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Oral saline consumption and pressor responses to acute physical stress

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ABSTRACT

Sodium induced volume loading may alter pressor responses to physical stress, an early symptom of cardiovascular disease. *Purpose:* Study 1: Determine the time point where total blood volume and serum sodium were elevated following saline consumption. Study 2: Examine the BP response to isometric handgrip (HG) and the cold pressor test (CPT) following saline consumption. *Methods:* Study 1: Eight participants drank 423 mL of normal saline (sodium 154 mmol/L) and had blood draws every 30 min for 3 h. Study 2: Sixteen participants underwent two randomized data collection visits; a control and experimental visit 90 min following saline consumption. Participants underwent 2 min of isometric HG, post exercise ischemia (PEI), and CPT. *Results:* Study 1: Total blood volume (3.8 ± 3.0 Δ%) and serum sodium (3.5 ± 3.6 Δ%) were elevated ($P < 0.05$) by the 90 min time point. Study 2: There were no differences in mean arterial pressure (MAP) during HG (EXP: 17.4 ± 8.2 ΔmmHg; CON: 19.1 ± 6.0 ΔmmHg), PEI (EXP: 16.9 ± 11.7 ΔmmHg; CON: 16.9 ± 7.8 ΔmmHg), or the CPT (EXP: 20.3 ± 10.8 ΔmmHg; CON: 20.9 ± 11.7 ΔmmHg) between conditions ($P > 0.05$). MAP recovery from the CPT was slower following saline consumption (1 min recovery: EXP; 15.7 ± 7.9 ΔmmHg, CON; 12.3 ± 8.9 ΔmmHg, $P < 0.05$). *Conclusion:* Data showed no difference in cardiovascular responses during HG or the CPT between conditions. BP recovery was delayed by saline consumption following the CPT.

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INTRODUCTION

With a majority of Americans consuming more sodium than is recommended [1], under-standing how sodium effects health is of the upmost importance. Chronic consumption of a high sodium diet is well known to increase the likelihood of cardiovascular disease and stroke [2], as well as raise blood pressure [3, 4]. Additionally, we know that blood sodium concentration and osmolality are controlled by the body to maintain a tight range [5]. When a large dose of sodium is ingested this will trigger the thirst mechanism in an attempt to balance the sodium consumed [6]. Therefore, increases in blood sodium will lead to an increase in blood volume [7]. Understanding how simultaneously elevated blood volume and blood sodium concentration effects blood pressure responses to common stressors such as muscle contraction and cold exposure is a topic that has been far less studied and may affect health outcomes.

Rodent studies have found that chronic consumption of high amounts of sodium combined with water causes enhanced responsiveness of the sympathetic regulatory neurons in the rostral ventrolateral medulla [8–11]. It is believed that both the increased blood sodium concentration and blood volume have an effect on blood pressure [12]. An increase in blood volume can increase stroke volume and cardiac output leading to increased blood pressure [13] if total peripheral resistance is not altered. Likewise, increased plasma osmolality resulting from increased blood sodium enhances baroreflex control of sympathetic activity during intravenous hypertonic saline infusions [14], which may counteract stimulatory effects of sodium and volume loading. Therefore, it is unclear what the effects of high sodium consumption with concomitant fluid intake will have on the acute blood pressure response to physical stress.

No previous studies have examined the effects of a controlled simultaneous oral fluid and sodium load in humans with the induction of physical stress. This will allow for a scientifically controlled model to examine how these two mechanisms impact cardiovascular responsiveness when both are present. Therefore, the purpose of this study was to determine how acute oral fluid and sodium consumption effects blood pressure responses to physical stress. Two studies were performed and presented within this manuscript. Study-1: Participants consumed 423 mL of a 154 mmol/L sodium saline solution followed by a series of blood draws over 3 h. This was done to determine the digestion time required to ensure that blood volume and serum sodium concentration were elevated. Study-2: The same saline solution was consumed, and isometric handgrip (HG) and a cold pressor test (CPT) were performed to examine the effects of a simultaneous increase in blood volume and serum sodium on cardiovascular responses. We hypothesized that there would be an exaggerated pressor response to HG and the CPT after the consumption of the saline solution when compared to a control trial.

