Protocol Title: Peripheral Dopamine in Postural Tachycardia Syndrome

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Rare Diseases Clinical Research Network

Peripheral Dopamine after Carbidopa Administration in Postural Tachycardia Syndrome

Autonomic Rare Diseases Clinical Research Consortium

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1. Synopsis

Protocol Number:	ARD6101
Protocol Title:	Peripheral Dopamine after Carbidopa Administration in Postural Tachycardia Syndrome
Study Chair:	Emily Garland, PhD and David Robertson, MD
Statistician:	[redacted]
Consortium:	Autonomic Rare Diseases Clinical Research Consortium
Participating Sites:	Vanderbilt University Medical Center
Activated by Vanderbilt, Date:	May 2008
Activated by RDCRN, Date:	April 2011
Sample Size:	16/group (32 total for participants with POTS and healthy controls) To allow for participant drop-out prior to study completion, we will plan to obtain informed consent from 35 participants in total (18 POTS, 17 Controls).
Target Enrollment Period:	5 yr
Study Design:	Randomized, double-blind, placebo-controlled crossover
Primary Study Objective:	The purpose of the proposed research is to determine how changes in kidney dopamine (DA) activity influence urinary sodium excretion. Dopamine in the kidney plays an important role in maintaining sodium balance. We will decrease DA activity in the kidney by inhibiting DA synthesis via carbidopa administration. We will compare urinary sodium excretion following the active agent and a placebo in participants with POTS and healthy controls. Urinary and plasma catecholamines will be measured to assess changes produced by carbidopa treatment. A dose escalation study with doses of 50mg, 100mg and 200mg will first be conducted to assess how well these doses are tolerated when given every 6 hours.
Secondary Study Objective:	We also want to compare findings in normal volunteers and in participants with postural tachycardia syndrome (POTS). These patients are characterized by an excessive increase in heart rate with standing. To determine whether some of these patients do not effectively regulate sodium excretion, the catecholamine, diuretic, and cardiovascular responses following orally administered carbidopa in participants with POTS will be compared with those of healthy volunteers. The dose escalation study will therefore include both POTS and controls.

Study Population and Main Eligibility/ Exclusion Criteria:	Inclusion Criteria:
	• Healthy volunteers,free from symptoms of orthostatic intolerance and without any chronic medical condition
	  ○ Non-smoking
	  ○ Free of medications with the potential to influence blood pressure (BP)
	  ○ Age between 18-60 years
	  ○ Male and female participants are eligible
	  ○ Able and willing to provide informed consent
	• Patients diagnosed with POTS by the Vanderbilt Autonomic Dysfunction Center based on the following stringent criteria: 1) history of daily orthostatic symptoms for at least 6 months; 2) increase in heart rate (HR) of at least 30 bpm with standing or a standing HR≥ 120 bpm; 3) absence of orthostatic hypotension (defined as a fall in BP>20/10 mm Hg); and 4) absence of conditions, such as dehydration, substantial weight loss, or systemic illnesses, that could provoke orthostatic intolerance
	  ○ Non-smoking
	  ○ Free of medications with the potential to influence BP

	○ Age between 18-60 years ○ Male and female participants are eligible ○ Able and willing to provide informed consent Exclusion Criteria: • Overt cause for postural tachycardia (such as acute dehydration) • Significant cardiovascular, pulmonary, hepatic, or hematological disease by history or screening results • Positive urine b-hcg pregnancy test or breastfeeding • Evidence of cardiac structural disease (by clinical examination or prior echocardiogram) • Hypertension defined as a BP>145/95 (off medications) or need for antihypertensive medications • Evidence of significant conduction system delay (QRS duration >120 ms) on electrocardiogram • Known allergy to FD&C Yellow dye 6 • Inability to give, or withdraw, informed consent • Other factors which in the investigator's opinion would prevent the participant from completing the protocol, including poor compliance during previous autonomic studies or an unpredictable schedule • Participants in the dose escalation part of the study are excluded from participation in the main study.
Primary Outcome Measures:	For the dose escalation study, results from the labs, ECG, Psychiatric Questionnaire and vital signs will be evaluated. For the main study, the primary outcome is the urinary sodium concentration normalized to creatinine.
Secondary Outcome Measures:	• Plasma and urinary catecholamines • Blood pressure and heart rate • Plasma sodium • Plasma renin activity
Statistical Considerations (sample size and analysis plan):	Based on our preliminary findings of a standard deviation for urinary sodium excretion of 30 mEq/g creatinine, a sample size of 16/group (32 total) will have 80% power to detect a difference in group means (control vs. POTS) of 31 mEq/g creatinine with a 0.05 two-sided significance level. To allow for participant drop-out prior to study completion, we will plan to obtain informed consent from 35 participants in total. Differences in urinary sodium in samples (1) collected at baseline vs. those collected following treatment (time effect) and (2) collected after placebo vs. carbidopa (treatment effect) will be assessed using a paired t-test and Wilcoxon signed-rank test. Differences between the patient and control groups (group effect) will be assessed using a student's t-test and a Mann-Whitney U test. Similar methods will be used to compare secondary outcome measures, such as BP, HR, plasma and urinary catecholamines, plasma renin activity, plasma aldosterone, and plasma sodium. All data analyses will be performed using SPSS 14.0 (SPSS, Chicago, IL) or STATA 8.2 (StataCorp, College Station, TX). All statistical tests will be two-sided. If these analyses indicate that the response to carbidopa differs between patients and controls, a mixed-effects model will be developed to describe the time, medication and group effects.
Sponsors (federal, state, foundation and industry support):	National Institutes of Health (NIH)

1.A. Protocol Overview

The purpose of the proposed research is to determine how changes in kidney dopamine (DA) activity influence urinary sodium excretion. Dopamine in the kidney plays an important role in maintaining sodium balance. We will decrease DA activity in the kidney by inhibiting DA synthesis via carbidopa administration. We will compare the active agent with a placebo. We also want to compare findings in normal volunteers and in patients with postural tachycardia syndrome (POTS). Some of these patients may not effectively regulate sodium excretion.

1.B. Dose Escalation Study of Carbidopa

Prior to initiation of the main study, a dose escalation study will be conducted. A cohort consisting of one healthy volunteer and one participant with POTS will be administered a dose of 50mg carbidopa every 6 hours for a total of five doses. If this dosage is well-tolerated (see next paragraph), a second cohort will be given five doses of carbidopa 100mg with 6 hours between doses. If this dosage is well-tolerated, a final cohort will take the proposed dose of 200mg carbidopa every 6 hours for five doses. All participants in the dose escalation study will also take placebo every 6 hours for five doses, according to a crossover design, and will undergo the same measurements and procedures as described below for the main study. However, additional blood draws and monitoring will be included.

Specific aims of Dose Escalation Study.

1. To assess tolerability of increasing doses (50mg, 100mg, 200mg) of carbidopa, as assessed by ECG, complete blood count (CBC), chemistry panel, liver function biomarkers, and a Psychiatric Symptom Questionnaire.

2. To assess plasma carbidopa levels after different doses of carbidopa.

3. To obtain preliminary data on the changes in plasma and urinary levels of catecholamines and urinary sodium excretion following oral administration of different doses of carbidopa.

4. To obtain preliminary data on the effect of oral administration of different doses of carbidopa on orthostatic changes in heart rate and blood pressure, as well as symptoms.

5. To compare the tolerability, as well as catecholamine, diuretic, and cardiovascular responses following orally administered carbidopa in participants with POTS with those of healthy volunteers.

To accomplish these aims:

- Pre-study assessments consist of 1) 12-lead ECG; 2) complete blood count (CBC) with platelets; 3) chemistry panel including albumin, total bilirubin, alkaline phosphatase, serum glutamic oxaloacetic transaminase (SGOT), and serum glutamic pyruvic transaminase (SGPT) to evaluate liver function; and 4) plasma carbidopa.
- Participants will be provided a 200 mEq/day sodium diet, free of methylxanthines and low in monoamines, by the kitchen of the Clinical Research Center (CRC).
- After achieving sodium balance on the study diet over 2-3 days, participants will collect urine over 24hr for baseline assessment of sodium and catecholamines and to confirm adherence to the study diet.
- On this day, the participants will be admitted to the CRC.
- An 18 gauge intravenous catheter will be inserted in order to draw blood.
- The participants will fast from 7 pm until after the next morning's testing.
- In the morning, while still supine after the overnight sleep, heart rate (HR) and blood pressure (BP) will be recorded, and blood will be drawn. The participants will then stand for 10 minutes. HR and BP will be measured at intervals, and an upright blood sample will be collected.
- The participants will be asked to collect their urine at the end of the 24hr urine collection. Another 24hr urine collection will then be started.

- Treatment A (carbidopa or placebo) will be given orally following the void, at approximately 7 am. Additional doses will be taken every 6 hours with the last dose at 7 am the following morning.
- Participants will remain inpatients on the CRC during the day. They will need to consume the 200 mEq sodium/day study diet for each meal, collect all urine, and take study medication on schedule. Supine BP and HR will be measured and blood will be collected for plasma carbidopa 2hr after each dose.
- The participants will fast after midnight except for water and medication.
- In the morning, supine and standing HR and BP will be recorded, and the participants will be asked to collect their urine to end the 24hr urine collection.
- The final dose of study medication (carbidopa or placebo) will be given orally following the void, at approximately 7 am.
- Supine HR and BP will be measured and supine blood samples will be collected hourly for 4 hours after the last dose and at 8 hours after the dose. Participants must rest supine for at least 30 minutes before each blood draw. Plasma carbidopa will be measured at 2hr, 4hr and 8hr after the 5th dose. The intravenous catheter will be removed following the 8-hour blood draw.
- At 2 hours after the 5th dose, participants will stand for 10 minutes for upright BP and HR measurements and collection of an upright blood sample, as described above. Participants will be asked to rate the severity of common orthostatic symptoms while supine and upright.
- As part of the safety assessment, the 12-lead ECG, CBC and chemistry panel will be repeated 2hr after the fifth dose.
- Urine will be collected for two 4-hour periods after the 5th dose followed by a 16-hour collection to finish the 24-hour cycle
- Participants may be discharged approximately 8 hours after the last dose or, if they prefer, they may remain on the CRC for the washout day.
- After at least a 1 day washout period, the study will be repeated with Treatment B. Treatment B consists of exactly the same regimen as Treatment A. The participant will be randomized to receive placebo or carbidopa (whichever was not given during Treatment A).

Throughout the dosing period, participants will be monitored (HR and BP measurement, Psychiatric Symptom Questionnaire, and questioning by study personnel 2hr after each dose) for adverse events, including allergic reaction, nausea, worsening hypotension or tachycardia, arrhythmia, neuroleptic malignant syndrome, hallucinations or other psychiatric symptoms. No more doses will be given to a participant who experiences an allergic reaction, arrhythmia, increased body temperature >100.4°F, or >38°C, changes in supine BP>20mmHg or changes in supine HR>30bpm, hallucinations or psychiatric symptoms (as determined by our Psychiatric Symptom Questionnaire). Adverse events and post-study changes in ECG or laboratory values (in relation to pre-study assessments) following carbidopa and placebo will be summarized for each cohort. Adverse events will be defined according to the Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE). [redacted], the Independent Medical Monitor (IMM) for this study, will review the data and use clinical judgment to decide whether to proceed to the next higher dosage of the dose escalation study. In general, a grade 2 event in more than one participant or a grade 3 event judged to be drug-related in any one participant will lead to study termination. Post-dose laboratory assessments may be repeated to confirm abnormalities.

Participants in the dose escalation study will not be allowed to also participate in the main study.

1.C. Detailed Description of Main Study:

This study will only be conducted if the results of the dose escalation study indicate that the 200mg dosage of carbidopa is well tolerated when given every 6hr for 5 doses. We will determine whether inhibition of renal

dopamine formation by carbidopa administration leads to a decrease in urinary excretion of dopamine and sodium and whether the response differs in POTS and control populations. Carbidopa effects will be compared to those of a matching placebo, and the sequence of treatments (carbidopa before placebo or placebo before carbidopa) will be randomized.

Each participant will undergo a complete history and physical examination, including an electrocardiogram (EKG).

- Participants will be provided a 200 mEq/day sodium diet, free of methylxanthines and low in monoamines, by the kitchen of the Clinical Research Center (CRC).
- After achieving sodium balance on the study diet over 2-3 days, participants will collect urine over 24hr for baseline assessment of sodium and catecholamines and to confirm adherence to the study diet.
- On this day, the participants will be admitted to the CRC.
- An 18 gauge intravenous catheter will be inserted in order to draw blood.
- The participants will fast from 7 pm until after the next morning's testing.
- In the morning, while still supine after the overnight sleep, heart rate and blood pressure will be recorded, and blood will be drawn. The participants will then stand for 10 minutes. Heart rate and blood pressure will be measured at intervals, and an upright blood sample will be collected.
- The participants will be asked to collect their urine to end the 24hr urine collection. Another urine collection will be started. This may take the form of one 24 hr sample or two 4 hr collection samples followed by a 16 hr sample collected from approximately 3 pm to 7am the following morning. The second schedule will facilitate comparison to urinary excretion after the final dose.
- Treatment A (Carbidopa 200mg or placebo) will be given orally following the void, at approximately 7 am. Additional doses will be taken every 6 hours with the last dose at 7 am the following morning.
- Participants will remain inpatients on the CRC during the day. They will need to consume the 200 mEq sodium/day study diet for each meal, collect all urine, and take study medication on schedule. Supine BP and HR will be measured 2hr after each dose.
- The participants will fast after midnight except for water and medication.
- In the morning, supine and standing heart rate and blood pressure will be recorded, and the participants will be asked to collect their urine to end the 24hr urine collection.
- The final dose of study medication (Carbidopa 200mg or placebo) will be given orally following the void, at approximately 7 am.
- Supine heart rate and blood pressure will be measured and supine blood samples will be collected hourly for 4 hours after the last dose and at 8 hours after the treatment. Participants must rest supine for at least 30 minutes before each blood draw. The intravenous catheter will be removed following the 8-hour blood draw.
- At 2 hours after the 5th dose, participants will stand for 10 minutes for upright blood pressure and heart rate measurements and collection of an upright blood sample, as described above. Participants will be asked to rate the severity of common orthostatic symptoms while supine and upright.
- Urine will be collected for two 4-hour periods after the last dose followed by a 16-hour collection to finish the 24-hour cycle.
- Participants may be discharged approximately 8 hours after the last dose or, if they prefer, they may remain on the CRC for the washout day(s).
- Fixed-sodium and low monoamine and methylxanthine-free study diet will be provided after the 4-hour measurements and in the evening.

After at least a 1 day washout period, the study will be repeated with Treatment B

2. Objective and Research Question of the Main Study

Specific aims.

1. To assess normal changes in plasma and urinary levels of catecholamines following oral carbidopa administration.
   We are giving 200mg of carbidopa every 6 hours for 5 doses. We expect that this treatment will decrease the formation of dopamine in the kidney so that urinary dopamine will be lowered and its precursor, urinary dopa, will be raised.

2. To assess the relationship between catecholamines and urinary sodium excretion following oral carbidopa administration.
   Because of the important role of kidney dopamine in regulating urinary sodium excretion, we expect that urinary sodium excretion will be decreased as urinary dopamine falls.

3. To assess the effect of oral carbidopa administration on orthostatic changes in heart rate and blood pressure, as well as symptoms.
   Because of the relationship between sodium excretion and blood pressure control, we expect that a carbidopa-mediated decrease in urinary sodium excretion may be associated with an increase in blood pressure.

