The Impact of Cardiopulmonary Baroreceptors on Pain Perception in Individuals at Differing Risk for Hypertension

A dissertation presented to
the faculty of
the College of Arts and Sciences of Ohio University

In partial fulfillment
of the requirements for the degree
Doctor of Philosophy

Erin L. Hockman Matson
March 2010

© 2010 Erin L. Hockman Matson. All Rights Reserved
This dissertation titled
The Impact of Cardiopulmonary Baroreceptors on Pain Perception in Individuals at
Differing Risk for Hypertension

by

ERIN L. HOCKMAN MATSON

has been approved for
the Department of Psychology
and the College of Arts and Sciences by

Christopher R. France
Professor of Psychology

Benjamin M. Ogles
Dean, College of Arts and Sciences
Abstract

MATSON, ERIN L. H., M.S., March 2010, Psychology

The Impact of Cardiopulmonary Baroreceptors on Pain Perception in Individuals at Differing Risk for Hypertension (102 pp.)

Director of Dissertation: Christopher R. France

The current study examined cardiopulmonary baroreflex stimulation as a potential mechanism of decreased pain sensitivity in both young men and women at differing risk for hypertension. Risk for hypertension was defined by a positive parental history of hypertension and/or elevated resting systolic blood pressure (SBP) levels. Concurrent and retrospective subjective pain ratings were collected in response to both electrical and thermal stimulation of the forearm. A tilt table was used to elicit inhibition (head-up tilt) and stimulation (head-down tilt) of the cardiopulmonary baroreflex in a controlled manner. Cardiovascular activity was measured to provide a manipulation check.

Consist with the previous literature, findings of the current study revealed that individuals at risk for hypertension demonstrated higher electrical and thermal pain thresholds. However, cardiopulmonary baroreflex manipulation did not impact pain perception in the expected manner. Across all participants, concurrent numerical pain ratings increased in both of the tilt conditions, whereas retrospective pain ratings decreased over time. Except for a small subsample of females responding to thermal stimulation in the cardiopulmonary baroreflex inhibition (head-up tilt) condition, cardiopulmonary baroreflex effects were not enhanced in those at increased risk for hypertension.
Ultimately, findings of the current study did not support the notion that cardiopulmonary baroreceptor stimulation can dampen pain in people at risk for hypertension. However, continued investigation into the role of cardiopulmonary baroreceptors in pain seems warranted given that the findings in the literature to date have been both limited and mixed.

Approved: ____________________________________________________________

Christopher R. France

Professor of Psychology
Acknowledgements

I would like to take this opportunity to thank the many people that played a significant role in making this document and journey possible. First, I owe much gratitude to the hundreds of participants and parents who expressed interest in and took the time to complete the study protocol. I would also like to acknowledge and thank Sarah McGlone, who spent numerous hours assisting me with the study. To my advisor, Chris France, I cannot thank you enough for your support, guidance, and availability throughout the entirety of this project; I will always remember and be grateful for your unselfish willingness to assist me to the finish line. Finally, none of this would have been possible without the unconditional support and encouragement of my family – to each and every one of you, my sincerest thanks.
Table of Contents

Abstract ........................................................................................................................................... 3
Acknowledgements ......................................................................................................................... 5
List of Tables ................................................................................................................................... 9
List of Figures ................................................................................................................................. 11
Introduction ..................................................................................................................................... 13
Methods ......................................................................................................................................... 21
  Participants ..................................................................................................................................... 21
  Measures ......................................................................................................................................... 22
    Session One Questionnaire .......................................................................................................... 22
    Session Two Questionnaire .......................................................................................................... 22
    Parental Blood Pressure History Survey .................................................................................... 22
    McGill Pain Questionnaire – Short Form ..................................................................................... 23
    Numerical Pain Rating Scale ........................................................................................................ 23
Procedure ......................................................................................................................................... 24
  Laboratory Testing Procedure: Session One ............................................................................... 24
    Introduction .................................................................................................................................... 24
    Thermode and Electrode Placement .............................................................................................. 26
    Preparation for Measurement of Blood Pressure and Heart Rate ............................................. 26
    Assessment of Thermal and Electrical Subjective Pain Thresholds ........................................ 27
    Acclimatization Procedure ............................................................................................................ 28
    Assessment of Pain Responses During and Following Cardiopulmonary
Baroreflex Manipulation………………………………………………………….29
Assessment of Blood Pressure and Heart Rate During Baroreflex Manipulation………………………………………………………….29
Assessment of Hydration Status……………………………………………………..31
Debriefing……………………………………………………………………………….31
Laboratory Testing Procedure: Session Two……………………………………………………….32
Results……………………………………………………………………………………..32
Participants…………………………………………………………………………………..32
Participant Characteristics……………………………………………………………..33
Analysis of Pain Thresholds………………………………………………………35
   Electrical Stimulation Pain Threshold……………………………………………..37
   Thermal Stimulation Pain Threshold…………………………………………….37
Analysis of Pain Ratings and MPQ Scores During Cardiopulmonary Baroreflex Stimulation and Inhibition……………………………………………………………………..41
   Mean Electrical Stimulation Pain Ratings…………………………………………43
   Electrical Stimulation MPQ Scores…………………………………………………47
   Mean Thermal Stimulation Pain Ratings…………………………………………47
   Thermal Stimulation MPQ Scores………………………………………………….48
Analysis of Cardiopulmonary Baroreflex Effects in those at Increased Risk for Hypertension………………………………………………………………………48
   Changes in Electrical Stimulation Pain Ratings…………………………………49
   Changes in Electrical Stimulation MPQ Scores…………………………………49
List of Tables

