Higher postural heart rate increments on head-up tilt correlate with younger age but not orthostatic symptoms

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Submitted 8 March 2013; accepted in final form 6 June 2013

Ives CT, Kimpinski K. Higher postural heart rate increments on head-up tilt correlate with younger age but not orthostatic symptoms. J Appl Physiol 115: 525–528, 2013. First published June 13, 2013; doi:10.1152/japplphysiol.00292.2013.—Reports have shown that younger individuals present with higher postural heart rate increments on head-up tilt (HUT). However, a correlation between the degree of heart rate increment and symptoms of orthostatic intolerance has not been determined. The objective of this study was to determine whether higher postural heart rate increments during HUT correlate with symptoms of orthostatic intolerance in healthy subjects. Postural heart rate increment on HUT did not differ between men and women (P = 0.48) but did show a significant decrease by age group (P < 0.0001). There was a significant negative correlation between heart rate increment on HUT and age [r = −0.63 (−0.73, −0.51), r² = 0.400; P < 0.0001]. There was a significant difference with respect to symptoms of orthostatic intolerance by sex (P = 0.03) but not age (P = 0.58). There was no significant correlation between either symptoms of orthostatic intolerance and age [r = −0.13 (−0.31, 0.06), r² = 0.017; P = 0.17] or heart rate increment on HUT and symptoms of orthostatic intolerance [r = 0.15 (−0.04, 0.33), r² = 0.022; P = 0.13]. The results demonstrate that higher postural heart rate increments in younger individuals do not result in an increase in orthostatic intolerance. This highlights the potential need for a reevaluation of the diagnostic criteria for postural orthostatic tachycardia syndrome in younger individuals.

Postural orthostatic tachycardia syndrome; aging; orthostatic intolerance; autonomic nervous system diseases; diagnosis

Orthostatic intolerance is the development of symptoms such as lightheadedness and dizziness during upright standing relieved by recumbency. A subset of individuals can manifest an excessive postural heart rate increase with standing that, when associated with symptoms of orthostasis, is termed postural tachycardia syndrome (POTS). POTS is strictly defined by symptoms of orthostatic intolerance associated with heart rate increments greater than 30 beats/min on head-up tilt (HUT) (10). More severe cases are associated with standing heart rates of greater than 120 beats/min (10). Symptoms related to orthostatic changes most often include lightheadedness, palpitations, and presyncope, with symptom exacerbations often caused by heat or exercise as well as prolonged standing, dehydration, psychological stress, etc. (23). For those individuals who meet the criteria for POTS, or those with milder forms of postural tachycardia, these symptoms can have a significant impact on day-to-day functioning.

POTS is more prevalent in younger individuals and women (2, 10, 13, 23). Recent studies have emphasized the importance of orthostatic disorders including POTS in pediatric and adolescent populations, as these disorders have significant social and health impacts on patients in these age groups (1, 3, 12).

Recent reports have focused on the degree of postural tachycardia in younger individuals. It has become clear that younger individuals more frequently manifest postural tachycardia at levels greater than 30 beats/min with HUT (11, 14). This has brought into question the diagnostic criteria of orthostatic disorders such as POTS and whether higher heart rate increments should be required in younger individuals. Furthermore, orthostatic symptoms can diverge from clinical data, in that patients’ symptoms may improve with continuing postural tachycardia on HUT (4).

The objective of the current manuscript was to determine whether higher postural heart rate increments during HUT correlate with symptoms of orthostatic intolerance.

