Effect of Midodrine vs Abdominal Compression on Cardiovascular Risk Markers in Autonomic Failure Patients

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1.0 Background

Blood Pressure Abnormalities in Autonomic Failure.- Autonomic failure is a chronic disabling disorder characterized by severe impairment of central or peripheral autonomic pathways. It can be due to a primary neurodegenerative disease or can be secondary to systemic conditions that affect peripheral nerves such as diabetes, amyloidosis, or paraneoplastic syndromes. The primary forms of autonomic failure are caused by deposits of alpha-synuclein, that impair CNS pathways involved in cardiovascular control forming glial cytoplasmic inclusions (Multiple system atrophy, MSA) or postganglionic autonomic fibers forming neuronal Lewy bodies (pure autonomic failure, PAF and Parkinson's disease, PD). Regardless of the level of the lesion, the clinical picture of autonomic failure is dominated by neurogenic hypotension (nOH, exaggerated drop in blood pressure upon standing), supine hypertension (high blood pressure when lying flat) and high blood pressure variability.

Neurogenic orthostatic hypotension is one of the most disabling symptoms in patients with autonomic failure. OH not only impairs the functional status and quality of life of affected patients but is also associated with a 2.6-fold increase in the risk of falls. OH is associated with coronary artery disease, stroke and heart failure, its presence doubles the risk of developing chronic kidney disease, and is an independent risk factor for cardiovascular morbidity and all-cause mortality.

Paradoxically, supine hypertension affects at least 50% of patients with primary autonomic failure. In the long-term, it is associated with cardiac and renal end-organ damage. In the short-term, it complicates the management of these patients because antihypertensive treatment can worsen OH. More important, supine hypertension during the night begets daytime orthostatic hypotension by inducing pressure natriuresis with significant volume loss during the night.

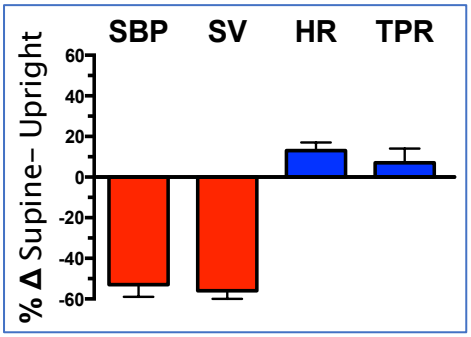


Figure 1. Hemodynamics of nOH

Treatment of Neurogenic Orthostatic Hypotension.- Improving upright BP has been at the centerpiece of efforts to develop new treatments for nOH, but currently available therapies do not consider important features of the underlying pathophysiology of nOH:

- First, our hemodynamic studies in nOH confirmed that BP falls mainly because of a decrease in stroke volume and cardiac output, compounded by the lack of a compensatory increase in arterial vascular resistance (Figure 1).[1] Thus, an important if not crucial hemodynamic cause of nOH is a decrease in venous return due to orthostatic venous pooling.
- Second, most of this orthostatic venous pooling occurs in the abdomen, with little contribution of the lower limbs (Figure 2). [2] Thus, the primary cause of nOH is a gravity-induced increase in splanchnic capacitance which reduces the

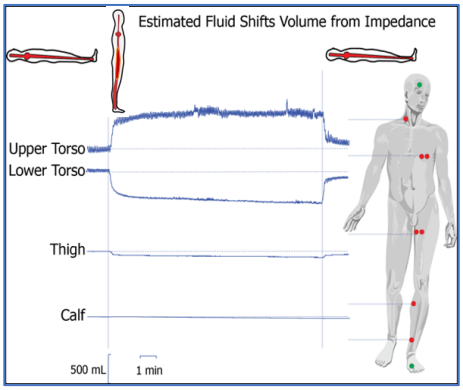


Figure 2. Segmental impedance during upright tilt. Most of the loss in thoracic volume (increase in impedance) is due to a gain in abdominal capacitance

amount of blood available in the central circulation to maintain BP.