Table 1. Protocol for Session One.................................................................................25
Table 2. Characteristics of the Participant Sample.........................................................34
Table 3. Descriptive Statistics for Electrical and Thermal Stimulation Pain
Thresholds.....................................................................................................................36
Table 4. Results of a 2 Group (Negative Parental History of Hypertension, Positive
Parental History of Hypertension) x SBP (Entered as a Continuous Variable)
x 2 Sex (Male, Female) ANOVA for Electrical Stimulation Pain Thresholds……38
Table 5. Results of a 2 Group (Negative Parental History of Hypertension, Positive
Parental History of Hypertension) x SBP (Entered as a Continuous Variable)
x 2 Sex (Male, Female) ANOVA for Thermal Stimulation Pain Thresholds……40
Table 6. Results of a 2 Tilt Condition (Baroreflex Stimulation, Baroreflex Inhibition)
x 3 Time Interval (Baseline, Tilt, Baseline) x 2 Sex (Male, Female) Repeated
Measures MANOVA for Mean Electrical Stimulation Pain Ratings, Electrical
Stimulation MPQ Scores, Mean Thermal Stimulation Pain Ratings, and
Thermal Stimulation MPQ Scores..............................................................................44
Table 7. Results of a 2 Group (Negative Parental History of Hypertension, Positive
Parental History of Hypertension) x 2 Tilt Condition (Baroreflex Stimulation,
Baroreflex Inhibition) x 2 Sex (Male, Female) x SBP (Entered as a Continuous
Variable) ANOVA for Changes in Electrical Stimulation Pain Ratings............50
Table 8. Results of a 2 Group (Negative Parental History of Hypertension, Positive Parental History of Hypertension) x 2 Tilt Condition (Baroreflex Stimulation, Baroreflex Inhibition) x 2 Sex (Male, Female) x SBP (Entered as a Continuous Variable) ANOVA for Changes in Electrical Stimulation MPQ Scores……..51

Table 9. Results of a 2 Group (Negative Parental History of Hypertension, Positive Parental History of Hypertension) x 2 Tilt Condition (Baroreflex Stimulation, Baroreflex Inhibition) x 2 Sex (Male, Female) x SBP (Entered as a Continuous Variable) ANOVA for Changes in Thermal Stimulation Pain Ratings………….54

Table 10. Results of a 2 Group (Negative Parental History of Hypertension, Positive Parental History of Hypertension) x 2 Tilt Condition (Baroreflex Stimulation, Baroreflex Inhibition) x 2 Sex (Male, Female) x SBP (Entered as a Continuous Variable) ANOVA for Changes in Thermal Stimulation MPQ Scores………….58

Table 11. Results of a 2 Tilt Condition (Baroreflex Stimulation, Baroreflex Inhibition) x 3 Time Interval (Post-1st Baseline, Post-Tilt, Post-2nd Baseline) Repeated Measures MANOVA for the Cardiovascular Measurements Taken Throughout the Cardiopulmonary Baroreflex Manipulation Protocol…………………………59

Table 12. A Summary of the Significant Findings related to the Study Hypotheses…….65
List of Figures

Figure 1. Illustration of baroreflex manipulation protocol…………………………...30

Figure 2. Correlation between electrical stimulation pain threshold and average resting systolic blood pressure………………………………………………………39

Figure 3. Correlation between thermal stimulation pain threshold and average resting systolic blood pressure in individuals with and without a parental history of hypertension………………………………………………………………...……42

Figure 4a. Mean electrical stimulation pain ratings for males and females across 1st baseline, tilt, and 2nd baseline time intervals……………………………………...……45

Figure 4b. Mean thermal stimulation pain ratings for participants across 1st baseline, tilt, and 2nd baseline time intervals……………………………………………….45

Figure 5a. Electrical stimulation MPQ scores for participants across 1st baseline, tilt, and 2nd baseline time intervals………………………………………………...…46

Figure 5b. Thermal stimulation MPQ scores for participants across 1st baseline, tilt, and 2nd baseline time intervals…………………………………………….……..46

Figure 6. Correlation between SBP and electrical stimulation MPQ change scores in females without a parental history of hypertension in the cardiopulmonary baroreflex inhibition condition……………………………………………..……53

Figure 7. Correlation between SBP and thermal stimulation pain rating change scores in females with a parental history of hypertension in the cardiopulmonary baroreflex inhibition condition…………………………………………..………56