MATERIALS AND METHODS

Subjects. Subject characteristics are described in Table 1. Subjects included in this study ranged in age from 14 to 76 years. Subjects were reviewed to assure they did not have a history of orthostatic and/or autonomic dysfunction. Preliminary evaluations were performed by a neurologist (KK) and included a neurological exam and nerve conduction studies in the lower extremity to help exclude neuropathy. Further exclusion criteria included one or more of the following: 1) pregnant or lactating women, 2) the presence of another cause of autonomic failure, 3) the presence of failure of other organ systems or systemic illness that can affect autonomic function or the subject’s ability to cooperate (these included dementia, pheochromocytoma, heart failure, hypertension, renal or hepatic disease, severe anemia, alcoholism, malignant neoplasms, hypothyroidism, sympathectomy, or cerebrovascular accidents), 4) concomitant therapy with anticholinergic, alpha- and beta-adrenergic antagonists or other medication which could interfere with testing of autonomic function, and 5) clinically significant coronary artery disease. We did not exclude female subjects taking oral contraceptive pills. Subjects were recruited locally over a 2-yr period, with a total of 120 healthy subjects included in the study. Ethical approval for the study was obtained from the local institutional ethics review board and written informed consent was obtained from each participant prior to study commencement.

Clinical autonomic testing. Standardized autonomic testing was performed as previously described (6, 9) in the Autonomic Disorders Laboratory at Western University, London, Ontario. The quantitative sudomotor axon reflex test (QSART) evaluates the postganglionic sympathetic sudomotor axon using a Q-Sweat device (WR Medical Electronics, Stillwater, MN) and multicompartamental sweat capsules. The resulting sweat response was recorded from four routine sites (forearm, proximal leg, distal leg, and foot). Results were compared with normative data derived from studies on 357 healthy subjects aged 10–83 yr (8). Cardiovagal function was assessed using heart rate response to deep breathing and Valsalva ratio with the results compared with normative data derived from 376 and 425 healthy subjects, respectively, aged 10–83 yr (8). In brief, subjects were asked to

Address for reprint requests and other correspondence: K. Kimpinski, Rm. C7-131, Univ. Hospital, London Health Sciences Centre, 339 Windermere Rd., London, Ontario, Canada, N6A 5A5 (e-mail: kkimpin@uwo.ca).
perform deep breathing cycles using visual cueing (heart rate response to deep breathing) and a Valsalva maneuver by way of forced exhalation (Valsalva ratio). Cardiovascular adrenergic function was evaluated by measuring blood pressure and heart rate responses to Valsalva maneuver and HUT (6, 9).

**Head-up tilt.** Subjects were placed in the supine position for 15 min prior to testing. The subject’s beat-to-beat blood pressure and heart rate responses were measured throughout testing using a BMeye Nexfin device (Amsterdam, The Netherlands) and an ECG device (Model 3000 Cardiac Trigger Monitor, IVY Biomedical Systems, Branford, CT) with ECG electrodes (Ambu Blue Sensor SP, Glen Burnie, MD), respectively. All recordings were made using WR TestWorks software (WR Medical Electronics, Stillwater, MN). Baseline recordings were obtained for a minimum of 1 min. The subject was passively tilted to a 70° angle for a period of 5 min. Afterward, the subject was tilted back down to the supine position for a period of 5 min. Average heart rate was obtained prior to tilt and compared with the maximal heart rate between the 2nd and 5th min of HUT. The line recordings were obtained for a minimum of 1 min. The subject was tilted back down to the supine position for a period of 5 min. Average heart rate was obtained prior to tilt and compared with the maximal heart rate between the 2nd and 5th min of HUT. The postural heart rate increment was then obtained by subtracting the average heart rate in the supine position from the maximal heart rate in the upright position.

**Composite autonomic severity score.** The composite autonomic severity score (CASS) is derived from the autonomic reflex screen as previously described (7). The CASS provides a measure of the severity and distribution of autonomic failure and has been previously validated to quantify autonomic dysfunction on standard autonomic testing (7). The 10-point CASS is divided into three subscores: sudomotor (0–3), cardiovagal (0–3), and adrenergic (0–4). Each score is normalized for the confounding variables of age and sex (8).

