Distinct neurohumoral biomarker profiles in children with hemodynamically defined orthostatic intolerance may predict treatment options

Ashley L. Wagoner,1,2 Hossam A. Shaltout,2,3 John E. Fortunato,2,4,5 and Debra I. Diz1,2,4
1Neuroscience Graduate Program, Wake Forest Graduate School of Arts and Sciences, Winston-Salem, North Carolina; 2Hypertension and Vascular Research Center, Wake Forest School of Medicine, Winston-Salem, North Carolina; 3Department of Obstetrics and Gynecology, Wake Forest School of Medicine, Winston-Salem, North Carolina; 4Department of General Surgery, Wake Forest School of Medicine, Winston-Salem, North Carolina; and 5Department of Pediatrics, Virginia Commonwealth University School of Medicine, Richmond, Virginia

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Wagoner AL, Shaltout HA, Fortunato JE, Diz DI. Distinct neurohumoral biomarker profiles in children with hemodynamically defined orthostatic intolerance may predict treatment options. Am J Physiol Heart Circ Physiol 310: H416–H425, 2016. First published November 25, 2015; doi:10.1152/ajpheart.00583.2015.—Studies of adults with orthostatic intolerance (OI) have revealed altered neurohumoral responses to orthostasis, which provide mechanistic insights into the dysregulation of blood pressure control. Similar studies in children with OI providing a thorough neurohumoral profile are lacking. The objective of the present study was to determine the cardiovascul ar and neurohumoral profile in adolescent subjects presenting with OI. Subjects at 10–18 yr of age were prospectively recruited if they exhibited two or more traditional OI symptoms and were referred for head-up tilt (HUT) testing. Circulating catecholamines, vasopressin, aldosterone, renin, and angiotensins were measured in the supine position and after 15 min of 70° tilt. Heart rate and blood pressure were continuously measured. Of the 48 patients, 30 patients had an abnormal tilt. Subjects with an abnormal tilt had lower systolic, diastolic, and mean arterial blood pressures during tilt, significantly higher levels of vasopressin during HUT, and relatively higher catecholamines and ANG II during HUT than subjects with a normal tilt. Distinct neurohumoral profiles were observed when OI subjects were placed into the following groups defined by the hemodynamic response: postural orthostatic tachycardia syndrome (POTS), orthostatic hypotension (OH), syncope, and POTS/syncope. Key characteristics included higher HUT-induced norepinephrine in POTS subjects, higher vasopressin in OH and syncope subjects, and higher supine and HUT aldosterone in OH subjects. In conclusion, children with OI and an abnormal response to tilt exhibit distinct neurohumoral profiles associated with the type of the hemodynamic response during orthostatic challenge. Elevated arginine vasopressin levels in syncope and OH groups are likely an exaggerated response to decreased blood flow not compensated by higher norepinephrine levels, as observed in POTS subjects. These different compensatory mechanisms support the role of measuring neurohumoral profiles toward the goal of selecting more focused and mechanistic-based treatment options for pediatric patients with OI.

orthostatic intolerance; head-upright tilt test; postural orthostatic tachycardia syndrome; orthostatic hypotension; arginine vasopressin

tachycardia syndrome, orthostatic hypotension, and syncope, revealing different compensatory mechanisms. This first comprehensive neurohumoral profile in children with orthostatic intolerance provides a basis for future strategic treatment options in children.

ORTHOSTATIC INTOLERANCE (OI) affects 500,000 Americans, rendering them unable to maintain adequate blood perfusion during an upright position (42). When standing, patients often experience lightheadedness, sweating, and nausea (22, 42). An abnormal cardiovascular response to head-up tilt (HUT) orthostatic challenge can be broadly grouped into the following: postural orthostatic tachycardia syndrome (POTS), orthostatic hypotension (OH), and syncope. Management and treatment of OI is typically dependent on the specific cardiovascular diagnosis, with most treatments having variable effectiveness in adult and adolescent populations (4, 8, 13, 30, 39). The pathophysiological mechanisms responsible for these cardiovascular changes are not well defined as presentation and symptoms are often heterogenous (14). This heterogeneity leads to the empirical treatment of symptoms without a evidence-based approach related to their underlying cause (3, 6).