METHODS

Screening visits

All experimental procedures and protocols were approved by the Montclair State University Institutional Review Board, and the study conformed to the standards outlined in the Declaration of Helsinki. Verbal and written consent were obtained voluntarily from all participants before participation. Participants were asked to fill out a health history questionnaire and a general physical activity questionnaire. Height, weight, and body mass index (BMI) were

measured. The study participants were then given a standard sodium free meal (oats and brown sugar) to take home and instructed to consume the meal no less than 4 hours prior to their experimental and control visits. With the exception of plain water, participants were asked to fast following the controlled meal until after the visit. Participants were also instructed to avoid consuming caffeine 12 h prior to the visit and avoid strenuous activity, over the counter drug use, and alcoholic beverages 24 h prior to each visit. Exclusion criteria for this study included a history of cardiovascular disease, hypertension, tobacco use, and obesity (BMI > 30 kg/m^2). All participants were generally healthy and between the ages of 18–50 yrs. Research visit time of day varied based on subject availability.

Oral saline protocol

Upon arrival to the laboratory, participants were asked to provide a urine sample for determination of urine specific gravity. If the participant had a urine specific gravity ≥1.020 [15] (Cambridge Instruments Inc., NY, USA), they were sent home and their visit was rescheduled. If urine specific gravity was appropriate, participants were asked to consume a saline beverage with a sodium concentration equivalent to normal saline, 423 mL of deionized water with 3.8 g of table salt (Na$^+$: 1500 mg, 154 mmol/L), over a span of less than 5 min. The researchers utilized a 1500 mg dose of sodium as it is in line with the American Heart Association's recommended upper limit of sodium per day, and because it is a dose of sodium that is plausible for a single high sodium meal (e.g. Big MAC$^®$ Combo Meal = 1635 mg; Bacon & Cheese WHOPPER$^®$ Sandwich = 1560 mg).

Study 1: Time course of plasma volume and serum sodium alterations

Eight young healthy adults (5 men, 3 women) participated in study 1 (age: 27 ± 2 years; height 173 ± 5 cm; body mass 81.8 ± 6.1 kg; body mass index 27.2 ± 1.5 kg/m^2). A baseline blood sample was taken from each participant in a supine position prior to saline consumption. Following oral saline consumption, a supine blood sample was obtained every 30 min for 3 h. Between blood draws participants rested quietly in the seated position. Blood samples were obtained within ~1 min of laying supine at each timepoint. Hemoglobin (HemoCue America, CA, USA), hematocrit (microcapillary reader, International Equipment Company, MA, USA), and serum sodium (EasyLyte Electrolyte Analyzer, Medica Corporation, MA, USA) were assessed. Changes in hemoglobin and hematocrit were used to calculate changes in plasma volume, red blood cell volume, and total blood volume [16]. The results of study 1 were used to determine that 90 min of digestion time are necessary for both total blood volume and serum sodium to be elevated following normal saline consumption (see Results section). Therefore, a 90 min digestion period was used in study 2.

Study 2: Cardiovascular responses to physical stress following normal saline consumption

Sixteen participants were tested for study 2 (9 men, 7 women; age 26 ± 1 years, height 169 ± 3 cm, weight 71.2 ± 3.7 kg, and body mass index 24.9 ± 0.9). Study 2 participants were not the same participants as study 1. A control visit with no saline consumption, and an experimental visit with saline consumption were performed during study 2. These visits were randomized for each

participant. During the experimental visit a 90 min waiting period (see study 1 results) was given to allow for digestion following saline consumption prior to HG and CPT trials.

