Orthostatic Hypotension

Efficacy of Servo-Controlled Splanchnic Venous Compression in the Treatment of Orthostatic Hypotension
A Randomized Comparison With Midodrine


Abstract—Splanchnic venous pooling is a major hemodynamic determinant of orthostatic hypotension, but is not specifically targeted by pressor agents, the mainstay of treatment. We developed an automated inflatable abdominal binder that provides sustained servo-controlled venous compression (40 mmHg) and can be activated only on standing. We tested the efficacy of this device against placebo and compared it to midodrine in 19 autonomic failure patients randomized to receive either placebo, midodrine (2.5–10 mg), or placebo combined with binder on separate days in a single-blind, crossover study. Systolic blood pressure (SBP) was measured seated and standing before and 1-hour post medication; the binder was inflated immediately before standing. Only midodrine increased seated SBP (31±5 versus 9±4 placebo and 7±5 binder, P=0.003), whereas orthostatic tolerance (defined as area under the curve of upright SBP [AUCsup]) improved similarly with binder and midodrine (AUCsup 195±35 and 197±41 versus 19±38 mmHg×minute for placebo; P=0.003). Orthostatic symptom burden decreased with the binder (from 21.9±3.6 to 16.3±3.1, P=0.032) and midodrine (from 25.6±3.4 to 14.2±3.3, P<0.001), but not with placebo (from 19.6±3.5 to 20.1±3.3, P=0.756). We also compared the combination of midodrine and binder with midodrine alone. The combination produced a greater increase in orthostatic tolerance (AUCsup 326±65 versus 140±53 mmHg×minute for midodrine alone; P=0.028, n=21) and decreased orthostatic symptoms (from 21.8±3.2 to 12.9±2.9, P<0.001). In conclusion, servo-controlled abdominal venous compression with an automated inflatable binder is as effective as midodrine, the standard of care, in the management of orthostatic hypotension. Combining both therapies produces greater improvement in orthostatic tolerance.

Clinical Trial Registration—URL: https://www.clinicaltrials.gov. Unique identifier: NCT00223691.

Key Words: autonomic nervous system ■ blood pressure ■ hemodynamic ■ midodrine ■ orthostatic hypotension ■ splanchnic circulation

Orthostatic hypotension (OH) is a significant medical problem; it occurs in ≈6% of healthy elderly in the community, 18% to 54% of nursing home residents and ≤60% in hospitalized elderly.1 The incidence of OH increases exponentially after the age of 65 years, and its importance is likely to increase as our population ages.2 OH is not only a cause of disability and impaired quality of life but it is also associated with a 2.6-fold increase in the risk of falls,3 and is an independent risk factor for the development of chronic kidney disease, comparable with having coronary artery disease, smoking, hypertriglyceridemia, and other risk factors that receive more attention.4 Moreover, OH is an independent risk factor for increased mortality.5 OH is particularly disabling in patients with severe impairment of autonomic pathways (neurogenic OH), who cannot engage the hemodynamic mechanisms that normally prevent the drop in blood pressure (BP) on standing. Despite its clinical importance, there are only 2 drugs approved for the treatment of neurogenic OH, the α-1 agonist midodrine and the norepinephrine prodrug droxidopa. The use of these drugs, however, is often limited by the development or worsening of supine hypertension, a common comorbidity in these patients.

Received January 21, 2016; first decision February 11, 2016; revision accepted March 31, 2016.
The online-only Data Supplement is available with this article at http://hyper.ahajournals.orglookup/suppl/doi:10.1161/HYPERTENSIONAHA.116.07199/DC1.
Correspondence to Italo Biaggioni, 560A RRB, Vanderbilt University Medical Center, 2222 Pierce Ave, Nashville, TN 37232. E-mail Italo.biaggioni@vanderbilt.edu
© 2016 American Heart Association, Inc.
Hypertension is available at http://hyper.ahajournals.org
DOI: 10.1161/HYPERTENSIONAHA.116.07199
It is also unlikely that these drugs will have a beneficial effect on the comorbidities associated with OH, namely renal impairment, heart failure, and increased risk of overall mortality. Finally, they do not specifically target a major hemodynamic mechanism of OH, which is a reduction in stroke volume and venous return because of venous pooling, particularly in the splanchnic circulation. There is a need, therefore, to develop therapeutic approaches that address these limitations.

Compression of venous capacitance beds with lower body compression garments improve venous return and can be useful in treating OH. The main advantages of this approach are that immediate presissor responses could be achieved only when required (ie, standing); and that it can be safely combined with virtually any drug therapy. Nonetheless, compliance is low because they are difficult to use at compression levels that are effective. Therefore, we developed an automated inflatable binder that can be selectively activated in the upright posture to produce a sustained compression level of 40 mm Hg, a level known to produce compression of the venous splanchnic circulation. In this study, we present proof-of-concept studies showing that servo-controlled splanchnic venous compression with this inflatable binder is as effective as midodrine, the current standard of care, in improving orthostatic tolerance and reducing orthostatic symptoms in patients with primary autonomic failure. In addition, we evaluated whether the binder combined with midodrine provided additional improvement in orthostatic tolerance and symptoms, compared with midodrine alone.

