Body Compression in Postural Tachycardia Syndrome: Effects on Orthostatic Tolerance

1.0 BACKGROUND – POSTURAL TACHYCARDIA SYNDROME

1.1 Postural Tachycardia Syndrome

Postural Tachycardia Syndrome (POTS) is a chronic form of orthostatic intolerance marked by a significant and sustained increase in heart rate (HR) upon positional change from supine to standing (≥30 beats/min [bpm])[1] in the absence of orthostatic hypotension (≥20/10 mmHg decrease)[2]. Symptoms must be present for ≥6 months[3] and other causes of orthostatic tachycardia must be ruled out[1]. Individuals with POTS report orthostatic symptoms including palpitations, light-headedness, dizziness, chest pain, and mental clouding, which improve on recumbence[2]. 80-85% of individuals diagnosed with POTS are women age 13-50[3]. Current treatment of POTS involves pharmacological and non-pharmacological intervention including salt and fluid loading, exercise, and physical countermanuevers[4].

1.2 Physiology

Upon standing, approximately 500 mL of blood immediately redistributes from the thorax down to the abdomen, buttocks and legs[2]. Blood return to the heart is decreased[5] and therefore stroke volume and arterial pressure decreases[2]. This leads to sympathetic activation as the baroreceptors sense less pressure[2]. In a healthy individual, HR initially increases 10-20 bpm, and the systolic blood pressure (BP) decreases by approximately 5 mmHg[2]. However, in an individual with POTS, this compensatory mechanism is impaired and HR will increase by ≥30 bpm and remain at this elevated rate for the duration of standing[2]. In some individuals with POTS, upon standing cerebral blood flow velocity decreases[5]. In other individuals, oscillation of cerebral blood flow due to failure of cerebral autoregulatory mechanisms is observed[6].

2.0 COMPRESSION GARMENTS

2.1 Compression Garment Mode of Action

Lower extremity compression garments provide pressure to the blood vessels in the legs, thighs and abdomen which can minimize blood pooling and lead to improved blood return to the heart[4].

2.2 Use of Compression Garments in Postural Tachycardia Syndrome

A study of compartmental fluid shifts on head up tilt found that in POTS patients, splanchnic blood volume increased on tilt[7]. In 2 subsets of POTS patients, this increase in blood volume was significant when compared to the healthy control group[7]. As well, blood volume in the pelvis and leg also increased upon head up tilt[7]. Interesting, in one subset of POTS patients, blood flow to the splanchnic region also increased significantly on 70° head up tilt[7]. GL Heyer evaluated the use of compression in children and teens with POTS[4]. They completed 3 head-up tilt table tests (HUTT), the first without compression, the second using the Zoex non-inflatable antishock garment (20-40 mmHg to the abdomen) and the third without compression[4]. The Zoex non-inflatable antishock garment has 6 flexible straps that fasten tightly around the legs, thigh, waist, and abdomen as well as a thin bladder on the attached to the abdominal straps. This bladder compresses the abdominal wall and the garment provides overall compression of 20-40 mmHg[4]. It was shown that the compression garment reduced orthostatic tachycardia and

orthostatic symptoms on tilt, and that both the tachycardia and symptoms returned on the third tilt test, when no compression was applied[4]. Despite the evidence of blood pooling in the abdomen, pelvis and leg,[7] and these promising findings with a non-commercial compression garment, there is relatively little other research indicating the benefits of abdominal and lower extremity compression garments in POTS. There are no data on the use of these compression garments in adult POTS patients with upright stress. Further, it is not known where compression is most effective in an individual with POTS (e.g. abdomen, thigh, lower leg, combination of these).

2.3 LifeWrap Non-Pneumatic Anti-Shock Garment (NASG)

The LifeWrap Non-Pneumatic Anti-Shock Garment (NASG)[8] is used as a treatment for postpartum hemorrhage in developing countries, and is comprised of neoprene fabric with a compression ball and Velcro closures that can be adjusted for use[8]. This garment consists of 3 leg segments and 2 pelvic/abdominal segments, and applies pressure to the external body surface in order to maintain adequate blood flow to the heart, lungs and brain, countering the effects of hypovolemic shock[8]. This garment is a Health Canada class I medical device.

