Dietary Salt in Postural Tachycardia Syndrome

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1.0 Background

Assumption of upright posture leads to major hemodynamic changes, including a decrease in cardiac output and stroke volume and an increase in heart rate. There is substantial pooling of blood in the lower extremities, the buttocks, and in the splanchnic vascular beds that is felt to be responsible for much of the heart rate increase that occurs with standing. Blood pooling lessens the absolute blood volume in the heart and central circulation, leading to activation of low and high-pressure baroreceptors, causing activation of the sympathetic nervous system and withdrawal of the parasympathetic nervous system. In conditions of low baseline blood volume, cardiovascular responses to standing are more dramatic.

Angiotensin II (ANG II) is synthesized from angiotensinogen via the sequential actions of renin and angiotensin-converting enzyme (ACE). Renin catalyzes the rate-limiting step in this pathway. Renin secretion is stimulated by a fall in NaCl concentration at the macula densa, a decrease in arterial pressure, and an increase in sympathetic tone. ANG II stimulates sodium reabsorption in the proximal tubule, causes arteriolar vasoconstriction, and stimulates aldosterone production, thereby decreasing sodium excretion and maintaining or increasing plasma volume.

Postural tachycardia syndrome (POTS) occurs in approximately 500,000 Americans, predominantly in young women. POTS is a chronic condition of consistent orthostatic tachycardia (> 30 bpm increase) and symptoms that are worse on standing but relieved by lying down. Orthostatic symptoms include palpitations, lightheadedness, chest pains, dyspnea, tremulousness, blurred vision, and mental clouding. When studied in balance on 150 mEq sodium/day, many patients with POTS have a low plasma volume. Furthermore, POTS patients have inappropriately low plasma renin activity and aldosterone for their level of hypovolemia.

Physicians often prescribe a high-sodium diet for the treatment of POTS. The rationale behind this approach is that sodium in the diet will help subjects to retain fluid, and thereby raise blood volume and/or blood pressure. We have preliminary evidence that a high-salt diet raises plasma volume (as determined by changes in hematocrit) and blunts the tachycardia with standing. This treatment is also felt to decrease symptoms in some patients with POTS. We will now use the DAXOR BVA-100 Blood Volume Analyzer to test whether patients with POTS have a blunted plasma volume expansion in response to a high-sodium diet and assess the influences of dietary sodium on components of the renin-angiotensin-aldosterone systems.

2.0 Rationale and Specific Aims

Patients with POTS may not adequately expand their plasma volume in response to a high-sodium diet. Mechanisms involved in the regulation of plasma volume, such as the renin-angiotensin-aldosterone system and renal DA, may be impaired in POTS and may respond inappropriately to changes in dietary sodium.The purpose of this study is to determine (1) whether a high dietary sodium level appropriately expands plasma volume in POTS; (2) whether

plasma renin activity and aldosterone are modified appropriately by changes in dietary sodium in POTS; and (3) whether patients with POTS have improvements in their orthostatic tachycardia and symptoms as a result of a high dietary sodium level.

3.0 Animal Studies and Previous Human Studies

In an unpublished study (Biaggioni et al., Vanderbilt University) comparing 150 mEq sodium versus 10 mEq sodium in the daily diet, there was a significant effect on the orthostatic change in heart rate in some patients with POTS. The orthostatic tachycardia was diminished in the moderate sodium diet (30±3 bpm) compared with the low-sodium diet (53±7 bpm). In another small unpublished study, we fed POTS patients diets consisting of 10 mEq/day sodium (low), 150 mEq/day sodium (normal) and 300 mEq/day sodium (high) for 5 days each. Our preliminary findings in 5 patients indicated greater orthostatic tachycardia in the low-salt diet (43±12 bpm) than with either a normal (29±9 bpm) or high-salt diet (29±10 bpm).

