Lower body muscle preactivation and tensing mitigate symptoms of initial orthostatic hypotension in young females

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BACKGROUND Initial orthostatic hypotension (IOH) is a form of orthostatic intolerance defined by a transient decrease in blood pressure upon standing. Current clinical recommendations for managing IOH includes standing up slowly or lower body muscle tensing (TENSE) after standing. Considering that IOH is likely due to a large muscle activation response resulting in excessive vasodilation with a refractory period (<2 minutes), we hypothesized that preactivating lower body muscles (PREACT) before standing would reduce the drop in mean arterial pressure (MAP) upon standing and improve presyncope symptoms.

OBJECTIVE The purpose of this study was to provide IOH patients with effective symptom management techniques.

METHODS Study participants completed 3 sit-to-stand maneuvers, including a stand with no intervention (Control), PREACT, and TENSE. Continuous heart rate and beat-to-beat blood pressure were measured. Stroke volume and cardiac output were then estimated from these waveforms.

RESULTS A total of 24 female IOH participants (mean ± SD: 32 ± 8 years) completed the study. The drops in MAP following PREACT (−21 ± 8 mm Hg; P < .001) and TENSE (−18 ± 10 mm Hg; P < .001) were significantly reduced compared to Control (−28 ± 10 mm Hg). The increase in cardiac output was significantly larger following PREACT (2.6 ± 1 L/min; P < .001) but not TENSE (1.9 ± 1 L/min; P = .2) compared to Control (1.4 ± 1 L/min). The Vanderbilt Orthostatic Symptom Score following PREACT (9 ± 8 au; P = .033) and TENSE (8 ± 8 au; P = .046) both were significantly reduced compared to Control (14 ± 9 au).

CONCLUSION Both the drop in MAP and symptoms upon standing improved with either PREACT or TENSE. These maneuvers provide novel symptom management techniques for patients with IOH.

KEYWORDS Initial orthostatic hypotension; Lightheadedness; Orthostatic intolerance; Physical counter-maneuvers; Presyncope; Syncope

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occasionally syncope as a result of cerebral hypoperfusion, and usually recovers within 45–60 seconds due to triggering of the arterial baroreflex. The exaggerated BP drop characterizing IOH most likely is explained by rapid and excessive vasodilation occurring in the active lower body muscles required in standing due to local metabolic pathways. Alternative explanations include the muscle pump, which is engaged during the muscular effort of standing, and the cardiopulmonary receptor reflex, which is triggered in response to the increase in right atrial pressure (RAP) from the muscle pump. However, the time course of these 2 responses do not align with the time course of the hypotension seen in IOH.

IOH symptoms often present during an active stand but not with a passive tilt-table test, suggesting that a muscle activation response plays an important role in the pathophysiology of IOH. This muscle activation response refers to the rapid and excessive vasodilation that occurs in response to the brief lower body muscle contraction required to stand due to local mechanisms. Additional factors involved in this response include the increase in heart rate, initially due to the muscle heart reflex and secondarily in response to the arterial baroreflex triggered by the drop in BP as well as the increase in peripheral resistance, which is also triggered by the arterial baroreflex.

Presyncope or syncope may occur on a daily basis in IOH patients. In a recent study, 1 in 10 patients with unexplained syncope had IOH, making IOH the second most common form of orthostatic intolerance in the cohort. Despite the high incidence of presyncope and IOH, few validated management options are available.

Current literature on managing IOH explores lower body muscle tensing (TENSE) after standing from a squat. There is no literature exploring the effects of TENSE before standing as a pre-emptive measure, or from a seated position. We recently reported that a short seated period (<2 minutes) preceding a stand blunts the drop in BP seen in IOH compared to a long seated period (>2 minutes), suggesting that the underlying response has a refractory period that could be harnessed therapeutically. We hypothesized that lower body muscle preactivation (PREACT) prior to standing, as well as TENSE following a sit-to-stand maneuver, would blunt the BP drop seen in IOH and improve symptoms.