- Third, nOH is commonly associated with supine hypertension.[3] This is not surprising given that both hypertension and nOH are highly prevalent in the elderly, and loss of baroreflex buffering unmasks and worsens hypertension. Supine hypertension is frequently present in nOH patients. This not only complicates their management, but importantly, supine hypertension can worsen nOH by promoting pressure diuresis.

Thus, if one were to design the ideal treatment for nOH, it would specifically target splanchnic venous pooling to selectively improve upright BP without worsening supine hypertension. In contrast, most therapies focus on pressor agents that increase arterial vascular resistance as a way to elevate BP. This results in a greater increase in supine than upright BP. Thus, novel approaches to treat nOH by improving venous pooling, the main cause of orthostatic BP falls, are needed.

Abdominal Venous Compression in the Treatment of nOH.- Compression of venous capacitance beds in the lower body has been shown in laboratory settings to improve upright BP and orthostatic symptoms in patients with primary autonomic failure by increasing stroke volume and cardiac output.[4] Compression of the abdominal vascular bed was by far the most effective at improving standing BP. Leg compression alone was much less effective presumably because it is a much smaller volume reservoir compared to the larger capacity of the abdominal vascular bed.[4, 5]

Studies using anti-gravity suits have shown that ***abdominal compression of 40 mmHg significantly improved standing BP in patients with autonomic failure, whereas lower compression levels (15-20 mmHg) were less effective.***[4, 5] ***These pressure levels are safe and selective for the venous circulation***; arterial blood flow starts to decrease only with abdominal compression levels ≥60 mmHg. [6]

2.0 Rationale and Specific Aims

Epidemiological studies have shown that OH not only increases the risk of falls and causes disability but is also an independent risk factor for increased mortality. Currently available treatments with pressor agents can improve OH and quality of life, but it is unclear that they will have a beneficial impact on mortality. Outcome mortality trials are not feasible or timely in this patient population, but we believe important to assess the impact of OH and its treatments on markers of cardiovascular risk. Aortic stiffness, measured as carotid-femoral pulse wave velocity (cfPWV), and indexes of central hemodynamics such as aortic augmentation index (AIx) and central SBP are considered stronger predictors of cardiovascular events than peripheral BP.[7] Previous studies in OH patients have shown that these markers of cardiovascular risk are increased compared to healthy controls.[8] Interestingly, the majority of the nOH patients in these studies (≥ 60%) were on pharmacologic treatment with the alpha 1-adrenoreceptor agonist midodrine. Given that arterial vasoconstrictors can increase aortic AIx and central SBP by increasing the amplitude of the reflected wave, shifting the arterial reflection sites proximally and/or by increasing aortic PWV, [9, 10] it is possible that treatment of nOH with midodrine could have contributed to the increase in these parameters. In support of this, previous studies have shown that arterial vasoconstriction with the α 1-agonist phenylephrine acutely increased AIx and aortic PWV in animals and humans. [11 12]

This provides the rationale for developing new targets for the treatment of nOH that have little or no impact on these markers of cardiovascular risk. In our previous studies, we

showed that abdominal compression with our inflatable abdominal binder was as effective as midodrine in improving upright BP in nOH patients (see Section 3.0; Figure 4), [13] but its effects on arterial stiffness and AIx are not unknown. Thus, our ***primary objective*** is to compare the effect of abdominal compression with an inflatable binder with midodrine on aortic AIx, cfPWV, and aortic SBP during HUT. If we assume that abdominal compression with the binder (inflated to 40 mmHg) has little effect on the arterial tree, we hypothesize that the binder will be associated with lower AIx and cfPWV than that of midodrine for the same improvement in upright SBP. A ***secondary objective*** will be to compare the same outcomes measured at the end of the supine period between treatment groups. We expect that supine aortic AIx, cfPWV, aortic and brachial SBP will be higher with midodrine compared to the binder given that it will remain deflated in the supine position.