Methods

Subjects

We studied a total of 23 patients with neurogenic OH and severe autonomic failure (11 with pure autonomic failure, 5 with Parkinson disease, 5 with probable multiple system atrophy, 1 with dementia with Lewy bodies, and 1 with autonomic failure of unknown pathogenesis) recruited from referrals to Vanderbilt University Autonomic Dysfunction Center between November 2011 and October 2014 (Figure S1 in the online-only Data Supplement). Clinical diagnoses were defined using current diagnostic criteria. OH was defined as ≥20-mm Hg decrease in systolic BP (SBP) or ≥210 mm Hg of diastolic BP within 3 minutes on standing. Patients were excluded if they were bedridden, if they had secondary causes of autonomic failure such as diabetes mellitus or amyloidosis, or if they had contraindications to administration of pressor agents (eg, coronary artery disease) or to any increase in intra-abdominal pressure (eg, severe gastroesophageal reflux and aortic aneurism). The Vanderbilt University Investigational Review Board approved this study, and written informed consent was obtained from each subject before initiating the study (ClinicalTrials.gov NCT00225601).

Screening Procedures

Patients were admitted to the Clinical Research Center at Vanderbilt University and were fed a low-monoamine, methylxanthine-free diet containing 150-mEq sodium and 60- to 80-mEq potassium per day. Medications affecting BP, blood volume, and the autonomic nervous system were withheld for ≥2 half-lives before admission. All other medications were held constant during admission. The screening consisted of a medical history, physical examination, 12-lead ECG, laboratory assessments, and standardized autonomic function tests, including orthostatic stress test, Valsalva maneuver, hyperventilation, cold pressor test, isometric handgrip, and sinus arrhythmia. BP and heart rate (HR) were obtained intermittently using an automated oscillometric sphygmomanometer (Dinamap ProCare, GE Healthcare) and continuously with finger photoplethysmographic volume-clamp BP device (Finometer, FMS, or Nexfin, BMEYE). HR was measured by continuous ECG. During the orthostatic test, blood samples were obtained for norepinephrine while patients were supine and upright, as described previously. Plasma norepinephrine was measured by high-performance liquid chromatography with electrochemical detection.

General Protocol

Patients were studied on 4 separate days in a randomized, crossover manner to receive either a single oral dose of placebo, midodrine 2.5 to 10 mg (Shire Pharmaceuticals Inc, Wayne, PA), placebo combined with abdominal binder (40 mm Hg), or midodrine 2.5 to 10 mg combined with abdominal binder (40 mm Hg). The order of interventions was randomized using computer-generated random numbers. Medications were blinded to patients. The dose of midodrine was chosen based on their regular dose at home (standard of care), and it was kept the same for both study days with midodrine. We used an abdominal compression level of 40 mm Hg based on previous studies in autonomic failure patients showing that sustained abdominal compression of ≤40 mm Hg for short periods of time was safe, tolerable, and produced the greatest pressor effects on upright BP compared with lower compression levels (10–20 mm Hg). Lower compression levels of ≥20 mm Hg, however, were allowed if a patient could not tolerate 40 mm Hg.

Acute medication trials were performed in a post void state and ≥2.5 hours after meals to avoid any confounding effects from postprandial hypotension. Participants were seated comfortably on a chair with their feet on the floor. BP and HR were recorded every 5 minutes with an automated brachial BP cuff (Dinamap ProCare, GE Healthcare). After 30 minutes of baseline measurements, patients were asked to stand for ≤10 minutes or until they developed symptoms of presyncope. BP and HR were measured at 1, 3, 5, and 10 minutes of standing (or as tolerated). The amount of time patients were able to stand was recorded by the study nurse using a timer. Immediately after sitting, the study medication was given and, on the study days with abdominal compression, the binder was placed (deflated) around the abdomen. BP and HR were measured for the next 60 minutes. At the end of this period, the binder was inflated to 40 mm Hg, and the 10-minute assessment of orthostatic tolerance was then repeated as described above, but this time with the binder inflated. Patients were asked to rate the severity of their orthostatic symptoms immediately after the orthostatic tolerance tests using the Orthostatic Hypotension Symptom Assessment (OHSAs) Score. The questionnaire consisted of 6 items, including the following: (1) light-headedness, dizziness, feeling faint, or like passing out; (2) blurring vision, seeing spots, or tunnel vision; (3) trouble concentrating; (4) weakness; (5) fatigue; and (6) head, neck, or shoulder discomfort. Each item was scored on a 0 to 10 scale (with 0 reflecting absence of symptoms), and the total scores (range: 0–60) before and after treatment were used as a measure of symptom burden. We further tested the acute effect of the binder on standing BP by deflating the binder at the end of the postintervention orthostatic tolerance test. Standing BP and HR were recorded for one more minute with the binder deflated.