Materials and methods

Research study and subjects

The study was approved by the Calgary Conjoint Health Research Ethics Board (REB19-0792), and all participants provided written informed consent. The study was registered on the United States National Institutes of Health Clinical Trials website (ClinicalTrials.gov Identifier: NCT03970551). The research reported in this paper adhered to the CONSORT guidelines.

Participants with IOH were recruited from the University of Calgary research study Web site and from the Calgary Autonomic Investigation and Management Clinic for participation. Participants with IOH were required to meet the following criteria: (1) presyncope symptoms immediately upon standing, with recovery occurring within 1 minute of ongoing stand; (2) More than 4 episodes of presyncope or syncope per month; or (3) prior faint immediately after standing. An additional criterion was checked on the day of the study: participants were required to have a BP drop of at least 40 mm Hg upon standing. This threshold was used, as it is the best data currently present on identifying IOH. This drop in BP was previously observed from supine-to-stand, whereas the participants in this study performed sit-to-stands. All participants met these criteria on the day of the study or on a previous clinic visit.

Participants were excluded if they (1) only fainted or experienced presyncope symptoms while already standing for over 1 minute; or (2) were diagnosed with another form of orthostatic hypotension, including classic neurogenic orthostatic hypotension or delayed orthostatic hypotension.

Participants arrived at the research study between 08:00 and 09:00 hours in a fasting state. Participants were asked to withhold any medications that could affect BP or heart rate (HR), including beta-blockers, midodrine, stimulants, and nonsteroidal anti-inflammatory drugs, whenever possible (Supplemental Table 1). These medications were withheld for a minimum 24 hours given their short half-lives. None of the participants were taking medication that would be expected to lower BP, such as diuretics or vasodilators. Participants were instructed to refrain from all food and drink, aside from water, for at least 8 hours before testing.

There were 26 participants who consented. One participant was found to have fainted earlier the day of the study and was excluded. Data from 1 additional participant were excluded due to technical analysis issues (Figure 1). Data for the remaining 24 participants were included in the analysis. Of these participants, 2 had inadequate HR recordings during the PREACT stand. Thus, 22 participants were included in the HR analysis.

Overall study design

Each participant performed 3 sit-to-stand maneuvers with physical interventions (Figure 2). First was no intervention (Control), which was performed in an earlier portion of the
study on the same day, then 1 of the 2 interventions, in random order, followed by the other intervention. One was lower body muscle preactivation through repeated knee raises prior to standing (PREACT), and the other was lower body muscle tensing through leg crossing and tensing after standing (TENSE). Each stand lasted for 2 minutes and was preceded by a 10-minute seated baseline. The PREACT intervention was performed for 30 seconds while sitting, at the end of the 10-minute seated baseline, immediately before standing. The TENSE intervention was performed for 30 seconds immediately after the onset of standing.

Symptoms upon standing were recorded immediately following each stand according to the Vanderbilt Orthostatic Symptom Score (VOSS) rating system. This is a self-reported symptoms rating that consisted of 9 symptoms and rated on a scale from 0 (no symptoms) to 10 (worst).

Statistical analysis
The primary analysis was the comparison of the drop in MAP from baseline to BPNadir (delta) following muscle preactivation and muscle tensing compared to Control. Secondary analyses included comparisons of HR, determined SV, CO, and SVR at BPNadir following PREACT and TENSE compared to Control. We tested the distribution of each variable using the Shapiro-Wilk normality test. Comparisons of each individual VOSS rating and delta hemodynamic parameter MAP, HR, SV, CO, and SVR between muscle preactivation, muscle tensing, and Control were performed using a repeated-measures analysis of variance with Bonferroni correction for the 3 comparisons.

For the Control, PREACT, and TENSE interventions, an additional analysis was done comparing the raw baseline hemodynamics to the BPNadir hemodynamics. For the PREACT intervention, 2 additional analyses were done comparing baseline hemodynamics to intervention hemodynamics as well as intervention to BPNadir. This included MAP, HR, SV, CO, and SVR. These comparisons were performed using paired t tests. These were secondary analyses, and the P values were not adjusted.