3.0 Animal Studies and Previous Human Studies

Markers of Cardiovascular Risk in Autonomic Failure,- Huijben et al. performed a study comparing the central BP, AIx, and PWV during head-up-tilt (HUT) between 10 patients with severe autonomic failure and 14 healthy controls.[14] During supine rest, brachial and central BP, AIx and PWV were higher in patients than in controls. In patients, 30 and 60 degrees of HUT decreased brachial and central BP, AIx and PWV, whereas, in controls, central or peripheral BP did not change, AIx decreased and PWV increased.

Another study by Milazzo et al. assessed cardiac organ damage (assessed as left ventricular mass), arterial stiffness, central hemodynamics in autonomic failure patients (n=27), and compared them with essential hypertension patients (n=27) and healthy controls (n=27).[8] Autonomic failure and essential hypertensive patients had similarly high left ventricular mass and PWV compared to healthy subjects. Compared with essential hypertensive subjects, autonomic failure patients had higher AIx and central BP, despite similarly high 24-hr peripheral (brachial) SBP levels.

Taken together, these studies showed that 1) compared to healthy subjects, autonomic failure patients had increased levels of markers of cardiovascular risk such as central BP, AIx and PWV during supine rest, and 2) these patients develop hypertensive heart disease (increased left ventricular mass) and increased arterial stiffness, similar to essential hypertension patients with comparable peripheral (brachial) BP values. Whether these markers are associated with OH severity or supine hypertension, and the effects of treatment for these conditions on these markers are not known.

Abdominal Compression with an Inflatable Abdominal Binder Improves Upright BP.- We studied 13 patients with disabling nOH who were asked to stand for 10 minutes or as tolerated before and after application of the binder.[13] The severity of nOH in our patients was evidenced by the fact that during screening, 50% of patients were not able to stand for the 10-minute period, systolic BP dropped by -67±7 mmHg on standing, and upright systolic BP ranged from 61 to 114 mmHg. Figure 3 shows the standing systolic BP at 1 minute without the binder, at 1 minute with the binder inflated, and at 10 minutes with the binder inflated. With the patient still standing

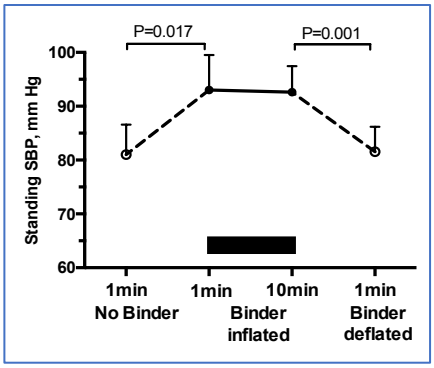


Figure 3. Standing systolic blood pressure (SBP) without the binder (No Binder), and with the binder inflated or deflated.

the binder was then deflated and data were recorded for one more minute. As shown in Figure 3, upright BP with the binder remained ≥ 90 mmHg, above the threshold pressure below which cerebral blood flow autoregulation fails and symptoms of cerebral hypoperfusion become apparent.

