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EDITORIAL

Mechanisms of post-prandial symptoms in postural tachycardia syndrome and other updates on recent autonomic research

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Most patients with postural tachycardia syndrome (POTS) report worsening of symptoms after meals rich in carbohydrates, however, the precise underlying mechanism is unknown. In their recent study, "Worsening postural tachycardia syndrome is associated with increased glucose-dependent insulinotropic polypeptide secretion," Breier and colleagues [1] evaluated the secretion of glucose-dependent insulinotropic polypeptide (GIP), a splanchnic vasodilator, to investigate the pathophysiological mechanisms involved in post-prandial symptom exacerbation in POTS.

The authors enrolled 12 patients with POTS who reported symptom exacerbation after eating. The patients were compared to 13 controls matched by age and BMI. The participants ingested glucose dissolved in water (acetaminophen was added to detect differences in glucose absorption between groups). Orthostatic vital signs, blood pressure (BP) and heart rate (HR) variability, and systemic hemodynamic were obtained in the supine position and after 10 min of standing at baseline, 30, 60, 90, and 120 min post glucose ingestion. Plasma glucose, GIP, insulin, C-peptide, glucagon and other gastrointestinal hormones levels were assessed at the various time points.

Orthostatic HR changes in patients with POTS were greater than controls (48.7 ± 11.2 vs. 23.3 ± 8.1 bpm, $p = 0.012$). The increase in standing HR after oral glucose ingestion was greater in patients with POTS compared to controls ($+21.2 \pm 11.9\%$ vs. $+6.0 \pm 19.9\%$, $p = 0.033$). GIP levels after the oral glucose challenge were higher in patients with POTS compared to controls ($p = 0.001$), with a maximum concentration after 90–120 min. Interestingly, levels of GIP were directly correlated with the timing of maximum upright tachycardia and minimum stroke volume in patients with POTS.

The authors found a lower hematocrit in POTS compared to controls ($38.3 \pm 2.8\%$ vs. $35.9 \pm 2.2\%$, $p = 0.029$), suggestive of lower plasma volume in POTS. In addition, patients with POTS had higher standing norepinephrine (NE) levels compared to controls (835.2 ± 368.4 vs. 356.9 ± 156.7 pg/mL, $p = 0.004$), suggesting a hyperadrenergic state in most patients. Fasting glucose and insulin levels were normal in both groups, however, C-peptide was higher in the POTS group, suggestive of insulin resistance. Glucose absorption was similar in both groups.

These findings suggest that patients with POTS may have some degree of insulin resistance, that they release greater amounts of GIP after glucose ingestion, and that this greater GIP release may contribute to the exacerbation of orthostatic symptoms via splanchnic vasodilation. Study limitations include the small sample size, the fact that medications were not held for five half-lives in patients with POTS, and the fact that only patients who reported post-prandial symptom exacerbation were included in the study. In addition, most patients had a hyperadrenergic response to standing, and it has been demonstrated that elevated NE levels are correlated with insulin resistance. Thus, a more heterogeneous sample of patients with POTS may have produced different results. Nonetheless, this is an important study that advances our understanding of post-prandial symptoms in POTS. It also brings to light the role of GIP receptor antagonists as a potential future treatment in POTS.

Mitigating initial orthostatic hypotension through stress and muscle contraction

Initial orthostatic hypotension (IOH) is a common cause of orthostatic intolerance. IOH is defined by a drop in systolic blood pressure by >40 mm Hg or a drop in diastolic blood by >20 mm Hg within 15 s of standing with recovery to

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baseline within 60 s. The pathophysiology of IOH is thought to reflect a temporal mismatch between cardiac output and vascular resistance [2]. In a recent study, Sheikh and colleagues [3] attempted to determine the roles of skeletal muscle contraction and sympathetic activation in the BP response during IOH.

The authors enrolled 26 female participants with a history of presyncope immediately after standing with recovery within 1 min, >4 presyncopal or syncopal episodes per month, and a history of syncope immediately after standing. Participants were asked to refrain from taking medication that could affect HR or BP for 1 day before the study. Participants who could not safely hold these medications were studied on medications. Three participants were excluded (unable to complete the protocol or technical difficulties).

Each participant performed 4 sit-to-stand maneuvers with interventions before standing including serial 7 mental arithmetic stress test (S7T), cold pressor test (CPT), and electrical stimulation (ES). A sit-to-stand maneuver without intervention was used as a control. The S7T and CPT increased sympathetic activity with minimal lower muscle activation. The ES increased lower extremity muscle contraction with minimal sympathetic simulation. HR and BP were measured continuously while sitting and standing. Stroke volume (SV), cardiac output (CO), and systemic vascular resistance (SVR) were calculated from waveform analysis. In addition, the Vanderbilt Orthostatic Symptom Score (VOSS) was administered to assess symptom burden. The order of the 4 interventions was randomized. The final 30 s of each 10-min seated baseline was used as the baseline hemodynamics (BSL). The intervention hemodynamics (INTV) were calculated as the mean of the 30 s while the intervention was performed seated before standing and following the seated baseline period. The lowest systolic BP within the first 15 s of each stand was used as the nadir BP (BPnadir).