2.4 Significance

There are no approved medications for use in POTS and patients are usually managed with a combination of off-label medications and non-pharmacological treatments[3]. Compression garments are often prescribed as one of these non-pharmacological management strategies[3]. However, there is no data to validate their efficacy, and also no data to determine which type of compression is most beneficial (e.g. lower leg only, abdomen only, combination) in adults. We will endeavour to complete a 4-way randomized crossover study of head up tilt tests (HUTTs) with compression applied by the LifeWrap NSAG in at attempt to demonstrate decreased orthostatic tachycardia and increased orthostatic tolerance in individuals with POTS. If successful, this study could provide needed evidence that compression in POTS is a successful non-pharmacological treatment modality, and as well, what type of compression is the most beneficial to patients with this syndrome. These findings could rapidly translate to the clinical setting and improve patient care.

3.0 HYPOTHESIS

3.1 Hypothesis

Full abdominal and lower extremity compression will reduce orthostatic tachycardia (lower HR increase on standing) and orthostatic symptoms in patients with POTS.

4.0 INCLUSION/EXCLUSION CRITERIA:

Inclusion Criteria:

- Physician diagnosis of Postural Tachycardia Syndrome (POTS)
- Age 18-60 years
- Male and Female
- Able and willing to provide informed consent
- Ability to travel to Libin Cardiovascular Institute of Alberta Autonomic Testing Lab at the University of Calgary, Calgary, AB.

Exclusion Criteria:

- Overt cause for postural tachycardia, i.e., acute dehydration
- Participants with somatization or severe anxiety symptoms will be excluded
- Pregnant
- Inability to tolerate compression garment for the duration of the study
- Other factors which in the investigator's opinion would prevent the participant from completing the protocol, including poor compliance during previous studies

5.0 ENROLLMENT, RANDOMIZATION and BLINDING

5.1 Recruitment

Patients will be recruited from the Calgary Autonomic Investigation and Management Clinic, and the practices of Drs. Satish R. Raj, Carlos A Morillo, and Robert S. Sheldon, including past research study participants. We will also recruit participants who contact us directly about their interest in our studies.

5.2 Randomization:

Each study participant will complete 4 HUTT on a single day:

i. one wearing the LifeWrap NASG Garment with all segments fastened;
ii. one wearing the LifeWrap NASG Garment with the lower leg components fastened;
iii. one wearing the LifeWrap NASG with the abdominal and pelvic components fastened; and
iv. one without the garment entirely.

The order of the interventions will be randomized to account for diurnal variation of HR and BP observed in POTS[9], and any possible training effect with repeated HUTT. Randomization will be performed using a pre-prepared randomization table.

5.3 Blinding

None. It will not be possible to blind the subject to the compression intervention.

6.0 STUDY PROCEDURE

6.1 Holding Pre-Existing Medications

Since this will be a crossover study and each subject will acts as their own control, we will not need to preclude the use of medications for this protocol. This will also make the study more clinically relevant and generalizable, as compression would most likely be recommended to patients in addition to medications. We will make note of the medications being used by each participant at the time of the study.

6.2 Study Design

6.2.1 General

This study will utilize a single-day, 4-way randomized crossover design, with assessments of HUTT with:

i. no compression;
ii. lower leg compression only;
iii. abdomen/pelvic compression only; and
iv. both abdomen/pelvic and lower leg compression.

The study will be conducted on a tilt table in a human physiology research and procedure room. Each intervention phase in the protocol will involve a baseline assessment period of 10 minutes followed by a 10 min HUTT (80 degrees). There will be a 20 min recovery periods between each HUTT. The study will take approximately 4 hours.

6.2.2. Interventions

The Lifewrap NSAG Compression Garment has been developed to treat postpartum hypovolemic shock and provides external compression to the abdomen, pelvis and lower extremities[8]. A pressure sensor will be used to ensure standardized compression application throughout the study.