Efficacy of Abdominal Compression with an Inflatable Abdominal Binder Compared to Midodrine and Placebo in Improving Orthostatic Tolerance.-We randomized 19 nOH patients to receive either placebo pill, midodrine (at their previously-determined effective dose, 2.5-10 mg) or placebo pill combined with binder on separate days in a single-blind, crossover study.[13] Systolic BP (SBP) was measured seated and standing before and 1-hour post-intervention; the binder was inflated immediately before standing. As an endpoint of orthostatic tolerance, we used the area under the curve of upright SBP (AUC_{SBP}), a composite score that integrates both the standing time and the upright systolic BP. Orthostatic symptom burden was measured by the Orthostatic Hypotension Symptom Assessment score (OHSA) Midodrine increased seated SBP (31±5 vs. 9±4 placebo and 7±5 binder, P=0.003 1-way ANOVA, Figure 4A) and, as expected, neither placebo nor binder had an effect on seated BP, given that the binder was deflated while patients were seated. Orthostatic tolerance improved significantly with inflation of the binder, and with midodrine compared to placebo (AUC_{SBP}, 195±35 and 197±41 vs. 19±38 mmHg*min for placebo, P=0.003 1-way ANOVA, Figure 4B). Total symptom burden improved with the abdominal binder and midodrine but not with placebo when compared to their corresponding baseline stand periods (Figure 4C). When compared to placebo, however, total symptom burden tended to improve after the abdominal binder (-4.9±2.0 vs. 0.5±1.8 for placebo) and midodrine (-6.7±2.7) but the difference did not reach statistical significance because of the relatively small number of subjects (n=17 patients completed OHSA scores; P=0.179)*.* The combination of midodrine and the binder produced a greater increase in orthostatic tolerance than midodrine alone (AUC_{SBP}, 326±65 vs. 140±53 mmHg*min, respectively, P=0.028, n=21, not shown).

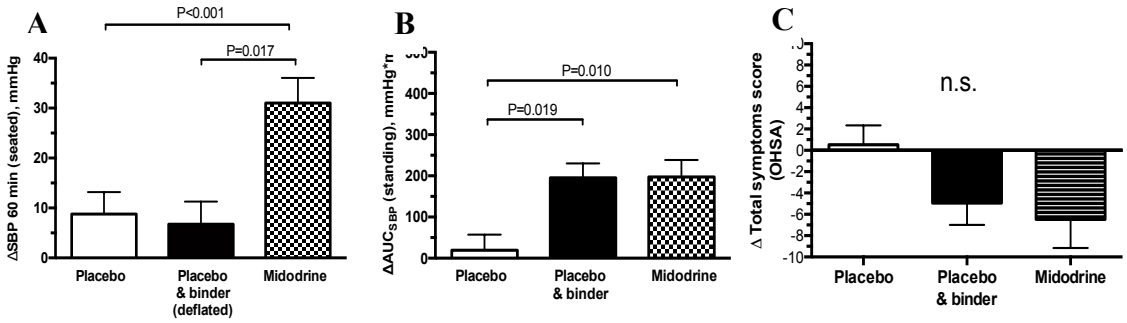


Figure 4. Changes from baseline in (A) seated SBP (ΔSBP), (B) areas under the curve of standing SBP (ΔAUC_{SBP}), and (C) orthostatic symptoms after 1-hour postdrug

4.0 Inclusion/Exclusion Criteria

Inclusion Criteria:

- Male and female subjects, age 40-80 years, with autonomic failure including pure autonomic failure, multiple system atrophy and Parkinson disease.
- Neurogenic OH, defined as a ≥20-mmHg decrease in SBP within 3 minutes of standing associated with impaired autonomic reflexes determined by autonomic testing in the absence of other identifiable causes.
- Patients who are willing and able to provide informed consent.

Exclusion Criteria:

- Pregnancy.
- Patients with any contraindication or intolerant to abdominal compression including history of aortic aneurysms, thoracic, abdominal or pelvic surgery within 6 months of study participation; symptomatic abdominal or inguinal hernias; severe gastrointestinal reflux; recent fractures or fissures of ribs, thoracic or lumbar spine; medical devices implanted on the abdominal wall or abdomen that would interfere with the abdominal compression.
- Pre-existing sustained supine hypertension ≥180/110mmHg
- Bedridden patients or those who are unable to stand due to motor impairment or severe OH.
- Patients who cannot tolerate the medication withdrawal, defined as those who are unable to stand for at least one minute after the medication withdrawal period or those with sustained supine hypertension ≥180/110mmHg.
- Clinically unstable coronary artery disease, or major cardiovascular or neurological event in the past 6 months.
- Clinically significant pulmonary, renal, hematopoietic, hepatic disease, or other factors which in the investigator's opinion would prevent the subject from completing the protocol including clinically significant abnormalities in clinical, mental, or laboratory testing.