Study Objectives

Our primary objective was to test the efficacy of abdominal compression with the inflatable binder against that of placebo in improving orthostatic tolerance in autonomic failure patients, and to compare it with midodrine, the standard of care. Orthostatic tolerance (primary outcome) was defined as the area under the curve of upright SBP (ΔAUCSBP; upright SBP multiplied by standing time). Secondary outcomes included orthostatic symptoms and seated SBP, as outlined in the Statistical Methods section of this article. Comparisons were made between placebo, midodrine, and placebo combined with binder, and included all patients who were able to complete these 3 treatment arms. Patients who were unable to stand in one of the study arms were not included in the final analysis.

A secondary objective of the study was to test the hypothesis that abdominal compression with the inflatable binder in combination with midodrine would produce a greater improvement in orthostatic...
tolerance compared with midodrine alone. Outcome measurements were compared in patients who completed these 2 treatment groups.

**Description of the Inflatable Abdominal Binder**

We developed an inflatable abdominal binder from off-the-shelf components that applies a sustained servo-controlled compression pressure, programmable from 20 to 40 mm Hg. The device consisted of a commercially available abdominal band or lumbar support garment (Airform back support, Ossur North America) made of polyester cloth with adjustable Velcro, and an inflatable cuff (commercially available BP cuff) placed underneath. The binder was attached to patients around the abdomen with the inflatable bladder placed at the level of the umbilicus. The inflatable bladder was pressurized by an automated inflator, which also monitored and maintained the compression level by inflating or deflating the bladder. We initially used a commercial inflator (Rapid Cuff Inflator E20, D.E. Hockason, Inc) and air pump (AG101 Air Source, D.E. Hockason, Inc) located in a cart next to the patient. We then developed a portable automated air pump and controller box that was attached to the binder. Both inflators were manually activated to provide a compression level of ≈40 mm Hg <2 minutes before the postintervention orthostatic tolerance test. The inflation pressure was maintained constant by a servo-controlled circuit. The time taken to inflate or deflate the bladder with either pump was <30 s. A detailed description of the automated binder is available in the Data Supplement.

**Statistical Methods**

The primary outcome was the change from baseline in orthostatic tolerance, defined as the AUC of upright SBP calculated by the trapezoidal rule (ΔAUCSBP; upright SBP multiplied by standing time). This is a composite score that integrates both the standing time and ΔSBP differences in t tests with significant overall treatment difference was found, paired comparisons of groups were analyzed using repeated-measures ANOVA. If a significant difference was found, paired comparisons between treatment groups were performed with SPSS version 22.0 (IBM Corp). A value of <0.05 was considered significant. Analyses were 2-tailed, and a P value of <0.05 was considered significant. Analyses were performed with SPSS version 22.0 (IBM Corp).

**Results**

**Patient Characteristics and Autonomic Testing**

We studied a total of 23 patients with severe autonomic failure (15 men; 67±2 years): 19 patients completed the 3 treatment arms required for the primary objective (placebo, midodrine, and placebo combined with binder) and 21 patients completed the 2 treatment arms required for the secondary objective (midodrine and midodrine combined with binder; Figure S1).

The presence of severe autonomic failure was evidenced by a profound decrease in SBP on standing (OH), with an inadequate compensatory increase in HR, and by impaired autonomic reflexes (Tables 1 and 2). Respiratory sinus arrhythmia was markedly reduced in all patients, suggesting parasympathetic dysfunction. Evidence of sympathetic dysfunction included blunted pressor responses to isometric handgrip and cold pressor tests, and an exaggerated decrease in SBP during phase II and absence of BP overshoot during phase IV of the Valsalva maneuver.

**Primary Objective: Comparison of the Effects of the Inflatable Abdominal Binder, Placebo, and Midodrine on Orthostatic Tolerance**

Nineteen of the 23 patients completed the 3 treatment arms. In 2 patients, we were unable to obtain upright BP during one of the treatment arms; in 2 other patients 1 of the study arms was not done for logistical reasons (Figure S1). The dose of midodrine previously determined to be effective in individual patients was used on this study: 8 patients received a single dose of 10 mg of midodrine, 10 patients received 5 mg and 1 patient received 2.5 mg. The compression level of 40 mm Hg was well tolerated in all patients except for one, in whom a lower compression level (20 mm Hg) was used. Average baseline-seated SBP was similar among treatment groups (placebo 105±6 mm Hg, placebo with binder 106±8 mm Hg, placebo with binder 100±5 mm Hg). The difference in median SBP between midodrine and midodrine combined with binder was analyzed using repeated-measures ANOVA. If a significant overall treatment difference was found, paired comparisons between treatment groups were performed with paired t tests with Bonferroni correction as post hoc test. For the secondary objective, differences in ΔAUCSBP and ΔSBP between midodrine and midodrine combined with binder were analyzed using paired t tests. Wilcoxon signed-rank test was used to test whether each treatment decreased the orthostatic symptom score compared with the baseline in both objectives. Power calculation was based on preliminary data from 3 patients. The difference in ΔAUCSBP mean values between placebo combined with binder and placebo alone 1 hour after drug administration was of 302 mm Hg per minute, with SD of difference of 188 mm Hg per minute. Assuming a minimally clinically significant effect size of 150 mm Hg per minute (≈50% of the observed effect) with similar variance, a sample size of 19 patients would have 90% power to detect a difference in mean values between treatments with an α level of 0.05 using paired t test analysis (PS Dupont, version 3.0.34). The study, however, was not powered for a noninferiority comparison between midodrine and placebo combined binder. Data are presented as mean±SEM unless otherwise noted. All of the tests were 2-tailed, and a P value of <0.05 was considered significant. Analyses were performed with SPSS version 22.0 (IBM Corp).