In response to HUT, a reduction in blood volume or pressure at the level of the heart or carotid arteries is associated with reflex increases in catecholamines, arginine vasopressin (AVP), renin, ANG II, and aldosterone (Aldo) (8a). Although there are many additional nonreflex regulators that influence these systems, previous studies in adults with OI have revealed exaggerated neurohumoral responses to upright posture, including elevated catecholamines (16, 24), ANG II (34, 35), and AVP (11, 25, 37, 54). Neurohumoral responses also differ among OI subtypes, underscoring the possibility of differential mechanisms related to specific hemodynamic profiles. Adults with POTS have been observed to have elevated levels of plasma norepinephrine (NE) and epinephrine (Epi) at the time of orthostatic challenge, suggesting disproportionally higher sympathetic activation likely compensating for low blood pressure (BP) (16, 34, 58). Elevated supine ANG II is also associated with POTS subjects with hypovolemia (49). In adults with OH, greater supine AVP and endothelin-1 concentrations have shown to be predictive of decreases in systolic BP (SBP) during HUT (37). Increases in AVP and Epi during HUT have also been observed in both adult OH and vasovagal syncope subjects (23, 32, 37). OI is also observed in pediatric patients (12) but is particularly difficult to diagnose and treat as it is underrecognized, and testing, such as HUT, can be invasive for children. Characterization of the neurohumoral response to orthostatic challenge in children with OI has not been well

NEW & NOTEWORTHY

Distinct neurohumoral profiles were detected in blood collected during head-up tilt in children with postural orthostatic

Address for reprint requests and other correspondence: D. I. Diz, Hypertension and Vascular Research Center, Wake Forest School of Medicine, Medical Center Blvd. Hanes 6, Winston-Salem, NC 27157-1032 (e-mail: ddiz@wakehealth.edu).
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described, but dysregulation of these systems likely plays a role in its pathogenesis (12, 13).

We hypothesized that children with OI undergoing HUT would demonstrate distinct neurohumoral responses in association with specific patterns of changes in BP and heart rate (HR). We further suggest that specific cardiovascular responses in OI subtypes such as POTS, OH, syncope, and syncope are associated with unique neurohumoral profiles. To test this, we measured circulating levels of Epi, NE, AVP, Aldo, renin, and angiotensins [ANG-(1–7) and ANG II] both in the supine position and during HUT and compared these findings with the hemodynamic response in pediatric subjects with OI.

METHODS

Patients

Forty-eight male and female subjects at 10–18 yr of age were recruited from the pediatric clinic at Wake Forest Baptist Medical Center if they experienced two or more symptoms consistent with OI, in which HUT was deemed necessary, for at least 2 mo before testing. These OI symptoms included nausea, dizziness, lightheadedness, abdominal pain/bloating, syncope, excessive sweating, or chronic fatigue. Patients were excluded if a metabolic, mechanical, or mucosal inflammatory finding was identified as the cause for their symptoms. All subjects were required to undergo a 45-min HUT test during which blood was drawn to measure Epi, NE, AVP, Aldo, renin, and AVP after 15 min in the supine position and after 15 min of HUT. The Institutional Review Board of Wake Forest Baptist Medical Center approved this study. Parents and children provided written consent/assent before study participation.

HUT

Each subject was positioned supine on the tilt table for 15 min before HUT followed by an immediate upright tilt from 0 to 70° for up to 45 min. Continuous measures of BP and HR were obtained using noninvasive finger arterial pressure measurements and analyzed by BIOPAC acquisition software (Santa Barbara, CA). An average of BP s and HR s in the last 5 min of the supine period were used for baseline measures. Average HUT BP s and HR s were calculated in the 2 min before blood samples were collected (after 15 min of HUT) to compare with baseline supine BP and HR. After 45 min, the tilt table was brought back to the supine position for an additional 15 min. The test was terminated early for excessive gastrointestinal symptoms (nausea or abdominal pain), syncope, cardiac arrhythmia, or at the request of the patient for severe discomfort.