5.0 Enrollment/Randomization

Patients with neurogenic OH due to autonomic failure will be recruited from the PI and the Vanderbilt Dysfunction Center (ADC) databases of previous participants, new referrals to the Vanderbilt ADC, clinic patients, former patients, autonomic patient support groups, and subjects that read about our center on our Vanderbilt website (www.mc.vanderbilt.edu/gcrc/adc) or about this study on clinicaltrials.gov. This study can also be offered to patients with autonomic failure who are admitted to the CRC for clinical evaluation or participation in other research studies.

A study investigator, research nurse, or trained research assistant will provide potential participants with information regarding the proposed research, including procedures involved and potential risks. Patients will be given the opportunity to ask questions. A signed informed consent form (hard copy or e-consent) will be obtained from all subjects before any study procedures, and a copy will be given to the participant. No exceptions to the informed consent process will be required.

The order of the study days will be randomized in a crossover fashion using a computer-generated allocation sequence generated by the investigators.

6.0 Study Procedures

Screening Procedures.
Potential participants will be admitted to the Clinical Research Center. Screening procedures may be done for 1-2 days and will include:

- Medications affecting BP and the autonomic nervous system such as pressor medications will be withdrawn for at least 5 half-lives before studies, except for fludrocortisone. Other medications will be held constant throughout the study.

Antihypertensive medications will also be discontinued for ≥5 half-lives before the study procedures.

- Patients will undergo a complete history and physical examination, ECG, and routine clinical laboratory analysis and blood pregnancy test for women with childbearing potential. This includes about 1 tablespoon of blood and a urine sample.
- Autonomic testing will include a Valsalva maneuver, sinus arrhythmia, and a posture study with blood samples for plasma catecholamines.
- Medical history information and results from any of the screening procedures obtained for other studies within this research group may be utilized. Screening procedures could also be done on a separate previous admission.

Study Procedures: Study Day 1 and 2

Participants will be studied in a randomized, single-blind, crossover fashion on two separate days with placebo pill + abdominal compression of 40 mmHg (or as tolerated) and midodrine 5-10 mg + sham abdominal compression (about 5 mmHg). Each study day will take about 3 hours and will include two tilt table tests performed as described below (Figure 5):

- After instrumentation, baseline measurements will be taken in the supine position for up to 30 minutes, and during head-up tilt (HUT) for 10 minutes at 60 degrees. The degree and duration of the HUT may be lower based on the patient's tolerance and investigator's criteria, but the same degree of HUT will be used in all study days. BP, HR, and impedance will be monitored continuously. Hemodynamic parameters and markers of cardiovascular risk will be estimated at the end of the supine period and at 1, 3, 5, and 10 min of HUT or as tolerated. At the end of the HUT, patients will be asked to rate the severity of their orthostatic symptoms using a validated questionnaire, the Orthostatic Hypotension Symptom Assessment (OHSA) score.
- Patients will then be placed in the seated position and will receive a single oral dose of placebo or midodrine 5-10mg, and a deflated inflatable binder will be placed around the abdomen at the level of the umbilicus.
- After 30 minutes, supine post-drug baseline measurements will be taken for 30 min and a second HUT test will be performed at 1-hour post drug (peak effect of midodrine) with the binder inflated at sham or active compression level. After 5 min of the second HUT on study day 2, the tilt angle will be increased or decreased to match the brachial systolic BP with the corresponding values of study day 1. Outcome measures will be repeated during the second HUT with the active/sham compression.