**Table 1. Patient Characteristics**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Primary Objective (n=19)</th>
<th>Secondary Objective (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male/female</td>
<td>12/7</td>
<td>14/7</td>
</tr>
<tr>
<td>Age, y</td>
<td>66±2</td>
<td>68±2</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.3±0.7</td>
<td>27.9±0.7</td>
</tr>
<tr>
<td>Diagnosis, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAF</td>
<td>9 (47)</td>
<td>10 (48)</td>
</tr>
<tr>
<td>PO+OH</td>
<td>4 (21)</td>
<td>5 (24)</td>
</tr>
<tr>
<td>Probable MSA</td>
<td>4 (21)</td>
<td>4 (19)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (11)*</td>
<td>2 (9)*</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>153±4</td>
<td>151±5</td>
</tr>
<tr>
<td>Upright</td>
<td>76±4</td>
<td>75±3</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>65±2</td>
<td>67±2</td>
</tr>
<tr>
<td>Upright</td>
<td>78±3</td>
<td>79±3</td>
</tr>
<tr>
<td>Norepinephrine, pg/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>102±22</td>
<td>124±23</td>
</tr>
<tr>
<td>Upright</td>
<td>221±73</td>
<td>235±64</td>
</tr>
</tbody>
</table>

Data are presented as mean±SEM. Primary objective, efficacy comparison of the binder vs placebo and midodrine. Secondary objective, efficacy comparison between the binder combined with midodrine and midodrine alone. BMI indicates body mass index; MSA, multiple system atrophy; PAF, pure autonomic failure; and PO+OH, Parkinson disease with neurogenic orthostatic hypotension. *One patient with autonomic failure of unknown pathogenesis and 1 patient with dementia with Lewy bodies.
Inflatable Binder for Orthostatic Hypotension

Okamoto et al

111±5 mm Hg, and midodrine 105±4 mm Hg; P=0.338 by repeated-measures ANOVA), suggesting that no significant carryover effects were present between treatment groups.

One hour after drug administration, midodrine significantly increased seated SBP compared with placebo (31±5 versus 9±4 mm Hg, respectively; P<0.001; Figure 1A), and to placebo and binder (7±5 mm Hg; P=0.017). As expected, the binder combined with placebo had a similar effect on seated SBP to that of placebo alone, given that the binder was deflated while patients were seated.

On standing, inflation of the abdominal binder and midodrine produced a similar significant increase in AUC$_{ap}$ (ie, improved orthostatic tolerance) compared with placebo (195±35 and 197±41 versus 19±38 mm Hg×minute on the placebo day; P=0.019 and P=0.010, respectively; Figure 1B). This represents an average increase in SBP of 19.5 mm Hg during the 10-minute standing period for the binder group versus 1.9 mm Hg for the placebo group.

The same number of patients in the binder and midodrine groups (n=14) was able to stand for the full 10 minutes of the postintervention orthostatic test, whereas only 10 did in the placebo group. The increase in 1-minute standing SBP from preintervention was 5±4 mm Hg in the placebo day, 12±4 mm Hg in the placebo combined with binder day, and 16±3 mm Hg in the midodrine day. Compared with placebo, the group averaged SBP at 3, 5, and 10 minutes of standing was significantly higher with midodrine and with placebo combined with binder while it was similar between these 2 groups (P=0.001 for drug effect, P<0.001 for time effect, and P=0.191 for inter action; 2-way ANOVA; Figure S3). Orthostatic symptom scores were obtained at baseline and 1 hour after placebo (n=18), placebo and binder (n=17), and midodrine (n=18). Compared with the baseline values, the total orthostatic symptom burden after 1 hour post
intervention significantly decreased with inflation of the abdominal binder (21.9±3.6 versus 16.3±3.1, respectively; \( P=0.032 \); Figure 1C) and with midodrine (25.6±3.4 versus 14.2±3.3, respectively; \( P<0.001 \)), but not with placebo (19.6±3.5 versus 20.1±3.3, respectively; \( P=0.756 \)). Similar results were obtained if the analysis was restricted to patients with orthostatic symptom scores in all of the treatment arms.

Individual responses and a responder analysis are included in the Data Supplement (Figure S4). Compared with placebo, midodrine, and the binder had a lower proportion of nonresponders at all response levels (ΔAUC\(_{SBP}\); Figure S4B). If we arbitrarily assign an increase from baseline in upright SBP of 15 mm Hg during the 10-minute standing period as a clinically significant improvement (ΔAUC\(_{SBP}\) ≥150 mm Hg×minute; Figure S4A and S4B), 63% (n=12) of patients were responders to the binder versus 16% (n=3) for placebo (\( P=0.016 \) by McNemar test; Figure S4B and S4C). There was no difference in the percentage of responders between the binder and midodrine (68%;n=13, \( P=1.000 \) by McNemar test; Figure S4B and S4C). The number of nonresponders was too small to determine if they differed in any clinical characteristic.