Patients were diagnosed as having an abnormal HUT [HUT(+)] if they met criteria for POTS, OH, syncope, or POTS/syncope (P/S). Otherwise, patients were defined as having a normal HUT [HUT(–)]. POTS was defined as either a HR of >120 beats/min or a ≥40-beats/min increase in HR from mean supine HR in the first 10 min of HUT and sustained for at least 2 min (46). OH was defined as a 25-mmHg decrease in SBP from mean supine SBP in the first 10 min of HUT sustained for a minimum of 2 min without an associated increase in HR (14). Syncope was defined as a temporary loss of consciousness during 45-min HUT. Subjects were classified as P/S if they met criteria for POTS as defined above followed by syncope at any time during the 45-min HUT.

Measurements of Blood Hormones

Measures of Aldo, renin, and angiotensins were carried out in the Clinical Laboratory Improvement Amendment-certified Hypertension Core Assay Laboratory at Wake Forest. Measures of catecholamines (Epi, NE, and dopamine) and AVP were carried out in the Pathology laboratory at Wake Forest Baptist Health. Radioimmunoassays (RIAs) previously described for human studies were used to measure three angiotensin peptides [ANG I, ANG II, and ANG-(1–7)] (27, 28). ANG I was measured using a modified version of the Peninsula assay, ANG II was measured using ALPCO (Windham, NH), and ANG-(1–7) was measured using an in-house antibody. AVP was measured using an ALPCO Diagnostics RIA (Windham, NH). Serum Aldo and plasma renin were measured as previously described (34). Epi, NE, and dopamine were measured after whole plasma extraction by HPLC. Dopamine was not detectable in plasma of any of the subjects.

Statistical Analysis

For continuous variables, means and SEs were calculated; for categorical variables, counts and percentages were calculated. Two-way ANOVA tests were conducted to examine the effect of HUT on HUT(+) versus HUT(–) groups as well as HUT(–), OH, POTS, syncope, and P/S groups. When appropriate, post hoc t-tests and one-way ANOVAs were conducted to identify specific effects of HUT on hemodynamic and neurohumoral variables between and among groups. Unpaired t-tests were performed to compare HUT(+) and HUT(–) groups followed by a Welch’s correction if there were unequal variances. Mann-Whitney tests were conducted when data sets were not normally distributed. One-way ANOVAs followed by Tukey’s post hoc multiple-comparisons tests were performed to define differences between HUT(–), POTS, OH, syncope, and P/S groups. Kruskal-Wallis tests were performed when group data were not normally distributed. Pearson’s correlation test was performed to compare neurohumoral and hemodynamic variables. Spearman’s correlation test was performed when data sets were not normally distributed. All statistical analyses were performed using GraphPad Prism 5.0. Results with P < 0.05 were considered statistically significant.

RESULTS

Forty-eight patients (36 female subjects and 12 male subjects) presenting with OI symptoms for at least 2 mo prior underwent HUT testing. The median age (±SE) was 15.2 ± 0.3 yr. Eighteen patients were HUT(–) and 30 patients were HUT(+) over the 45-min HUT. The 30 HUT(+) subjects met criteria for one of the four groups [POTS (n = 7), OH (n = 5), syncope (n = 8), or P/S (n = 10)]. There were no differences in age or weight between groups. The body mass index was significantly higher in HUT(–) subjects than HUT(+) subjects. As expected, HUT(–) subjects were able to sustain HUT significantly longer than HUT(+) subjects. Syncope and P/S subjects sustained significantly less time on HUT compared with HUT(–) subjects, and POTS subjects were able to stay on HUT longer than syncope subjects (Table 1).

HUT(+) Versus HUT(–) Subjects

Hemodynamic measurements. There were no significant differences between HUT(+) and HUT(–) subjects for BP and HR in the supine position (Fig. 1). During tilt, HUT(+) subjects had significantly lower SBP and diastolic BP (DBP) compared with HUT(–) subjects [interaction, P < 0.05; HUT(+) vs. HUT(–), P < 0.0005; Fig. 1, A and B]. Similar patterns were observed for mean arterial pressure (MAP). Additionally, HUT(–) subjects had a significant increase in DBP upon HUT compared with supine (P < 0.05). No other significant BP changes were observed from supine to HUT in either group. Both groups had a significant increase of HR
from supine to HUT, but there were no differences at supine or HUT between groups (Fig. 1C).