HG protocol

The isometric HG trial was performed similarly to previous studies [17–19]. Briefly, maximal voluntary contraction (MVC) was assessed by a handgrip dynamometer (ADInstruments, Colorado Springs, CO, USA) using their dominant hand. Participants underwent three MVC trials separated by approximately 1 min, and the highest stable value was used as the MVC. A 5 min resting baseline was collected followed by a 2 min period of isometric HG at ≈30% MVC. Visual feedback was given to allow the participants to maintain the proper HG force. In the final 5 s of the 2 min of HG, an occlusion cuff was inflated to suprasystolic pressure (>240 mmHg) and maintained for 2 min to cause a period of post exercise ischemia (PEI). Following the 2 min of PEI, an additional 2 min of recovery data was recorded. Following the HG trial, at least 10 min of quiet rest was given, and it was confirmed that resting blood pressure was stable and near baseline levels before any other tests were performed.

CPT protocol

Following the HG trial a CPT was then administered to determine the BP and heart rate (HR) responses to a non-exercise pressor stimulus [20]. Two minutes of baseline measurements were recorded. The participants then placed their dominant hand in an ice bath for 2 min, and immediately followed by a 2 min recovery period.

Instrumentation

Automated brachial artery blood pressures (Omron BP785N, Omron Healthcare Inc., Lake Forest, IL, USA) were taken to obtain accurate absolute resting values. Beat-by-beat finger blood pressure was measured by a Human Non-Invasive Blood Pressure Continuous Monitor placed on the middle finger of the non-dominant hand (ADInstruments, Colorado Springs, CO, USA). Heart rate was measured using a lead II electrocardiogram (ADInstruments, Colorado Springs, CO, USA). Respiratory movements were monitored using a strain-gauge pneumograph (Pneumotrace II, ADInstruments, Colorado Springs, CO, USA) which was placed over the abdomen and done to ensure that the participant did not perform a Valsalva maneuver during the HG protocol. HG force, occlusion cuff pressure, HR, respiratory abdominal movement, finger blood pressure, and model flow derived cardiac output, stroke volume, and peripheral resistance [21] were recorded continuously using ADInstruments PowerLab with LabChart 8 Pro software (ADInstruments, Colorado Springs, CO, USA).

Statistical analysis

Blood alterations from study 1 were analyzed for the effect of time (treatment follow up) using a one-way ANOVA with repeating measures. The Dunnett's multiple comparison post hoc test was used when appropriate to compare time point results compared to the baseline for all one-way ANOVA results. Resting values were compared between conditions using paired t-tests. Comparisons of cardiovascular variables for the HG/PEI and the CPT were compared in 60 s intervals using repeated measures two-way ANOVA with the main factors of treatment and

time. Scheffe post hoc correction was performed when appropriate to determine differences between time points within and between conditions. The immediately preceding rest period was used for the baseline values of each trial. Results were reported as means $\pm$ SD, and the α-level was set at $P <0.05$. All data, including data not shown, is available at: https://digitalcommons.montclair.edu/data/7/.

RESULTS

Study 1

The baseline values taken immediately prior to saline consumption were: serum sodium 132.2 $\pm$ 6.6 g/dL; urine specific gravity 1.007 $\pm$ 0.007 sgu; systolic blood pressure (SBP) 117 $\pm$ 14 mmHg; diastolic blood pressure (DBP) 70 $\pm$ 7 mmHg; and mean arterial pressure (MAP) 86 $\pm$ 7 mmHg. Hemoglobin decreased ($P < 0.05$) from baseline starting at 60 min (each $P < 0.05$) and remained depressed for the remainder of the time trial (base 13.9 $\pm$ 0.9, 30 min 13.5 $\pm$ 1.0, 60 min 13.6 $\pm$ 1.0, 90 min 13.4 $\pm$ 1.1, 120 min 13.5 $\pm$ 1.2, 150 min 13.5 $\pm$ 1.1, 180 min 13.3 $\pm$ 1.1 g/dL). Hematocrit also decreased from baseline, but did not reach significance (each $P < 0.05$) until 150 min (base 45.0 $\pm$ 3.6, 30 min 44.5 $\pm$ 3.2, 60 min 43.8 $\pm$ 3.0, 90 min 43.4 $\pm$ 3.7, 120 min 43.7 $\pm$ 3.6, 150 min 42.5 $\pm$ 2.9, 180 min 42.7 $\pm$ 3.5%). Total blood volume increased ($P < 0.05$) from baseline by 90 min, and remained elevated throughout the trial (Fig. 1). Serum sodium increased significantly from baseline at each time point ($P < 0.05$), except 60 min ($P > 0.05$) (Fig. 1). Plasma volume increased ($P < 0.05$) from baseline by 60 min (Fig. 1). There was no change in red blood cell volume throughout the trial (all time points $P < 0.05$). HR decreased from baseline at all time points (base 67 $\pm$ 8, 30 min -8 ± 8, 60 min -8 ± 9, 90 min -9 ± 9, 120 min -8 ± 6, 150 min -12 ± 6, 180 min -11 ± 7 %Δbpm; all $P < 0.05$). Neither SBP, DBP, or MAP were altered by saline consumption ($P > 0.05$).