**Acute Pressor Effect of the Inflatable Abdominal Binder**

Fourteen patients were able to stand until the end of the orthostatic test with the binder inflated. In 13 of them, we deflated the binder while they were still standing, and measured standing SBP for an additional minute. Figure 2 shows the standing SBP at 1 minute without the binder (No Binder), at 1 and 10 minutes with the binder inflated, and after 1 minute with the binder deflated. Abdominal compression with the binder significantly increased upright SBP at 1 minute, from 81±6 mm Hg with no binder to 93±7 mm Hg (\( P=0.017 \) by paired \( t \) test). After 10 minutes standing with the binder inflated, SBP remained the same (93±5 mm Hg) and significantly decreased to baseline levels (82±5 mm Hg; \( P=0.001 \) by paired \( t \) tests) when the binder was deflated. In 9 of the 13 patients, SBP remained ≥90 mm Hg after 10 minutes standing, above the threshold pressure below which cerebral blood flow autoregulation fails in these patients and triggers symptoms of cerebral hypoperfusion.21

**Secondary Objective: Comparison of the Effects of the Inflatable Abdominal Binder in Combination With Midodrine versus Midodrine Alone on Orthostatic Tolerance**

Twenty-one patients completed the 2 study arms required for the secondary objective; in the other 2 patients one of the study days were not done for logistical reasons (Figure S1). Eight patients received a 10-mg dose of midodrine, 11 patients received 5 mg, and 2 patients received 2.5 mg. An abdominal compression level of 20 mm Hg was used in 1 patient. Baseline-seated SBP was similar between groups (midodrine 105±4 mm Hg and midodrine combined with binder 108±6 mm Hg; \( P=0.691 \)). As expected, the change from baseline in seated SBP after 1 hour postdrug did not differ between midodrine alone and midodrine combined with the binder deflated (30±5 versus 32±5 mm Hg, \( P=0.808 \); Figure 3A). On standing, the combination of midodrine and binder produced a greater increase in AUC\(_{SBP}\) (improved orthostatic tolerance) compared with midodrine alone (326±65 versus 140±53 mm Hg×minute, respectively; \( P=0.028 \); Figure 3B). Seventeen patients with the combination were able to stand for the full 10 minutes of the postintervention orthostatic test compared with 14 in the midodrine group. The increase in standing SBP at 1 minute from preintervention was greater with the combination than with midodrine alone, but the difference did not reach statistical significance (23±4 versus 14±3 mm Hg, respectively; \( P=0.068 \)). Orthostatic symptom scores were obtained at baseline and 1 hour post intervention in 20 patients with midodrine alone and in 19 patients with the combination. Total symptom burden was significantly reduced with midodrine alone (from 26.0±3.1 to 16.7±3.2; \( P=0.005 \); Figure 3C) and with midodrine combined with binder (from 21.8±3.2 to 12.9±2.9; \( P<0.001 \)).

**Adverse Events**

One subject reported mild abdominal discomfort with a compression level of 40 mm Hg, but deflation to a lower compression level (20 mm Hg) improved the discomfort, and allowed the patient to complete the studies. All other patients tolerated the procedure and no other adverse events were reported with the binder.

**Discussion**

We found that servo-controlled splanchnic venous compression, using an inflatable automated abdominal binder at a compression level of 40 mm Hg, was as effective as midodrine, the current standard of care, in improving upright BP, and reducing orthostatic symptoms. Greater beneficial effects were obtained when both the treatments were applied simultaneously. Abdominal compression has been previously used for the treatment of OH, but the use of a servo-controlled automated inflatable binder that can be activated only when required (ie, standing) is a novel approach.
Despite the clinical importance of OH, there are few available options for its treatment. Midodrine and droxidopa are the only drugs approved by the FDA for the treatment of neurogenic OH. Both are prodrugs that are activated through their conversion, respectively, to desglymidodrine, a selective \( \alpha_1 \)-adrenoreceptor agonist, and norepinephrine.\(^{22}\) Fludrocortisone is also commonly used in the treatment of OH, and it is generally regarded as a volume expander. The increase in plasma volume, however, is transient and its long-term pressor effect relies on an increase in peripheral resistance.\(^{23,24}\)

Not only are treatment options scarce but current therapies for neurogenic OH have limitations. Midodrine and other pressor agents can induce or worsen supine hypertension, given that these drugs increase both supine and standing BP, so that OH (the difference between supine and standing BP) is often not selectively improved. Thus, it is less likely that these drugs help to reduce the risk of renal disease, heart failure, and overall mortality associated with OH, and they may be contraindicated in patients with significant cardiovascular disease. Moreover, side effects of these drugs (eg, urinary retention and piloerection for midodrine, exaggerated fluid retention and hypokalemia for fludrocortisone) further limit their use. Finally, direct vasoconstrictors such as midodrine do not specifically target a major hemodynamic mechanism responsible for neurogenic OH, the reduction in venous return because of failure of sympathetically mediated contraction of capacitance beds.