**The autonomic symptom profile.** The autonomic symptom profile (ASP) is a validated self-report instrument designed to provide an index of autonomic symptom severity (21). It yields a total score (COMPASS) reflecting overall severity of autonomic symptoms and 11 subscale scores that assess severity of symptoms within the following domains: orthostatic intolerance, sexual failure, bladder dysfunction, diarrhea, gastroparesis, secretomotor dysfunction, syncope, sleep disorder, constipation, vasomotor symptoms, and pupilmotor symptoms. In this study, the orthostatic subscore was used as a measure of orthostatic intolerance. The score ranged from 0 to 40, with higher scores indicative of greater orthostatic intolerance.

**Statistical analyses.** The Pearson’s r correlation coefficient was used to determine significant correlation between variables. As the data were found to be normally distributed, an unpaired t-test was used to compare male and female postural heart rate increments on HUT. The data for each of the other comparisons was non-normally distributed, and thus the Mann Whitney test and Kruskal-Wallis tests were used for two and multiple group comparisons, respectively. A P value of <0.05 was considered statistically significant. All statistical analyses were performed using GraphPad Prism 4.02 (GraphPad Software, San Diego, CA).

### RESULTS

Subject characteristics are presented in Table 1. Low CASS total scores were found for all subjects [0.26(0.50), men [0.29(0.57)] and women [0.24(0.43)], indicative of the absence of significant autonomic dysfunction. Similarly, CASS total scores for subjects aged 14–25 yr [0.08(0.27)], 26–40 yr [0.36(0.49)], 41–75 yr [0.39(0.69)] revealed no significant autonomic dysfunction. The overall and subgroup median scores were consistently 0.

Postural heart rate increment on HUT did not differ between men and women t(118) = 0.71, P = 0.48 (−5.99, 2.82), but did show a significant decrease by age group: H(2) = 47.48, P < 0.0001 (see Table 2). In line with these results, there was a significant negative correlation between heart rate increment on HUT and age [r = −0.63 (−0.73, −0.51), r² = 0.400; P < 0.0001; see Fig. 1]. Conversely, there was a significant difference with respect to symptoms of orthostatic intolerance by sex (U = 1,098, P = 0.03) but not age [H(2) = 1,082, P = 0.58; see Table 2]. As a result, there was no significant correlation between either symptoms of orthostatic intolerance and age [r = −0.13 (−0.31, 0.06), r² = 0.017; P = 0.17] or heart rate increment on HUT and symptoms of orthostatic intolerance [r = 0.15 (−0.04, 0.33), r² = 0.022; P = 0.13].

### DISCUSSION

This study reveals three main findings. First, younger individuals have higher heart rate increments on HUT as previously described. Second, subjects with greater postural heart rate increments did not demonstrate a greater degree of orthostatic intolerance. Third, younger individuals (who had statistically higher heart rate increments on HUT) did not experience a greater degree of orthostatic intolerance. A large retrospec-

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**Table 1. Subject characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>n = 120</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>35 (17)</td>
<td>27</td>
</tr>
<tr>
<td>Sex</td>
<td>57 m, 63 w</td>
<td></td>
</tr>
<tr>
<td>Height, cm</td>
<td>171 (9)</td>
<td>150–192</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>72.4 (15.0)</td>
<td>45.4–145.5</td>
</tr>
<tr>
<td>Age group:</td>
<td>n = 49</td>
<td>21 m, 28 f</td>
</tr>
<tr>
<td>14–25 yr</td>
<td>n = 41</td>
<td>20 m, 21 f</td>
</tr>
<tr>
<td>26–40 yr</td>
<td>n = 30</td>
<td>16 m, 14 f</td>
</tr>
</tbody>
</table>

Values expressed as mean(SD). Data in parentheses indicate range. m, men; w, women.