IBM SPSS Statistics 24 (IBM Corp., Armonk, NY) was used for all statistical analyses. GraphPad Prism 8 (GraphPad Software, San Diego, CA) was used to create all figures. Data are reported as mean ± SD.

Sample size calculation
A sample size of 26 IOH patients was considered robust (90% power) in detecting a difference in nadir SBP of 15 mm Hg following PREACT (or TENSE) compared to Control, assuming SD of 15 mm Hg, using a paired test of continuous data and a .05 2-sided significance level. This was based on previous data indicating the lack of a normal (15–20 mm Hg) drop in SBP during a stand following a physical countermaneuver in IOH patients.

Results
Participant demographics
Median participant age of the 24, all female, participants was 31 years (25 to 38 years) (Table 1). Most (18 [75%]) were
Comparisons of absolute values during baseline and after standing

**PREACT vs Control**

MAP during the seated baseline was not significantly different between control and PREACT; however, after standing (at the BPnadir time point), MAP was significantly higher following PREACT compared to Control (66 ± 10 mm Hg vs 59 ± 10 mm Hg; \( P < .001 \)) (Figure 3A). HR and SVR both were not significantly different at baseline or BPnadir following PREACT compared to Control. SV and CO both were significantly higher after standing at BPnadir following PREACT compared to Control despite not being significantly different during baseline. Data are given in Table 2 and Figure 3.

**TENSE vs Control**

MAP during baseline was not significantly different between Control and TENSE; however, after standing at the BPnadir time point, MAP was significantly higher following TENSE compared to Control (70 ± 10 mm Hg vs 59 ± 10 mm Hg; \( P < .001 \)) (Figure 3A). HR, SV, and SVR were not significantly different during baseline between TENSE and Control. HR was significantly lower at BPnadir following TENSE compared to Control. SV and SVR both were significantly higher at BPnadir following TENSE compared to Control. CO was not significantly different during baseline or at BPnadir following the TENSE intervention compared to Control. Data are given in Table 2 and Figure 3.

**PREACT vs TENSE**

MAP at BPnadir following muscle preactivation was not significantly different than muscle tensing (66 ± 10 mm Hg vs 70 ± 10 mm Hg; \( P = .10 \)) (Figure 3A). HR, SV, and CO were not significantly different during baseline or at BPnadir following PREACT compared to TENSE. SVR was significantly lower at BPnadir following PREACT compared to TENSE, but there was no statistical difference during baseline. Data are given in Table 2 and Figure 3.

**Delta values comparisons**

**PREACT vs Control**

The drop in MAP following muscle preactivation through seated knee raises was significantly reduced compared to Control (−21 ± 8 mm Hg vs −28 ± 10 mm Hg; \( P < .001 \)) (Table 2 and Figure 4A). The increase in HR following PREACT was not significantly reduced compared to Control (19 ± 7 bpm vs 23 ± 8 bpm; \( P = .90 \)) (Table 2 and Figure 4B). The increases in SV and CO were significantly higher following PREACT compared to Control. There was no significant difference in the change in SVR when comparing PREACT to Control. The VOSS symptom score following PREACT was significantly reduced compared to Control (9 ± 8 au vs 14 ± 9 au; \( P = .033 \)) (Table 2 and Figure 4F). Data are given in Table 2 and Figure 4.

**TENSE vs Control**

The drop in MAP following muscle tensing through leg crossing was significantly reduced compared to Control (−18 ± 10 mm Hg vs −28 ± 10 mm Hg; \( P < .001 \)) (Table 2 and Figure 4A). The increase in HR following

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**Table 1**

<table>
<thead>
<tr>
<th>Participant demographics (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (y)</strong></td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
</tr>
<tr>
<td>Height (cm)</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
</tr>
</tbody>
</table>

Values are given mean ± SD or %. 
BMI = body mass index.
TENSE was significantly reduced compared to Control (17 ± 8 bpm vs 23 ± 8 bpm; *P* = .001) (Table 2 and Figure 4B). The increases in SV and CO were significantly higher following TENSE compared to Control. There were no significant changes in SVR when comparing TENSE to Control. The VOSS symptom score following the TENSE intervention was significantly reduced compared to Control (8 ± 8 au vs 14 ± 9 au; *P* = .046) (Table 2 and Figure 4F). Data are shown in Table 2 and Figure 4.