4. To compare the catecholamine, diuretic, and cardiovascular responses following orally administered carbidopa in participants with POTS with those of healthy volunteers.
   One of the most consistent findings in POTS is a reduction in plasma volume or blood volume. Previous findings by our research group suggest that mechanisms involved in orthostatic and absolute volume regulation contribute to POTS pathophysiology. We have preliminary data showing that patients with POTS do not decrease urinary sodium excretion after 30-60 minutes of upright posture, whereas healthy control participants do. We also reported that plasma renin activity (PRA) and aldosterone are paradoxically low in POTS in view of the reduced plasma volume. This indicates that sodium handling is perturbed in POTS. We therefore expect that patients with POTS may benefit from a reduction in urinary sodium excretion or that carbidopa-mediated changes in sodium excretion may differ between patients with POTS and healthy volunteers.

Hypothesis: In these studies, we will test the null hypothesis (H_o) that the effect of oral carbidopa administration on urinary sodium excretion will not differ between participants with POTS and healthy volunteers.

Research Question: Does orally administered carbidopa, by blocking the formation of renal dopamine from dopa, decrease urinary dopamine and sodium excretion in POTS and normal participants?

3. Background

Synthesis and degradation of catecholamines. The synthesis of catecholamines is summarized in Figure 1. Tyrosine hydroxylase (TH) is the rate-limiting step in norepinephrine (NE) synthesis under almost all circumstances. NE acts as a feedback inhibitor of this enzyme. L-dopa (dopa) is the amino acid precursor of the endogenous catecholamines and the immediate product of TH. L-Aromatic amino acid decarboxylase (AADC; also known as dopa decarboxylase or DDC) converts dopa to dopamine (DA) in both nonneural and neural tissues. Dopamine-ß-hydroxylase (DBH), which converts DA to NE, is localized in vesicles of noradrenergic neurons in the central and peripheral nervous systems and in the adrenal medulla. Phenylethanolamine-N-methyltransferase (PNMT; NE to epinephrine (EPI)) is restricted to the adrenal medulla, the brain, and the heart, with only trace amounts in other locations.

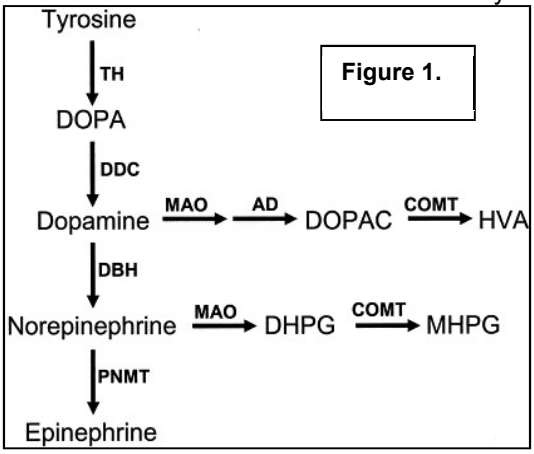


Figure 1.

The fate of released catecholamines includes a) uptake into the neuron by the norepinephrine transporter (NET; uptake I), b) uptake by the extraneuronal monoamine transporter (EMT; uptake II), or c) metabolic transformation. Intraneuronal NE is converted to dihydroxyphenylglycol (DHPG) by monoamine oxidase (MAO)[7]. Catechol-O-methyltransferase (COMT) converts extraneuronal NE into normetanephrine (NMN), EPI into metanephrine (MN), and DA into 3-methoxytyramine (MT). DA that is not transported into the DBH-containing vesicles is deaminated by MAO to 3,4-dihydroxyphenylacetic acid (DOPAC) which is subsequently O-methylated by COMT to homovanillic acid (HVA). The corresponding metabolite for NE is vanillylmandelic acid (VMA).

Functions of dopamine. In the brain, dopamine functions as a neurotransmitter, activating the five main types of dopamine receptor - D1, D2, D3, D4 and D5. Brain DA has been implicated in the control of movement and reward systems. Dopamine, administered as a medication clinically, acts on the sympathetic nervous system to produce effects such as increased heart rate and blood pressure. Effects of DA are dose-related and dependent on the localization and characteristics of the receptors with which it interacts. At very low doses (1 to 2 ug/kg/min), it dilates renal and mesenteric blood vessels and increases renal blood flow, principally by actions on dopaminergic receptors. At dosages of 2 to 10 ug/kg/min, dopamine stimulates myocardial β1 adrenergic receptors, increasing cardiac output but inducing relatively little tachycardia. At higher doses, it also stimulates α-adrenergic receptors and elevates arterial pressure. Since it cannot cross the blood-brain barrier, peripherally given dopamine does not directly affect the central nervous system.

Dopamine as an autocrine/paracrine substance. In addition to its role as a neurotransmitter and as a precursor to NE and EPI, non-neuronal DA also acts as a paracrine or autocrine substance, originating in the gastrointestinal tract and the kidney. In the gut, DA is produced endogenously and is also derived from dietary sources. DA undergoes sulfate conjugation in gastrointestinal tissues, and at least 95% of circulating DA occurs in the sulfoconjugated form. Ingestion of a standard meal or bananas raise plasma dopamine sulfate concentration more than 50-fold, whereas plasma dopa and DA increase much less[5;13]. Twelve hours of fasting have been shown to eliminate dopamine sulfate that comes from a dietary source[23]. Sulfoconjugation may contribute to a gut-blood barrier and limit the amount of ingested catecholamines that enter the bloodstream[13].

Renal dopamine and sodium excretion. In the kidney, DA is synthesized from circulating dopa in non-neuronal tissue and exerts local effects to facilitate natriuresis. Renal DA is metabolized by COMT and MAO. The supply of dopa to the kidney is the primary regulatory factor for intrarenal non-neuronal DA synthesis[9]. Dopa is taken up into proximal tubule cells by a sodium-dependent process[27] and is rapidly converted to DA by the high concentrations of AADC found there. Intrarenal DA induces natriuresis by inhibition of tubule sodium reabsorption via the Na^+K^+-ATPase pump and the Na-H exchanger. High salt intake in Caucasians produces a significant and sustained increase in urine DA output[12]. An increase in the filtered load of sodium promotes uptake of dopa by the proximal tubule cells[26;32], and AADC activity is also up-regulated by sodium[14]. Saline loading may also be associated with decreased renal degradation of DA by COMT[25] to 3MT and eventually to HVA. Carbidopa, by blocking the synthesis of DA from dopa, will prevent a rise in renal DA under high-sodium conditions. A low-salt diet, in contrast, decreases renal and urinary dopa and DA, without significantly changing plasma dopa[12]. DA exerts its renal actions through two families of receptors, designated D1-like and D2-like[20], which are identical in the brain and in peripheral tissues. The two D1-like receptors (D1 and D5) are linked to stimulation of adenylyl cyclase. D2, D3, and D4 are linked to inhibition of adenylyl cyclase. Inhibition by DA of the Na^+K^+-ATPase pump is thought to be mediated by D1 receptors. D2 receptors may increase glomerular filtration rate and possibly contribute to natriuresis in the cortical collecting duct cells, but their role in the regulation of sodium excretion is not well understood[2].

The renin-angiotensin-aldosterone system interacts with the renal dopaminergic system to regulate plasma volume in humans. In response to DA, hypovolemia, a decrease in sodium, or an increase in renal sympathetic nerve activity, plasma renin activity is stimulated to produce angiotensin II. Angiotensin stimulates sodium reabsorption directly and also stimulates the release and synthesis of aldosterone, a mineral corticoid hormone that causes the retention of sodium, increasing fluid volume. Further modulation of natriuresis is achieved by DA-mediated attenuation of aldosterone secretion[4].

Dopamine in cardiovascular regulation. This renal autocrine-paracrine function, which has heretofore been most evident during extracellular fluid volume expansion, is lost in essential hypertension[1] and in some animal models of genetic hypertension[3;18;21;24]. Animal models and genetic forms of hypertension demonstrate decreased

signal transduction by DA receptors in proximal tubule cells, and an impaired ability to increase urinary sodium excretion following a DA agonist[8], resulting in decreased sodium reabsorption[19]. This has been linked to an uncoupling of the D1 receptor from the G protein complex as a result of a GRK4 polymorphism[19].

Postural tachycardia syndrome. Postural tachycardia syndrome (POTS) is the most common form of orthostatic intolerance, affecting an estimated 500,000 Americans, principally young women. POTS refers to an excessive increase in heart rate (>30 beats per minute) on standing in the absence of orthostatic hypotension. Patients typically experience symptoms of excessive sympathetic activation with physical or emotional exertion. POTS can produce substantial disability among otherwise healthy people. The pathophysiology of POTS is heterogeneous and poorly understood. Many of these patients have elevated levels of plasma NE, particularly when upright. Subgroups of patients have a primary hyperadrenergic state, while others suffer from a partial dysautonomia affecting the lower limbs.

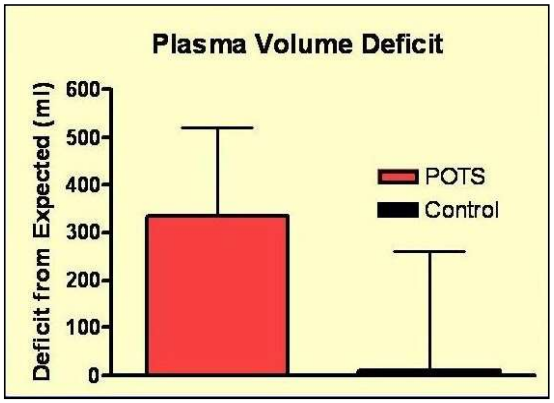


Figure 2. Plasma volume deficit in patients with POTS and healthy controls(2)

Plasma volume and its orthostatic shift in POTS. One of the most consistent findings in POTS is a reduction in plasma volume or blood volume **(Figure 2**)[10;11;17;29;31]. Furthermore, there are additional decrements in plasma volume due to orthostatic volume shifts[16;28]. The marked interindividual variation in the POTS group, with some patients having a volume shift that is well within the normal range, suggests that the POTS population is quite heterogeneous in terms of this variable.

Previous findings by our research group suggest that mechanisms involved in orthostatic and absolute volume regulation contribute to POTS pathophysiology. We have preliminary data showing that patients with POTS do not decrease urinary sodium excretion after 30-60 minutes of upright posture, whereas healthy control participants do (**Figure 3**). We also reported that PRA and aldosterone are paradoxically low in POTS in view of the reduced plasma volume. This indicates that sodium handling is perturbed in POTS. Several investigators have implicated dopamine in the control of natriuresis in other disorders. Approximately 50% of sodium excretion appears to be under dopaminergic regulation.

Uptake of dopa into the proximal tubule cells and its subsequent decarboxylation to DA are stimulated by a high salt diet. Carbidopa inhibits the activity of AADC in the periphery. By blocking the conversion of dopa to DA, it has the potential to attenuate the effects of the sodium load on renal DA production and urinary sodium excretion. However, since carbidopa also inhibits dopa decarboxylation in peripheral neurons, it can increase plasma dopa levels and the filtered load of dopa in the kidney. The final effect of carbidopa on renal DA production is therefore the result of increased substrate and decreased decarboxylation[12].

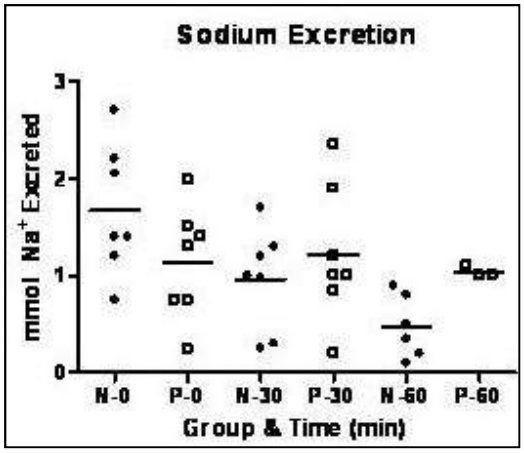


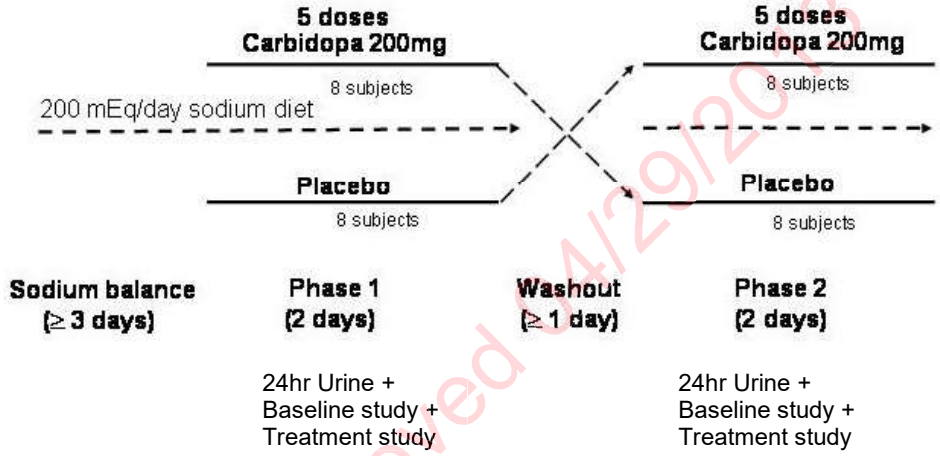
Figure 3

Recommended dosages of carbidopa for the treatment of Parkinson's disease, as Sinemet®, are at least 70-100 mg, up to 200 mg daily (AHFS Drug Information 2007). Yet, Durso et al.[6] speculated that "doses used in current practice" are not saturating for the decarboxylase enzyme. Kaufmann et al.[22] and Hershey et al.[15] administered one dose of 200 mg carbidopa to ensure that the decarboxylase was completely inhibited. Stokes et al.[30] proposed that more than one dose of carbidopa must be given to see an effect on renal salt handling. Based on this information and a carbidopa half-life of about 2 hours, we have chosen to administer 200 mg of carbidopa every 6hr. We believe that with repeated dosing of 200 mg, we will be able to assess the influence of decarboxylase inhibition on urinary sodium excretion. Nevertheless, since this dosage is higher than that which is FDA approved, we will first conduct a dose escalation study with 50mg, 100mg and 200mg of carbidopa to confirm that these dosages are well tolerate

The following studies are designed to compare the influence of plasma dopa levels on plasma and urinary catecholamines in participants with POTS and healthy volunteers and to assess subsequent effects on sodium excretion. We will evaluate the roles of peripheral dopa and DA in POTS by comparing the effects of placebo and carbidopa on urinary DA and sodium excretion in patients and controls. Study participants will consume a relatively high-salt diet to "turn on" the dopaminergic regulation of sodium excretion. The dosage of carbidopa may be modified to attenuate or intensify the responses, not to exceed 1000mg in a 24hr period.

4. Study Design and Methods

We will determine whether inhibition of renal DA formation by carbidopa administration leads to a decrease in urinary excretion of DA and sodium and whether the response differs in POTS and control populations. Carbidopa effects will be compared to those of a matching placebo, and the sequence of treatments (carbidopa before placebo or placebo before carbidopa) will be randomized. The study is double-blinded. The investigational pharmacy at Vanderbilt Medical Center determines the randomization and the treatment order. The same crossover design is used for both the dose escalation and main studies.