**Table 2. Heart rate increment on head-up tilt and orthostatic intolerance values**

<table>
<thead>
<tr>
<th>Sample</th>
<th>Heart Rate Increment, beats/min</th>
<th>Orthostatic Intolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean(SD)</td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td>All participants</td>
<td>27.9 (12.1)</td>
<td>28.3</td>
</tr>
<tr>
<td>Men</td>
<td>27.1 (10.3)</td>
<td>27.9</td>
</tr>
<tr>
<td>Women</td>
<td>28.7 (13.7)</td>
<td>28.9</td>
</tr>
<tr>
<td>14–25 yr</td>
<td>35.1 (10.2)</td>
<td>33.6</td>
</tr>
<tr>
<td>26–40 yr</td>
<td>28.3 (9.3)</td>
<td>27.4</td>
</tr>
<tr>
<td>41–76 yr</td>
<td>15.6 (8.5)</td>
<td>11.7</td>
</tr>
</tbody>
</table>

Orthostatic intolerance values represent the subscore of the Autonomic Symptom Profile. *Significant difference from 14–25 yr. †Significant difference from 26–40 yr. ‡Significant difference from men (P = 0.03). Heart rate increment 14–25 yr vs. 26–40 yr (P < 0.05), 14–25 yr vs. 41–76 yr (P < 0.001), 26–40 yr vs. 41–76 yr (P < 0.001).
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The current study shows a divergence between symptoms and heart rate increment, further adding to the growing number of studies questioning the diagnostic criteria used for POTS in adult populations and their relevance to pediatric populations (14, 15). Our study did not involve POTS patients in younger groups, as the diagnosis of these patients remains difficult for the reasons stated above. Prior prospective studies looking at treatment and prognosis in POTS have focused on older individuals (4). However, additional studies focusing on younger persons with POTS are needed to better define diagnostic criteria and treatment. Issues such as the unclear relationship between symptom improvement and reduction of postural tachycardia in response to treatment may be similar in pediatric, young adult, and older adult populations (4, 22).

The pathophysiological mechanisms of orthostatic dysfunction in POTS have been well studied in younger populations, revealing specific roles for hypovolemia and peripheral and splanchnic blood flow and their relationship to the renin-aldosterone system. The renin-aldosterone system in addition to angiotensin II levels has been strongly implicated in the pathophysiology of POTS (13, 19, 20). In younger patients with POTS, angiotensin II is increased, with an associated low distal lower extremity peripheral blood flow and hypovolemia (16). Furthermore, these patients with decreased peripheral blood flow and decreased angiotensin II levels have lower body mass indexes (19, 20). Other associations with reduced splanchnic blood flow, blunt arterial vasoconstriction and passive redistribution (pooling) of blood in peripheral venous beds, have been shown in younger patients with POTS (17, 18). More recently, a correlation between flow-mediated vasodilatation and nitric oxide synthase activity was seen in younger patients with POTS (5). Lastly, elevated hydrogen sulfide levels may distinguish patients with POTS from control subjects (24). We are currently following asymptomatic individuals with higher postural heart rate increments on HUT in a prospective manner to examine the role these mechanisms may play in this particular population. Such a prospective study will also help to elucidate the potential role of these mechanisms in the development of the syndrome.

In conclusion, our study supports previous data showing higher heart rate increments on HUT in younger individuals. However, those individuals with increased postural heart rate increments did not demonstrate a greater degree of orthostatic symptoms. These findings lend further support to those previously raised concerns regarding the degree of postural tachycardia on HUT as it relates to the diagnostic criteria for POTS in younger individuals. Additional prospective studies are planned to determine whether individuals with higher postural heart rates increments develop symptoms of orthostasis and subsequently meet the diagnostic criteria for POTS.

GRANTS
This work was supported by unrestricted grant funds from the Department of Clinical Neurological Sciences Internal Research Fund.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS
Author contributions: C.T.I. and K.K. conception and design of research; C.T.I. and K.K. performed experiments; C.T.I. and K.K. analyzed data; C.T.I.
and K.K. interpreted results of experiments; C.T.I. and K.K. prepared figures; C.T.I. and K.K. edited and revised manuscript; C.T.I. and K.K. approved final version of manuscript; K.K. drafted manuscript.

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J Appl Physiol • doi:10.1152/japplphysiol.00292.2013 • www.jappl.org