### PREACT vs TENSE

Activating the lower body muscles before standing vs after standing did not result in significantly different MAP values (−21 ± 8 mm Hg vs −18 ± 10 mm Hg; *P* = .62) (Figure 4A). The increase in HR following PREACT was not significantly reduced compared to TENSE. There was no significantly different increase in SV or CO following the PREACT intervention compared to the TENSE intervention after standing. The drop in SVR was significantly larger following PREACT compared to TENSE. The VOSS symptom score following PREACT was similar to TENSE (9 ± 8 au vs 8 ± 8 au; *P* = 1) (Figure 4F and Table 2). Data are shown in Figure 4.

### Discussion

The key findings of this study are that (1) preactivating lower body muscles before standing reduces the drop in MAP as well as symptoms in young female IOH patients by increasing cardiac output; and (2) mechanically compressing lower body muscles following a stand reduces the drop in MAP as well as symptoms in young female IOH patients by increasing stroke volume.

### Physiology underlying IOH

IOH most likely is explained by excessive vasodilation occurring in the lower body muscles due to local metabolic pathways. Alternative explanations include the muscle pump and the cardiopulmonary receptor reflex. The brief leg and abdominal muscle contraction required to stand translocates blood from the venous vasculature toward the thorax (muscle pump), effectively increasing RAP. This increase in RAP activates the cardiopulmonary mechanoreceptors, which initiates a reflex withdrawal of sympathetic vasoconstrictor tone, resulting in a fall of peripheral resistance lasting for 6–8 seconds. Although both these mechanisms still play important roles during a stand, the time course of these 2 responses do not align with the time course of the hypotension seen in IOH.

### Physical counter-maneuvers following a stand

Physical counter-maneuvers have been shown to effectively improve symptoms in other orthostatic intolerance disorders such as vasovagal syncope and classic orthostatic hypotension. Previous research has explored lower body muscle tensing in IOH following a stand from a squatting position. It has been shown that performing this intervention after rising from a squat significantly attenuates the drop in BP. Additionally, using static handgrip 30 seconds before standing and continued through standing also has been shown to minimize orthostatic symptoms in IOH patients by evoking the exercise pressor reflex. However, these maneuvers have not previously been tested in the clinically relevant situation of standing up from a seated position.