On standing, there is normally an orthostatic shift of 500 to 700 mL of blood from the chest to the venous capacitance system below the diaphragm, and most of this venous pooling occurs in the splanchnic circulation.\(^{25}\) The splanchnic circulation contains a large and highly compliant venous bed, which normally stores \( \approx25\% \) of the blood volume at rest,\(^{26}\) and receives \( \leq25\% \) of the resting cardiac output.\(^{27}\) Splanchnic veins are highly innervated by sympathetic nerves and represent the largest blood volume reservoir in the human body. Veins of the extremities, however, are less compliant and have relatively insignificant sympathetic innervation; thus, their role as blood volume reservoir is relatively minor.\(^{27}\) This is consistent with the observation that patients who underwent selective bilateral splanchnic sympathectomy often developed OH, whereas those with sympathetic denervation of lower limbs by bilateral lumbar sympathectomy did not.\(^{28}\) Taken together, these observations support the notion that splanchnic capacitance vessels play an important role in the regulation of upright BP.

Thus, nonpharmacological approaches targeting capacitance vessels, particularly splanchnic veins, not only may be effective in increasing standing BP but also may address the limitations of pressor agents. Indeed, mechanical compression of venous capacitance beds in the lower body has been shown to improve upright BP and orthostatic symptoms by increasing stroke volume and cardiac output in patients with primary autonomic failure.\(^{6}\) Compression of the abdominal vascular bed was by far the most effective site to improve standing BP, whereas leg compression alone was much less effective presumably because it is a much smaller volume reservoir.\(^{6,29}\) For it to be effective, however, compression of the abdomen has to be sustained and intense enough to produce a measurable effect on OH while being tolerable to patients. In this study, we used a maximal compression level of 40 mm Hg based on our pilot studies and the literature. Smit et al\(^{6}\) has shown that abdominal compression with air-pressurized antigravity suits increased standing SBP by 11 to 17 mm Hg at a compression level of 15 to 20 mm Hg, whereas higher compression levels (40 mm Hg) had greater pressor effects. Furthermore, several acute studies have documented that abdominal compression of \( \leq40 \) mm Hg was safe, tolerable, and did not

---

**Figure 3.** Changes from baseline in seated systolic blood pressure (\( \Delta \text{SBP} \), A), and areas under the curve of standing SBP (\( \Delta \text{AUC}_{\text{SBP}} \), B) after 1 h post drug and orthostatic symptom scores (C) at baseline (pre) and after 1 h of the intervention (post). The binder was inflated immediately before standing. The total score ranges from 0 to 60, with lower scores reflecting lower symptom burden. Values are expressed as mean±SEM.
increase supine BP. More important, abdominal compression of 40 mm Hg provides selective venous compression without affecting aortic blood flow. 

Unfortunately, current compression garments have low patient compliance. Waist-high compression stockings require substantial time and significant effort to put on, and once on it is impractical for patients to take them off even for periods when they are no longer needed. Elastic abdominal binders are easier to put on and off, but are difficult to apply at the required compression level for them to be effective (20–40 mm Hg). Most patients may require assistance applying them, making it difficult to selectively use abdominal compression only while standing. Furthermore, applying abdominal compression while patients are supine results in a reduction in cardiac preloading and stroke volume, suggesting that compression garments should be used only in the upright posture. Thus, abdominal binders are effective treatments in laboratory settings, but their effectiveness is limited by difficulty of use and low compliance. The automated abdominal binder was developed to overcome these limitations. The main advantages of this device would be that (1) it can apply effective abdominal compression (manually or automatically) only when needed (when the patient stands) and (2) our servo-controlled design ensures that a predefined sustained compression level is maintained, by automatically inflating and deflating the bladder. This latter feature would avoid excessive, and potentially harmful, increases in intra-abdominal pressure when performing physiological maneuvers such as coughing, sneezing, breathing deeply, etc; or while bending over or lifting heavy objects.

Our results indicate that the automated abdominal binder improved standing BP and reduced orthostatic symptoms in a magnitude similar to that of midodrine, the standard of care. Furthermore, the abdominal binder provides a greater increase in orthostatic tolerance when added to midodrine compared with midodrine alone (Figure 3B). This suggests that the binder and midodrine have complementary hemodynamic effects (venous compliance and arterial vasoconstriction, respectively) so that combination therapy would be additive. Desglymidodrine, the active metabolite of midodrine, constricts peripheral human veins in vitro and in healthy volunteers. Thus, in theory, midodrine could reduce splanchnic capacitance. However, selective α1-adrenoreceptor stimulation with systemic infusion of phenylephrine failed to increase venous return and cardiac output in normal subjects, and in autonomic failure patients midodrine 10 mg did not decrease calf venous compliance. Taken together, these observations suggest that the pressor effects of midodrine are mediated predominantly by resistance vessels, whereas its effect on capacitance vessels, particularly those in the splanchnic circulation, is less important. This also agrees with our observation that selective splanchnic venous compression with the binder produced additional improvement in orthostatic tolerance when combined with midodrine.