Study 2

Baseline readings for the control and experimental visits were taken immediately prior to the HG trial. There were no significant differences ($P > 0.05$) between the experimental and control visits for resting brachial artery SBP (EXP: 118 $\pm$ 15 mmHg; CON: 121 $\pm$ 25 mmHg), DBP (EXP: 58 $\pm$ 13 mmHg; CON: 58 $\pm$ 11 mmHg), and MAP (EXP: 76 $\pm$ 12 mmHg; CON: 75 $\pm$ 13 mmHg). Resting HR was significantly lower ($P < 0.05$) following saline consumption (EXP: 59 $\pm$ 10 bpm) vs the control visit (CON: 63 $\pm$ 12 bpm). Urine specific gravity was not different between conditions (EXP: 1.009 $\pm$ 0.006; CON: 1.008 $\pm$ 0.006 sgu).

Handgrip

During HG the two-way ANOVA time effect was statistically significant for all variables ($P < 0.05$), but the condition and interaction effects were not significant ($P > 0.05$) for any variable.

In both the saline and control visits, SBP, DBP, and MAP were significantly elevated ($P < 0.05$) during HG and PEI when compared to baseline (see Fig. 2 for MAP data). SBP remained elevated above baseline ($P < 0.05$) in both conditions during the first minute of recovery, while DBP and MAP returned immediately to baseline levels. In both conditions HR increased ($P < 0.05$) during HG. HR returned to baseline ($P > 0.05$) during minute one of PEI in the control condition and
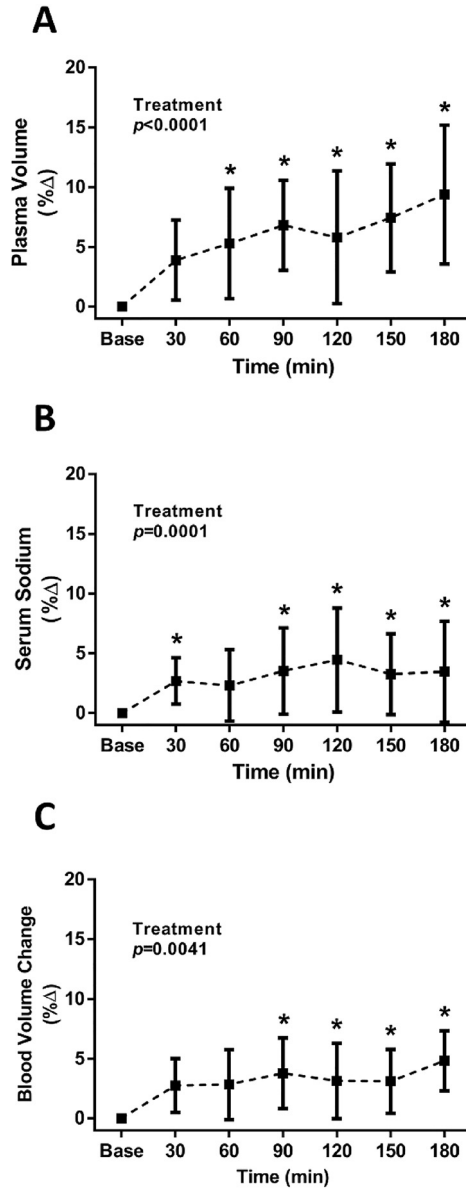