**Neurohumoral measurements.** There were no significant differences between HUT(−) and HUT(+) subjects for neurohumoral measures in the supine position (Fig. 2). Plasma levels of NE (Fig. 2A), Epi (Fig. 2B), renin (Fig. 2D), and ANG II (Fig. 2F) significantly increased from supine to HUT for both HUT(−) and HUT(+) groups, but there were no differences in these hormones between groups during HUT. Plasma AVP concentrations increased in both groups from supine to HUT \( P < 0.05 \) for HUT(−) and \( P < 0.001 \) for HUT(+) but were higher in HUT(+) versus HUT(−) subjects during HUT \( P < 0.05 \); interaction, \( P = 0.08 \); Fig. 2C). There were no differences in Aldo or ANG-(1–7) levels between or among groups (Fig. 2, E and G).

**Correlative Assessment of Neurohumoral Biomarkers and Hemodynamics**

Based on our findings, we applied regression analysis to further elucidate the association between these neurohumoral biomarkers and hemodynamics at supine and in response to HUT considering all 48 subjects and HUT(+) and HUT(−) groups alone (Table 2). Supine NE had a negative correlation with Epi and ANG-(1–7) in both supine and HUT positions and positive correlation with supine AVP. As expected, NE during HUT had a positive relationship with both supine and HUT HR. These relationships were also observed in HUT(+) subjects but not in HUT(−) subjects. HUT levels of NE correlated in a positive manner with supine AVP and negatively with HUT ANG-(1–7). The negative relationship between HUT NE and HUT ANG-(1–7) was also observed in HUT(−) subjects. Supine Epi correlated directly with supine HR, whereas HUT Epi had an inverse relationship with MAP. HUT Epi also directly correlated with ANG-(1–7) in both supine and HUT positions considering all 48 subjects and HUT(+) subjects alone (Table 2).

In addition to relationships with NE and Epi, AVP associated with MAP in the supine position and during HUT. In the supine position, AVP showed a positive correlation with MAP. In contrast, during HUT, a significant negative correlation between MAP and AVP during HUT was observed.
supine to HUT and higher plasma levels of NE compared with all other abnormal HUT subgroups ($P < 0.01$). P/S subjects were the only other group to have a significant change from supine to HUT in these variables, with a significant increase in NE with HUT ($P < 0.05$). OH ($P = 0.1$), syncope ($P = 0.2$), and P/S ($P = 0.07$) groups showed a trending increase in Epi levels from supine to HUT. HUT(−) subjects had a significant increase from supine to HUT in NE and Epi (Fig. 4, A and B).

**Vasopressin measurements.** At baseline, there were no differences among groups in plasma AVP concentrations. OH ($P < 0.05$) and syncope ($P < 0.01$) subjects had significantly higher AVP during HUT than POTS and HUT(−) subjects. Syncope subjects also had a significant increase in AVP from supine to HUT ($P < 0.001$), and OH subjects had a variably high but not statistically significant increase in AVP (Fig. 4C). These two subgroups did not show a significant decrease in BP during HUT, but both had lower BP during HUT compared with the HUT(−) group, and the OH subgroup had lower pressure than most other groups during HUT.

**Renin-angiotensin-Aldo system measurements.** There were no differences among groups for renin in the supine position or during HUT. An increase in renin from the supine position to HUT was observed in HUT(−) and syncope subjects ($P < 0.01$; Fig. 4D). There was no change in serum Aldo from the supine position to HUT in any group. OH subjects had higher Aldo measurements than HUT(−) and POTS subjects in the supine position and HUT(−), POTS, and syncope subjects during HUT (Fig. 4E).

For ANG II, there were no differences in supine values among subgroups. HUT(−), POTS, syncope, and P/S groups had a significant increase from the supine position to HUT. There was a trend for group differences ($P = 0.054$), likely driven by the higher ANG II during HUT in P/S subjects relative to HUT(−) and syncope subjects (Fig. 4F). There were no changes in ANG-(1–7) elicited by HUT and no differences among subgroups (Fig. 4G).

**DISCUSSION**

The objective of our study was to better characterize the neurohumoral phenotype and its relationship with hemodynamic changes to HUT in children with OI (14, 46). The neurohumoral profile included measurements of circulating catecholamines (Epi and NE), the renin-angiotensin-aldosterone system axis, and AVP to provide a comprehensive panel for subjects with OI to test the effects of orthostatic challenge. Our methodology was unique in that the neurohumoral profile was measured during HUT as opposed to previous studies in adults in which sample collection was taken in the supine position alone, after completion of a 30-min test, or after an evoked HUT response (11, 19, 20, 34, 37). Our approach aimed to more accurately reflect real-time neurohumoral changes as they related to cardiovascular symptoms including HR and BP changes, especially for neurohumoral factors that are less stable and metabolized quickly (1).