### Table 2 Delta hemodynamics values and mean hemodynamic values at baseline and BP nadir for each stand

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Time point*</th>
<th>Control</th>
<th>PREACT</th>
<th>*Control vs PREACT</th>
<th>TENSE</th>
<th>*Control vs TENSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>Baseline</td>
<td>86 ± 9</td>
<td>87 ± 8</td>
<td>.001‡</td>
<td>88 ± 7</td>
<td>.48‡</td>
</tr>
<tr>
<td>BP nadir</td>
<td>59 ± 10</td>
<td>66 ± 10</td>
<td>.001‡</td>
<td>70 ± 10</td>
<td>.001‡</td>
<td></td>
</tr>
<tr>
<td>Delta</td>
<td>−28 ± 10</td>
<td>−21 ± 8</td>
<td>.001‡</td>
<td>−18 ± 10</td>
<td>.001‡</td>
<td></td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>Baseline</td>
<td>81 ± 9</td>
<td>80 ± 9</td>
<td>.1</td>
<td>83 ± 10</td>
<td>.34</td>
</tr>
<tr>
<td>BP nadir</td>
<td>104 ± 12</td>
<td>103 ± 16</td>
<td>.01‡</td>
<td>100 ± 14</td>
<td>.01‡</td>
<td></td>
</tr>
<tr>
<td>Delta</td>
<td>23 ± 8</td>
<td>19 ± 7</td>
<td>.89</td>
<td>17 ± 8</td>
<td>.001‡</td>
<td></td>
</tr>
<tr>
<td>SV (mL)</td>
<td>Baseline</td>
<td>75 ± 14</td>
<td>77 ± 15</td>
<td>.62</td>
<td>76 ± 15</td>
<td>1</td>
</tr>
<tr>
<td>BP nadir</td>
<td>76 ± 15</td>
<td>88 ± 18</td>
<td>.001†</td>
<td>86 ± 19</td>
<td>.01†</td>
<td></td>
</tr>
<tr>
<td>Delta</td>
<td>1 ± 9</td>
<td>11 ± 10</td>
<td>.002‡</td>
<td>9 ± 12</td>
<td>.02‡</td>
<td></td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>Baseline</td>
<td>6 ± 1.2</td>
<td>6 ± 1.1</td>
<td>.1</td>
<td>6 ± 1.1</td>
<td>1</td>
</tr>
<tr>
<td>BP nadir</td>
<td>7 ± 1.4</td>
<td>9 ± 1.7</td>
<td>.001‡</td>
<td>8 ± 1.6</td>
<td>.05</td>
<td></td>
</tr>
<tr>
<td>Delta</td>
<td>1 ± 1</td>
<td>3 ± 1</td>
<td>.001‡</td>
<td>2 ± 1</td>
<td>.17</td>
<td></td>
</tr>
<tr>
<td>SVR (dyne·s/cm²)</td>
<td>Baseline</td>
<td>1226 ± 320</td>
<td>1211 ± 255</td>
<td>1</td>
<td>1217 ± 264</td>
<td>1</td>
</tr>
<tr>
<td>BP nadir</td>
<td>700 ± 161</td>
<td>683 ± 162</td>
<td>1</td>
<td>683 ± 160</td>
<td>.045‡</td>
<td></td>
</tr>
<tr>
<td>Delta</td>
<td>−527 ± 253</td>
<td>−528 ± 185</td>
<td>1</td>
<td>−434 ± 223</td>
<td>.22</td>
<td></td>
</tr>
</tbody>
</table>

Continuous data are given as absolute value (± SD) of each hemodynamic parameter during baseline and after standing at BP nadir as well as the delta hemodynamic values of each parameter.

BP nadir = nadir blood pressure; CO = cardiac output; Control = no intervention; HR = heart rate; MAP = mean arterial pressure; PREACT = lower body muscle preactivation; SV = stroke volume; SVR = systemic vascular resistance; TENSE = lower body muscle tensing.

*Baseline values are 30-second averages taken during the final 30 seconds of the seated periods. BP nadir values are the nadir values taken at BP nadir following the stand. Delta values are BP nadir minus baseline values.

†P values are for a repeated-measures analysis of variance with Bonferroni correction for multiple comparisons.

‡Indicates significance.
The results of this study have shown that TENSE following a sit-to-stand significantly attenuated the drop in MAP and was driven by an increase in SV. This could be explained by the mechanical compression of the lower body muscles including the abdomen, pushing blood from the splanchnic vessels back up toward the heart, resulting in an increase in SV. Additionally, there did also seem to be a slight attenuation of the drop in SVR when comparing the absolute nadir SVR values. This could be explained by the mechanical compression of the leg vasculature through leg crossing.

Mechanism of muscle preactivation in IOH
We have previously shown that there is a refractory period to the muscle activation response underlying IOH. Symptoms did not reappear upon standing if IOH participants remained seated for only a short period of time (30 seconds to 2 minutes) before the stand. This led to the idea that muscle preactivation through knee raises before standing may simulate the thigh muscle activation of standing, and increase SV and/or SVR and subsequently result in reduced symptoms upon standing.

This study found that PREACT significantly reduces the drop in MAP and symptoms upon standing in IOH. This has not previously been demonstrated. This attenuation of the MAP drop likely is due to an overall increase in CO following the stand, which was driven by an increase in SV. However, SVR decreased the same amount following muscle preactivation vs Control, indicating that the vasodilation that occurs due to local mechanisms in the skeletal muscle in response to the brief muscle contraction required to stand in IOH was not attenuated by muscle preactivation; rather, it was combatted with increased cardiac output.