Figure 1. Percent change following oral saline consumption of plasma volume (A), serum sodium (B), and total blood volume (C) over time from baseline (Base). Values are mean ± SD. *$P < 0.05$ for percent change from baseline
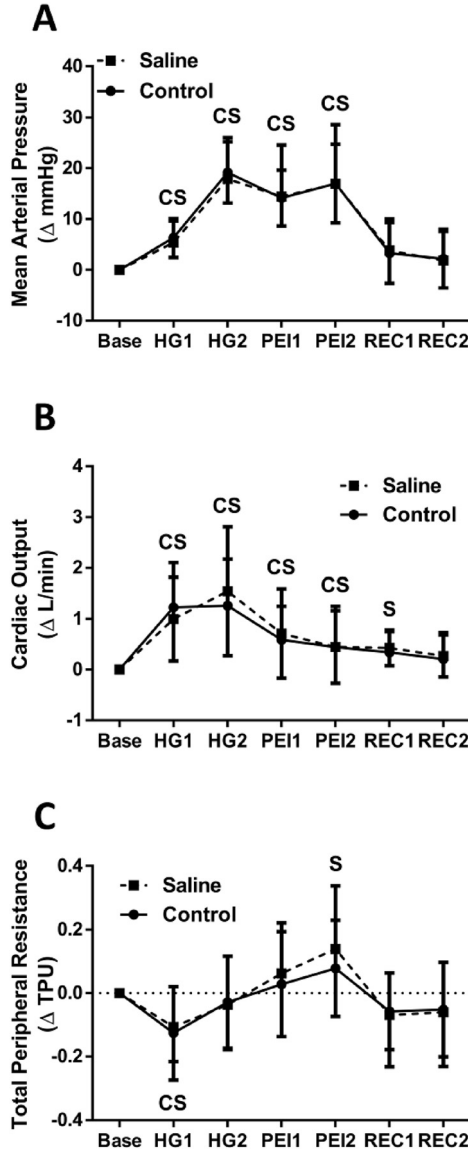
Figure 2. Percent change following oral saline consumption (dashed line with squares) vs. control (solid line with circles) of mean arterial pressure (A), cardiac output (B), and total peripheral resistance (C) over time from baseline (Base) during the handgrip protocol. Hand grip 1st minute (HG1), hand grip 2nd minute (HG2), post-exercise ischemia 1st minute (PEI1), post-exercise ischemia 2nd minute (PEI2), recovery 1st minute (REC1), recovery 2nd minute (REC2). Values are mean ± SD. **C** $P < 0.05$ for control condition vs. baseline value. **S** $P < 0.05$ for saline condition vs. baseline
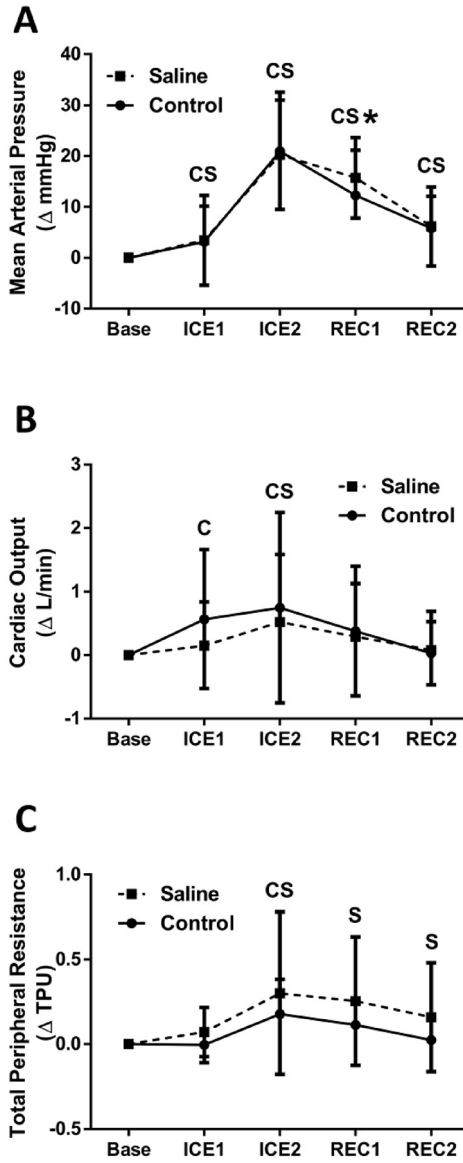
Figure 3. Percent change following oral saline consumption (dashed line with squares) vs. control (solid line with circles) of mean arterial pressure (A), cardiac output (B), and total peripheral resistance (C) over time from baseline (Base) during the cold pressor test. Cold pressor test 1st minute (ICE1), cold pressor test 2nd minute (ICE2), recovery 1st minute (REC1), recovery 2nd minute (REC2). Values are mean ± SD. **C** P < 0.05 for control condition vs. baseline value. **S** P < 0.05 for saline condition vs. baseline. *P < 0.05 for experimental condition vs. control

