130 bpm if ≤ 12 years<br>≥125 bpm if 13–18 years | The presence of chronic OI symptoms (e.g., fatigue, headache, light-headedness, blurring of vision, palpitations, tremulousness, and even syncope)                                                                                                                                      |
| Zhang et al. 2014 <sup>40</sup>     | 37 (POTS diagnosis)            | 11.04 (6–15)            | HUT (10 min)          | Within 10 min   | ≥40                                        | Sustained rate of 120 bpm in the first 10 min     | None specified.                                                                                                                                                                                                                                                                         |
| Heyer et al. 2016 <sup>18</sup>     | 34 (PPCS)                      | 16.0 (13–18)            | HUT (10 min)          | 5, 10 min       | ≥30                                        | >120bpm                                           | Light-headedness and at least one of headache, dimming or blurring of vision, nausea, fatigue, diaphoresis or confusion corresponding with HR changes.                                                                                                                                  |

## Abbreviations:

Δ = Change

AST = Active Stand Test

bpm = Beats per minute

HC = Healthy control

HR = Heart rate

HUT = Head Up Tilt

mTBI = Mild traumatic brain injury

OI = Orthostatic intolerance

PANS = Pediatric acute-onset neuropsychiatric syndrome

POTS = Postural orthostatic tachycardia syndrome

PPCS = Postconcussion symptom

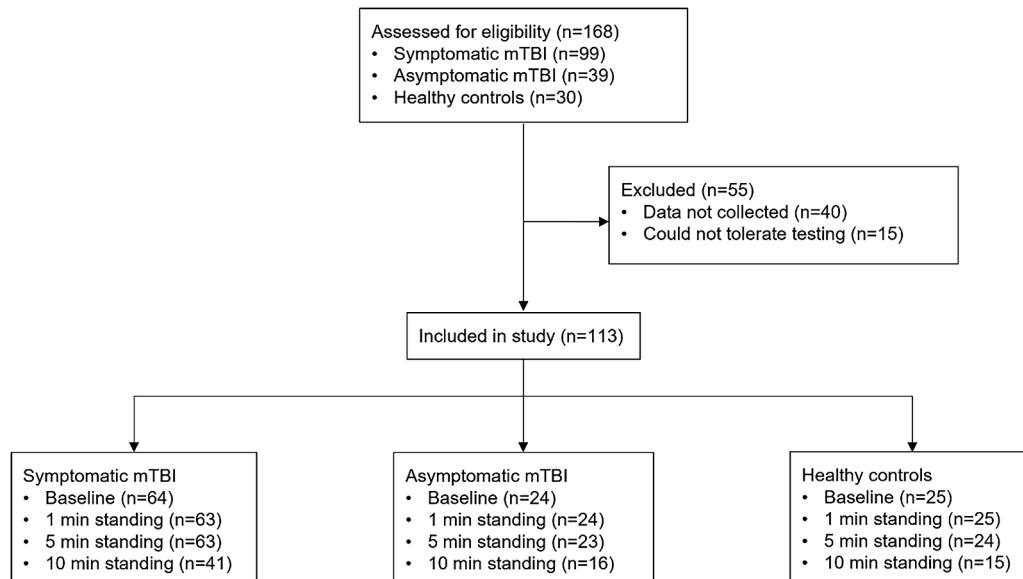


**FIGURE 1.** Consolidated Standards of Reporting Trials (CONSORT) study flow diagram. mTBI = Mild traumatic brain injury

increase in total PCSI score compared to preinjury scores and a score  $\geq 1$  to the PCSI question 'In general, to what degree do you feel "differently" than before the injury (rated from "0" no difference to "4" major difference)?'.<sup>46</sup> Participants were considered as recovered (i.e., asymptomatic) if there was no increase in symptoms compared to their preinjury score, a score of zero on the "feeling different" question, and if they had returned to normal activities.<sup>47</sup> All female participants had urinary pregnancy testing performed. Healthy controls (without a history of TBI) were recruited from friends and siblings of mTBI participants and the same exclusion criteria applied.