4.0 Inclusion/Exclusion Criteria

Inclusion:

- Diagnosed with postural tachycardia syndrome by the Vanderbilt Autonomic Dysfunction Center
    - Increase in heart rate ≥30 beats/min with position change from supine to standing (10 minutes)
    - Chronic symptoms consistent with POTS that are worse when upright and get better with recumbence
- Age between 18-50 years old
- Non-smokers
- Premenopausal patients with POTS and healthy volunteers
- Only female participants are eligible.
    - Since 80-90% of POTS patients are female, and there can be differences in measures with the menstrual cycle, including a small number of males might introduce a significant amount of noise.
- Able and willing to provide informed consent

Exclusion:

- Smokers
- Overt cause for postural tachycardia, i.e., acute dehydration
- Significant cardiovascular, pulmonary, hepatic, or hematological disease by history or screening results
- Pregnant (positive pregnancy test) or breastfeeding
- Hypertension defined as supine resting BP>145/95 mmHg off medications or needing antihypertensive medication
- Other factors which in the investigator's opinion would prevent the participant from completing the protocol, including poor compliance during previous studies or an unpredictable schedule
- Unable to give informed consent

5.0 Enrollment/Randomization

The participants with POTS will be recruited from patients referred to the Vanderbilt University Autonomic Dysfunction Center. Healthy volunteers will be recruited from a population of previous participants in autonomic studies, through the ResearchMatch.org database, and through advertising and emails around the Vanderbilt community.

When contacting appropriate study candidates, the investigator will describe the complete protocol. The participants will then be given a written informed consent form that has been approved by the Vanderbilt Institutional Review Board. The subject will be given adequate time to read the consent form, ask questions, and if satisfied by the responses, sign the form. Consent or refusal to participate in this study will not affect medical care. No modifications or waiver of the elements of consent will be necessary in the execution of this study. Consent procedures will take place in the Autonomic Dysfunction Center at Vanderbilt University Medical Center.

Randomization tables will be used to determine whether the 10 mEq sodium/day or 300 mEq sodium/day diet will be consumed first. Both diets will be completed on each subject (randomized crossover study), so all of the below study procedures (after screening) will be repeated.

6.0 Study Procedures

6.1 Screening and Pre-Admission

6.1.1 Healthy Controls Subjects

- Consent obtained (with signature)
- History and physical examination
- Orthostatic vital signs
- Meet with dietician

6.1.2 POTS Patients

- Patients will often be identified from a prior assessment at the Vanderbilt Autonomic Dysfunction Center, so screening visit might not be in person
- Consent obtained (phone, email and signature)
- Withdraw medications prior to admission
    - Research Nurse and study physician will be available by phone if new symptoms or problems appear during this medication washout.

6.2 Study Day 1

- Admit to CRC (POTS patients only; healthy volunteers will do initial part as outpatients)
- Start 150 mEq Na^+/day diet (POTS patients as inpatients; healthy control subjects with CRC provided outpatient diet)
- Start a 24h urine collection (for Na^+, K^+, Cr, fractionated catecholamines)
- Blood work
    - BMP (for Na^+, K^+, Cl^-, Cr)
    - CBC
    - Serum β-hCG pregnancy test

6.3 Study Day 2

- Complete 24h urine
- Start STUDY DIET (10 mEq Na^+/day or 300 mEq Na^+/day in a random order) after 3 meals of 150 mEq Na^+/day are complete; water ad lib
    - Blood volume – carbon monoxide rebreathing
        - We will measure blood volume. Subject will be asked to sit comfortably with their legs flat for about 30 minutes breathing through a mouthpiece, and we will measure the total amount of hemoglobin (protein in the blood that carries oxygen) and myoglobin (protein in the muscle that transports oxygen into the muscle cell) in their body. The procedure is called carbon monoxide (CO) rebreathing. During this procedure, one teaspoon of blood will be taken before and after a small amount of CO (equivalent to sitting in a smoky room for ~3 hours) has been absorbed into the bloodstream. The concentration of CO in the blood is measured.
        - A valve is used to switch the mouthpiece over to a self-contained "rebreathing" circuit initially containing 100% oxygen. The rebreathing circuit is a closed system from which the subject will breathe in and out during the test. It contains a carbon-dioxide (the waste product in the air of exhaled breath) absorber so that the air that the subject breathes in will always be 100% oxygen. A small amount (about 1 tablespoon) of CO is introduced into the rebreathing circuit and rebreathed for 10 minutes. A venous blood sample (about 1 teaspoon) is then taken and another larger dose of CO is introduced into the circuit (approximately 100 ml or about one-half cup) and again, rebreathed for 10 minutes. A final blood sample (about 1 teaspoon) is taken and the test is completed.