minute two of PEI in the saline condition. Stroke volume was significantly elevated ($P < 0.05$) by the second minute of HG, with significant values remaining throughout PEI in both conditions. Stroke volume was significantly elevated ($P < 0.05$) in both conditions during minute one of recovery, but only in the control condition during minute two of recovery. Cardiac output (Q) increased ($P < 0.05$) from baseline throughout HG and PEI for both conditions, with only the saline condition remaining elevated into minute one of recovery (Fig. 2). In both conditions, total peripheral resistance (TPR) showed a transient decrease ($P < 0.05$) from baseline during minute one of HG, with significant elevation ($P < 0.05$) found in minute two of PEI for the saline condition only (Fig. 2).

Cold pressor test

The CPT two-way ANOVA time effect was statistically significant for all variables ($P < 0.05$), but the condition effect was not significant for any variable ($P > 0.05$). However, there was a significant interaction effect for all blood pressure variables, i.e. SBP, DBP, and MAP ($P < 0.05$).

SBP increased from baseline during the second minute of the CPT, and remained significantly elevated ($P < 0.05$) throughout recovery in both conditions. The saline condition was significantly greater ($P < 0.05$) than the control condition during the first minute of recovery (Saline REC1 17.8 ± 13.6 ΔmmHg, Control REC1 12.3 ± 11.4 ΔmmHg) suggesting a slower SBP recovery. Both DBP and MAP were significantly elevated ($P < 0.05$) from baseline from minute one through minute two of recovery (see Fig. 3 for MAP data). Similar to SBP, both DBP (Saline REC1 12.5 ± 6.0 ΔmmHg, Control REC1 9.7 ± 7.3 ΔmmHg) and MAP (Saline REC1 15.7 ± 7.9 ΔmmHg, Control REC1 12.3 ± 8.9 ΔmmHg) were slower to recovery in the saline condition. In both conditions, HR significantly increased ($P < 0.05$) from baseline during minute one of the CPT, and showed a significant decrease ($P < 0.05$) during minute two of recovery. The control condition showed a significant increase ($P < 0.05$) in SV during minute two of the CPT, which remained during minute one of recovery. The saline condition only showed a significant SV increase ($P < 0.05$) from baseline during minute one of recovery. Q significantly increased ($P < 0.05$) from baseline in minutes 1–2 in the control condition, while only minute two for the saline condition (Fig. 3). Both conditions showed increases in TPR during minute two of the CPT, with only the saline condition remaining significantly elevated ($P < 0.05$) throughout recovery (Fig. 3).