#### Orthostatic testing procedures

At 4–6 weeks postinjury, all children were clinically evaluated by a clinician experienced in mTBI/concussion assessment before undergoing the AST. Participants were asked to lie supine and motionless on a bed in a quiet environment for at least 20 minutes before the test.<sup>19,23</sup> Parents and staff were asked to remain silent and to stand away from the participant before or during the standing test to allow the participants to be relaxed and in a state of ease before standing. Measurements were conducted in a quiet room and participants were asked to refrain from unnecessary talking. BP and HR were measured using a digital Welch Allyn vital signs monitor. Measurements were taken after lying supine for 20 min, and then after standing without support for one, 5, and 10 minutes. These time periods were chosen due to the inconsistencies in the literature regarding the necessary length of time the participant should be supine and standing, and if movement should be permitted while supine.<sup>48</sup> During the testing, participants were questioned about any dizziness or lightheadedness on standing, and participants could terminate the test at any time or if they experienced any presyncopal symptoms (e.g., light headedness, faintness, or marked dizziness).

#### Outcomes

The primary outcome was change in HR at 5 min and 10 min<sup>19,23</sup> alongside clinical OI symptoms consistent with POTS diagnosis reported during testing according to the 2015 Heart

Rhythm Society Expert Consensus Statement,<sup>42</sup> i.e., an increase in HR of  $\geq 40$  bpm when moving from recumbent to standing position or absolute HR of  $\geq 120$  bpm ( $\geq 130$  bpm if  $< 12$  years) with the absence of orthostatic hypotension ( $> 20$  mm Hg drop in systolic BP) in addition to one of the following clinical symptoms: lightheadedness, palpitations, tremor, generalized weakness, blurred vision, exercise intolerance, and fatigue.

Secondary outcomes were changes in mean arterial pressure and clinical criteria for orthostatic hypotension and health-related quality of life. To assess perceived quality of life of the child and their family, the Child Health Questionnaire (CHQ)<sup>49</sup> was completed by both the parent and child. The CHQ is designed to capture the physical and psychosocial wellbeing of children 5 years of age or older, and consists of 50 items, taking into account the past 4-week period. Scores are transformed onto a scale of 0 to 100, with a higher score indicating better functioning and wellbeing. Postconcussion Symptom Inventory scores recorded at 28 days postinjury were used to categorize patients as symptomatic or asymptomatic. The PCSI<sup>37</sup> is a 26-item questionnaire (child and parent versions) requiring a child to rate their symptoms on a scale of 0–6. Along with current symptoms, a retrospective set of questions from before the injury were completed to determine a preinjury PCSI score.

#### Statistical analysis

Demographic and clinical characteristics were compared between groups using parametric (analysis of variance and Students t-tests) and nonparametric tests (Kruskal-Wallis test and Mann-Whitney U-Test) where data normality was violated. Analysis of group proportions was performed using the Chi-squared or Fisher's exact tests. Statistical analysis was performed using IBM SPSS (version 28; IBM SPSS Inc, Chicago, IL).

## Results

#### Participant demographics

A total of 168 participants were assessed for eligibility and 113 participants underwent orthostatic assessment (25 controls, 24

asymptomatic participants, 64 symptomatic participants; Fig 1). Participants who underwent orthostatic testing did not differ in age ( $t = -0.75$ ,  $P = 0.2$ ), sex ( $\chi^2 = 0.4$ ,  $P = 0.8$ ) or body mass index ( $t = 0.59$ ,  $P = 0.4$ ) from those without orthostatic testing. Demographics and injury details of the patients who underwent orthostatic testing are shown in Table 2. Groups (symptomatic, asymptomatic and healthy controls) did not statistically differ in age (mean 13.86, S.D. 2.64 years;  $F = 0.03$ ,  $P = 0.97$ ), sex ( $n = 55$ , 48.7% male;  $\chi^2 = 3.27$ ,  $P = 0.20$ ), body mass index (mean 20.66, S.D. 4.45;  $F = 0.39$ ,  $P = 0.68$ ), or family income (median CAD\$116,717, interquartile range 50,765; Kruskal-Wallis = 2.91,  $P = 0.23$ ). A significantly greater number of symptomatic participants reported one or more previous concussions (46.1% in symptomatic, compared to 16.7% in asymptomatic;  $\chi^2 = 12.30$ ,  $P = 0.18$ ), as well as the presence of OI symptoms (52% of symptomatic participants, 13% of asymptomatic participants and 44% of controls;  $\chi^2 = 33.3$ ,  $P < 0.001$ ). The majority of participants were injured while playing sports (75.0% in both asymptomatic and symptomatic participants).