Muscle preactivation vs muscle tensing
When comparing the overall response to the muscle preactivation and muscle tensing interventions, both resulted in an attenuated drop in MAP as well as a reduction in orthostatic symptoms. However, when looking at the underlying physiological response resulting in this reduction in MAP and symptoms, the 2 interventions differed slightly. All 3 stands resulted in a drop in MAP, likely due to the large drop in SVR following each stand. However, PREACT and TENSE experienced significantly smaller drops in MAP despite the reduction in SVR being the same in preactivation and tensing compared to Control. This large drop in vascular resistance in theory should cause a large reduction in MAP, as seen in Control, but the drop in MAP was reduced following both PREACT and TENSE. PREACT reduced the drop in MAP by increasing HR and SV while seated, with SV remaining elevated through the stand resulting in an increase in CO. This increase in CO combatted the drop in SVR, which allowed the drop in MAP to be attenuated following PREACT.

TENSE showed an increase in SV, likely due to an increase in venous return from the lower body as a direct result of mechanically compressing the leg vasculature through the TENSE maneuver (leg crossing). However, the increase in HR was reduced upon standing in TENSE, unlike PREACT, resulting in no overall change in CO. The TENSE intervention also showed a reduced drop in SVR when compared to PREACT but not compared to Control. These results indicate that an increase in preload, which in turn resulted in an increase in SV, combatted the drop in SVR and was the driving factor in the reduced drop seen in MAP following TENSE.

Comparatively, the reduced drop in MAP following PREACT was a result of an overall increase in CO, which started during the intervention while seated and continued through the stand. The TENSE intervention, however, attenuated the drop in MAP by increasing SV through mechanical compression of the leg vasculature after standing.

Figure 4  Delta hemodynamic changes following lower body muscle preactivation (PREACT), tensing (TENSE), and no intervention (Control). Delta MAP (A), HR (B), SV (C), CO (D), SVR (E), and Vanderbilt Orthostatic Symptom Score (VOSS) (F) following Control (blue), PREACT (pink), and TENSE (purple). P values obtained from a repeated-measures analysis of variance with Bonferroni correction for multiple comparisons. Abbreviations as in Figure 3. (Figure created using GraphPad Prism 8. GraphPad Software, San Diego, CA.)
Clinical implications
Current management options for IOH patients include being told to “stand up slowly” or to perform lower body muscle tensing after standing if they feel symptomatic. This study provides a novel pre-emptive management option that IOH patients can utilize every day before standing. The information from this study can be used when recommending management options to IOH patients who experience symptoms multiple times a day. Combining muscle preactivation and muscle tensing could be another possible management option, but this requires further prospective testing.

Study limitations
The Control stand was always performed before the PRE-ACT and TENSE stands, as it was part of an earlier portion of the study. In theory, there could have been a training effect, but based on interventions in other portions of the study, this does not seem to be the case. The Control stand was performed at 2 separate portions of the study, and when compared there was no significant difference. This indicates that there was no training effect.

IOH occurs in males and females, but all participants in this study were female. We made a decision to actively recruit male participants; however, this was just before our clinical research was shut down because of restrictions due to the coronavirus disease 2019 (COVID-19) pandemic. Females with reflex syncope have a greater relative decrease of thoracic blood volume compared to males upon standing, resulting in lower orthostatic tolerance and a higher rate of reflex syncope in females. Future IOH studies should aim to include males to better understand whether there are any sex differences in the response to these interventions.

Conclusion
This study demonstrated that lower body muscle preactivation attenuates the BP drop, and symptoms, of IOH upon standing. This study also confirmed that leg crossing with muscle tensing after standing attenuates the MAP drop, and symptoms, of IOH upon standing. These are simple, effective, and cost-free interventions that patients can use to prevent their symptoms from IOH.

Acknowledgment
We thank our participants for making this study possible.

Appendix

Supplementary data
Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2021.12.030.

References