The key results of the study are as follows. The fall in BP from BSL to BPnadir was blunted following S7T (-26 ± 12 mm Hg; $p = 0.004$), CPT (-20 ± 15 mm Hg; $p < 0.001$), and ES (-28 ± 12 mm Hg; $p = 0.01$) compared to the control condition (-34 ± 11 mm Hg). The fall in BP from INTV to the BPnadir was blunted following ES (-28 ± 12 mm Hg; $p = 0.01$) but not S7T or CPT compared to the control condition. The fall in SVR following S7T (-391 ± 206 dyne × s/cm^5; $p = 0.006$) and CPT (-386 ± 179 dyne × s/cm^5; $p = 0.011$) were also reduced when compared to controls (-488 ± 173 dyne × s/cm^5) but not following ES (-456 ± 165 dyne × s/cm^5; $p = 0.39$). BP and HR increased from BSL to INTV with both S7T and CPT but not with ES. Lastly, CO increased upon standing compared with during the sit for S7T (6 ± 1 vs 8 ± 2 L/min; $p < 0.001$), CPT (6 ± 1 vs 7 ± 2 L/min; $p < 0.001$), ES (6 ± 1 vs 7 ± 2 L/min; $p < 0.001$) and control (6 ± 1 vs 7 ± 1 L/min; $p < 0.001$). ES was the only intervention that resulted in reduced VOSS compared to the control sit-to-stand (10 ± 10 vs. 14 ± 9; $p = 0.009$).

This study demonstrates that both the skeletal muscle pump and sympathetic activation mitigate the BP response in IOH. The reduction in the fall in BP following sympathetic activation is likely driven by a blunted reduction in SVR, whereas stimulation of skeletal muscle reduces the fall in BP with standing but also improves symptoms. The large drop in BP following sympathetic activation was due to the increase in BP and HR while seated during the stress tests. On the other hand, involuntary muscle contractions are not associated with an increase in HR and BP before standing suggesting that the effects of muscle contraction in modulating the BP response during IOH occur after standing.

A limitation of this study is that only female participants were included. Some participants found the electrical stimulus for muscle contraction to be uncomfortable, which could have increased sympathetic activity. Participants had difficulty sitting still during electrical stimulation, which could also have influenced the results. Lastly, medications that could affect HR and BP may have affected the results. Nevertheless, this study improves our understanding of how both skeletal muscle contraction and sympathetic activation mitigate the BP response during IOH.

Neuromodulation of the baroreflex to treat resistant hypertension

Resistant hypertension is defined as blood pressure (BP) that remains above 140/90 mmHg despite optimal use of at least three antihypertensive medications. Persistent, uncontrolled HTN increases cardiovascular disease mortality. Pharmacotherapies for HTN may lead to sympathetic activation, which is thought to be a major contributing factor to resistant HTN. Therefore, devices to reduce excessive sympathetic activation have been studied including renal sympathetic denervation and baroreflex activation therapies with electrical stimulation of the baroreceptors [4]. Activation of the baroreceptors by an implantable electric stimulator effectively lowers the BP; however, there are possible side effects due to the open surgical approach. Stretching of the baroreceptors has been proposed as another method to reduce excessive sympathetic activation in patients with resistant HTN. An endovascularly delivered device (Mobius HD) can be inserted near the carotid bulb and slowly changes the carotid sinus geometry, which stimulates baroreceptor firing with resultant sympathetic outflow inhibition and a decrease in BP.

An earlier publication presented promising short-term safety and efficacy outcomes 6 months after the procedure [5]. In a recent study, Van Kleef and colleagues presented

the results from two prospective, open-label studies designed to determine the long-term safety and effectiveness of endovascular baroreflex amplification (EVBA) in patients with resistant hypertension [6]. A total of 47 patients (30 in Europe, 17 in the United States; mean age 54 years, 23 women) were studied. Five serious adverse events (hypotension, $n=2$; hypertension, $n=1$; vascular access complications, $n=2$) and 2 transient ischemic attacks occurred within 30 days post-procedure. Two ischemic strokes and 1 transient ischemic attack occurred more than 2 years post-implantation. Mean office BP decreased by 25/12 mm Hg (95% CI: 17–33/8–17 mm Hg) at 6 months and 30/12 mm Hg (95% CI: 21–38/8–17 mm Hg) at 3 years. Mean 24-h ambulatory BP decreased by 20/11 mm Hg (95% CI: 14–25/8–15 mm Hg) at 6 months.

The persistent reduction in BP after 3 years is promising as there were concerns that ongoing stretching at the carotid body might lose its effectiveness with time with baroreflex resetting. There were, however, delayed ischemic events with at least one stroke in the vascular territory ipsilateral to the device. Further studies are necessary to investigate the role of EVBA for the treatment of resistant hypertension, and the degree of improvement in open-label studies does not always predict the long-term outcomes of more rigorous trials [7]. If this device is proven to be effective in randomized sham-controlled trials, it may become a promising treatment for patients with resistant hypertension.

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Declarations

Conflict of interest None.

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