Child-rated PCSI and CHQ scores are presented in Table 2. PCSI scores were significantly different across groups at preinjury and postinjury timepoints. Child-rated CHQ scores differed significantly across groups in all domains except for Global Health and Change in Health (Table 2). Comparing sport-related mTBI/concussion with all other causes of mTBI, there were no differences between groups in any CHQ domain scores, or in preinjury or postinjury child-rated PCSI scores (preinjury PCSI: sport median 3.0, 95% confidence interval [CI] 4.7–9.6 vs nonsport median 3.5, 95% CI 3.5–11.8,  $U = 734$ ,  $P = 0.98$ ; postinjury PCSI: sport median 27.0, 95% CI 25.2–37.4, nonsport median 37.0, 95% CI 25.1–60.4,  $U = 670.5$ ,  $P = 0.53$ ).

### Changes in HR after one, 5, and 10 minutes of standing

There were no significant differences in HR or mean arterial pressure across the groups at baseline, or one min, 5 min, and 10 min of standing (see Table 3). At baseline, symptomatic participants displayed an average HR of 71 bpm (95% CI, 68–74), compared to 73 bpm (68–78) in the asymptomatic group and 74 bpm (68–80) in the control group ( $F = 0.75$ ,  $P = 0.5$ ). After 5 minutes of standing, average HR had increased by 21 bpm (18–24) in symptomatic participants, 19 bpm (13–24) in asymptomatic participants and 16 bpm (10–21) in controls (Fig 2). After 10 minutes of standing, average HR had increased by 18 bpm (14–21) in the symptomatic group, compared to 24 bpm in the asymptomatic group (17–30) and 18 bpm (10–26) in the control group compared to baseline. Although at one, 5, and 10 minutes of standing a greater number of participants in the symptomatic group developed a change in HR  $\geq 40$  bpm compared to the asymptomatic and control groups (Table 3), this difference did not reach significance across groups.

There were no significant differences in the proportion of participants across groups who satisfied various element of the POTS diagnostic criteria (Table 4). By the 10-minute timepoint, 5 (7.9%) symptomatic participants, one (4.3%) asymptomatic, and one (4.2%) control participant satisfied physiological criteria for POTS. Three (4.8%) symptomatic and one (4.2%) asymptomatic participant reported OI symptoms during testing (Table 5). Overall, only 3 (4.8%) symptomatic participants and one (4.2%) control participant satisfied both physiological and clinical symptoms of POTS (including either chronic or provoked OI symptoms). All three of the symptomatic participants who met POTS diagnosis criteria had sustained a sports-related injury. These participants continued to