As we have previously reported (12, 13), pediatric subjects presenting with various OI symptoms frequently demonstrated an abnormal HUT, raising the possibility of a cardiovascular basis for their OI, including gastrointestinal symptoms. The majority (62.5%) of patients with reported orthostatic dizziness were HUT(+), consistent with findings in adults (36) in which sample collection was taken in the supine position alone, after completion of a 30-min test, or after an evoked HUT response (11, 19, 20, 34, 37). Our approach aimed to more accurately reflect real-time neurohumoral changes as they related to cardiovascular symptoms including HR and BP changes, especially for neurohumoral factors that are less stable and metabolized quickly (1).
patients experienced syncope later in the HUT (10). Subjects with P/S or syncope sustained significantly less time on HUT compared with HUT(−) subjects. POTS subjects were able to endure the HUT for a longer time compared with syncope subjects. While there was no statistical significance, P/S subjects were only able to sustain half as much time on HUT compared with POTS subjects (Table 1). This is most likely due to P/S subjects experiencing syncope after 10 min of HUT compared with POTS subjects who were able to sustain the 45-min HUT.

When all HUT(+) subgroups were analyzed collectively, an increase in hormone secretion from the supine position to HUT included AVP, NE, Epi, renin, and ANG II. Although ANG-(1–7) has been reported to influence AVP and NE release and baroreflex function in animal studies (7, 17, 44, 57), there were no differences in ANG-(1–7) between groups. A negative relationship was observed between ANG-(1–7) and NE, consistent with evidence of a neuromodulatory action of ANG-(1–7) on the release of NE (7, 17, 48, 57). Overall, only AVP was markedly elevated between HUT(+) and HUT(−) patients. These findings, taken in the context of decreased BP upon HUT in OI, suggests that AVP release is in response to a reduction in blood volume and perfusion of heart and atrial vessels as well as carotid arteries. Whether the hormone is effectively contributing to an increase in vasoconstriction and volume expansion (5, 25, 54), albeit insufficient to maintain normal arterial pressure, is not clear.

To determine whether the hemodynamic pattern presented by specific OI phenotypes was associated with specific neurohumoral profiles, HUT(+) patients were divided into four diagnostic subgroups. Adult POTS patients compensate for a reduction in blood perfusion during orthostatic challenge by increasing HR to prevent a decrease in BP (38, 42, 43), while different compensatory mechanisms and neurohumoral patterns occur relative to adult OH and syncope subjects (3, 14, 23, 32, 55). Our findings in children were similar to adults in that POTS subjects showed an elevation in NE compared with HUT(−) subjects, consistent with a hyperadrenergic state (16,
There was little to no change during HUT in renin or Aldo. The lack of an Aldo response in POTS subjects is consistent with other studies in which an increase in Aldo secretion was absent despite increases in ANG II during HUT (34, 38, 49). Plasma ANG II increased significantly from the supine position to HUT in POTS subjects; however, ANG II levels were not statistically different from those of HUT (34, 38, 49). Plasma ANG II increased significantly from the supine position to HUT in POTS subjects; however, ANG II responses were variable in this subgroup. In contrast to the subjects with POTS alone, the NE response was not elevated. This may suggest that those with POTS who progress to syncope may have a disproportionate reliance on the renin-angiotensin-Aldo system compared with other vasoconstrictor systems versus those with POTS alone who may rely on sympathetic nervous system activation. Traditionally, this distinction between POTS and P/S has not been made when analyzing neurohumoral changes in adults, but the unique findings support the concept that subjects in this category require additional compensatory mechanisms to maintain sufficient perfusion over the longer HUT timeframe and perhaps in daily activity.