DISCUSSION

This investigation examined a controlled simultaneous oral consumption of fluid and sodium to determine its effect on blood pressure responsiveness to physical stress. The major findings of this study were that acute saline consumption causes 1) increased in blood volume (via plasma volume) and serum sodium; 2) decreased resting HR, but does not affect cardiovascular responses to isometric HG or the CPT; and 3) slowed blood pressure recovery following the CPT likely driven by a slower recovery of total peripheral resistance. Collectively, these results suggest that while sodium and volume loading may not affect cardiovascular responsiveness to physical stress, it may slow cardiovascular recovery following a strong stimulus such as a CPT.

Previous studies have looked at the effect of chronic high dietary sodium consumption on sympathetic regulatory networks in rats [8–11] and humans [22] and found that high dietary

sodium causes elevated sympathetic nerve activity. Interestingly, having greater sodium sensitivity is also associated with greater resting sympathetic nerve activity [23]. The effects of acute high dietary sodium consumption have been studied with mixed results. Some studies have shown that acute sodium loading can lead to an increase in cardiovascular and sympathetic responses in rats [24] and humans [25]. Other studies have determined that pressor and sympathetic responses to hypertonic saline infusions were not significant [26]. Recently, an acute high sodium meal was shown not to effect blood pressure responses to maximal dynamic exercise [27]. The current investigation is the first to examine the effects of an acute high sodium meal on blood pressure responses to isometric muscle contraction.

It is possible that the volume loading that was incorporated with the sodium loading during this investigation counteracted the effects of sodium through stimulation of the baroreflex. Baroreflex stimulation through vascular volume loading causes a depressor response to sympathetic excitation and blood pressure [28]. Previous studies where volume loading occurred found significant increases in the control of sympathetic activity [29, 30]. When plasma osmolality increases it can enhance the sensitivity of the baroreflex to control muscle sympathetic nerve activity [14]. The exercise pressor reflex responsiveness is heavily modulated by the baroreflex [28] and may have been dampened by baroreflex activation via volume loading in the present investigation.

Altered cardiovascular reactivity to the CPT has been shown to exist in diseases such as hypertension [31]. In fact, high reactivity to the CPT has been shown to be a predictor of future hypertension [31]. The current investigation found that saline consumption delayed the recovery of blood pressure following the CPT, but not isometric HG. The neural mechanisms are different between HG and the CPT which leads to different response patterns [32]. The CPT primarily brings upon a cardiovascular response via cold induced pain [33], while HG combines feed forward (central command) [34] and efferent (exercise pressor reflex) [35] neural input to drive the cardiovascular responses. Also the CPT is a very strong stimulus [36] while using a 30% MVC HG is a more moderate intensity stimulus [37]. The differences in neural input or stimulus intensity could explain the differences in blood pressure recovery patterns found in the current investigation.

We recognize that there are some limitations to this study. One limitation is that the participants were in a supine position during the HG and CPT protocols. In the supine position, venous return is maximized leading to high stroke volume and cardiac output [38]. This is different from the upright posture that is most common during waking hours. In the upright posture our bodies must overcome the effects of gravity to return blood to the heart [39]. We also recognize that using a larger muscle group and having participants engage in dynamic exercise, as opposed to isometric exercise, may yield different results. Future investigations should examine the effects of sodium and volume loading during upright, large muscle mass dynamic exercise. The current investigation also has a small sample size which limited our ability to find effects smaller than Cohen's f = 0.4 (a strong effect).

CONCLUSION

The hypothesis of this study was that there would be an exaggerated pressor response to HG and the CPT after the consumption of saline when compared to a control condition. Our data does not support this hypothesis and showed no significant difference in cardiovascular responses

during HG or the CPT between conditions. However, a modest delay in the recovery of blood pressure and total peripheral resistance was found following the CPT in the saline condition. These findings are important because any increase in the length of time the arteries experience high pressures may increase the blood pressure related cardiovascular damage and the risk of a cardiovascular event.

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