**TABLE 2.**  
Baseline Demographics of Study Participants

| Total n = 113                               | Controls n = 25  | Asymptomatic n = 24 | Symptomatic n = 64 | Test Statistic                   |
|---------------------------------------------|------------------|---------------------|--------------------|----------------------------------|
| Age (years) mean $\pm$ S.D.                 | 13.61 $\pm$ 3.2  | 13.78 $\pm$ 2.7     | 13.87 $\pm$ 2.58   | $F = 0.03$ , $P = 0.97$          |
| Males n, (%)                                | 13 (52.0)        | 15 (62.5)           | 27 (41.5)          | $\chi^2 = 3.27$ , $P = 0.20$     |
| BMI mean $\pm$ S.D.                         | 21.36 $\pm$ 4.0  | 20.69 $\pm$ 2.9     | 20.39 $\pm$ 5.1    | $F = 0.39$ , $P = 0.68$          |
| Family income (CAD) median (IQR)            | 117,492 (39,424) | 112,646 (31,900)    | 118,859 (65,662)   | KW = 2.91, $P = 0.23$            |
| Previous concussion(s) n, (%)               |                  |                     |                    | $\chi^2 = 12.29$ , $P = 0.018^*$ |
| One concussion                              | NA               | 1 (4.2)             | 19 (29.2)          |                                  |
| 2 concussions                               | NA               | 2 (8.3)             | 5 (7.7)            |                                  |
| 3+ concussions                              | NA               | 1 (4.2)             | 6 (9.2)            |                                  |
| Mechanism of injury n, (%)                  |                  |                     |                    | $\chi^2 = 13.80$ , $P = 0.18$    |
| Sports                                      | NA               | 18 (75.0)           | 49 (75.4)          | $\chi^2 = 0.00$ , $P = 1.00$     |
| Fall                                        | NA               | 3 (12.5)            | 10 (15.4)          |                                  |
| Motor vehicle accident                      | NA               | 1 (4.2)             | 4 (6.2)            |                                  |
| Other                                       | NA               | 2 (8.3)             | 2 (3.1)            |                                  |
| Loss of consciousness n, (%)                | NA               | 5 (13.8)            | 15 (15.3)          | $\chi^2 = 0.29$ , $P = 0.72$     |
| Days since injury mean $\pm$ S.D.           | NA               | 39.67 $\pm$ 10.1    | 37.06 $\pm$ 6.8    | $t = 1.45$ , $P = 0.15$          |
| PCSI (child report, preinjury) median, IQR  | 3.0 (7.0)        | 0.0 (2.5)           | 5.0 (12.5)         | KW = 16.6, $P < 0.001^\dagger$   |
| PCSI (child report, postinjury) median, IQR | NA               | 4.0 (10.0)          | 38.0 (42.0)        | $U = 1381$ , $P < 0.001^\dagger$ |
| CHQ (child report) mean $\pm$ S.D.          |                  |                     |                    |                                  |
| Global health                               | 88.13 $\pm$ 17.1 | 84.13 $\pm$ 20.4    | 76.77 $\pm$ 25.2   | $F = 2.50$ , $P = 0.09$          |
| Physical functioning                        | 93.96 $\pm$ 6.3  | 92.11 $\pm$ 11.7    | 73.96 $\pm$ 22.9   | $F = 16.9$ , $P < 0.001^\dagger$ |
| Role/social limitations                     | 98.14 $\pm$ 5.4  | 88.41 $\pm$ 16.9    | 62.72 $\pm$ 37.5   | $F = 15.0$ , $P < 0.001^\dagger$ |
| Bodily pain                                 | 77.50 $\pm$ 24.2 | 72.6 $\pm$ 16.8     | 48.06 $\pm$ 29.9   | $F = 14.2$ , $P < 0.001^\dagger$ |
| General health perception                   | 76.84 $\pm$ 16.2 | 74.78 $\pm$ 11.7    | 66.73 $\pm$ 16.7   | $F = 4.60$ , $P = 0.01^*$        |
| Change in health                            | 3.58 $\pm$ 0.8   | 3.78 $\pm$ 0.9      | 3.36 $\pm$ 1.2     | $F = 1.50$ , $P = 0.23$          |

#### Abbreviations:

BMI = Body mass index

CAD = Canadian Dollars

CHQ = Child Health Questionnaire

IQR = Interquartile range.

KW = Kruskal-Wallis

mTBI = Mild traumatic brain injury

PCSI = Postconcussion Symptom Inventory

\* Indicates  $P < 0.05$ .

† Indicates  $P < 0.001$ .

**TABLE 3.**  
Changes in HR and MAP After One, 5, and 10 Minutes

| Variable                          | Controls          | Asymptomatic      | Symptomatic       | Test Statistic     |
|-----------------------------------|-------------------|-------------------|-------------------|--------------------|
| Mean baseline HR, bpm (95% CI)    | 73.92 (68.1–79.8) | 73.13 (67.9–78.4) | 70.73 (67.9–73.6) | F = 0.75, P = 0.47 |
| Mean baseline MAP, mm Hg (95% CI) | 84.83 (79.8–89.8) | 82.51 (79.6–85.5) | 81.95 (79.5–84.1) | F = 0.83, P = 0.44 |
| Mean $\Delta$ HR, bpm (95% CI)    |                   |                   |                   |                    |
| 1 min                             | 15.20 (10.3–20.1) | 19.46 (13.9–25.0) | 20.08 (17.2–23.0) | F = 1.55, P = 0.22 |
| 5 min                             | 15.75 (10.1–21.4) | 18.83 (13.3–24.4) | 21.03 (18.0–24.0) | F = 1.59, P = 0.21 |
| 10 min                            | 18.00 (10.0–26.0) | 23.50 (16.6–30.4) | 17.61 (13.9–21.4) | F = 1.30, P = 0.28 |
| Mean $\Delta$ MAP, mm Hg (95% CI) |                   |                   |                   |                    |
| 1 min                             | 5.05 (2.0–8.1)    | 5.35 (2.4–8.3)    | 4.68 (2.3–7.1)    | F = 0.06, P = 0.94 |
| 5 min                             | 3.49 (–0.3–7.3)   | 3.99 (0.9–7.1)    | 3.32 (1.0–5.6)    | F = 0.05, P = 0.95 |
| 10 min                            | 3.07 (–1.6–7.7)   | 5.33 (1.1–9.6)    | 6.07 (2.2–9.9)    | F = 0.42, P = 0.66 |