6.4 Study Day 3
- Continue STUDY DIET; water ad lib

6.5 Study Day 4
- Continue STUDY DIET; water ad lib

6.6 Study Day 5
- 24h Holter combined ECG monitor and BP monitor put on subject
- Continue STUDY DIET; water ad lib

6.7 Study Day 6
- Admit to CRC in afternoon (healthy control subjects only as POTS patients will already have been admitted to the CRC)
- Continue STUDY DIET; water ad lib
- Remove 24h Holter combined ECG monitor and BP monitor from subject
- Start a 24h urine collection (for Na^+, K^+, Cr, fractionated catecholamines)
- NPO after midnight for study next day

6.8 Study Day 7 (BIG DAY)
- Awaken early (~6am) to void (still collecting 24h urine)

- Patient returns to bed
- IV catheter inserted

- **Posture Study** (in morning; between 7-8am ideally)
    - Blood pressure and heart rate will be measured while supine and then while standing for up to 30 minutes
    - We will draw 3 tablespoons of blood in each body position to measure hormones that regulate blood pressure and blood volume
    - Estradiol and progesterone levels to verify the subject's phase of menstrual cycle
    - Serum/plasma aliquots for future analysis
    - Subjects will rate symptoms during supine period and at end of stand using Vanderbilt Orthostatic Symptoms Score (VOSS)
- **Total Blood Volume (DAXOR)**
    - using injection of iodinated I-131 tagged human serum albumin nominally 25 micro-Ci of radiation
    - blood samples drawn through IV catheter before injection and for ~30 minutes post-injection (total – 25 ml)
    - This will be done after supine assessment, but before standing the subject up
- Late breakfast
- Wait ≥1h hour post breakfast

- **Autonomic Function Test with Cardiac Output and Brief Tilt**
    - Tests of how the involuntary nervous system is working
    - We will measure:
        - heart rate using an electrocardiogram
        - blood pressure using a cuff around one arm and/or finger
        - the shift of fluids in the body (body impedance)
        - Cardiac output will be measured by analyzing the air that is breathed out. This will be done using the acetylene rebreathing test. For this last test, subject will breathe normally for about 5 minutes through a mouthpiece connected to a bag. This bag will contain air and small amounts of the inactive gasses methane and acetylene.
        - The autonomic function tests include asking the subject to breathe deeply for two minutes and breathing as fast and as hard as they can for 30 seconds, maintaining a handgrip for 3 minutes, breathing against pressure for 15 seconds, and placing one hand in ice water for 1 minute.
        - The subject will be tilted up to 60-75 degrees head-up tilt for up to 10 minutes to measure the changes in heart rate and blood pressure and symptoms with upright challenge.
        - All these tests are meant to stimulate the autonomic nervous system to produce changes in blood pressure and heart rate of short duration that reflect how well the involuntary nervous system is working.
- Blood volume – carbon monoxide rebreathing
        - We will measure blood volume.
        - Subject will be asked to sit comfortably with their legs flat for about 30 minutes breathing through a mouthpiece, and we will measure the total amount of hemoglobin (protein in the blood that carries oxygen) and myoglobin (protein in the muscle that transports oxygen into the muscle

cell) in their body. The procedure is called carbon monoxide (CO) rebreathing. During this procedure, one teaspoon of blood will be taken before and after a small amount of CO (equivalent to sitting in a smoky room for ~3 hours) has been absorbed into the bloodstream. The concentration of CO in the blood is measured.