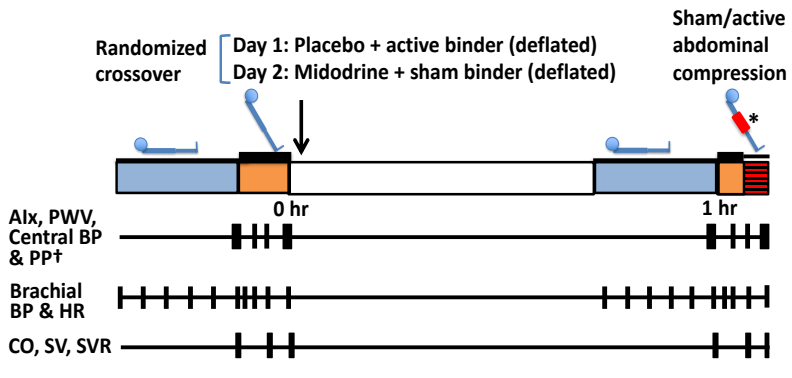


Figure 5. Protocol outline. *At 5 min of the post-intervention head up tilt on study day 2, brachial systolic blood pressure (SBP) will be matched with the corresponding SBP of study day 1 by increasing or decreasing the tilt angle. AIx; augmentation index, PP, pulse pressure; HR, heart rate; CO, cardiac output; SV, stroke volume; SVR, systemic vascular resistance.

- At the end of the second HUT, we may include the estimation of splanchnic venous capacitance using the modified method of Schmitt et.al. In this technique, segmental impedance is monitored, while continuous positive airway pressure (CPAP) is applied. ***The investigator may decide not to perform this procedure (e.g., due to a longer than anticipated study day duration, the inability of patients to tolerate longer periods of HUT or patient's intolerance to the CPAP). In this case, the study will include only the outcome measurements during the drug trials.***

7.0 Risks

Assessment of markers of cardiovascular risk: There is no known risk associated with the tonometric or oscillometric methods. The oscillometric method is similar to a standard blood pressure measurement with an inflatable BP cuff placed around the arm. It may produce some discomfort and occasional bruising of the upper arm. The tonometric method uses a pen-size pressure transducer (tonometer) positioned over the common carotid, common femoral and/or radial arteries to assess pressure waveforms. Applying the tonometer over the neck, wrist and inguinal region (upper thigh) might feel uncomfortable. Applying ECG patches during the tonometric method may cause skin rash.

Holding Medications: Holding medication for OH may worsen OH symptoms and may increase the risk of injury due to fainting. Holding medications for hypertension may cause an increase in blood pressure. Patients will be closely monitored by the study staff during this period. If participants cannot tolerate the withdrawal, we will restart the medications immediately.

Peripheral venous catheterization might cause pain and bruising at the insertion site.

Orthostatic tests and head-up tilt table tests: can cause lightheadedness, tiredness, dizziness, or syncope.

Midodrine is a drug approved for the treatment of orthostatic hypotension. Administration of midodrine results in a rise in supine, sitting and standing blood pressure. Common side effects include goosebumps, itching mainly of the scalp; rare side effects are numbness or tingling, changes in urinary function.

Placebo (sugar pill) - Rarely, people may react to the coloring of the capsules.

Abdominal compression: Applying external pressure to the abdomen may produce some temporary abdominal/back pain, occasional bruising, discomfort, or difficulty breathing deeply. Some people may also experience chest discomfort (e.g., heartburn and/or acid reflux)**.**

Cardiac output and segmental fluid measurements by impedance: There is no known risk associated with the measurement of the heart's pumping capacity by bioimpedance. Measurements are made by recording changes in the transmission of a very weak electrical current at the patches placed on the skin, which is not felt by participants.

Blood pressure cuff: Some may find it uncomfortable to hold their arms with an inflated cuff placed around the forearm, or finger in a relatively fixed position or to have the cuff inflated frequently.

Electrodes: Sticky patches will be put on the chest and limbs of participants to record electrical activity from the heart. This might be uncomfortable. This can occasionally cause a rash.