In contrast to POTS subjects, OH and syncope subjects had no change in NE, increased Epi, and exaggerated increases in AVP. There was a failure to significantly increase renin and ANG II in OH subjects with HUT, whereas syncope subjects showed normal renin and ANG II responses. Both groups had a trending increase in Epi and a failure to increase NE, which is consistent with a previous report (18) of sympathoadrenal imbalance in OH and syncope subjects. This study showed drastic increases in Epi before syncopal episodes, suggesting that vasodilation in neurocardiogenic syncope is, at least in part, humorally mediated (10, 18). Furthermore, intravenous infusion of NE maintained BP in OH subjects during HUT, temporarily eliminating OH (19). Thus, the imbalance of NE and Epi, with higher circulating Epi, most likely contributes to vasodilation or impairments in peripheral vascular resistance by stimulating vasodilating $\beta_2$-adrenergic receptors in skeletal blood vessels, which results in low BP/cardiac output in OH and syncope subjects (15). However, in the present study, the sympathoadrenal imbalance was accompanied by a trend for exaggerated increases in AVP in syncope and OH subjects and increased Aldo in OH subjects.

Surprisingly, OH subjects exhibited significantly higher serum Aldo compared with HUT(−) subjects, with higher levels in both supine and HUT positions. All other groups had lower Aldo levels while in the supine position, with little to no increase from the supine position to HUT. A trend for higher AVP in the supine position was also observed in the OH group.
Fig. 3. Orthostatic changes in SBP (A), DBP (B), and HR (C) in children from the following five diagnostic HUT subgroups: HUT(-), orthostatic hypotension (OH), postural orthostatic tachycardia syndrome (POTS), syncope (Syn), and POTS/syncope (P/S). HUT(-) subjects (n = 18) had significantly higher SBP than all other groups during HUT. OH subjects (n = 5) had significantly lower SBP than P/S subjects (n = 10) during HUT. The pattern of response in SBP was similar to that in DBP. HUT(-) (n = 7), Syn (n = 8), and P/S groups had elevated HR from the supine position to HUT. POTS subjects had significantly higher HR and a more exaggerated increase from the supine position to HUT. Supine position vs. HUT: *P < 0.05, **P < 0.01, and ***P < 0.001; HUT(-) vs. HUT(+) subgroups: #P < 0.05, ##P < 0.01, and ###P < 0.001.

The higher AVP may be a reflection of a chronically lower BP, as has been suggested when copeptin was used as an indirect measure of chronically elevated AVP (59). The increase in AVP may be due to lower pressures in the OH group compared with the syncope group at the time of the hormonal measurement, given that syncope occurred later in the HUT. A combination of high Aldo and AVP has also recently been associated with hospitalized neonatal foals with clinical hypoperfusion, providing further evidence for these clinical biomarkers to identify subjects with volume depletion and/or poor tissue perfusion (9). Considering that AVP release is most sensitive to reduced serum osmolality followed by sensitivity to decreases in BP, our findings are consistent with the reduction in effective BP and perfusion as the stimulus for release of this hormone. However, the trigger for this response is still unclear. Thus, while accompanied by an imbalance in NE and Epi, higher Aldo and AVP at baseline and the exaggerated increase in AVP in response to HUT in OH subjects appear to be compensating for the lack of response in multiple other vasoconstrictive and fluid retention systems.

The relationship between AVP and reduced BP has been described in both animal and human studies in which increased secretion of plasma AVP is triggered by unloading of arterial baroreceptors in the hypotensive state (26, 54). This is similar to our observations after HUT in both OH and syncope subjects with the reduction in BP. However, stimulation of AVP also occurs independently of the baroreflex (41). Baroreflex sensitivity and HR variability are reduced during HUT in normal subjects, and there is an even greater suppression of these indexes of BP and HR regulation in those with OH and HUT(+) (45). In fact, AVP release is reportedly greater in situations when the baroreflex is impaired (41), which would be consistent with the observed AVP responses during HUT given the negative correlation between AVP and BP during the upright position in HUT(+) subjects. Thus, the trigger for AVP release, low BP, and an exaggerated impairment in baroreflex remains unclear in the present study.