6.2.3 Instrumentation

- The patient will be instrumented in a fasting state on an empty bladder. Patients will be allowed to drink water on the morning of study.
- The entire study will take place with the subject on the tilt table (supine or tilted)
- The skin electrodes will be applied for continuous ECG and HR monitoring.
- BP will be monitored continuously using a finger volume clamp method (Nexfin, BMEYE Inc.) and calibrated with intermittent brachial cuff measurements (Vital-Guard 450C Patient Care Monitor, IVY Medical).
- From the continuous BP waveform, we can get an estimate of stroke volume, cardiac output, and systemic vascular resistance (Modelflow).
- Middle cerebral blood flow velocity will be assessed using Spencer Technologies ST^3 Digital Transcranial Doppler System Model PMD150 (TCD).
- Oxygen saturation will be assessed from a finger probe.
- End-tidal CO_2 will be measured using nasal prongs.

6.2.4 Study Day

- The participant will be asked about co-morbid disorders, and current pharmacological and non-pharmacological treatments of POTS
- The participant will be instrumented in a fasting state (aside from water as needed).
- The compression garment will be worn, but not initially strapped tight. The compression garment will be tightened around segments as determined by the order of randomization
- Participant will be strapped onto the tilt table (for their safety)
- Supine for 20 minutes prior to baseline data collection
- For each intervention:
    - Physiological signals will be digitally sampled throughout the study
    - 10 minute baseline data collection (supine)
    - Table will be tilted up to 80 degrees (head up) for 10 minutes
        1. Tilt will be terminated early if the patient has syncope or if the patient requests that the table be returned to the supine position. If the tilt is terminated early, the duration of the tilt will be recorded.
        2. Symptoms will be assessed using the brief Vanderbilt Orthostatic Symptom Score before the end of tilt.
    - Table will be returned to the supine position

- The next compression garment intervention will be applied, removed or fastening modified depending on randomization scheme
- After completion of the 4th intervention, the study is over
    - The compression garment will be removed.
    - Study participant will be de-instrumented

6.3 Study Outcome Measures

- The primary outcome measure will be the magnitude of ΔHR from supine to head up tilt (max between 5-10 min of HUTT) for each intervention

- Secondary outcome measures for each intervention will include the peak standing HR between 5-10 min HUTT, VOSS Symptom Rating at end of each 10min HUTT, BP, advanced hemodynamics & CBF at peak standing HR during 5-10 min HUTT.

7.0 STATISTICAL CONSIDERATIONS

7.1 Primary Analysis

The primary analysis will compare the magnitude of ΔHR from supine to head up tilt (max between 5-10 min of HUTT) when the participant is wearing the LifeWrap NASG with full compression applied compared to when the patient has no compression applied. The comparison will use a paired t-test (or a Wilcoxon Signed-Rank test if the data are non-normally distributed).

7.2 Secondary Analysis

The secondary analyses will compare the magnitude of ΔHR from supine to head up tilt (max between 5-10 min of HUTT) with partial compression to no compression and to full compression. Other secondary analyses will include patient reported orthostatic symptoms on tilt with different compression garment configurations, and assessments of other hemodynamic parameters in different garment configurations as well as a regression analysis of orthostatic heart rate and orthostatic symptoms. We will also consider biological sex differences in response to the compression garment. Additionally, co-morbid medical conditions and the medications each participant is prescribed will be evaluated to investigate possible differences in response to the compression garment.

7.3 Sample Size Calculation

Since this is a proof of concept study, there is no preliminary data about the effect of compression on orthostatic HR change in adults. In a pediatric study[4], the mean orthostatic HR change upon the addition of abdominal and leg compression was about 25bpm. Orthostatic tachycardia is physiologically greater in children and decreases with increasing age, so a more conservative assumption is required. A clinically meaningful reduction in orthostatic tachycardia of 10 bpm would be clinically significant. We estimate a standard deviation of about 15 bpm for our sample. With the aforementioned assumptions for a paired test of continuous data and a 0.05 two-sided significance level, a sample size of 26 POTS patients would allow for 90% power to detect this difference. To account for study withdrawal and dropout we will enroll **40 POTS patients in total**.