Abbreviations:

$\Delta$  = Change in

95% CI = 95% Confidence interval

bpm = Beats per minute

HR = Heart rate

MAP = Mean arterial pressure

mm Hg = Millimeters of mercury

See Consolidated Standards of Reporting Trials (CONSORT) diagram for number of participants at each timepoint.

gradually increase activity and exercise and were asymptomatic 4 weeks later with normal AST results. Notably, upon clinical review, one participant who developed symptoms during testing had onset of a migraine attack. An additional symptomatic participant with OI symptoms consistent with POTS diagnosis showed borderline physiological changes (38 bpm increase in HR, 129bpm max HR).

## Discussion

Autonomic dysfunction is a recognized symptom following TBI, where previous literature has reported changes in HR variability<sup>50</sup> and cerebral blood flow<sup>51</sup> in adults with acute concussion. Autonomic dysfunction during the acute phases of TBI is thought to result from injury to areas of the brain important in autonomic control, including the anterior temporal, insular, orbitofrontal, and hypothalamic regions,<sup>52</sup> although the mechanisms following mTBI are unclear. Despite important treatment implications, there is limited research in this area following pediatric mTBI.<sup>16,33,53</sup>

This is the only study to date that investigates the prevalence of POTS in a previously healthy population of children and adolescents relative to their recovery at 4 weeks following a mild TBI. Our hypothesis was not upheld as we found no difference in provoked physiological changes during the AST following mTBI compared to healthy controls, nor did we find a significantly increased prevalence of POTS in children with PPCS. Although the tolerability of the AST was similar across children with PPCS, asymptomatic children, and healthy controls, only four children developed OI during testing: two children with PPCS whose testing was suspicious for POTS, one child with an onset of a migraine attack, and another child who developed orthostatic hypotension. All children with either orthostatic tachycardia or POTS had normal testing one month later. Our data suggest that, although POTS and OI can occur following mTBI, dysautonomia is unlikely to explain symptom persistence for most children with PPCS.

Previous research has alerted the clinician to the possibility of POTS when symptoms persist after mTBI and concussion;<sup>16,33,53</sup> yet it is unclear as to what degree dysautonomia contributes to

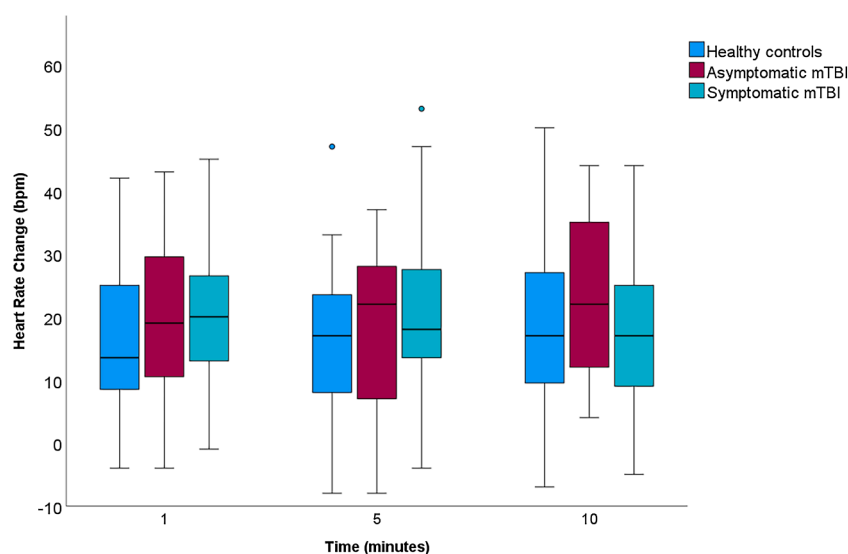


**FIGURE 2.** Change in heart rate in control, asymptomatic and symptomatic groups during Active Stand Test at intervals of one, 5, and 10 minutes. Boxes represent median and IQR (Q1 and Q3), and whiskers extend to largest data point within 1.5 times the IQR above Q3. Blue and green dots represent outliers within 3 times the IQR. bpm = Beats per minute; IQR = Interquartile range. The color version of this figure is available in the online edition.