The positive correlation observed between AVP and BP in the supine position was an unexpected finding. In light of the association between dysautonomia and hypertension, this does raise some concern for future elevated BP in HUT(+) subjects (most notably, the OH subgroup with higher supine Aldo) (2, 40). For example, autonomic indexes, including decreased HR variability and baroreflex sensitivity, are accepted as risk factors and indicators for the development and progression of cardiovascular problems such as hypertension and stroke (29, 31, 33). Future studies may include measuring copeptin levels to further elucidate this question. Copeptin, a stable component of AVP, is a marker of treatment effectiveness for OH, with lower levels of copeptin observed in patients effectively treated with vasoconstrictors (59). Whether OH, Aldo, or AVP/copeptin may also serve as biomarkers for the development of hypertension in this patient population warrants further attention, particularly in light of the absence of long-term cardiovascular longitudinal studies in these patients.

The findings in the present study underscore the distinct nature of HUT(+) hemodynamic subgroups, raising the question as to the need for more specific treatment strategies based on individual subgroup characteristics. The exaggerated release of several hormones in the face of minimally maintained or lower pressure in POTS or P/S may suggest that vascular responsiveness to the constrictors is impaired. In contrast, deficits in the release of neurohumoral factors other than AVP appear to have a role in OH. POTS patients do not have high levels of Aldo or AVP either in the supine position or during HUT, suggesting that volume expansion with the use of Aldosterone drugs such as fludrocortisone may be sufficient, particu-
larly when coupled with increased NE, to mitigate their pronounced orthostatic response. In contrast, fludrocortisone may be less effective in OH patients based on the observed increases in Aldo. The exaggerated AVP response in this group supports this possibility. In fact, fludrocortisone is not effective in 35% of adolescents treated for OI (12). Therefore, prospective placebo-controlled studies are needed to determine the potential role for other treatment modalities, such as vasoconstrictor therapy (e.g., midodrine), in OH subjects (3, 39, 51).

The limitations of the study include the following. First, while HUT subjects served as controls, all those studied with HUT had reported symptoms of OI before the study. Thus, future study designs require HUT and neurohumoral assessment of asymptomatic, healthy controls. Second, the sample size was relatively small, particularly when considering HUT(+) subgroups. To better define potential differences among patients with POTS, OH, syncope, and P/S as well as the correlation between hemodynamic and neurohumoral measures, a larger cohort of OI patients is required. To better determine the feasibility of conducting such a study, understanding the prevalence of OI in the pediatric population will be necessary. The timing of blood collection also requires further consideration. As discussed above, neurohumoral markers were measured 15 min after HUT to optimally capture orthostatic symptoms. However, by performing a 45-min HUT, several patients with syncope did not manifest orthostatic and cardiovascular changes until later in the study. Therefore, changes in the neurohumoral profile in this subgroup may be more pronounced at different times during the HUT. Finally, while the hormone panel we measured was comprehensive, it...
did not include cortisol. Cortisol levels may be relevant as anxiety can be a comorbid symptom in pediatric patients with OI (52). Assessing cortisol levels during HUT may help delineate the potential role of physiological stress in these children.

In conclusion, a distinct neurohumoral profile related to OI subgroup diagnoses was demonstrated during HUT in pediatric patients presenting with orthostatic symptoms and gastrointestinal symptoms. These findings support the need for a better understanding of the relationship between these hormones and cardiovascular changes with orthostatic challenge. By studying these potential causes and effects in OI patients, it is anticipated that more focused and possibly more effective treatments can be started in this group of patients, thereby leading to an evidence-based approach.

Perspectives

Since dysautonomia, which can manifest as OI, is a potential risk factor for cardiovascular disease, understanding the mechanisms involved in producing symptoms of OI is warranted, particularly at an early age. The heterogeneity of clinical presentation in OI patients with symptoms ranging from syncope to migraine headaches to gastrointestinal complaints favors a multidisciplinary approach to their care. In the present study, we measured a panel of neurohormones in OI subjects. To determine the impact of orthostatic challenge, we measured these hormones both while in the supine position and during HUT and attempted to define differences among specific HUT(+) subgroups. We demonstrated that elevated AVP was associated with lower BP and that OH subjects have elevated Aldo independent of upright posture. Further evaluation of AVP, the renin-angiotensin-Aldo system, and catecholamines in subjects with orthostatic symptoms may elucidate the mechanisms involved in the cause of these OI subtypes. It may further provide insight into their long-term cardiovascular prognosis, including risk of hypertension and cardiovascular disease.

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DISCLOSURES

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

AUTHOR CONTRIBUTIONS


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