Continuous positive airway pressure (CPAP). Participants will wear a face mask to apply a low air pressure in their airway. There is no known risk associated with this procedure. The mask might feel uncomfortable to wear, and the machine might be noisy. Rarely, CPAP can cause congestion, runny nose, dry mouth, or nosebleeds

8.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

The PI will review the records of the study subjects following the participation of each subject to ensure patient safety. Any adverse events (AE) will be rated on a 0-5 scale (0-no AE; 1-mild AE, no treatment required; 2-moderate AE that responds to treatment; 3-severe AE that would limit normal activities and require a prolongation of hospitalization; 4-life-threatening or disabling AE; 5-fatal AE). Any AE rated 3 or greater will be reported in writing to the Vanderbilt IRB and DSMB within 7 days of the PI's notification of the event. All adverse events and instances of protocol noncompliance will be summarized once a year as part of the annual review report to the IRB.

The DSMB will provide objective review of treatment results as they relate to human safety and data quality. The committee will be chaired by **Dr. Charles M. Stein,** Professor of Medicine and Pharmacology, Division of Clinical Pharmacology, and will be comprised of **James M. Luther,** Associate Professor of Medicine, Division of Clinical Pharmacology and **Daniel Byrne**, Senior Associate in Biostatistics. The DSMB will review and assess the PI's reports of recruiting, safety data including common and serious adverse events, and data quality (e.g., protocol noncompliance) at yearly intervals or more often if needed, as determined by its Chair. The PI will be responsible for providing all the information required, including all clinical data regarding the AE occurrence. The DSMB may choose to perform an interim analysis and/or break the blind; however, it is expected that this would not occur without reasonable concern related to either patient safety or data validity. The DSMB will have the authority to modify the protocol or to terminate the study if it deems such actions to be warranted.

9.0 Study Withdrawal/Discontinuation

The investigators or Vanderbilt may stop participants from taking part in this study at any time if it is in their best interest, if they do not follow the study rules, or if the study is stopped.

Participants are free to withdraw from this study at any time. We will cease to collect study information at the time of withdrawal of consent. Withdrawal of consent or refusal to participate will not prejudice their health care or their participation in other research studies.

10.0 Statistical Considerations

Statistical Analysis Plan:
In our ***primary objective***, we will test the null hypothesis *that the increase in aortic augmentation index (AIx) during HUT would not be different between active compression*

and midodrine. The ***primary outcome*** will be the *aortic AIx* at 10 min of the post-intervention HUT. ***Secondary outcomes*** will include brachial SBP, carotid-femoral pulse wave velocity (cfPWV), aortic SBP, aortic pulse pressure (PP) and hemodynamic parameters (cardiac output, stroke volume and systemic vascular resistance) during the post-intervention HUT. If the distribution of an outcome is skewed, a transformed outcome will be used. The main comparison will be between the placebo pill + active compression and midodrine + sham compression groups. The data analysis will be conducted using multiple regression models to assess whether the means of each outcome would be different between the active and sham compression, after adjusting for the corresponding measurement at baseline (pre-intervention HUT), fludrocortisone treatment, mean arterial pressure, height and other potential confounding variables such as age, gender, and autonomic diagnosis.

11.0 Privacy/Confidentiality Issues

Protected Health Information will be used in this study. The investigators will comply with the patient privacy guidelines of Vanderbilt University Medical Center and the rules outlined by the Health Insurance Portability and Accountability Act (HIPAA).

The research team is comprised of experienced research nurses and research assistants who are aware of the importance of confidentiality of health information. Research records will be stored in a locked office. Digital records will be stored on password-protected computers/servers (REDCap). Digital data files will be coded so that the subject name is not in the filename or other such identifiers. Every effort will be made to publish and present the data from this study. At no time will any subject be identified in any such publication.

12.0 Follow-up and Record Retention

There will be no further study follow-up after the study is completed. The research material obtained in this proposal will be recording data obtained specifically for research purposes and kept indefinitely. Data will be maintained in paper at CRC office and computer files that will be locked and password-protected in PI's office and VU CRC server. Only the investigators and members of the study team will have access to identifying information.