Title: Local Passive Heat for the Treatment of Hypertension in Autonomic Failure
NCT: NCT02417415
Date: 9/13/21

Subjects

Patients with primary autonomic failure (AF) were recruited from referrals to Vanderbilt University Autonomic Dysfunction Center. Clinical diagnoses were defined using current criteria. All patients had neurogenic orthostatic hypotension (OH) and supine hypertension defined as systolic BP (SBP) ≥150 mmHg or diastolic BP (DBP) ≥90 mmHg. Nineteen patients participated in Protocol 1. Patients were excluded if they had secondary causes of AF (e.g., diabetes mellitus or amyloidosis), if they were bedridden or if they had any significant cardiac or renal illness. The Vanderbilt University Institutional Review Board approved this study, and written informed consent was obtained from each patient before initiating the study (http://clinicaltrials.gov identifier: NCT02417415).

General Protocol

Patients were studied as inpatients in the Clinical Research Center at Vanderbilt University Medical Center, and were fed a low-monoamine, caffeine-free diet containing 150-mEq sodium and 70-mEq potassium per day. Medications affecting BP, blood volume and the autonomic nervous system, including fludrocortisone, pressor drugs or antihypertensive medications, were withheld for ≥5 half-lives before studies. All other medications were held constant during admission. The screening consisted of a medical history, physical examination, ECG, routine safety laboratory assessments, and standardized autonomic function tests, including orthostatic stress test, respiratory sinus arrhythmia and Valsalva maneuver. BP and HR were obtained using an automated oscillometric sphygmomanometer (Dinamap ProCare, GE Healthcare), finger photoplethysmography (Nexfin, BMEYE), and continuous ECG. During the orthostatic test, blood samples were obtained for norepinephrine while patients were supine and upright, as described previously. Plasma norepinephrine was measured by high-performance liquid chromatography with electrochemical detection. All patients were screened for nocturnal supine hypertension by assessing BP in duplicate at 2-hour intervals from 8:00 PM to 8:00 AM with an automated sphygmomanometer (Dinamap ProCare, GE Healthcare).

Protocol 1: Acute Hemodynamic Effects of Local Controlled Passive Heating

Patients were studied on 2 separate days in a randomized crossover manner with either local controlled passive heat stress (40-42ºC) or sham control. Studies were conducted in a temperature-controlled room (24-26ºC) in the afternoon when BP is higher, in a post-void state, and ≥2.5 hours after meals.

On each study day, patients remained supine throughout the study covered by a thin blanket for comfort. BP and HR were measured every 5 minutes with an automated oscillometric sphygmomanometer (Dinamap ProCare, GE Healthcare), and continuously with finger photoplethysmographic volume-clamp BP device (Nexfin, BMEYE) and ECG. Skin temperature was monitored with a wireless temperature sensor (Dermal Patch, VitalSense, Philips Respironics) placed on the right lower abdominal quadrant (underneath the heating pad). Core body temperature (Tcore) was monitored with a telemetric thermometer pill (Jonah™ ingestible capsule, VitalSense, Mini Mitter) that was swallowed >2 hours before studies.

After 30 minutes of normothermic baseline measurements, passive heat was applied over the abdomen and pelvis with a commercial electric heating pad (61 x 30 cm, Sunbeam Products), placed over 2 layers of clothing, to provide local heating at 40-42ºC ("high" temperature setting) continuously for up to 2 hours. Outcome measurements were recorded during the intervention

and for ≤30 minutes of recovery. All procedures were identical in the sham control day, but the heating pad was turned off.

In a subset of participants, we included measurements of systemic and skin hemodynamics at baseline and at 2 hours after each intervention to assess the hemodynamic mechanisms underlying the BP effects of passive heat (secondary objective). Specifically, stroke volume (SV) was estimated using impedance cardiography, as described previously. Cardiac output (CO) was then calculated by multiplying SV by the heart rate (HR) obtained from oscillometric BP measurements. Systemic vascular resistance (SVR) was estimated by dividing oscillometric mean arterial pressure (MAP) by CO. Skin blood flow was measured on the right lower abdominal quadrant (underneath the heating pad), and on the right lateral calf (a distal site unexposed to heat) using laser-Doppler flow probes (DRT4, Moor Instruments Inc.), to assess local (abdomen) and reflex-induced (calf) vascular changes due to local heating. Skin temperature on the right lateral calf was monitored with a wireless temperature sensor (Dermal Patch, VitalSense, Philips Respironics). Cutaneous vascular conductance (CVC) was estimated as the ratio of skin blood flow to arm cuff MAP, to assess changes in vasomotor tone. Systemic and skin hemodynamic data were reduced to average values measured during a 5-15 minute period and expressed as percent changes from baseline.

Statistical Analysis

In Protocol 1, our primary objective was to test the hypothesis that local controlled passive heat stress would decrease supine BP compared to sham control (normothermia) in AF patients with supine hypertension. The primary outcome was the change from the averaged baseline in supine SBP (ΔSBP) during the 2-hour intervention period. Secondary outcomes included changes from baseline in DBP, MAP, HR, pulse pressure (PP) and abdominal skin temperature and Tcore during the intervention and recovery periods. We used 2-way repeated-measures ANOVA to test effects of treatment, time, and their interaction on primary and secondary outcomes. If a significant overall treatment difference was found, paired comparisons of outcome variables across time were performed using paired t tests with Bonferroni correction as post hoc test. In the secondary objective, BP, HR and percent changes from baseline in CO, SV, SVR, skin blood flow and CVC at 2 hours post-intervention were compared between treatments using Wilcoxon signed-rank tests or paired t tests depending on the data distribution.

Sample size and Power Calculations

In Protocol 1, power calculation was based on preliminary data from 4 patients. The difference in the change from baseline in supine SBP between local controlled passive heating and sham control groups at 2 hours post-intervention was of 29 mmHg, with SD of the difference of 33 mmHg, which was consistent with the clinically significant hypotensive effect of nitric oxide potentiation with sildenafil and other antihypertensive tested in the same patient population. Assuming this effect size and variance, a sample size of 22 patients would have 97% power to detect a difference in mean values between treatments with an α level of 0.05 using paired t test analysis.