8.0 RISKS and INCOVENIENCES

BP 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 your heart. This might be uncomfortable to you. This can occasionally cause a rash.

Compression Garments: The LifeWrap garment may be uncomfortable to wear.

***Tilt-table test (HUTT)*:** There might be light-headedness, dizziness, tremor, headache or nausea during the tilt table test. These symptoms usually resolve rapidly upon lowering of the table.

Transcranial Dopppler (TCD): Ultrasound gel will be applied which may cause a rash. The Doppler probe will be in direct contact with the head, which may be uncomfortable. The headband/apparatus will be snug, but there will be opportunities to loosen it off during the recovery periods. Extended use of TCD at a high power may cause tissue heating, however we will keep the TCD at low power, and turn off the data acquisition during recovery periods.

Syncope: A small portion of individuals may experience fainting (syncope) while tilted upright. We will continuously monitor your blood pressure and heart rate and lower you immediately if you faint or request to be lowered. If you faint, you may chose to stop the study or continue with the next tilt table test, if you feel well and are willing.

We cannot foresee any other risks, but there may be previously unknown or unforeseen risks.

9.0 DATA and SAFETY PLAN

9.1 Adverse Event (or Unanticipated Problem) Reporting

Any adverse events of a serious nature will be reviewed immediately with the principal investigator. Serious adverse events will be reported in writing to the CHREB within 10 days of the PI's notification of the event. All study adverse events will be summarized once a year, during the annual review reporting, for the CHREB. The research coordinator will be responsible for tracking adverse events in this study.

The adverse event will be described with the following information: description of the event, outcome of the event, how long it lasted, whether the event required treatment or intervention, and the outcome.

The definition of events is as follows:
Mild – transient and mild in nature, with no treatment necessary.
Moderate – some intervention and treatment necessary, but participant completely recovers.
Severe – an event that results in hospitalization, disability, death or is life threatening.

9.2 Data & Safety Monitor

There will be no external Data & Safety monitor for this study.

10.0 STUDY WITHDRAWAL or DISCONTINUATION

10.1 Principal Investigator Initiated Withdrawal

The principal investigator reserves the right to withdraw the participant from the study after they have provided informed consent, but before study completion. This could occur for one of many reasons, which include, but are not limited to: non-compliance with the protocol, a concern for participant safety, the availability of new knowledge that might affect continued participation in the study, or study termination.

10.2. Study Participant Initiated Withdrawal

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

10.3 Data Post-Withdrawal

If the participant is taken out of the study, or if the participant chooses to no longer be in the study, then we will stop collecting any information on the participant. With the participant's permission we will keep the data already collected, and this will still be used for analysis.

11.0 COMPENSATION

Participants will be financially compensated for parking costs related to this study. Participants will not be financially compensated for their time involved in this study. We are doing assessments that might generate knowledge about their medical condition and may indirectly be of benefit to them.

12.0 PRIVACY and CONFIDENTIALITY ISSUES

Protected Health Information will be used in this study. The investigators will comply with the patient privacy guidelines of the University of Calgary and applicable provincial and federal rules.

The research team is comprised of experienced research nurses and research assistants who are aware of the importance of confidentiality of health information. Paper research records will be stored in a locked office. Digital records will be stored on password-protected University of Calgary computers/servers and in the University of Calgary Clinical Research Unit REDCap Database.

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.

13.0 FOLLOW-UP AND RECORD RETENTION

13.1 Follow Up

There is no follow-up in this study. Once the physiological study day has been completed, the participant will be finished in this protocol. We may approach participants who participate in this study for further studies related to POTS.

14.0 Study Sponsor

Departmental Funds and the start-up package of Dr. Satish R Raj will support this study. We may later apply for independent funding.

15.0 Reference List

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