Finally, the ideal treatment for OH would preferentially increase upright BP while having less of an effect in supine or seated BP. This concept is shown graphically in Figure 4; that is, the increase in BP produced by an ideal agent would fall above the line of identity. We found, however, that pressor agents such as midodrine increase seated BP to a greater degree than standing BP (Figure 4), so that symptoms are improved by an increase in standing BP, rather than a true improvement in OH (difference between standing and seated BP). By contrast, the binder selectively improves upright BP by design, a characteristic of the ideal treatment for OH that avoids worsening of supine hypertension. It also improved the response to midodrine, by shifting it toward the line of identity (Figure 4, arrows).

There are some potential limitations to this study. First, we only tested responses to the inflatable binder during ≤10 minutes of standing. This was designed as a proof-of-concept study to show acute effects of the binder in BP and symptoms in autonomic failure patients. Further studies are needed to assess the long-term efficacy, tolerability, and practical use of the inflatable binder for the treatment of neurogenic OH. Second, a sham binder was not used as a control because adequate blinding of patients wearing a sham device would not have been possible given our cross-over study design. To overcome this limitation, we further tested the pressor effects of the binder by deflating it at the end of orthostatic tolerance test. As shown in Figure 2, standing BP decreased to baseline levels after 1 minute of abdominal decompression. Future parallel-group studies are needed to compare the efficacy of the binder with a sham device control group, and between the automated binder with a manually applied one. Third, a relatively small number of patients were included in this study. Autonomic failure is a rare disease, and our sample size is similar to other clinical studies for OH in these patients. Finally, we enrolled patients with severe autonomic failure referred to a tertiary care center, who may not reflect the broader and less severe disease population. Nonetheless, the results of our proof-of-concept studies suggest that our inflatable binder is as effective as midodrine, the current standard of care, in the treatment of OH.

**Perspectives**

The inflatable binder we report has several potential advantages over currently available therapies. Venous pooling is a
major hemodynamic determinant of OH, and the inflatable binder specifically targets the venous splanchnic circulation. It can be activated (manually or with an automated posture detector) only when needed (when patients stand). The servo controller ensures a predefined sustained compression level. It does not worsen supine hypertension (a common comorbidity of other treatment options). Its effects have immediate onset and offset (compared with short-acting pressor agents that have a peak effect of 1 hour and last several hours). It can be combined with pressor agents (to produce a greater effect on upright BP). It relies less on patient compliance or their ability to apply an effective compression level. Further studies are needed to determine the long-term effectiveness, safety, and tolerability of this approach, particularly in comparison with pressor agents and conventional compression garments (eg, elastic abdominal binders).

Acknowledgments
We acknowledge the patients who volunteered for these studies and the Clinical Research Center nurses who made this study possible.

Sources of Funding
This work was supported by National Institutes of Health (NIH) grants PO1 HL66903-, US4 NS065736, R01 HL122847, and ULI TR000445 (National Center for Advancing Translational Sciences). Additional support was provided by American Heart Association grant 14CRP20380211. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Advancing Translational Sciences or the NIH.

Disclosures
L.E. Okamoto, A. Diedrich, F.J. Baudenbacher, R. Harder, and I. Biaggioni have submitted a patent application for the use of an automated inflatable abdominal binder as a medical device. The other authors report no conflicts.

References


---

**Novelty and Significance**

**What Is New?**
- Abdominal venous compression with a servo-controlled automated abdominal binder is as effective as midodrine, the standard of care, in improving orthostatic tolerance in patients with neurogenic orthostatic hypotension.
- Combining the automated abdominal binder with midodrine provides additional improvement in orthostatic tolerance.

**What Is Relevant?**
- Splanchnic venous pooling is a major hemodynamic determinant of orthostatic hypotension, but is not specifically targeted by current treatment approaches.

**Summary**

In this proof-of-concept study, the automated inflatable abdominal binder acutely improved orthostatic tolerance. Longer-term studies are required to assess the effectiveness, safety, and tolerability of this device.
Efficacy of Servo-Controlled Splanchnic Venous Compression in the Treatment of Orthostatic Hypotension: A Randomized Comparison With Midodrine


_Hypertension._ 2016;68:418-426; originally published online June 6, 2016;
doi: 10.1161/HYPERTENSIONAHA.116.07199

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2016 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/68/2/418

Data Supplement (unedited) at:
http://hyper.ahajournals.org/content/suppl/2016/06/06/HYPERTENSIONAHA.116.07199.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Hypertension_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Hypertension_ is online at:
http://hyper.ahajournals.org//subscriptions/
ONLINE DATA SUPPLEMENT

EFFICACY OF SERVO-CONTROLLED SPLANCHNIC VENOUS COMPRESSION IN THE TREATMENT OF ORTHOSTATIC HYPOTENSION. A RANDOMIZED COMPARISON WITH MIDODRINE

Luis E. Okamoto (1,2,3), André Diedrich (1,2,3,6), Franz J. Baudenbacher (6), René Harder (7), Jonathan S. Whitfield (3), Fahad Iqbal (6), Alfredo Gamboa (1,2,3), Cyndya A. Shibao (1,2,3), Bonnie K. Black (1,2,3), Satish R. Raj (1,2,3,4), David Robertson (1,2,3,4,5), Italo Biaggioni (1,2,3,4).