Recruitment. The participants with POTS will be recruited for both dose escalation and main studies from patients referred to the Vanderbilt University Autonomic Dysfunction Center. Control participants will be recruited from healthy volunteers known to the Autonomic Dysfunction Center, through the ResearchMatch.org database, and through emails to the Vanderbilt community

4.A Inclusion criteria

Healthy Volunteers

- Free of orthostatic symptoms
- No chronic medical conditions
- Free of medications with the potential to influence BP
- Non-smoking
- Ages between 18-60
- Males and females
- Able and willing to provide consent

POTS Participants

- Patients diagnosed with POTS by the Vanderbilt Autonomic Dysfunction Center based on the following stringent criteria: 1) history of daily orthostatic symptoms for at least 6 months; 2) increase in heart rate (HR) of at least 30 bpm with standing or a standing HR≥ 120 bpm; 3) absence of orthostatic hypotension (defined as a fall in blood pressure (BP)>20/10 mm Hg); and 4) absence of conditions, such as dehydration, substantial weight loss, or systemic illnesses, that could provoke orthostatic intolerance
- Non-smoking
- Free of medications with the potential to influence BP

- Age between 18-60 years
- Male and female participants are eligible
- Able and willing to provide informed consent

4.B Exclusion Criteria

- Overt cause for postural tachycardia (such as acute dehydration)
- Significant cardiovascular, pulmonary, hepatic, or hematological disease by history or screening results
- Positive urine b-hcg pregnancy test or breastfeeding
- Evidence of cardiac structural disease (by clinical examination or prior echocardiogram)
- Hypertension defined as a BP>145/95 (off medications) or need for antihypertensive medications
- Evidence of significant conduction system delay (QRS duration >120 ms) on electrocardiogram
- Known allergy to FD&C Yellow dye 6
- Inability to give, or withdraw, informed consent
- Other factors which in the investigator's opinion would prevent the participant from completing the protocol, including poor compliance during previous autonomic studies or an unpredictable schedule
- Participants in the dose escalation phase will not be able to participate in the main study.

4.C Recruitment of Participants for Dose Escalation and Main Studies

The patients with POTS will be recruited from patients referred to the Vanderbilt University Autonomic Dysfunction Center. Control participants will be recruited from healthy volunteers known to the Autonomic Dysfunction Center, through the ResearchMatch.org database, and through emails to the Vanderbilt community.

Prospective participants come from several sources, including clinic patients, former patients and participants that read about our center on our Vanderbilt website. We do not advertise active studies on that site but we receive calls asking to be seen, evaluated or studied. If a potential participant is identified, a sample consent form is mailed to the participant for review. During a follow-up telephone or email contact, the participant decides if he/she wishes to be screened for the study. Clinic patients that are known to us may be offered the study and known to qualify in advance. Participants enrolled in the dose escalation part of the study will not be eligible to participate in the main study.

All participants with POTS will have been previously evaluated with a posture study (orthostatic vital signs with supine and upright blood work to assess hormones). Control participants will undergo a brief history and physical examination to ensure that they are healthy.

The history will include (but not be limited to):

- Framingham risk factors (age, gender, smoking, hypertension, dyslipidemia)
- Metabolic diseases (metabolic syndrome, polycystic ovary syndrome, diabetes)
- Inflammatory diseases (e.g., rheumatoid arthritis)
- Review of medication
- Date that last menstrual period started (if female).

The physical examination will include (at minimum):

- Height
- Weight
- Orthostatic vital signs (HR and BP)
- EKG
- Complete blood count
- Metabolic panel

4.D Retention Strategies

Follow-up. Study participation will be complete following the inpatient evaluation. There will be no further study follow-up.

Record retention. Study records will be kept for at least 7 years following the publication or presentation of the data collected as part of this study.

4.E Data Elements-Dose Escalation Study

- A dose escalation study will be conducted prior to the main study. A cohort consisting of one healthy volunteer and one patient with POTS will be administered a dose of 50mg carbidopa every 6 hours for a total of five doses. If this dose is well tolerated, a second cohort will be given five doses of carbidopa 100mg with 6 hours between doses. If this dose is well tolerated, a final cohort will take the proposed dose of 200mg carbidopa every 6 hours for five doses. A minimum of 9 days is needed to complete the study with 2 nights on the CRC for the active compound and 2 nights for the placebo.
- Pre-study assessments consist of 1) 12-lead ECG; 2) complete blood count (CBC:WBC, Hgb, PCV, Plt-Ct, RBC, MCV, MCH, MCHC, RDWSD, RDW, Neut, Lym, Monocy, Eos, Baso) with platelets; 3) chemistry panel (CMP: Na, K, Cl, CO2, BUN, Creat, Gluc, Ca, Tprot) including albumin, total bilirubin, alkaline phosphatase, serum glutamic oxaloacetic transaminase (SGOT), and serum glutamic pyruvic transaminase (SGPT) to evaluate liver function; and 4) plasma carbidopa.
- Participants will be provided a 200 mEq/day sodium diet, free of methylxanthines and low in monoamines, by the kitchen of the Clinical Research Center (CRC).
- After achieving sodium balance on the study diet over 2-3 days, participants will collect urine over 24hr, starting at 0700hr, for baseline assessment of sodium, potassium and catecholamines and to confirm adherence to the study diet.
- Participants will be admitted to the CRC that afternoon or evening.
- In the morning, while still supine and NPO after the overnight sleep, HR and BP will be recorded with a Dinamap electrocardiographic and BP (brachial cuff) recorder, and blood will be drawn for a basic metabolic panel, fractionated catecholamines, aldosterone and plasma renin activity. The participants will then stand for 10 minutes or for as long as they are able to tolerate. They may sit for short intervals if necessary. HR and BP will be measured at 1, 3, 5, and 10 minutes of standing, and an upright blood sample will be collected at 10 minutes for catecholamines, plasma renin activity, and aldosterone.
- The participants will be asked to void while recumbent, if able, or after the upright measurements, to end the first 24hr urine collection. Another 24hr urine collection will then be started for analysis of sodium, potassium and creatinine.
- Treatment A (carbidopa or placebo) will be given orally following the void, at approximately 0700hr. Additional doses will be taken every 6 hours with the last dose at 0700hr the following morning. BP and HR will be measured and plasma carbidopa will be measured 2 hours after each dose. Participants will remain on the CRC for monitoring.
- In the next morning, supine and standing HR and BP will be recorded with a Dinamap recorder, and the participants will be asked to void and collect the urine to end the 2nd 24hr urine collection.
- The final dose of study medication (carbidopa or placebo) will be given orally following the void, at approximately 0700hr.
- Supine HR and BP will be measured by Dinamap and supine blood samples will be collected hourly for 4 hours after the 5th dose and at 8 hours after the treatment. Participants must rest supine for at least 30 minutes before each blood draw. These samples will be analyzed for catecholamines (all samples), and plasma renin activity and aldosterone (only at 2 hr after treatment). In addition, a basic metabolic panel will be run for the 4-hour and 8-hour samples.
- Plasma carbidopa will be measured at 2hr, 4hr and 8hr after the final dose.
- As part of the dose escalation assessment, the 12-lead ECG, CBC and Comprehensive Metabolic Panel will be repeated 2hr after the 5th dose.
- At 2 hours after the 5th dose, participants will stand for 10 minutes for upright BP and HR measurements and collection of an upright blood sample, as described above. Participants will be asked to rate the severity of common orthostatic symptoms while supine and upright.
- Urine will be collected for two 4-hour periods after the last dose followed by a 16-hour collection to finish the 24-hour cycle for analysis of sodium, potassium, catecholamines, and creatinine.
- Participants may be discharged from the CRC approximately 8 hours after the last dose.
- After at least 24 hours, the protocol will be repeated with treatment B (carbidopa or placebo, whichever was not administered during treatment A). Depending on the interval, participants will either remain on the study diet or re-start the diet 2-3 days before admission for the 2nd phase.
- Throughout the dosing period, participants will be monitored (HR and BP measurement, Psychiatric Symptom Questionnaire, and questioning by study personnel 2hr after each dose) for adverse events,

including allergic reaction, nausea, acute psychosis, worsening hypotension or tachycardia, arrhythmia, neuroleptic malignant syndrome, hallucinations or other psychiatric symptoms.

4.F Schedule of Events-Dose Escalation Study

Table 1 Study Schedule-Dose Escalation

Dosing Regimen	Time of Dose	Monitoring/Labs
Predose	NA	24hr urine for catecholamines, sodium, potassium, creatinine to start 24hr prior to 1st dose; 12-lead ECG; CBC with platelets; chemistry panel including liver enzymes; supine and upright BP and HR; supine and upright plasma catecholamines, serum aldosterone, plasma renin activity; plasma carbidopa; metabolic panel; start a 2nd 24hr urine for catecholamines, sodium, potassium, creatinine
Dose #1	0700	0900: supine BP and HR; Psychiatric Symptom Questionnaire; monitoring; plasma carbidopa
Dose #2	1300	1500: supine BP and HR; Psychiatric Symptom Questionnaire; monitoring; plasma carbidopa
Dose #3	1900	2100: supine BP and HR; Psychiatric Symptom Questionnaire; monitoring; plasma carbidopa
Dose #4	0100	0300: supine BP and HR; Psychiatric Symptom Questionnaire; monitoring; plasma carbidopa
Pre-Dose #5	0645	Supine and upright BP and HR; finish 24hr urine and start 4hr urine for catecholamines, sodium, potassium, creatinine
Dose #5	0700	0800: supine BP and HR; plasma catecholamines
		0900: supine and upright BP and HR; 12-lead ECG; CBC with platelets; chemistry panel including liver enzymes; Psychiatric Symptom Questionnaire; Orthostatic Symptom Questionnaire; monitoring; plasma carbidopa; supine and upright plasma catecholamines, serum aldosterone, plasma renin activity
		1000: supine BP and HR; plasma catecholamines
		1100: supine BP and HR; metabolic panel; plasma catecholamines; plasma carbidopa; restart 4hr urine for catecholamines, sodium, potassium, creatinine
		1500: supine BP and HR; metabolic panel; plasma catecholamines; plasma carbidopa; start 16hr urine for catecholamines, sodium, potassium, creatinine

Table 2. Study Day Description-Dose Escalation

Day	Treatment	Time	Assessments for Tolerability	Obtain Consent	History & Physical	Pregnancy Test	Study Diet	Carbidopa or Placebo	Blood Draw	HR/BP	Urine
Pre-Study			X	X	X	X			X		
-3, -2							X				Start study diet
-1		0700					X				Start 24hr urine #1
1		0645					X		X	X	End & restart 24hr urine
	A	0700, 1300, 1900					X	Doses 1, 2, 3			Continue 24hr urine #2
		0900, 1500, 2100	X				X		X	X	Continue 24hr urine #2
2		0100					X	Dose 4			Continue 24hr urine #2
		0300	X				X		X	X	Continue 24hr urine #2
		0645-0700					X	Dose 5		X	End 24hr, start 4hr urine #1
		0800					X		X	X	Continue 4hr urine #1
		0900	X				X		X	X	Continue 4hr urine #1
		1000					X		X	X	Continue 4hr urine #1
		1100					X		X	X	End 4hr urine #1 & start 4hr urine #2
May be discharged		1500					X		X	X	End 4hr urine #2 & start 16hr
3(washout day)		0700					X				End 16hr urine
4		0700					X				Start 24hr urine
5		0645					X		X	X	End & restart 24hr urine
	B	0700, 1300, 1900					X	Doses 1, 2, 3			Continue 24hr urine #2
		0900, 1500, 2100	X				X		X	X	Continue 24hr urine #2
6		0100					X	Dose 4			Continue 24hr urine #2
		0300	X				X		X	X	Continue 24hr urine #2
		0645-0700					X	Dose 5		X	End 24hr, start 4hr urine #1
		0800					X		X	X	Continue 4hr urine #1
		0900	X				X		X	X	Continue 4hr urine #1
		1000					X		X	X	Continue 4hr urine #1
		1100					X		X	X	End 4hr urine #1 & start 4hr urine #2
		1500					X		X	X	End 4hr urine #2 & start 16hr
7		0700									End 16hr urine

4.G Data Elements-Main Study

- A minimum of 9 days is needed to complete the study with 2 nights on the CRC for the active compound and 2 nights for the placebo.
- Participants will be provided a 200 mEq/day sodium diet, free of methylxanthines and low in monoamines, by the kitchen of the Clinical Research Center (CRC).
- After achieving sodium balance on the study diet over 2-3 days, participants will collect urine over 24hr starting at 0700hr, for baseline assessment of sodium, potassium and catecholamines and to confirm adherence to the study diet.
- Participants will be admitted to the CRC that afternoon or evening.
- In the morning, while still supine and NPO after the overnight sleep, HR and BP will be recorded with a Dinamap electrocardiographic and blood pressure (brachial cuff) recorder, and blood will be drawn for a basic metabolic panel, fractionated catecholamines, aldosterone and plasma renin activity. The participants will then stand for 10 minutes or for as long as they are able to tolerate. They may sit for short intervals if necessary. HR and BP will be measured at 1, 3, 5, and 10 minutes of standing, and an upright blood sample will be collected at 10 minutes for catecholamines, plasma renin activity, and aldosterone.
- The participants will be asked to void while recumbent, if able, or after the upright measurements, to end the first 24hr urine collection. Another 24hr urine collection will then be started for analysis of sodium, potassium and creatinine. This may take the form of one 24 hr sample or two 4 hr collection samples followed by a 16 hr sample collected from approximately 3 pm to 7am the following morning. The second schedule will facilitate comparison to urinary excretion after the final dose.
- Treatment A (Carbidopa 200mg or placebo) will be given orally following the void, at approximately 0700hr. Additional doses will be taken every 6 hours with the last dose at 0700hr the following morning. BP and HR will be measured 2 hours after each dose. Participants will remain on the CRC for monitoring.
- In the next morning, supine and standing HR and BP will be recorded with a Dinamap recorder, and the participants will be asked to void and collect the urine to end the 2nd 24hr urine collection.
- The final dose of study medication (Carbidopa 200mg or placebo) will be given orally following the void, at approximately 0700hr.
- Supine HR and BP will be measured by Dinamap and supine blood samples will be collected hourly for 4 hours after the 5th dose and at 8 hours after the treatment. Participants must rest supine for at least 30 minutes before each blood draw. These samples will be analyzed for catecholamines (all samples), carbidopa (at 2, 4 and 8hr) and plasma renin activity and aldosterone (only at 2 hr after treatment). In addition, a basic metabolic panel will be run for the 4-hour and 8-hr samples.
- At 2 hours after the last dose, participants will stand for 10 minutes for upright BP and HR measurements and collection of an upright blood sample, as described above. Participants will be asked to rate the severity of common orthostatic symptoms while supine and upright.
- Urine will be collected for two 4-hour periods after the last dose followed by a 16-hr collection to finish the 24-hour cycle for analysis of sodium, potassium, catecholamines, and creatinine.
- Participants may be discharged from the CRC approximately 8 hours after the last dose.
- After at least 24 hours, the protocol will be repeated with treatment B (Carbidopa 200 mg or placebo, whichever was not administered during treatment A). Depending on the interval, participants will either remain on the study diet or re-start the diet 2-3 days before admission for the 2nd phase.