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- Lunch
- **Exercise Capacity Test (in the afternoon)**
    - At least 2 hours after lunch
    - Will estimate maximal oxygen consumption (VO_2 max)
    - This test will be conducted on a stationary bicycle
    - Effort will be gradually increase while expired air is measured during exhaustive physical work.
    - The test will last approximately 30 minutes and be conducted in the CRC.
    - A mouthpiece with a one-way rebreathing valve attached to a breathing tube will be used to collect air samples during the exercise test. Essentially, subjects will breathe room air through a mouthpiece, and then exhale the air into a tube that connects to a machine (metabolic cart). This machine analyzes carbon dioxide and oxygen content, which allows us to calculate the amount of oxygen they are using under resting and exercise conditions.
    - A test will be considered valid and finished when two of the following three conditions are met:
        - (1) predicted maximal heart rate is obtained,
        - (2) the respiratory exchange ratio reaches 1.15 or higher,
        - (3) oxygen consumption plateaus.
    - Verbal encouragement will be given to help subjects achieve a valid exercise test.
    - To assess VO_2 max directly, an individual's expired air is measured during exhaustive physical work.
    - The workload will be gradually increased on the bike by increasing the resistance. As the workload increases, oxygen consumption also increases. Throughout the test period exhaled air will be collected. When subjects can no longer continue, the test will be stopped.
    - Blood pressure will be measured at the end of each resistance-stage. Heart rate data will be recorded continuously.

- Before and after completing the exercise test, subjects will be required to complete a "warm-up" and "cool-down" session including stretching exercises.

- **Saline Bolus (optional)**
  - Subject can receive an optional 2L saline bolus IV to prepare them for discharge to home
- **Study Phase Completed**
  - Discharge Subject to home

Schedule patient for 2nd Study phase and repeat all above (except screening).

7.0 Risks

Stopping intermittent medications might worsen symptoms. POTS patients will be supervised by a nurse and physician and will be monitored on the CRC during most of the duration of their medication withdrawal. If necessary, medications will be restarted. Healthy subjects will not be allowed to participate in this study if they routinely take medication that alters blood pressure or heart rate.

The **study diets** may not taste good and may be unpleasant to eat.

There are minor risks and discomforts associated with **blood sampling**. We will insert a plastic catheter into the vein to allow drawing blood while minimizing 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. 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. Rarely, an infection develops which can be treated.

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

Electrodes: Sticky patches will be put on your chest and your limbs to record electrical activity from the heart or for the body impedance measurements. This might be uncomfortable. This can occasionally cause a rash.

There might be lightheadedness, dizziness, tremor, headache, or nausea during the **tilt table test**. These symptoms usually resolve rapidly upon lowering of the table.

As part of this research study, participants will receive a **small amount of radioactive substance** (nominally 25 microCi, but usually less) called Iodine-131. The radiation dose that they will receive from each procedure is about the same amount that they would receive over a period of four months from natural background radiation. This procedure will be performed a maximum of 2 times at an interval of at least several weeks. **I-131 tagged human albumin** is a human blood product. This product has been screened and heat-treated for at least 10 hours at 60°C. Experts believe that this treatment kills the encapsulated viruses (like HIV and Hepatitis C). Recent studies have shown that the risk of getting a disease from human blood

products such as this is extremely small. However, some individuals may not want to receive human blood products for religious or other ethical concerns.

Immersing extremities in ice water: Immersing extremities in ice water is sometimes painful.

Acetylene rebreathing test: Subjects may find breathing through a mouthpiece uncomfortable. There are no reported side effects from using these gasses in the rebreathing device.

Body impedance: There is no known risk associated with the measurement of heart's pumping capacity using patches placed throughout the body; however this can be an inconvenience.

Exercise test. The risks involved in this exercise test may include abnormal blood pressure, fainting, irregular heartbeat, and in the most rare instances, heart attack, or even death. Every effort will be made to minimize these risks by continuously monitoring participants throughout the exercise testing. Participants will be encouraged to inform the study investigator if they feel dizzy, ill-feeling, or other symptoms, during or after the test.

24-hour urine collection. Collecting urine for 24 hours might be an inconvenience. We try to make it more convenient by fitting the toilet with a collection device and/or providing a urinal for their use.

We cannot foresee any other risks, but there may be previously unknown or unforeseen risks. By not allowing pregnant females to participate, we will eliminate any risks these procedures might have for a pregnant woman.

8.0 Costs and Compensation to Participants

8.1 Costs to Participants

Study related materials will be provided to the participants without charge. The Inpatient stays will be covered by a grant from the Vanderbilt Institute of Clinical and Translational Research (VICTR), and the assay and testing costs will be covered by an NIH grant. The participants will be responsible for their own travel expenses to come to Vanderbilt and any extraneous expenses related to their time in Nashville.