From Vanderbilt Autonomic Dysfunction Center,1 Division of Clinical Pharmacology,2 and Departments of Medicine,3 Pharmacology,4 Neurology,5 Biomedical Engineering6, and Electrical Engineering7, Vanderbilt University School of Medicine

Short Title: Inflatable Binder for Orthostatic Hypotension

Correspondence to:
Italo Biaggioni, MD
560A RRB
Vanderbilt University Medical Center
2222 Pierce Ave
Nashville, TN 37232
615-343-8010
615-343-5144 (fax)
Italo.biaggioni@vanderbilt.edu
**Supplemental Methods**

**Description of the inflatable abdominal binder**

The automated abdominal binder is an investigational device designed to improve tolerance to standing in patients with orthostatic hypotension due to autonomic failure. This device applies a sustained servo-controlled pressure over the abdomen, programmable from 20 to 50 mmHg, when the patient is in the upright posture by using an internal inflatable bladder. The device consists of a commercially available belt (Airform back support, Ossur North America) with an inflatable cuff (commercially available BP cuff) attached underneath, an Arduino Uno microprocessor board, a triple axis accelerometer (SparkFun MMA8452Q), a digital pressure transducer (Honeywell ASDXRRX005PG2A5), a miniature diaphragm pump (Parker T2-04), two miniature pneumatic solenoid valves (Parker X-Valve® 8mm) and three lithium-ion rechargeable batteries (Biopower LP-063450). The belt is an elastic band made of polyester attached to the abdomen with Velcro straps. The inflatable cuff (SC12, Hokanson, Bellevue, WA) was attached to inside of the belt with Velcro. The air pump and controller box are contained inside the abdominal belt and the accelerometer is worn on the thigh, fixed with an elastic band (Figure S2, for illustration purposes the controller box is shown outside the binder and the accelerometer is shown over the clothes). The accelerometer senses changes in body posture and triggers the pump to inflate the binder when the patient stands up, and to deflate it when the patient sits or lies down. For the present studies, however, the study personnel manually activated the pump by tilting the accelerometer to simulate the standing and seated positions. The pressure sensor and the pump maintain a pre-defined constant binder pressure by inflating (by activating the pump) or deflating (by opening the scape valve) the internal bladder. Thus, excessive abdominal compression is prevented by automatically adjusting for normal changes in intra-abdominal pressure such as those caused by coughing, deep breathing, bending over, lifting etc. The device has a battery capacity for continuous use for periods up to 20 hours.
Supplemental Figure S1

**Primary Objective:**
Allocated to intervention (n=23)
- Received allocated intervention (n=23)
- Did not receive allocated intervention (n=0)

Lost to follow-up (n=2)
- One of the treatment arms could not be done due to time conflicts (n=2)

Analysed (n=19)
- Excluded from analysis:(n=2): Unable to obtain upright blood pressures during one of treatment arms

**Secondary Objective:**
Allocated to intervention (n=23)
- Received allocated intervention (n=23)
- Did not receive allocated intervention (n=0)

Lost to follow-up (n=2)
- One of the treatment arms could not be done due to time conflicts (n=2)

Analysed (n=21)
- Excluded from analysis(n=0)

*Figure S1.* Enrollment, treatment allocation, and follow-up of study participants.
Supplemental Figure S2

Figure S2. Inflatable abdominal binder with controller box, air pump and accelerometer.
Figure S3. Time course of standing systolic blood pressure (SBP) after 1 hour of the intervention (post). Values are given as group-averaged SBP (mean±SEM). Both placebo combined with binder and midodrine produced a significantly higher SBP at 3, 5 and 10 minutes of standing compared with placebo (P=0.001 for main treatment effect, 2-way ANOVA).
Figure S4. Individual responses and response rate to midodrine and abdominal compression with the binder. Individual changes from baseline in areas under the curve of standing SBP (ΔAUCSBP) after 1 hour post-intervention are shown in Panel A. The discontinued line indicates a response definition of ΔAUCSBP ≥150 mmHg*min (or an average increase in SBP of 15 mm Hg over the 10 minute period). Panel B shows the cumulative percentage of patients having a response less than or equal to a particular value of ΔAUCSBP (nonresponders). Positive changes in ΔAUCSBP indicate improvement. Panel C shows the percentage of responders at 4 response levels. Placebo combined with binder had a response rate higher than placebo at all levels of ΔAUCSBP but it only reached statistical significance at 50 and 150 mmHg*min (P=0.061 at 100 mmHg*min, and P=0.077 at 200 mmHg*min by McNemar’s test). Midodrine had a significantly higher response rate than that of placebo at all response levels. *P<0.05 and †P<0.01 by McNemar’s test.