4.H Schedule of Events-Main Study

Table 3 Study Schedule-Main Study

Dosing Regimen	Time of Dose	Monitoring/Labs
Predose	NA	24hr urine for catecholamines, sodium, potassium, creatinine to start 24hr prior to 1st dose; supine and upright BP and HR; supine and upright plasma catecholamines, serum aldosterone, plasma renin activity; metabolic panel; start another urine collection over 24 hr for catecholamines, sodium, potassium, creatinine
Dose #1	0700	0900: supine BP and HR
Dose #2	1300	1500: supine BP and HR
Dose #3	1900	2100: supine BP and HR
Dose #4	0100	0300: supine BP and HR
Pre-Dose #5	0645	Supine and upright BP and HR; finish 24hr urine and start 4hr urine for catecholamines, sodium, potassium, creatinine
Dose #5	0700	0800: supine BP and HR; plasma catecholamines
		0900: supine and upright BP and HR; plasma carbidopa; Orthostatic Symptom Questionnaire; supine and upright plasma catecholamines, serum aldosterone, plasma renin activity
		1000: supine BP and HR; plasma catecholamines
		1100: supine BP and HR; metabolic panel; plasma catecholamines; plasma carbidopa; restart 4hr urine for catecholamines, sodium, potassium, creatinine
		1500: supine BP and HR; metabolic panel; plasma catecholamines; plasma carbidopa; start 16hr urine for catecholamines, sodium, potassium, creatinine

Table 4. Study Day Description-Main Study

Day	Treatment	Time	Obtain Consent	History & Physical	Pregnancy Test	Study Diet	Carbidopa or Placebo	Blood Draw	HR/BP	Urine
Pre-Study			X	X	X					
-3, -2						X				Start study diet
-1		0700				X				Start 24hr urine #1
1		0645				X		X	X	End & restart 24hr of urine collection
	A	0700, 1300, 1900				X	Doses 1, 2, 3			Continue urine collection
		0900, 1500, 2100				X			X	Continue urine collection
2		0100				X	Dose 4			Continue urine collection
		0300				X			X	Continue urine collection
		0645-0700				X	Dose 5		X	End 24hr of urine collection, start 4hr urine #1
		0800, 0900, 1000				X		X	X	Continue 4hr urine #1
		1100				X		X	X	End 4hr urine #1 & start 4hr urine #2
May be discharged		1500				X		X	X	End 4hr urine #2 & start 16hr urine
3(washout day)		0700				X				End 16hr urine
4		0700				X				Start 24hr urine
5		0645				X		X	X	End & restart 24hr of urine collection
	B	0700, 1300, 1900				X	Doses 1, 2, 3			Continue urine collection
		0900, 1500, 2100				X			X	Continue urine collection
6		0100				X	Dose 4			Continue urine collection
		0300				X			X	Continue urine collection
		0645-0700				X	Dose 5		X	End 24hr of urine collection, start 4hr urine #1
		0800, 0900, 1000				X		X	X	Continue 4hr urine #1
		1100				X		X	X	End 4hr urine #1 & start 4hr urine #2
		1500				X		X	X	End 4hr urine #2 & start 16hr urine
7		0700								End 16hr urine

5. Data and Safety Monitoring Plan

The NINDS has reviewed the risk associated with this study, and the following safety monitoring will be implemented:

The Study Chair will appoint an NINDS approved Independent Medical Monitor (IMM) to review all adverse events that are serious, unexpected, and possibly/probably/definitely related to the study intervention in real time.

The IMM will also review cumulative AEs. The frequency of review of cumulative AEs will be determined by the IMM in conjunction with the Study Chair and will occur at least once every 12 months.

The site's Primary Investigator and the research team (co-Investigators, research nurses, clinical trial coordinators, and data managers) are responsible for identifying adverse events. Aggregate report- detailed by severity, attribution (expected or unexpected), and relationship to the study drug/study procedures – will be available from the DMCC for site review. Adverse events will be reviewed regularly by the research team. A separate report detailing protocol compliance will also be available from the DMCC for site review on a monthly basis.

Adverse events will be monitored on an ongoing basis by Drs. David Robertson and Emily Garland. [redacted] RN will be responsible for tracking adverse events in this study. Any adverse event of a serious or greater nature will be reviewed immediately with the P.I. Drs Robertson and Garland and [redacted] will convene monthly to discuss the progress of the study and any issues concerning data collection and safety.

Serious adverse events will be reported in writing to the Vanderbilt IRB, with copies to the CRC Advisory Committee, within 24 hours of occurrence. All study adverse events will be summarized once a year, as part of the annual review report to the IRB.

The adverse event will be described with the following information: description of the event; outcome of the event; duration of the event; relationship to study procedure; requirement, if any, for treatment or intervention; and outcome.
Adverse events will be graded according to the following scale:

0 = No adverse event or within normal limits
1 = Mild adverse event (transient and mild in nature, and no treatment is necessary)
2 = Moderate adverse event (some intervention and treatment are necessary, but participant completely recovers
3 = Severe adverse event
4 = Life-threatening or disabling adverse event
5 = Death related to adverse event

The investigator will state his opinion on whether there is a reasonable possibility that the event or experience is related to a procedure performed as part of this study."

5.A Study Oversight

The study protocol will be reviewed and approved by the National Institutes of Health (NIH) before submission to individual center IRB's for approval. Participant enrollment may only begin with IRB approved consent forms. This is a phase II study that meets the federal definition of moderate risk.

The Study Chair has primary oversight responsibility of this clinical trial. The Autonomic Consortium will review accrual, patterns and frequencies of all adverse events, and protocol compliance at least every 6 months.

5.B Definitions and Standards

The Rare Diseases Clinical Research Network defines an adverse event as: "…an unfavorable and unintended sign, symptom or disease associated with a participant's participation in a Rare Diseases Clinical Research Network study."

Serious adverse events include those events that: "result in death; are life-threatening; require inpatient hospitalization or prolongation of existing hospitalization; create persistent or significant disability/incapacity, or a congenital anomaly/birth defects."

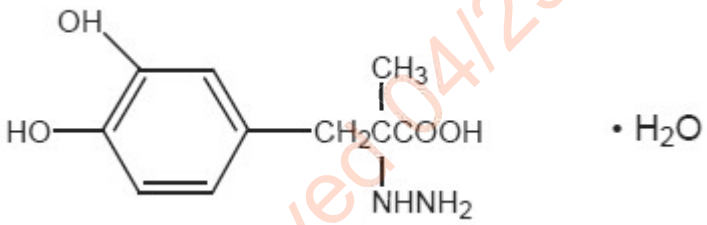
An unexpected adverse event is defined as any adverse experience…the specificity or severity of which is not consistent with the risks of information described in the protocol. Expected adverse events are those that are known to be associated with or have the potential to arise as a consequence of participation in the study

All reported adverse events will be classified using the current version of the Common Terminology Criteria for Adverse Events (CTCAE) developed and maintained by CTEP at National Cancer Institute.

5.C Expected/Known Risks/Discomforts/Adverse Events Associated with Study Intervention and Procedures: Definition of Expected Adverse Events

Study Drug/Intervention: Carbidopa / Placebo
Drug Information for STUDY DRUG

Carbidopa, an inhibitor of aromatic amino acid decarboxylation, is a white, crystalline compound, slightly soluble in water, with a molecular weight of 244.3. It is designated chemically as (—)-L-αhydrazino- α-methyl-β-(3,4-dihydroxybenzene) propanoic acid monohydrate. Its empirical formula is $C_{10}H_{14}N_2O_4 \cdot H_2O$, and its structural formula is:



Tablet content is expressed in terms of anhydrous carbidopa which has a molecular weight of 226.3.

LODOSYN (Carbidopa) tablets contain 25 mg of carbidopa. Inactive ingredients are cellulose, FD&C Yellow 6, magnesium stearate and starch.

Human Toxicity/ Adverse Events (adapted from package insert)
Carbidopa has not been demonstrated to have any overt pharmacodynamic actions in the recommended doses. The only adverse reactions that have been observed have been with concomitant use of carbidopa with other drugs such as levodopa, and with carbidopa-levodopa combination products. Common adverse events with the carbidopa-levodopa combination include abnormal body movements and nausea. Less common adverse effects are psychotic episodes (periods of confused thinking which can include hearing voices, seeing things that are not real, believing things that are not true and/or strange behavior), depression and dementia (loss of mental ability severe enough to cause problems with normal activities of daily living). Rarely, there is an allergic reaction to the FD&C Yellow 6 dye. The dose in this study is a much higher dose than used in clinical practice, and there may be additional side effects that are not known at this time. This medication has never been used at this dose or frequency.

Study Procedures:
Venipuncture: The vein in which the needle has been inserted to draw blood may become sore and red. A temporary "black and blue mark" may develop, and rarely fainting may occur.

5.D Reporting Timeline

- Withi **24 hours** (of learning of the event), investigators must report any reportable Serious Adverse Event (SAE) that:
  - Is considered life-threatening/disabling or results in death of participant

  -OR-
  - Is Unexpected/Unanticipated
- Investigators must report all other reportable SAEs within **5 working days** (of learning of the event).
- All other (suspected) reportable AEs must be reported to the RDCRN within **20 working days** of the notification of the event or of the site becoming aware of the event.

Local institutional reporting requirements to IRBs, any Vanderbilt Institute for Clinical and Translational Research/Clinical Research Center (VICTR/CRC) oversight committee and the FDA, if appropriate, remain the responsibility of the site investigator and the Study Chair.

5.E RDCRN Adverse Event Data Management System (AEDAMS)

Upon entry of a serious adverse event by a site investigator, the DMCC created Adverse Event Data Management System (AEDAMS) will immediately notify the Study Chair and the Independent Medical Monitor.
The Study Chair is responsible for notifying the appropriate NINDS staff.

Serious adverse events: The site investigator determines causality (definitely not related, probably not related, possibly related, probably related, definitely related) of the adverse event. The IMM will also review the SAE incident report.

The IMM may request further information if necessary and possibly suggest changes to the protocol or consent form to the NINDS as a consequence of adverse events. The Adverse Event Data Management System (AEDAMS) maintains audit trails and stores data (and data updated) and communication related to any adverse event in the study.

Non-serious expected adverse events: Except those listed above as immediately reportable, non-serious expected adverse events that are reported to or observed by the investigator or a member of his research team will be submitted to the DMCC in a timely fashion (within 20 working days). The events will be presented in tabular form and given to the IMM at least once every 12 months or as requested. Local site investigators are also required to fulfill all reporting requirements of their local institutions.

The DMCC will post aggregate reports of all adverse events (serious/not serious and expected, unexpected) for site investigators and IRBs.

5.F Study Discontinuation

The NIH and local IRB's (at their local site) have the authority to stop or suspend this trial at any time. This study may be suspended or closed:

- For safety concerns
- For other reasons as determined by the NIH or FDA

5.G Participant Discontinuation

An intent to treat approach will be used. All data acquired prior to termination for the reasons outlined below will be included in the primary analysis unless the participant withdraws consent. Every effort will be made to conduct a final study visit with the participant, and participants will be followed clinically until, if applicable, all adverse events resolve.

- Withdrawal of consent
- Withdrawal by the investigator
- Noncompliance to study diet and or urine collections
- Unanticipated reaction to study drug / placebo

5.H Data Quality and Monitoring Measures

As much as possible data quality is assessed at the data entry point using intelligent on-line data entry via visual basic designed screen forms. Data element constraints, whether independent range and/or format limitations or 'relative' referential integrity limitations, can be enforced by all methods employed for data input. QA reports assess data quality post-data entry. As we note, data quality begins with the design of the data collection forms and procedures and incorporates reasonable checks to minimize transcription and omission errors. Of the more important quality assurance measures are the internal validity checks for reasonableness and consistency.

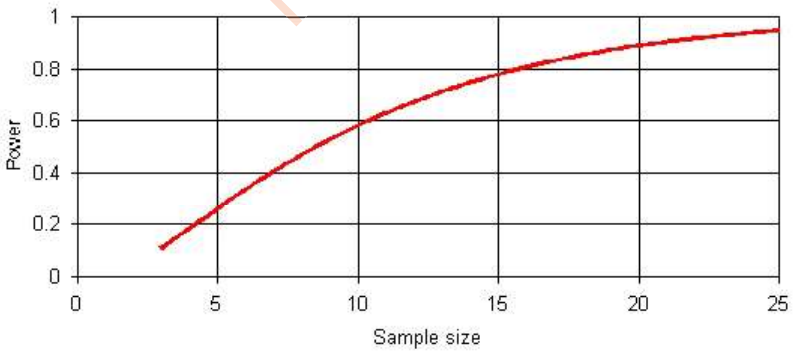
- Data Monitoring: The RDCRN DMCC identifies missing or unclear data and generates a data query to the consortium administrator contact.
- Data Delinquency Tracking: The Data Management and Coordinating Center will monitor data delinquency on an ongoing basis.

6. Statistical Considerations

Individual data will be reviewed for the Dose Escalation Study with the post-dose data compared to pre-dosing data. The data for each cohort will be summarized for review by Dr. David Robertson and the IMM of this study.The primary outcome is the urinary sodium concentration normalized to creatinine. Differences in urinary sodium in samples (1) collected at baseline vs. those collected following treatment (time effect) and (2) collected after placebo vs. carbidopa (treatment effect) will be assessed using a paired t-test and Wilcoxon signed-rank test. Differences between the patient and control groups (group effect) will be assessed using a student's t-test and a Mann-Whitney U test. Similar methods will be used to compare secondary outcome measures, such as BP, HR, plasma and urinary catecholamines, plasma renin activity, plasma aldosterone, and plasma sodium. All data analyses will be performed using SPSS 18.0 (SPSS, Chicago, IL) or STATA 8.2 (StataCorp, College Station, TX). All statistical tests will be two-sided. A mixed-effects model will be developed to describe the time, medication and group effects.

Sample Size Calculation. Based on our preliminary findings of a standard deviation for urinary sodium excretion of 30 mEq/g creatinine, a sample size of 16/group (32 total) will have 80% power to detect a difference in group means (control vs. POTS) of 31 mEq/g creatinine with a 0.05 two-sided significance level. To allow for participant drop-out prior to study completion, we will plan to obtain informed consent from 35 participants in total (18 POTS, 17 healthy controls).

Randomization procedures were performed by [redacted] and the results provided to Vanderbilt's Investigational Pharmacy. Prior to admission, the pharmacy is notified whether the participant is a patient or healthy volunteer and the Investigational Pharmacist determines the treatment order (placebo or carbidopa first). At the end of the study, the blinding will be broken by the Vanderbilt Investigational Pharmacy and the order of agents will be revealed to the investigators and to the participants, if they so request.



7. Data Management

The investigators, research personnel and nursing staff at the CRC will collect the majority of the data at the bedside in real time. Data will be handwritten on CRFs provided by Emily Garland, PhD. Routine labs are sent to

the hospital laboratory for analysis. Special study specific labs (ex: catecholamines) are sent to the GCRC Core Lab for analysis. Laboratory data will be obtained from Vanderbilt Medical Center's online medical chart system (StarPanel) and from the GCRC Core Laboratory website, both of which are password protected and only authorized personnel have access. After all data points have been retrieved, a member of the research team will enter the data into the DMCC database, which is also password protected and only accessible to authorized personnel. Data analysis will be performed routinely for periodic review. Hard copies of the CRFs will be maintained in the patient's research chart in a locked cabinet. Study participation will be complete following the inpatient evaluation. There will be no further study follow-up. Study records will be kept for at least 7 years following the publication or presentation of the data collected as part of this study.

All study data will be collected via systems created in collaboration with the RDCRN Data Management and Coordinating Center and will comply with all applicable guidelines regarding patient confidentiality and data integrity.

7.A Registration

Registration of participants on this protocol will employ an interactive data system in which the clinical site will attest to the participant's eligibility as per protocol criteria and obtain appropriate informed consent. IRB approval for the protocol must be on file at the DMCC before accrual can occur from the clinical site.

The DMCC will use a system of coded identifiers to protect participant confidentiality. Each participant enrolled will be assigned a local identifier by the enrollment site. This number can be a combination of the site identifier (location code) and a serial accession number. Only the registering site will have access to the linkage between this number and the personal identifier of the participant. When the participant is registered to participate in the study, using the DMCC provided web-based registration system, the system will assign a participant ID number. Thus each participant will have two codes: the local one that can be used by the registering site to obtain personal identifiers and a second code assigned by the DMCC. For all data transfers to the DMCC both numbers will be required to uniquely identify the participant. In this fashion, it is possible to protect against data keying errors, digit transposition or other mistakes when identifying a participant for data entry since the numbers should match to properly identify the participant. In this fashion, no personal identifiers would be accessible to the DMCC.

7.B Data Entry

Data collection for this study will be accomplished with online electronic case report forms. Using encrypted communication links, on-line forms will be developed that contain the requisite data fields.

7.C Laboratory data flow

Much of the data will be entered into the password-protected Autonomic Dysfunction Center Database. Hard copies of research results are maintained by the Autonomic Dysfunction Center research nurses in a locked room. Data will be accessible to the PI, other staff members of the Autonomic Dysfunction Center, and their collaborators. All data and research specimens will be maintained by David Robertson, M.D. following study termination for an indeterminate period of time.