**TABLE 4.**  
Number of Participants Meeting Elements of POTS Criteria

| Variable                         | Controls | Asymptomatic | Symptomatic | Test Statistic ( $\chi^2$ ) |
|----------------------------------|----------|--------------|-------------|-----------------------------|
| $\Delta$ HR $\geq 30$ bpm, n (%) |          |              |             |                             |
| 5 min                            | 3 (12.5) | 4 (17.4)     | 14 (22.2)   | 1.10, $P = 0.54$            |
| 10 min                           | 3 (20.0) | 6 (37.5)     | 9 (21.2)    | 1.7, $P = 0.47$             |
| $\Delta$ HR $\geq 40$ bpm, n (%) |          |              |             |                             |
| 5 min                            | 1 (4.2)  | 0 (0)        | 4 (6.3)     | 1.50, $P = 0.63$            |
| 10 min                           | 1 (6.7)  | 1 (6.3)      | 2 (4.9)     | 0.86, $P = 1.0$             |
| Max HR <sup>†</sup> , n (%)      |          |              |             |                             |
| 5 min                            | 0 (0)    | 1 (4.3)      | 3 (4.8)     | 1.15, $P = 0.65$            |
| 10 min                           | 0 (0)    | 1 (6.3)      | 0 (0)       | 3.49, $P = 0.44$            |
| OI symptoms during test, n (%)   | 0 (0)    | 1 (6.3)*     | 3 (4.7)     | 1.18, $P = 0.65$            |

Abbreviations:

 $\Delta$  = Change

bpm = Beats per minute

HR = Heart rate

OI = Orthostatic intolerance

PCSI = Postconcussion Symptom Inventory

POTS = Postural orthostatic tachycardia syndrome

See Consolidated Standards of Reporting Trials (CONSORT) diagram for number of participants at each timepoint.

\* Participant had symptoms and signs suggestive of orthostatic hypotension.

† Absolute HR  $\geq 130$  bpm for children aged  $\leq 12$  years, or  $\geq 120$  bpm in children aged 13–18 years.

symptom persistence. We found that a diagnosis of POTS was uncommon in children with PPCS, where 8% of children with PPCS met the physiological criteria of orthostatic tachycardia, which was similar in children who had recovered (4%) and healthy controls without a previous history of concussion (4%). Indeed, only 5% of children with PPCS satisfied POTS criteria (similar to healthy controls, 4%), even though over 50% reported POTS-like symptoms before testing. Our study has significant strengths in that we decreased the likelihood of a false positive test by ensuring cardiovascular stability before the AST (supine position for  $>10$  min) and ensuring a quiet, nonstressful environment for testing. In addition, we decreased the likelihood of false negative test by measuring physiological changes for 10 min following the AST. Our findings are similar to a study by Pearson et al. 2022,<sup>33</sup> where a similar prevalence of orthostatic tachycardia (7%) was reported,

**TABLE 5.**  
Demographics of Participants Who Developed Symptoms of Orthostatic Intolerance During Testing

| Group        | Age (Years) | Sex | Clinical Symptoms (5 min)                           | $\Delta$ HR, Max HR | $\Delta$ BP (mmHg) | Diagnosis               |
|--------------|-------------|-----|-----------------------------------------------------|---------------------|--------------------|-------------------------|
| Symptomatic  | 13.53       | F   | Dizziness, nausea, tinnitus, and migraine-like aura | +26, 109            | +11                | Migraine onset          |
| Symptomatic  | 10.43       | M   | Lightheaded                                         | +38, 129            | −9                 | Possible POTS           |
| Symptomatic  | 15.25       | M   | Dizzy                                               | +47, 107            | −3                 | POTS                    |
| Asymptomatic | 15.21       | M   | Dizzy                                               | +25, 100            | −17                | Orthostatic hypotension |

Abbreviations:

 $\Delta$ BP = Change in mean arterial blood pressure $\Delta$ HR = Change in heart rate

bpm = Beats per minute

mm Hg = Millimeters of mercury

POTS = Postural orthostatic tachycardia syndrome

although this was distinct from POTS and involved several methodological differences including an abbreviated AST (2 minutes supine, 2 minutes standing), a conservative maximum HR criterion of  $\geq 120$  bpm (rather than recommended  $\geq 130$  bpm in pediatric populations<sup>23</sup>), and variable time since injury.