8.2 Participant Compensation

Participants will be compensated at a rate of $500 for the entire study ($150 for each phase and an extra $200 at completion). Upon request, some subjects may receive the compensation amount in the form of a gift card instead of a check.

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

The PI and at least one co-investigator will review data from subjects enrolled in this study on a bi-monthly basis.

Adverse events will be monitored on an ongoing basis by Drs. Satish Raj and Victor Nwazue (both of whom 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.

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 (an event that results in hospitalization, disability, or death or is life-threatening)

The investigator will state his opinion on whether there is a reasonable possibility that the event or experience is elated to a procedure performed as part of this study. Serious adverse events will be reported in writing to the Vanderbilt IRB within 72 hours of occurrence. All study adverse events will be summarized once a year, as part of the annual review report to the IRB

10.0 Study Withdrawal/Discontinuation

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

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

11.0 Statistical Considerations

11.1 Statistical Analysis Plan

The primary statistical analysis will focus on the increase in plasma volume from low sodium (10 mEq Na+/day) to a high sodium (300 mEq Na+/day) diet between POTS patients and control subjects. Secondary endpoints will include the magnitude of suppression of aldosterone (from low sodium to high-sodium diets), and a reduction in orthostatic tachycardia and orthostatic symptoms (VOSS) in POTS patients with the high-sodium diet. We will develop repeated measures analyses of covariance to evaluate the two treatment groups (low vs. high-sodium diets). In these experiments, data collection will be balanced and we are primarily concerned with estimating marginal effects in our target population. For this reason, our method of choice will be generalized estimating equations (GEE). For well balanced data, this approach has the great advantage that the Huber-White sandwich estimator of the parameter variance covariance matrix is unaffected by the choice of the working variance-covariance matrix. This can make these analyses considerably more robust than other methods. We will include an indicator covariate for the study drug order in the statistical models. Each outcome will be the dependent variable in a GEE model with indicator variables used to designate high or low-sodium diets and patient groups. Also, interactions terms will be included in our models if appropriate. Such

terms will be used to evaluate whether the order of treatment has any effect on outcome. Exploratory data analysis will be performed using grouped strip plots (one dimensional scatter plots). Outliers will be reported if sufficiently extreme and the data will be transformed if the raw data are sufficiently skewed. In order to determine the effectiveness of a high-sodium diet in patients with low plasma volumes we will also perform a secondary analysis restricted to patients who have a plasma volume deficit (i.e. plasma volume less than expected for height, weight and gender) at the initial screening exam. We will use the xtgee program of Stata for these analyses.

Data will be entered into a Microsoft Excel spreadsheet or a CTSA generated, HIPAA compliant Research Data Capture (REDCap) web-based database 52. SPSS for Windows (version 17.0), *Stata 11.0*, and R (www.r-project.org) will be used for data analysis. The sample size calculations were performed using the software package PS Power and Sample Size Calculations version 3.0.1 53. A co-investigator on this grant, William Dupont, Ph.D., Professor of Biostatistics at Vanderbilt University, will be primarily responsible for the statistical analyses of this study.

11.2 Sample Size

There are no data available on the plasma volume change when changing diet from 10 mEq Na^+/day to 300 mEq Na^+/day. We estimated our required sample size from our prior paper documenting a plasma volume deficit of 354±193 ml in female POTS patients 11. We estimate that difference in augmentation of plasma volume might account for 50-60% of this deficit (~200 ml). A sample size of 22 in each group will have 90% power to detect a difference in mean plasma volume change of 200 ml assuming that the common standard deviation is 200ml using a two-sided, Student's t-test with alpha=0.05. We propose to enroll 30 subjects in each group to allow for data loss and drop-out.

12.0 Privacy/Confidentiality Issues

All the investigators have completed Vanderbilt training in compliance with the HIPAA regulations. Every effort will be made to protect and respect patient confidentiality and privacy within the limits of HIPAA. Research data will be entered into a password-protected database. The Principal Investigator's Assurance Statement has been submitted with the proposal.

13.0 Follow-up and Record Retention

The study will last 3-4 weeks for each participant, and it will likely take 3 years to enroll the required number of participants. The study results will be retained in our research records for at least six years after the study is completed. At that time any research information in the medical record will be kept indefinitely. Any research information not already in the medical record may be kept indefinitely.