Laboratory specimens, especially for catecholamine determination, are kept in the Core Lab. Specimens are secured in a frozen state in a locked –70° freezer. The results are entered into the CRC Core Lab password-protected database.

8. Human Participants

All patients who contact us with symptoms of orthostatic intolerance or tachycardia are in theory eligible for this study. Most of them find us because we have a website. If they complete the screening process (IRB #030751) and meet the criteria for the study, i.e. have difficulty maintaining a standing posture, have classic symptoms (palpitations, dizziness, difficulty thinking, chest tightness) while upright or have heart rate changes and high plasma catecholamines on standing, they may be eligible to participate.

The participants are screened on the CRC where pertinent heart rate, blood pressure, history and laboratory data are obtained to make sure that they are appropriate and can tolerate this study. Study personnel will be experienced in the conduct and completion of patient-oriented investigations.

This clinical trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and all applicable regulatory requirements.

8.A Human participants involvement and characteristics

Inclusion of vulnerable groups:
No ethnic group is targeted or excluded.

Inclusion of Women. To the extent possible, patient and control groups will include approximately equal numbers of males and females. However, postural tachycardia syndrome is far more common in women than in men. Based upon prior experience, we anticipate a patient population that is approximately 80% female and 20% male

Inclusion of Minorities. The ethnic composition of Nashville is ~79.4% non-Hispanic white American, 15.6% black American, 1.7% Asian and Pacific Islander, 0.3% American Indian and Alaska Native, and 3% Hispanic. In the literature on postural tachycardia syndrome, breakdown of study participants by race is frequently not reported. No one to our knowledge has reported a race-based difference in the frequency of this category of illness. However, investigators who see substantial numbers of tertiary referrals of patients with the postural tachycardia syndrome, including ourselves, encounter this disease only rarely in African-Americans, and believe this may reflect a true difference in susceptibility. Through the alliance between Vanderbilt and the historically African-American Meharry Medical College, in Nashville, we will attempt to enrich our study population by recruiting African-American patients for evaluation at our institution.

8.B Informed consent

Written informed consent will be obtained from each participant before any study-specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained. The participant's willingness to participate in the study will be documented in writing in a consent form, which will be signed by the participant with the date of that signature indicated. The investigator will keep the original consent forms and signed copies will be given to the participants. It will also be explained to the participants that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. Written and/or oral information about the study in a language understandable by the participant will be given to all participants.

See appendix 1a &1b

8.C Potential risks

1. There is the inconvenience of having to sleep on the CRC for several nights.
2. Intravenous catheter placement and blood sampling can cause bruising, pain and infection.
3. Collecting urine can be inconvenient and embarrassing.
4. Blood pressure measurements with a cuff on the arm can be uncomfortable.
5. Drawing blood for analysis can cause discomfort or bruising.
6. Standing upright may cause lightheadedness, blurred vision, rapid heartbeat, headache and nausea.
7. Carbidopa – only reported to have adverse effects when it is given with the drug levodopa for Parkinson's disease. Less common adverse effects are allergies, psychotic episodes, depression and dementia. However, the dosage used in this study is higher than typically administered. We will therefore do a dose escalation study to assess the tolerability of the 200mg carbidopa dose that we propose to use in the main study.
8. Consuming a sodium- and caffeine-controlled diet that needs to be picked up at the CRC might be inconvenient. If caffeine intake is stopped suddenly, participants might have headaches and fatigue for a few days.

8.D Protection against risk

Due to the dosage of carbidopa proposed for the main study, an IND (#108723) has been obtained by Dr. David Robertson. All procedures have been used previously by the staff of the CRC or ADC, and risks will be minimized by using trained, well-qualified personnel.

8.E Potential benefits of the proposed research to the participants and others

Although we cannot guarantee any benefit to the individuals who participate in this study, we hope to obtain knowledge from this study that will help us to better understand the causes of problems involving blood pressure and heart rate.

8.F Importance of the knowledge to be gained

It is possible that this study might provide insight into the effectiveness of a potential treatment for their disorder and provide either direct or indirect benefit to their medical care.

8.G Confidentiality

As part of the Vanderbilt application, the principal investigator signs the following statement of assurance.

PRINCIPAL INVESTIGATOR'S ASSURANCE STATEMENT

I certify that the information provided in this application is complete and accurate.

I understand that as Principal Investigator, I have ultimate responsibility for the conduct of the study, the ethical performance of the project, the protection of the rights and welfare of human participants, and strict adherence to the study protocol and any stipulations imposed by the Vanderbilt University Institutional Review Board.

I understand that, should I use the project described in this application as a basis for a proposal for funding (either intramural or extramural), it is my responsibility to ensure that the human participants' involvement as described in the funding proposal(s), is consistent in principle, to that contained in this application. I will submit modifications and/or changes to the IRB as necessary, in the form of an amendment, to ensure these are consistent.

I agree to comply with all VU policies and procedures, as well as with all applicable federal, state, and local laws regarding the protection of human participants in research, including, but not limited to:

- Ensuring all investigators and key study personnel have completed the VU human participants training program;
- Ensuring the project is conducted by qualified personnel following the approved IRB application and study protocol;
- Implementing no changes in the approved IRB application, study protocol, or informed consent document without prior IRB approval in accordance with VU IRB policy (except in an emergency, if necessary to safeguard the well-being of a human participant, and will report to the IRB within 5 days of such change);
- Obtaining the legally effective informed consent from human participants or their legally responsible representative, using only the currently approved date-stamped informed consent documents, and providing a copy to the participant, if applicable.
- Promptly report to the IRB, Data Safety and Monitoring Boards, sponsors and appropriate federal agencies any adverse experiences and all unanticipated problems involving risks to human participants or others that occur in the course of the research in accordance with Vanderbilt University IRB Policies and Procedures.
- If unavailable to conduct this research personally, as when on sabbatical leave or vacation, I will arrange for another investigator to assume direct responsibility for the study. Either this person is named as another investigator in this application, or I will notify the IRB of such arrangements;
- Promptly providing the IRB with any information requested relative to the project;
- Promptly and completely complying with an IRB decision to suspend or withdraw approval for the project;
- Obtaining Continuing Review approval prior to the date the approval for the study expires. I understand if I fail to apply for continuing review, approval for the study will automatically expire, and all study activity must cease until IRB approval is granted;
- Maintain accurate and complete research records, including, but not limited to, all informed consent documents for 3 years from the date of study completion;
- Maintain any authorization documents to use or disclose PHI for 6 years from the date authorization is obtained; and

- Fully informing the VU IRB of all locations in which human participants will be recruited for this project and being responsible for obtaining and maintaining current IRB approvals/letters of cooperation and Federal Wide Assurances (FWAs), when applicable.

_____ _____

Principal Investigator's Signature Date

By my signature, I certify that I have evaluated this research application for soundness of research design and scientific merit in accordance with departmental policy and the adequacy of facilities and resources.

_____ _____

Division Chief's Signature* Date

_____ _____

Department Chair's Signature* Date

Requires one signature other than PI

8.H Financial considerations

Participants with POTS will not be monetarily compensated for their participation in this study. Healthy control participants will be compensated $450 in the dose escalation study and $400 in the main study for their inconvenience and time involved in participating in this study. The investigator has no financial interest or compensation from the outcomes of the study.

8.I Conflict of interest

There are no known conflicts of interest between study participants, research personnel and other entities regarding the conduction of the study.

9. References

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10. APPENDICES

APPENDIX 1a Sample Informed Consent Form for Main Study - POTS

This informed consent applies to Participants with Postural Tachycardia Syndrome

Name of participant: _____ Age: _____

The following is given to you to tell you about this research study. Please read this form with care and ask any questions you may have about this study. Your questions will be answered. Also, you will be given a copy of this consent form.

You do not have to be in this research study. You can stop being in this study at any time. If we learn something new that may affect the risks or benefits of this study, you will be told so that you can decide whether or not you still want to be in this study.

1. What is the purpose of this study?

You are being asked to take part in this research study because you have been diagnosed with Postural Tachycardia Syndrome (POTS). A chemical in the kidney called dopamine plays an important role in maintaining your body's salt levels. We will give you a drug called carbidopa that interferes with the formation of dopamine in the kidney, and we will measure how much salt is then excreted in your urine. This drug has been used for many years at lower doses to treat Parkinson's disease. We will also measure your blood pressure and heart rate and some chemicals in your blood and urine that control them. We will compare the effects of this drug to those of a sugar pill. You will take the drug and the sugar pill on different days (Treatment A and Treatment B), but you will not be told which one you are taking on a given day. We expect to enroll 16 participants with POTS and 16 healthy volunteers.

2. What will happen and how long will you be in the study?

This study is being conducted at the Vanderbilt Clinical Research Center (CRC). You will be asked some questions about your health other than POTS. One of the investigators will explain the study to you and ask you to sign this consent form. A copy of the consent form will be given to you. Your participation is voluntary.

A minimum of 9 days will be required to complete this study. You will need to spend 4 nights on the CRC, 2 nights for the active drug and 2 nights for the sugar pill. Alternatively, you may stay as an inpatient on the CRC for the entire study period. On the morning after the first overnight, study day 1, we will collect pre-treatment data and then give you your first pill. You will take pills every 6 hours. You will need to be on the CRC so that we can measure your blood pressure and heart rate two hours after every dose. Studies on the second study day will last until about 3pm. Different parts of the study are described below.

Drug withdrawal

You must remain off any medications that could affect blood pressure, the composition of your urine, or the chemicals that we will measure for three days prior to the first treatment and during the entire study. This includes not only your usual scheduled medications, but also other drugs that might be taken intermittently. You should consult your primary care physician before stopping any drug and contact the Principal Investigator or his nurse if any problems occur prior to admission. Your symptoms, such as dizziness, fatigue, nausea, fainting or near fainting, might get worse, but they should be relieved by lying down. If necessary, we will admit you to the hospital and take you off your medications there. While you are an inpatient on the CRC, we will check your general condition, blood pressure and heart rate regularly to reduce any risk.

Pregnancy test

If you are a female, we will perform a pregnancy test on a sample of your blood when you are admitted to the hospital for this study. Pregnant females may not participate in this research study.

Diet

We will ask you to eat a standard diet with no caffeine and a controlled amount of salt for three days prior to each study day and during the study days. We will provide this food to you and ask you to eat all of it and no other food. We will check to be sure that you are doing this by having you collect all of your urine for 24 hours and measuring the amount of salt in it (see below).

Urine Collection
You will collect your urine for 24 hours before administration of the first pill (active drug or sugar pill) and for the next 24 hours (study day 1). After the last pill, on the second study day, you will collect samples over the first 4 hours, from 4-8 hours, and from 8-24 hours. The urine will be analyzed for sodium, potassium and for hormones that control blood pressure and heart rate.

Vital signs
Vital signs (blood pressure and heart rate) will be measured several times while you are lying down just before and after the treatment. Sometimes you will be asked to stand quietly for 10 minutes for additional measurements. A Dinamap, an automated blood pressure monitor that uses a cuff around your upper arm, is used for these measurements.

Blood sampling
For Treatments A and B, it will be necessary to collect 2 samples of your blood during study day 1 and 6 samples during study day 2 (a total of 6 tablespoons per treatment and 12 tablespoons for the complete protocol) for measurement of the hormones that control blood pressure. We will also measure sodium in your blood when you complete the pre-study 24hr-urine collection and the 2 4hr-urine collections. At some times, we will also measure carbidopa in your blood. To avoid sticking you repeatedly, we will place a small plastic tube (catheter) in your arm vein. The samples will be 2-3 teaspoons each.

Drug testing
In the evening prior to study day 1, you will be admitted to the Vanderbilt Clinical Research Center. In the morning, a small tube (catheter) will be placed in your arm vein in order to draw blood. Baseline blood pressure and heart rate readings will be obtained and blood samples will be collected in the supine (lying on your back) and upright positions. You will void to finish the pre-study 24hr urine collection. You will then be given a pill, either the active drug or the sugar pill. Whether you receive the active pill or the sugar pill as Treatment A will be decided by a procedure similar to tossing a coin. You will receive the other kind of pill as Treatment B. The medication will be given by mouth, every 6 hours, for 5 doses. You will remain on the CRC during the day and we will measure your blood pressure and pulse after each dose, including overnight. You will need to consume the study diet for each meal, collect all urine, and take your study medication on schedule. In the next morning, study day 2, blood pressure and heart rate readings will be obtained in the supine and upright positions. You will void to finish the study day 1 urine collection. After taking the last dose of Treatment A, your supine blood pressure and heart rate will be measured every hour for 4 hours and again at 8 hours after treatment. You will be able to sit up and move around during the study but you must lie supine for at least 30 minutes before each of the measurements. Standing vital signs will also be taken 2 hours after treatment. A sample of blood will be collected at every scheduled blood pressure measurement after the 5th dose of study drug. Urine will also be collected from 0-4 hours, 4-8 hours and 8-24 hours. If you live close enough to Vanderbilt, you may be discharged 8 hours after the last dose.

After at least another 24 hours, you will start collecting the pre-study urine for Treatment B. You may wait longer than 24 hours but you will need to eat the study diet for at least 3 days before study day 1 for Treatment B. Treatment B will follow the same schedule as Treatment A.

Table 1. Study Day Description

Day	Treatment	Time[a]	Pregnancy Test	Study Diet	Admit to CRC	Carbidopa or Placebo	Blood Draw	HR/BP	Urine
-3, -2				X					Start study diet
-1		0700	X	X					Start 24hr urine #1
		1600			X				
1		0645		X			X	X	End & restart 24hr urine
	A	0700, 1300, 1900		X		Doses 1, 2, 3			Continue 24hr urine #2
		0900, 1500, 2100		X				X	Continue 24hr urine #2
2		0100		X		Dose 4			Continue 24hr urine #2
		0300		X				X	Continue 24hr urine #2
		0645-0700		X		Dose 5		X	End 24hr, start 4hr urine #1
		0800, 0900, 1000		X			X	X	Continue 4hr urine #1
		1100		X			X	X	End 4hr urine #1 & start 4hr urine #2
May be discharged		1500		X			X	X	End 4hr urine #2 & start 16hr urine
3(washout day)		0700		X					End 16hr urine
Repeat with Treatment B after at least 1 day									

[a] these times are approximate

3. Costs to you if you take part in this study:

There will be no costs to you for any procedures done strictly for research. All of the procedures described in this consent form will be done for research.

4. Side effects and risks that you can expect if you take part in this study:

Stopping medications might worsen your symptoms.

Consuming a **sodium- and caffeine-controlled diet** that needs to be picked up at the CRC might be inconvenient. The diet might not be to your liking. If you drink caffeinated beverages regularly and you stop caffeine intake suddenly, you might have headaches and fatigue for a few days. You can avoid these symptoms if you cut down gradually on the amount of caffeine in your diet.

Staying in the hospital might be an inconvenience for you.

Being woken up during the night might be an inconvenience for you.

Frequent blood pressure measurements with the cuff around your arm may produce some discomfort and occasional bruising of the upper arm.

There are minor risks and discomforts associated with **blood sampling**. We will insert a plastic catheter into the vein to allow drawing blood without repeated sticks during the study. This may cause a brief period of pain and possibly a small bruise at the site. Occasionally, a person feels faint when their blood is drawn. Rarely, an infection develops which can be treated. There is a small risk of bleeding after removal of the catheter and possibly a bruise at the site which can be prevented by tight compression on the site.

Collecting your urine might be inconvenient for you. We try to make it more convenient by fitting the toilet with a collection device and/or providing a urinal for your use.

The **study days might seem tedious** and boring because they require you to lie down for an extended period of time before your blood pressure is monitored.