In comparison, our results differ from two previous studies where higher incidences of POTS and OI symptoms were reported. Kokorelis et al. 2020<sup>53</sup> found a higher prevalence of OI symptoms (29%) in a slightly older group of adolescents/young adults with PPCS (median age 15 years; range 10–22). This study used three screening questions for OI symptoms which included the presence of symptoms before concussion, current symptoms, and perceived worsening of motion sickness since concussion. Kokorelis et al. used similar diagnostic criteria and AST protocol to our study, in addition to using screening to identify those potentially at risk of POTS. However, there were important differences which are likely to explain the higher prevalence, such as higher risk of OI due to selection criteria, the slightly older age group, and longer time since injury. Furthermore, the authors also used a maximum HR criterion of  $\geq 120$  bpm for diagnosis which is conservative for the younger participants.<sup>54,55</sup> Nevertheless, the screening criteria used by Kokorelis et al. could be very useful in clinical practice. Another study by Heyer et al. 2016<sup>16</sup> also found a higher prevalence of POTS (41%). Here, the HUT was used to test for POTS in 34 adolescents with PPCS who complained of persistent light-headedness. Although using the adult physiological diagnostic criteria for POTS is likely to have inflated the prevalence of POTS (e.g., 27% in our study had orthostatic tachycardia when using adult criteria), the prevalence of POTS in Heyer et al. may be increased as the HUT enables longer physiological data capture compared to the AST where measurements are not possible after orthostatic symptom onset, which could have been missed in our study.

It was interesting to note that all three symptomatic children diagnosed with POTS in our study had sustained sports-related injuries. Until recently, concussion management guidelines have recommended physical rest until resolution of symptoms.<sup>56</sup> However, as highlighted in Kokorelis et al. 2020,<sup>53</sup> aerobic activity is an important lifestyle management strategy for OI,<sup>57</sup> and cessation of physical activity can lead to decompensation in orthostatic tolerance. It is therefore possible that decreases in aerobic activity in children who previously engaged in sport may contribute to the onset of POTS.

The parallel group design of this study (considering both asymptomatic and symptomatic participants at 4–6 weeks following TBI), observations at a consistent time point postinjury, and multiple physiological measurements are strengths of our study. Although all children with mTBI were recruited in a similar way, we acknowledge that the asymptomatic mTBI group in our study is small and may not reflect the general mTBI pediatric population, and so decreases the power of our study. Furthermore, a number of participants dropped out between the 5 and 10 minute measurements, which was mainly due to logistic requirements in the larger study (i.e., testing being conducted in a hospital setting where participants had many clinical appointments/commitments throughout the day) and was not due to participant symptoms. Overall, this attrition affected our sample size and resulted in poor power at the 10 minute timepoint. Nevertheless, as the orthostatic maximum HR is usually achieved within 5 minutes, it is not likely to have affected our results. We cannot generalize our results to children with significant preinjury medical or psychiatric comorbidity. Hydration status was not assessed before testing but is unlikely to have influenced our results given the low prevalence of significant physiological change. Although the literature supports the use of the AST, it may be that more physiological changes would be apparent if we had used the HUT

test.<sup>16</sup> Moreover, we cannot rule out delayed symptoms of POTS which can occasionally occur after 10 minutes of standing.<sup>21,48</sup> We also did not evaluate other symptoms of autonomic dysfunction such as sweating and gastrointestinal disturbances. Finally, the use of several different HR and BP monitors may have affected our findings although this would have occurred at random as groups were enrolled concurrently.

## Conclusions

Overall, POTS was found to be an uncommon complication following mTBI and although it should be considered, it is unlikely to play a major role in PPCS in general. Orthostatic tachycardia detected by the AST explains symptoms in only a few children with PPCS. Other physiological measures such as HR variability, cerebrovascular reactivity, baroreflex sensitivity, and pupillometry may increase the sensitivity for determining a dysautonomia PPCS phenotype.

## Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## CRediT authorship contribution statement

**Athena Stein:** Writing – review & editing, Writing – original draft, Visualization, Software, Formal analysis, Data curation. **Karen M. Barlow:** Writing – review & editing, Writing – original draft, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

## Declaration of competing interest

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