Carbidopa – When any medication is used in testing, there is a small risk of an unforeseeable life-threatening allergic reaction. Side effects of **Carbidopa have** only been reported when it is given with the drug levodopa for Parkinson's disease at lower dosages than are being evaluated in this study. Common adverse events with the carbidopa-levodopa combination include abnormal body movements and nausea. Less common adverse effects are allergies, psychotic episodes (periods of confused thinking which can include hearing voices, seeing things that are not real, believing things that are not true and/or strange behavior), depression and dementia (loss of mental ability severe enough to cause problems with normal activities of daily living). The dose you will receive in this study is a much higher dose than used in clinical practice, and there may be additional side effects that are not known at this time. This medication has never been used at this dose or frequency.

5. Risks that are not known:

Because the medications might be harmful to an unborn child, adequate birth control measures (i.e., oral, implanted or barrier methods) must be used by all participants and their sexual partners while participants are enrolled in this study. If you become pregnant or father a child while in this study, you must notify your physician immediately. In addition, women must not breastfeed while in this study. To rule out pregnancy prior to receiving treatment in this study, women of childbearing potential will have a pregnancy test.

6. Payment in case you are injured while in this study:

If you are injured because you are in this study, you can get reasonable, immediate, and necessary medical care for your injury at Vanderbilt without charge to you. There are no plans for Vanderbilt to pay for the costs of care beyond your injury, or to give you money for such injury. There is no program for compensation through the National Institute of Neurological Disorders and Stroke (NINDS)/National Institutes of Health (NIH).

7. Good effects that might result from this study:

The benefits to science and humankind that might result from this study are: a better understanding of the relationship between the plasma and urinary chemicals that we will measure and sodium excretion.

The benefits you might get from being in this study are: this study might provide insight into the effectiveness of a potential treatment for your disorder and provide either direct or indirect benefit to your medical care.

8. Other treatments you could get if you decide not to be in this study:

You may choose not to participate in this study.

9. Payments for your time spent taking part in this study or expenses:

You will not be paid for taking part in this study.

10. Reasons why the study doctor may take you out of this study:

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

11. What will happen if you decide to stop being in this study?

If you decide to stop being part of the study, you should tell your study doctor. We will cease to collect study information at the time of withdrawal of consent.

12. Who to call for any questions or in case you are injured:

If you should have any questions about this research study or if you feel you have been hurt by being a part of this study, please feel free to contact **Emily Garland, Ph.D.** at [redacted] **or David Robertson, M.D.** at [redacted]

For additional information about giving consent or your rights as a participant in this study, please feel free to contact the Vanderbilt University Institutional Review Board Office at (615) 322-2918 or toll free at (866) 224-8273.

13. Confidentiality:

All efforts, within reason, will be made to keep your personal information in your research record confidential but total confidentiality cannot be guaranteed. Research records will be stored in a locked office. Digital records will be stored on password protected computers/servers. Digital data files will be coded so that the participant's 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 participant be identified in any such publication.

14. Privacy:

All efforts, within reason, will be made to keep your protected health information (PHI) private. PHI is your health information that is, or has been gathered or kept by Vanderbilt as a result of your healthcare. This includes data gathered for research studies that can be traced back to you. Using or sharing ("disclosure") such data must follow federal privacy rules. By signing the consent for this study, you are agreeing ("authorization") to the uses and likely sharing of your PHI. If you decide to be in this research study, you are also agreeing to let the study team use and share your PHI as described below.

As part of the study, Dr. Garland and her co-investigators may report the results of your study and/or non-study related laboratory tests and electrocardiograms as well as parts of your medical record, to other members of *the* research team and to collaborators. If your research record is reviewed by any of these groups, they may also need to review your entire medical record. Your records may also be reviewed in order to meet federal or state regulations. Reviewers may include representatives from the Food and Drug Administration, representatives of the National Institutes of Health, or the Vanderbilt University Institutional Review Board. Federal privacy rules may not apply to these groups; they have their own rules and codes to assure that all efforts, within reason, will be made to keep your PHI private.

The study results will be kept in your research record for at least seven years after the study is finished. At that time, the research data that has not been put in your medical record will be maintained in your research file for an unknown length of time. Any research data that has been put into your medical record will be kept for an unknown length of time.

The clinical information collected for this study will be stored at the Data Management and Coordinating Center at the [redacted]. The data management center uses several layers of protection for the clinical data stored there. It meets all of the local and federal security requirements for research datacenters. Your information is stored only using a study ID.

Unless told otherwise, your consent to use or share your PHI does not expire. If you change your mind, we ask that you contact Dr. Emily Garland in writing and let her know that you withdraw your consent. Her mailing address *is*

[redacted]
Vanderbilt University
Nashville, TN [redacted]

At that time, we will stop getting any more data about you. The health data we stored before you withdrew your

consent may still be used for reporting and research quality.

If you decide not to take part in this research study, it will not affect your treatment, payment or enrollment in any health plans or affect your ability to get benefits. You will get a copy of this form after it is signed.

STATEMENT BY PERSON AGREEING TO BE IN THIS STUDY
I have read this consent form and the research study has been explained to me verbally. All my questions have been answered, and I freely and voluntarily choose to take part in this study.

_____
Date Signature of patient/volunteer

Consent obtained by:

_____
Date Signature

_____
Printed Name and Title

APPENDIX 1b: Sample Informed Consent Form for Main Study – Healthy Volunteer

This informed consent applies to Healthy Volunteers

Name of participant: _____ Age: _____

The following is given to you to tell you about this research study. Please read this form with care and ask any questions you may have about this study. Your questions will be answered. Also, you will be given a copy of this consent form.

You do not have to be in this research study. You can stop being in this study at any time. If we learn something new that may affect the risks or benefits of this study, you will be told so that you can decide whether or not you still want to be in this study.

1. What is the purpose of this study?

You are being asked to take part in this research study because you are a healthy volunteer. Data obtained from healthy persons will be compared with data from participants who have a condition called postural tachycardia syndrome. A chemical in the kidney called dopamine plays an important role in maintaining your body's salt levels. We will give you a drug called carbidopa that interferes with the formation of dopamine in the kidney, and we will measure how much salt is then excreted in your urine. This drug has been used for many years at lower doses to treat Parkinson's disease. We will also measure your blood pressure and heart rate and some chemicals in your blood and urine that control them. We will compare the effects of this drug to those of a sugar pill. You will take the drug and the sugar pill on two different days (Treatment A and Treatment B), but you will not be told which one you are taking on a given day. We plan to enroll 16 participants with POTS and 16 healthy volunteers.

2. What will happen and how long will you be in the study?

This study is being conducted at the Vanderbilt Clinical Research Center (CRC). You will be asked some questions to ensure that you are in good health. One of the investigators will explain the study to you and ask you to sign this consent form. A copy of the consent form will be given to you. Your participation is voluntary.

A minimum of 9 days will be required to complete this study. You will need to spend 4 nights on the CRC, 2 nights for the active drug and 2 nights for the sugar pill. On the morning after the first overnight, study day 1, we will collect pre-treatment data and then give you your first pill. You will take pills every 6 hours. You will need to be on the CRC so that we can measure your heart rate and blood pressure two hours after every dose. Studies on the second study day will last until about 3pm. Different parts of the study are described below.

Drug withdrawal
You must remain off any medications that could affect blood pressure, the composition of your urine, or the chemicals that we will measure for three days prior to the first treatment and during the entire study. This includes not only your usual scheduled medications, but also other drugs that might be taken intermittently.

Pregnancy test
If you are a female, we will perform a pregnancy test on a sample of your blood when you are admitted to the hospital for this study. Pregnant females may not participate in this research study.

Diet
We will ask you to eat a standard diet with no caffeine and a controlled amount of salt for three days prior to each study day and during the study days. We will provide this food to you and ask you to eat all of it and no other food. We will check to be sure that you are doing this by having you collect all of your urine for 24 hours and measuring the amount of salt in it (see below).

Urine Collection
You will collect your urine for 24 hours before administration of the first pill (active drug or sugar pill) and for the next 24 hours (study day 1). After the last pill, on the second study day, you will collect samples over the first 4 hours, from 4-8 hours, and from 8-24 hours. The urine will be analyzed for sodium, potassium and for hormones that control blood pressure and heart rate.

Vital signs

Vital signs (blood pressure and heart rate) will be measured several times while you are lying down just before and after the treatment. Sometimes you will be asked to stand quietly for 10 minutes for additional measurements. A Dinamap, an automated blood pressure monitor that uses a cuff around your upper arm, is used for these measurements.

Blood sampling

For Treatments A and B, it will be necessary to collect 2 samples of your blood during study day 1 and 6 samples during study day 2 (a total of 6 tablespoons per treatment and 12 tablespoons for the complete protocol) for measurement of the hormones that control blood pressure. We will also measure sodium in your blood when you complete the pre-study 24hr-urine collection and the 2 4hr-urine collections. At some times, we will also measure carbidopa in your blood. To avoid sticking you repeatedly, we will place a small plastic tube (catheter) in your arm vein. The samples will be 2-3 teaspoons each.

Drug testing

In the evening prior to study day 1, you will be admitted to the Vanderbilt Clinical Research Center. In the morning, a small tube (catheter) will be placed in your arm vein in order to draw blood. Baseline blood pressure and heart rate readings will be obtained and blood samples will be collected in the supine (lying on your back) and upright positions. You will void to finish the pre-study 24hr urine collection. You will then be given a pill, either the active drug or the sugar pill. Whether you receive the active pill or the sugar pill as Treatment A will be decided by a procedure similar to tossing a coin. You will receive the other kind of pill as Treatment B. The medication will be given by mouth, every 6 hours, for 5 doses. You will remain on the CRC during the day and we will measure your blood pressure and pulse after each dose, including overnight. You will need to consume the study diet for each meal, collect all urine, and take your study medication on schedule. In the next morning, study day 2, blood pressure and heart rate readings will be obtained in the supine and upright positions. You will void to finish the study day 1 urine collection. After taking the last dose of Treatment A, your supine blood pressure and heart rate will be measured every hour for 4 hours and again at 8 hours after treatment. You will be able to sit up and move around during the study but you must lie supine for at least 30 minutes before each of the measurements. Standing vital signs will also be taken 2 hours after treatment. A sample of blood will be collected at every scheduled blood pressure measurement after the 5th dose of treatment. Urine will also be collected from 0-4 hours, 4-8 hours and 8-24 hours. You may be discharged 8 hours after the last dose.

After at least another 24 hours, you will start collecting the pre-study urine for Treatment B. You may wait longer than 24 hours but you will need to eat the study diet for at least 3 days before study day 1 for Treatment B. Treatment B will follow the same schedule as Treatment A.

Table 1. Study Day Description

Day	Treatment	Time[a]	Pregnancy Test	Study Diet	Admit to CRC	Carbidopa or Placebo	Blood Draw	HR/BP	Urine
-3, -2				X					Start study diet
-1		0700	X	X					Start 24hr urine #1
		1600			X				
1		0645		X			X	X	End & restart 24hr urine
	A	0700, 1300, 1900		X		Doses 1, 2, 3			Continue 24hr urine #2
		0900, 1500, 2100		X				X	Continue 24hr urine #2
2		0100		X		Dose 4			Continue 24hr urine #2
		0300		X				X	Continue 24hr urine #2
		0645-0700		X		Dose 5		X	End 24hr, start 4hr urine #1
		0800, 0900, 1000		X			X	X	Continue 4hr urine #1
		1100		X			X	X	End 4hr urine #1 & start 4hr urine #2
May be discharged		1500		X			X	X	End 4hr urine #2 & start 16hr urine
3(washout day)		0700		X					End 16hr urine
Repeat with Treatment B after at least 1 day									

[a] these times are approximate

3. Costs to you if you take part in this study:

There will be no costs to you for any procedures done strictly for research. All of the procedures described in this consent form will be done for research.

4. Side effects and risks that you can expect if you take part in this study:

Stopping medications might worsen your symptoms. If you routinely take medications that can affect blood pressure or plasma volume, you will not be enrolled in the study.

Consuming a **sodium- and caffeine-controlled diet** that needs to be picked up at the CRC might be inconvenient. The diet might not be to your liking. If you drink caffeinated beverages regularly and you stop caffeine intake suddenly, you might have headaches and fatigue for a few days. You can avoid these symptoms if you cut down gradually on the amount of caffeine in your diet.

Staying in the hospital might be an inconvenience for you.

Being woken up during the night might be an inconvenience for you.

Frequent blood pressure measurements with the cuff around your arm may produce some discomfort and occasional bruising of the upper arm.

There are minor risks and discomforts associated with **blood sampling**. We will insert a plastic catheter into the vein to allow drawing blood without repeated sticks during the study. This may cause a brief period of pain and possibly a small bruise at the site. Occasionally, a person feels faint when their blood is drawn. Rarely, an infection develops which can be treated. There is a small risk of bleeding after removal of the catheter and possibly a bruise at the site which can be prevented by tight compression on the site

Collecting your urine might be inconvenient for you. We try to make it more convenient by fitting the toilet with a collection device and/or providing a urinal for your use.

The **study days might seem tedious** and boring because they require you to lie down for an extended period of time before your blood pressure is monitored.

Carbidopa – When any medication is used in testing, there is a small risk of an unforeseeable life-threatening allergic reaction. Side effects of **Carbidopa have** only been reported when it is given with the drug levodopa for Parkinson's disease at lower dosages than are being evaluated in this study. Common adverse events with the carbidopa-levodopa combination include abnormal body movements and nausea. Less common adverse effects are allergies, psychotic episodes (periods of confused thinking which can include hearing voices, seeing things that are not real, believing things that are not true and/or strange behavior), depression and dementia (loss of mental ability severe enough to cause problems with normal activities of daily living). The dose you will receive in this study is a much higher dose than used in clinical practice, and there may be additional side effects that are not known at this time. This medication has never been used at this dose or frequency.

5. Risks that are not known:

Because the medications might be harmful to an unborn child, adequate birth control measures (i.e., oral, implanted or barrier methods) must be used by all participants and their sexual partners while participants are enrolled in this study. If you become pregnant or father a child while in this study, you must notify your physician immediately. In addition, women must not breastfeed while in this study. To rule out pregnancy prior to receiving treatment in this study, women of childbearing potential will have a pregnancy test.

6. Payment in case you are injured while in this study:

If you are injured because you are in this study, you can get reasonable, immediate, and necessary medical care for your injury at Vanderbilt without charge to you. There are no plans for Vanderbilt to pay for the costs of care beyond your injury, or to give you money for such injury. There is no program for compensation through the National Institute of Neurological Disorders and Stroke (NINDS)/National Institutes of Health (NIH).

7. Good effects that might result from this study:

The benefits to science and humankind that might result from this study are: a better understanding of the relationship between the plasma and urinary chemicals that we will measure and sodium excretion. The benefits you might get from being in this study are: none anticipated.

8. Other treatments you could get if you decide not to be in this study:

You may choose not to participate in this study.

9. Payments for your time spent taking part in this study or expenses:

$200 for completing Treatment A and an additional $200 for completing Treatment B.

10. Reasons why the study doctor may take you out of this study:

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

11. What will happen if you decide to stop being in this study?

If you decide to stop being part of the study, you should tell your study doctor. We will cease to collect study information at the time of withdrawal of consent.

12. Who to call for any questions or in case you are injured:

If you should have any questions about this research study or if you feel you have been hurt by being a part of this study, please feel free to contact **Emily Garland, Ph.D.** at [redacted] **or David Robertson, M.D.** at [redacted].

For additional information about giving consent or your rights as a participant in this study, please feel free to contact the Vanderbilt University Institutional Review Board Office at (615) 322-2918 or toll free at (866) 224-8273.

13. Confidentiality:

All efforts, within reason, will be made to keep your personal information in your research record confidential but total confidentiality cannot be guaranteed. Research records will be stored in a locked office. Digital records will be stored on password protected computers/servers. Digital data files will be coded so that the participant's 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 participant be identified in any such publication.

14. Privacy:

All efforts, within reason, will be made to keep your protected health information (PHI) private. PHI is your health information that is, or has been gathered or kept by Vanderbilt as a result of your healthcare. This includes data gathered for research studies that can be traced back to you. Using or sharing ("disclosure") such data must follow federal privacy rules. By signing the consent for this study, you are agreeing ("authorization") to the uses and likely sharing of your PHI. If you decide to be in this research study, you are also agreeing to let the study team use and share your PHI as described below.

As part of the study, Dr. Garland and her co-investigators may report the results of your study and/or non-study related laboratory tests and electrocardiograms as well as parts of your medical record, to other members of *the* research team and to collaborators. If your research record is reviewed by any of these groups, they may also need to review your entire medical record. Your records may also be reviewed in order to meet federal or state regulations. Reviewers may include representatives from the Food and Drug Administration, representatives of the National Institutes of Health, or the Vanderbilt University Institutional Review Board. Federal privacy rules may not apply to these groups; they have their own rules and codes to assure that all efforts, within reason, will be made to keep your PHI private.

The study results will be kept in your research record for at least seven years after the study is finished. At that time, the research data that has not been put in your medical record will be maintained in your research file for an unknown length of time. Any research data that has been put into your medical record will be kept for an unknown length of time.

The clinical information collected for this study will be stored at the Data Management and Coordinating Center at the [redacted] The data management center uses several layers of protection for the clinical data stored there. It meets all of the local and federal security requirements for research datacenters. Your information is stored only using a study ID.

Unless told otherwise, your consent to use or share your PHI does not expire. If you change your mind, we ask that you contact Dr. Emily Garland in writing and let her know that you withdraw your consent. Her mailing address *is*

[redacted]
Vanderbilt University
Nashville, TN [redacted]

At that time, we will stop getting any more data about you. The health data we stored before you withdrew your

consent may still be used for reporting and research quality.

If you decide not to take part in this research study, it will not affect your treatment, payment or enrollment in any health plans or affect your ability to get benefits. You will get a copy of this form after it is signed.

STATEMENT BY PERSON AGREEING TO BE IN THIS STUDY

I have read this consent form and the research study has been explained to me verbally. All my questions have been answered, and I freely and voluntarily choose to take part in this study.

_____

Date Signature of patient/volunteer

Consent obtained by:

_____

Date Signature

_____

Printed Name and Title

APPENDIX 1c: Sample Informed Consent Form for Dose Escalation Study– POTS

This informed consent applies to Participants with POTS

Name of participant: _____ Age: _____

The following is given to you to tell you about this research study. Please read this form with care and ask any questions you may have about this study. Your questions will be answered. Also, you will be given a copy of this consent form.

You do not have to be in this research study. You can stop being in this study at any time. If we learn something new that may affect the risks or benefits of this study, you will be told so that you can decide whether or not you still want to be in this study.

1. What is the purpose of this study?

You are being asked to take part in this research study because you have Postural Tachycardia Syndrome (POTS) Data obtained from healthy persons will be compared with data from participants who have POTS. A chemical in the kidney called dopamine plays an important role in maintaining your body's salt levels. We will give you a drug called carbidopa that interferes with the formation of dopamine in the kidney, and we will measure how much salt is then excreted in your urine. This drug has been used for many years at lower doses to treat Parkinson's disease. We will also measure your blood pressure and heart rate and some chemicals in your blood and urine that control them. We will compare the effects of this drug to those of a sugar pill. You will take the drug and the sugar pill on two different days (Treatment A and Treatment B), but you will not be told which one you are taking on a given day. Because we do not know what the best dose of carbidopa is, we are first doing this study to compare the effects of different doses. You will take 50 mg, 100 mg or 200 mg of carbidopa every 6 hours for 5 doses. We will monitor you for the effects we are studying and for any problems. Only if no problems occur after the 50 mg dose, we will enroll two more people at 100 mg, then 200 mg. This is called "dose escalation". Although we do not expect the doses of carbidopa to cause any problems, we are doing this study to make sure that participants do not have any problems at each dose level before we enroll at a higher dose.

2. What will happen and how long will you be in the study?

This study is being conducted at the Vanderbilt Clinical Research Center (CRC). You will be asked some questions about your health other than POTS. One of the investigators will explain the study to you and ask you to sign this consent form. A copy of the consent form will be given to you. Your participation is voluntary.

A minimum of 9 days will be required to complete this study. You will need to spend 4 nights on the CRC, 2 nights for the active drug and 2 nights for the sugar pill. On the morning after the first overnight, study day 1, we will collect pre-treatment data and then give you your first pill. You will take pills every 6 hours. You will need to stay on the CRC during the day so that we can monitor your blood pressure and pulse and make sure that there are no health problems associated with the dose of carbidopa that you take. Studies on the second study day will last until about 3pm. Different parts of the study are described below.

Drug withdrawal

You must remain off any medications that could affect blood pressure, the composition of your urine, or the chemicals that we will measure for three days prior to the first treatment and during the entire study. This includes not only your usual scheduled medications, but also other drugs that might be taken intermittently. You should consult your primary care physician before stopping any drug and contact the Principal Investigator or his nurse if any problems occur prior to admission. Your symptoms, such as dizziness, fatigue, nausea, fainting or near fainting, might get worse, but they should be relieved by lying down. If necessary, we will admit you to the hospital and take you off your medications there. While you are an inpatient on the CRC, we will check your general condition, blood pressure and heart rate regularly to reduce any risk.

Pregnancy test

If you are a female, we will perform a pregnancy test on a sample of your blood when you are admitted to the hospital for this study. Pregnant females may not participate in this research study.

Diet
We will ask you to eat a standard diet with no caffeine and a controlled amount of salt for three days prior to each study day and during the study days. We will provide this food to you and ask you to eat all of it and no other food. We will check to be sure that you are doing this by having you collect all of your urine for 24 hours and measuring the amount of salt in it (see below).

Urine Collection
You will collect your urine for 24 hours before administration of the first pill (active drug or sugar pill) and for the next 24 hours (study day 1). After the last pill, on the second study day, you will collect samples over the first 4 hours, from 4-8 hours, and from 8-24 hours. The urine will be analyzed for sodium, potassium and for hormones that control blood pressure and heart rate.

Vital signs
Vital signs (blood pressure and heart rate) will be measured several times while you are lying down just before and following the last dose of the treatment. As part of the dose escalation evaluation, we will also measure your blood pressure and heart rate 2 hours after every dose while you are lying down, including overnight. Sometimes you will be asked to stand quietly for 10 minutes for additional measurements. A Dinamap, an automated blood pressure monitor that uses a cuff around your upper arm, is used for these measurements. An electrocardiogram (EKG) will be obtained before the first dose and after the 5th dose of Treatments A and B.

Blood sampling
For Treatments A and B, as part of the safety evaluation, 2 teaspoons of blood will be collected before the 1st dose and after the 5th dose of drug, in addition to smaller samples to be collected after every dose, including overnight. A total of 5 teaspoons of blood will be needed for the safety evaluation part of the study. It will also be necessary to collect 2 samples of your blood during study day 1 and 6 samples during study day 2 for measurement of the hormones that control blood pressure. We will also measure sodium in your blood when you complete the pre-study 24hr- urine collections and the 2 4hr-urine collections. At some times, we will also measure carbidopa in your blood. The study samples will be 2-3 teaspoons each. To avoid sticking you repeatedly, we will place a small plastic tube (catheter) in your arm vein. The total amount for the entire study with Treatments A and B will be about 16 tablespoons.

Drug testing
In the evening prior to study day 1, you will be admitted to the Vanderbilt Clinical Research Center. In the morning, a small tube (catheter) will be placed in your arm vein in order to draw blood. Baseline blood pressure and heart rate readings will be obtained and blood samples will be collected in the supine (lying on your back) and upright positions. You will void to finish the pre-study 24hr urine collection. You will then be given a pill, either the active drug or the sugar pill. Whether you receive the active pill or the sugar pill as Treatment A will be decided by a procedure similar to tossing a coin. You will receive the other kind of pill as Treatment B. The medication will be given by mouth, every 6 hours, for 5 doses. You will stay on the CRC for monitoring throughout day 1. In addition to the vital signs and the blood draws described above, at two hours after every dose, you will be questioned about any symptoms or unusual feelings you may be experiencing. We will need to wake you up around 3am for these measurements. In the next morning, study day 2, blood pressure and heart rate readings will be obtained in the supine and upright positions. You will void to finish the study day 1 urine collection. After taking the last dose of Treatment A, your supine blood pressure and heart rate will be measured every hour for 4 hours and again at 8 hours after treatment. You will be able to sit up and move around during the study but you must lie supine for at least 30 minutes before each of the measurements. Standing vital signs will also be taken 2 hours after treatment. A sample of blood will be collected at every scheduled blood pressure measurement after the 5th dose of treatment. Urine will also be collected from 0-4 hours, 4-8 hours and 8-24 hours. If you live close enough to Vanderbilt, you may be discharged 8 hours after the last dose.

After at least another 24 hours, you will start collecting the pre-study urine for Treatment B. You may wait longer than 24 hours but you will need to eat the study diet for at least 3 days before study day 1 for Treatment B. Treatment B will follow the same schedule as Treatment A.

Table 1. Study Day Description

Day	Treatment	Time[a]	Assessments for Tolerability	Pregnancy Test	Admit to CRC	Study Diet	Carbidopa or Placebo	Blood Draw	HR/BP	Urine
Pre-study			X							
-3, -2						X				Start study diet
-1		0700				X				Start 24hr urine #1
		1600			X					
1		0645[b]				X		X	X	End & restart 24hr urine
	A	0700, 1300, 1900				X	Doses 1, 2, 3			Continue 24hr urine #2
		0900, 1500, 2100	X			X		X	X	Continue 24hr urine #2
2		0100				X	Dose 4			Continue 24hr urine #2
		0300	X			X		X	X	Continue 24hr urine #2
		0645-0700				X	Dose 5		X	End 24hr, start 4hr urine #1
		0800				X		X	X	Continue 4hr urine #1
		0900	X			X		X	X	Continue 4hr urine #1
		1000				X		X	X	Continue 4hr urine #1
		1100				X		X	X	End 4hr urine #1 & start 4hr urine #2
May be discharged		1500				X		X	X	End 4hr urine #2 & start 16hr urine
3(washout day)		0700				X				End 16hr urine
Repeat with Treatment B after at least 1 day										

[a] times are approximate

[b] Blood pressure and heart rate will be measured and a blood sample will be collected before the first dose and at 2 hours after each dose as part of the safety evaluation.

3. Costs to you if you take part in this study:

There will be no costs to you for any procedures done strictly for research. All of the procedures described in this consent form will be done for research.

4. Side effects and risks that you can expect if you take part in this study:

Stopping medications might worsen your symptoms. If you routinely take medications that can affect blood pressure or plasma volume, you will not be enrolled in the study.

Consuming a **sodium- and caffeine-controlled diet** that needs to be picked up at the CRC might be inconvenient. The diet might not be to your liking. If you drink caffeinated beverages regularly and you stop caffeine intake suddenly, you might have headaches and fatigue for a few days. You can avoid these symptoms if you cut down gradually on the amount of caffeine in your diet.

Staying in the hospital might be an inconvenience for you.

Being woken up during the night might be an inconvenience for you.

Frequent blood pressure measurements with the cuff around your arm may produce some discomfort and occasional bruising of the upper arm.

There are minor risks and discomforts associated with **blood sampling**. We will insert a plastic catheter into the vein to allow drawing blood without repeated sticks during the study. This may cause a brief period of pain and possibly a small bruise at the site. Occasionally, a person feels faint when their blood is drawn. Rarely, an infection develops which can be treated. There is a small risk of bleeding after removal of the catheter and possibly a bruise at the site which can be prevented by tight compression on the site

Collecting your urine might be inconvenient for you. We try to make it more convenient by fitting the toilet with a collection device and/or providing a urinal for your use.

The **study days might seem tedious** and boring because they require you to lie down for an extended period of time before your blood pressure is monitored.

Carbidopa – When any medication is used in testing, there is a small risk of an unforeseeable life-threatening allergic reaction. Side effects of **Carbidopa have** only been reported when it is given with the drug levodopa for Parkinson's disease at lower dosages than are being evaluated in this study. Common adverse events with the carbidopa-levodopa combination include abnormal body movements and nausea. Less common adverse effects are allergies, psychotic episodes (periods of confused thinking which can include hearing voices, seeing things that are not real, believing things that are not true and/or strange behavior), depression and dementia (loss of mental ability severe enough to cause problems with normal activities of daily living). The dose you will receive in this study will be between 50 mg – 200 mg. There may be additional side effects that are not known at this time. This medication has never been used at the highest dose or frequency.

5. Risks that are not known:

Because the medications might be harmful to an unborn child, adequate birth control measures (i.e., oral, implanted or barrier methods) must be used by all participants and their sexual partners while participants are enrolled in this study. If you become pregnant or father a child while in this study, you must notify your physician immediately. In addition, women must not breastfeed while in this study. To rule out pregnancy prior to receiving treatment in this study, women of childbearing potential will have a pregnancy test.

6. Payment in case you are injured while in this study:

If you are injured because you are in this study, you can get reasonable, immediate, and necessary medical care for your injury at Vanderbilt without charge to you. There are no plans for Vanderbilt to pay for the costs of care beyond your injury, or to give you money for such injury. There is no program for compensation through the National Institute of Neurological Disorders and Stroke (NINDS)/National Institutes of Health (NIH).

7. Good effects that might result from this study:

The benefits to science and humankind that <u>might</u> result from this study are: a better understanding of the relationship between the plasma and urinary chemicals that we will measure and sodium excretion. The benefits you might get from being in this study are: none anticipated.

8. Other treatments you could get if you decide not to be in this study:

You may choose not to participate in this study.

9. Payments for your time spent taking part in this study or expenses:

You will not be paid for taking part in this study.

10. Reasons why the study doctor may take you out of this study:

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

11. What will happen if you decide to stop being in this study?

If you decide to stop being part of the study, you should tell your study doctor. We will cease to collect study information at the time of withdrawal of consent.

12. Who to call for any questions or in case you are injured:

If you should have any questions about this research study or if you feel you have been hurt by being a part of this study, please feel free to contact **Emily Garland, Ph.D.** at [redacted] **or David Robertson, M.D.** at [redacted]

For additional information about giving consent or your rights as a participant in this study, please feel free to contact the Vanderbilt University Institutional Review Board Office at (615) 322-2918 or toll free at (866) 224-8273.

13. Confidentiality:

All efforts, within reason, will be made to keep your personal information in your research record confidential but total confidentiality cannot be guaranteed. Research records will be stored in a locked office. Digital records will be stored on password protected computers/servers. Digital data files will be coded so that the participant's 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 participant be identified in any such publication.

14. Privacy:

All efforts, within reason, will be made to keep your protected health information (PHI) private. PHI is your health information that is, or has been gathered or kept by Vanderbilt as a result of your healthcare. This includes data gathered for research studies that can be traced back to you. Using or sharing ("disclosure") such data must follow federal privacy rules. By signing the consent for this study, you are agreeing ("authorization") to the uses and likely sharing of your PHI. If you decide to be in this research study, you are also agreeing to let the study team use and share your PHI as described below.

As part of the study, Dr. Garland and her co-investigators may report the results of your study and/or non-study related laboratory tests and electrocardiograms as well as parts of your medical record, to other members of *the* research team and to collaborators. If your research record is reviewed by any of these groups, they may also need to review your entire medical record. Your records may also be reviewed in order to meet federal or state regulations. Reviewers may include representatives from the Food and Drug Administration, representatives of the National Institutes of Health, or the Vanderbilt University Institutional Review Board. Federal privacy rules may not apply to these groups; they have their own rules and codes to assure that all efforts, within reason, will be made to keep your PHI private.

The study results will be kept in your research record for at least seven years after the study is finished. At that time, the research data that has not been put in your medical record will be maintained in your research file for an unknown length of time. Any research data that has been put into your medical record will be kept for an unknown length of time.

The clinical information collected for this study will be stored at the Data Management and Coordinating Center at the [redacted]. The data management center uses several layers of protection for the

clinical data stored there. It meets all of the local and federal security requirements for research datacenters. Your information is stored only using a study ID.

Unless told otherwise, your consent to use or share your PHI does not expire. If you change your mind, we ask that you contact Dr. Emily Garland in writing and let her know that you withdraw your consent. Her mailing address *is*

[redacted]
Vanderbilt University
Nashville, TN [redacted]

At that time, we will stop getting any more data about you. The health data we stored before you withdrew your consent may still be used for reporting and research quality.

If you decide not to take part in this research study, it will not affect your treatment, payment or enrollment in any health plans or affect your ability to get benefits. You will get a copy of this form after it is signed.

STATEMENT BY PERSON AGREEING TO BE IN THIS STUDY

I have read this consent form and the research study has been explained to me verbally. All my questions have been answered, and I freely and voluntarily choose to take part in this study.

_____
Date Signature of patient/volunteer

Consent obtained by:

_____ _____
Date Signature

_____
Printed Name and Title

APPENDIX 1d: Sample Informed Consent Form for Dose Escalation Study – Healthy Volunteers

This informed consent applies to Healthy Volunteers

Name of participant: _____ Age: _____

The following is given to you to tell you about this research study. Please read this form with care and ask any questions you may have about this study. Your questions will be answered. Also, you will be given a copy of this consent form.

You do not have to be in this research study. You can stop being in this study at any time. If we learn something new that may affect the risks or benefits of this study, you will be told so that you can decide whether or not you still want to be in this study.

1. What is the purpose of this study?

You are being asked to take part in this research study because you are a healthy volunteer. Data obtained from healthy persons will be compared with data from participants who have POTS. A chemical in the kidney called dopamine plays an important role in maintaining your body's salt levels. We will give you a drug called carbidopa that interferes with the formation of dopamine in the kidney, and we will measure how much salt is then excreted in your urine. This drug has been used for many years at lower doses to treat Parkinson's disease. We will also measure your blood pressure and heart rate and some chemicals in your blood and urine that control them. We will compare the effects of this drug to those of a sugar pill. You will take the drug and the sugar pill on two different days (Treatment A and Treatment B), but you will not be told which one you are taking on a given day. Because we do not know what the best dose of carbidopa is, we are first doing this study to compare the effects of different doses. You will take 50 mg, 100 mg or 200 mg of carbidopa every 6 hours for 5 doses. We will monitor you for the effects we are studying and for any problems. Only if no problems occur after the 50 mg dose, we will enroll two more people at 100 mg, then 200 mg. This is called "dose escalation". Although we do not expect the doses of carbidopa to cause any problems, we are doing this study to make sure that participants do not have any problems at each dose level before we enroll at a higher dose.

2. What will happen and how long will you be in the study?

This study is being conducted at the Vanderbilt Clinical Research Center (CRC). You will be asked some questions to ensure that you are in good health. One of the investigators will explain the study to you and ask you to sign this consent form. A copy of the consent form will be given to you. Your participation is voluntary.

A minimum of 9 days will be required to complete this study. You will need to spend 4 nights on the CRC, 2 nights for the active drug and 2 nights for the sugar pill. On the morning after the first overnight, study day 1, we will collect pre-treatment data and then give you your first pill. You will take pills every 6 hours. You will need to stay on the CRC during the day so that we can monitor your blood pressure and pulse and make sure that there are no health problems associated with the dose of carbidopa that you take. Studies on the second study day will last until about 3pm. Different parts of the study are described below.

<u>Drug withdrawal</u>
You must remain off any medications that could affect blood pressure, the composition of your urine, or the chemicals that we will measure for three days prior to the first treatment and during the entire study. This includes not only your usual scheduled medications, but also other drugs that might be taken intermittently.

<u>Pregnancy test</u>
If you are a female, we will perform a pregnancy test on a sample of your blood when you are admitted to the hospital for this study. Pregnant females may not participate in this research study.

<u>Diet</u>
We will ask you to eat a standard diet with no caffeine and a controlled amount of salt for three days prior to each study day and during the study days. We will provide this food to you and ask you to eat all of it and no other food.

We will check to be sure that you are doing this by having you collect all of your urine for 24 hours and measuring the amount of salt in it (see below).

Urine Collection
You will collect your urine for 24 hours before administration of the first pill (active drug or sugar pill) and for the next 24 hours (study day 1). After the last pill, on the second study day, you will collect samples over the first 4 hours, from 4-8 hours, and from 8-24 hours. The urine will be analyzed for sodium, potassium and for hormones that control blood pressure and heart rate.

Vital signs
Vital signs (blood pressure and heart rate) will be measured several times while you are lying down just before and following the last dose of the treatment. As part of the dose escalation evaluation, we will also measure your blood pressure and heart rate 2 hours after every dose while you are lying down, including overnight. Sometimes you will be asked to stand quietly for 10 minutes for additional measurements. A Dinamap, an automated blood pressure monitor that uses a cuff around your upper arm, is used for these measurements. An electrocardiogram (EKG) will be obtained before the first dose and after the 5th dose of Treatments A and B.

Blood sampling
For Treatments A and B, as part of the safety evaluation, 2 teaspoons of blood will be collected before the 1st dose and after the 5th dose of drug, in addition to smaller samples to be collected after every dose, including overnight. A total of 5 teaspoons of blood will be needed for the safety evaluation part of the study. It will also be necessary to collect 2 samples of your blood during study day 1 and 6 samples during study day 2 for measurement of the hormones that control blood pressure. We will also measure sodium in your blood when you complete the pre-study 24hr- urine collections and the 2 4hr-urine collections. At some times, we will also measure carbidopa in your blood. The study samples will be 2-3 teaspoons each. To avoid sticking you repeatedly, we will place a small plastic tube (catheter) in your arm vein. The total amount for the entire study with Treatments A and B will be about 16 tablespoons.

Drug testing
In the evening prior to study day 1, you will be admitted to the Vanderbilt Clinical Research Center. In the morning, a small tube (catheter) will be placed in your arm vein in order to draw blood. Baseline blood pressure and heart rate readings will be obtained and blood samples will be collected in the supine (lying on your back) and upright positions. You will void to finish the pre-study 24hr urine collection. You will then be given a pill, either the active drug or the sugar pill. Whether you receive the active pill or the sugar pill as Treatment A will be decided by a procedure similar to tossing a coin. You will receive the other kind of pill as Treatment B. The medication will be given by mouth, every 6 hours, for 5 doses. You will stay on the CRC for monitoring throughout day 1. In addition to the vital signs and the blood draws described above, at two hours after every dose, you will be questioned about any symptoms or unusual feelings you may be experiencing. We will need to wake you up around 3am for these measurements. In the next morning, study day 2, blood pressure and heart rate readings will be obtained in the supine and upright positions. You will void to finish the study day 1 urine collection. After taking the last dose of Treatment A, your supine blood pressure and heart rate will be measured every hour for 4 hours and again at 8 hours after treatment. You will be able to sit up and move around during the study but you must lie supine for at least 30 minutes before each of the measurements. Standing vital signs will also be taken 2 hours after treatment. A sample of blood will be collected at every scheduled blood pressure measurement after the 5th dose of treatment. Urine will also be collected from 0-4 hours, 4-8 hours and 8-24 hours. You may be discharged 8 hours after the last dose.

After at least another 24 hours, you will start collecting the pre-study urine for Treatment B. You may wait longer than 24 hours but you will need to eat the study diet for at least 3 days before study day 1 for Treatment B. Treatment B will follow the same schedule as Treatment A.

Table 1. Study Day Description

Day	Treatment	Time[a]	Assessments for Tolerability	Pregnancy Test	Admit to CRC	Study Diet	Carbidopa or Placebo	Blood Draw	HR/BP	Urine
Pre-study			X							
-3, -2						X				Start study diet
-1		0700				X				Start 24hr urine #1
		1600			X					
1		0645[b]				X		X	X	End & restart 24hr urine
	A	0700, 1300, 1900				X	Doses 1, 2, 3			Continue 24hr urine #2
		0900, 1500, 2100	X			X		X	X	Continue 24hr urine #2
2		0100				X	Dose 4			Continue 24hr urine #2
		0300	X			X		X	X	Continue 24hr urine #2
		0645-0700				X	Dose 5		X	End 24hr, start 4hr urine #1
		0800				X		X	X	Continue 4hr urine #1
		0900	X			X		X	X	Continue 4hr urine #1
		1000				X		X	X	Continue 4hr urine #1
		1100				X		X	X	End 4hr urine #1 & start 4hr urine #2
May be discharged		1500				X		X	X	End 4hr urine #2 & start 16hr urine
3(washout day)		0700				X				End 16hr urine
Repeat with Treatment B after at least 1 day										

[a] times are approximate
[b] Blood pressure and heart rate will be measured and a blood sample will be collected before the first dose and at 2 hours after each dose as part of the safety evaluation.

3. Costs to you if you take part in this study:

There will be no costs to you for any procedures done strictly for research. All of the procedures described in this consent form will be done for research.

4. Side effects and risks that you can expect if you take part in this study:

Stopping medications might worsen your symptoms. If you routinely take medications that can affect blood pressure or plasma volume, you will not be enrolled in the study.

Consuming a **sodium- and caffeine-controlled diet** that needs to be picked up at the CRC might be inconvenient. The diet might not be to your liking. If you drink caffeinated beverages regularly and you stop caffeine intake suddenly, you might have headaches and fatigue for a few days. You can avoid these symptoms if you cut down gradually on the amount of caffeine in your diet.

Staying in the hospital might be an inconvenience for you.

Being woken up during the night might be an inconvenience for you.

Frequent blood pressure measurements with the cuff around your arm may produce some discomfort and occasional bruising of the upper arm.

There are minor risks and discomforts associated with **blood sampling**. We will insert a plastic catheter into the vein to allow drawing blood without repeated sticks during the study. This may cause a brief period of pain and possibly a small bruise at the site. Occasionally, a person feels faint when their blood is drawn. Rarely, an infection develops which can be treated. There is a small risk of bleeding after removal of the catheter and possibly a bruise at the site which can be prevented by tight compression on the site

Collecting your urine might be inconvenient for you. We try to make it more convenient by fitting the toilet with a collection device and/or providing a urinal for your use.

The **study days might seem tedious** and boring because they require you to lie down for an extended period of time before your blood pressure is monitored.

Carbidopa – When any medication is used in testing, there is a small risk of an unforeseeable life-threatening allergic reaction. Side effects of **Carbidopa have** only been reported when it is given with the drug levodopa for Parkinson's disease at lower dosages than are being evaluated in this study. Common adverse events with the carbidopa-levodopa combination include abnormal body movements and nausea. Less common adverse effects are allergies, psychotic episodes (periods of confused thinking which can include hearing voices, seeing things that are not real, believing things that are not true and/or strange behavior), depression and dementia (loss of mental ability severe enough to cause problems with normal activities of daily living). The dose you will receive in this study will be between 50 mg – 200 mg. There may be additional side effects that are not known at this time. This medication has never been used at the highest dose or frequency.

5. Risks that are not known:

Because the medications might be harmful to an unborn child, adequate birth control measures (i.e., oral, implanted or barrier methods) must be used by all participants and their sexual partners while participants are enrolled in this study. If you become pregnant or father a child while in this study, you must notify your physician immediately. In addition, women must not breastfeed while in this study. To rule out pregnancy prior to receiving treatment in this study, women of childbearing potential will have a pregnancy test.

6. Payment in case you are injured while in this study:

If you are injured because you are in this study, you can get reasonable, immediate, and necessary medical care for your injury at Vanderbilt without charge to you. There are no plans for Vanderbilt to pay for the costs of care beyond your injury, or to give you money for such injury. There is no program for compensation through the National Institute of Neurological Disorders and Stroke (NINDS)/National Institutes of Health (NIH).

7. Good effects that might result from this study:

The benefits to science and humankind that might result from this study are: a better understanding of the relationship between the plasma and urinary chemicals that we will measure and sodium excretion. The benefits you might get from being in this study are: none anticipated.

8. Other treatments you could get if you decide not to be in this study:

You may choose not to participate in this study.

9. Payments for your time spent taking part in this study or expenses:

$225 for completing Treatment A and an additional $225 for completing Treatment B.

10. Reasons why the study doctor may take you out of this study:

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

11. What will happen if you decide to stop being in this study?

If you decide to stop being part of the study, you should tell your study doctor. We will cease to collect study information at the time of withdrawal of consent.

12. Who to call for any questions or in case you are injured:

If you should have any questions about this research study or if you feel you have been hurt by being a part of this study, please feel free to contact **Emily Garland, Ph.D.** at [redacted] **or David Robertson, M.D.** at [redacted]

For additional information about giving consent or your rights as a participant in this study, please feel free to contact the Vanderbilt University Institutional Review Board Office at (615) 322-2918 or toll free at (866) 224-8273.

13. Confidentiality:

All efforts, within reason, will be made to keep your personal information in your research record confidential but total confidentiality cannot be guaranteed. Research records will be stored in a locked office. Digital records will be stored on password protected computers/servers. Digital data files will be coded so' that the participant's 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 participant be identified in any such publication.

14. Privacy:

All efforts, within reason, will be made to keep your protected health information (PHI) private. PHI is your health information that is, or has been gathered or kept by Vanderbilt as a result of your healthcare. This includes data gathered for research studies that can be traced back to you. Using or sharing ("disclosure") such data must follow federal privacy rules. By signing the consent for this study, you are agreeing ("authorization") to the uses and likely sharing of your PHI. If you decide to be in this research study, you are also agreeing to let the study team use and share your PHI as described below.

As part of the study, Dr. Garland and her co-investigators may report the results of your study and/or non-study related laboratory tests and electrocardiograms as well as parts of your medical record, to other members of *the* research team and to collaborators. If your research record is reviewed by any of these groups, they may also need to review your entire medical record. Your records may also be reviewed in order to meet federal or state regulations. Reviewers may include representatives from the Food and Drug Administration, representatives of the National Institutes of Health, or the Vanderbilt University Institutional Review Board. Federal privacy rules may not apply to these groups; they have their own rules and codes to assure that all efforts, within reason, will be made to keep your PHI private.

The study results will be kept in your research record for at least seven years after the study is finished. At that time, the research data that has not been put in your medical record will be maintained in your research file for an unknown length of time. Any research data that has been put into your medical record will be kept for an unknown length of time.

The clinical information collected for this study will be stored at the Data Management and Coordinating Center at the [redacted]. The data management center uses several layers of protection for the clinical data stored there. It meets all of the local and federal security requirements for research datacenters. Your information is stored only using a study ID.

Unless told otherwise, your consent to use or share your PHI does not expire. If you change your mind, we ask that you contact Dr. Emily Garland in writing and let her know that you withdraw your consent. Her mailing address *is*

[redacted]
Vanderbilt University
Nashville, TN [redacted]

At that time, we will stop getting any more data about you. The health data we stored before you withdrew your consent may still be used for reporting and research quality.

If you decide not to take part in this research study, it will not affect your treatment, payment or enrollment in any health plans or affect your ability to get benefits. You will get a copy of this form after it is signed.

STATEMENT BY PERSON AGREEING TO BE IN THIS STUDY

I have read this consent form and the research study has been explained to me verbally. All my questions have been answered, and I freely and voluntarily choose to take part in this study.

_____
Date Signature of patient/volunteer

Consent obtained by:

_____
Date Signature

_____
Printed Name and Title