Figure 8. Diastolic blood pressure responses to changes in tilt…………………………...61
Figure 9. Heart rate responses to changes in tilt...............................63
Introduction

Hypertension has often been viewed in the medical community as a “silent killer.” Although individuals suffering from hypertension do not usually report any subjective symptoms, hypertension has convincingly been associated with at least one behavioral symptom – hypoalgesia, or decreased pain perception (France, 1999). Almost three decades of research on animals and humans alike has demonstrated that hypertension is often accompanied by a reduction in pain sensitivity (Dworkin, Filewich, Miller, Craigmyle, & Pickering, 1979; Eilam, Malach, Bergmann, & Segal, 1991; Ghione, Rosa, Mezzasalma, & Panattoni, 1988; Guasti et al., 1995; Guasti et al., 1998; Guasti, Zanotta et al., 1999; Naranjo & Fuentes, 1985; Nyklicek, Vingerhoets, & Van Heck, 1999; Rosa, Vignocchi, Panattoni, Rossi, & Ghione, 1994; Saavedra, 1981; Sheps, Bragdon, Gray, Ballenger, Usedom, & Maixner, 1992; Zamir & Segal, 1979; Zamir & Shuber, 1980; Zamir, Simantov, & Segal, 1980).

The relationship between hypertension and decreased pain perception has been demonstrated across a range of pain stimulation techniques, including electrical, thermal, and mechanical pain stimulation. Moreover, diminished sensitivity to painful physical stimulation has been reported in studies that have examined both animals and humans with varying hypertensive conditions (see Ghione, 1996, for a comprehensive review of empirical evidence for hypertension-associated hypoalgesia).

Consequently, investigators began to ask whether risk for hypertension was associated with hypoalgesia in humans, following the lead of the available animal literature that provided initial support for this association (Maixner, Touw, Brody,
Gebhart, & Long, 1982; Sitsen & de Jong; 1983; Wendel & Bennett, 1981). It was thought that an answer to this question would provide valuable information regarding a potential common physiological mechanism involved with both hypertension and hypoalgesia (France & Ditto, 2000). Eventually, a growing body of literature provided strong evidence of decreased pain perception in normotensive individuals at risk for developing hypertension (see France, 1999, for a comprehensive review of empirical evidence of decreased pain perception in normotensive individuals at risk for hypertension). Individuals at risk for hypertension have been identified using a variety of indicators, including parental history of hypertension, elevated resting blood pressure, and/or exaggerated blood pressure reactivity to stress. Moreover, it has been suggested that a combination of risk factors for hypertension may be most reliably associated with differences in pain perception (France & Ditto, 1996). Studies that have examined multiple risk factors have, in fact, demonstrated that hypertension risk factors combine both additively and interactively to determine sensitivity to pain (D’Antono, Ditto, Rios, & Moskowitz, 1999; Ditto, France, & France, 1997; Ditto, Seguin, Boulerice, Pihl, & Tremblay, 1998; France & Stewart, 1995; Page & France, 1997).

In examining the question as to whether hypoalgesia is a cause, consequence, or correlate of hypertension, the above line of research provided substantial confirmation that hypoalgesia is not a consequence of hypertension. Rather, the findings lent support to the notion that hypoalgesia and hypertension may best be described as correlated phenomena. As such, it has been hypothesized that the relationship between hypoalgesia and hypertension may result from a common underlying physiological dysfunction.
(France, 1999). Investigation into this apparent overlap between cardiovascular and pain regulatory mechanisms has been an evolving focus of researchers.

Although early studies with human participants were not focused on identifying the mechanism(s) involved with hypertension-associated hypoalgesia, research in this area has progressed. Given the evidence suggesting that pain inhibitory circuitry is linked with cardiovascular regulatory systems in man and laboratory animals (Zamir & Maixner, 1986), investigators have focused increased attention on the possibility of a common underlying physiological mechanism(s) for both hypoalgesia and hypertension. Although the underlying mechanism(s) responsible for this connection has not yet been fully delineated, several important aspects have been explicated throughout the years. To date, the most widely studied hypothesis in this arena has focused on the inhibitory influence of baroreceptor stimulation on the central nervous system. It has been suggested that enhanced stimulation of baroreflex arcs may be one mechanism of hypoalgesia in individuals prone to hypertension (France, 1999). Particularly, hypoalgesia in the context of elevated blood pressure may be a result of baroreceptor stimulation having dampening effects on the central nervous system. To date, an impressive body of animal and human literature exists in this area.

Over the years, in several experimental models of acute and chronic blood pressure elevation, it has been found that a reduction or interruption in arterial baroreceptor input by various techniques leads to a marked attenuation or elimination of hypertension-associated hypoalgesia in animals (Dworkin et al., 1979; Ghione, 1996; Randich & Hartunian, 1983; Randich & Maixner, 1984; Zamir & Maixner, 1986).
Similarly, the research on cardiopulmonary baroreflex stimulation in animals suggests a relationship between stimulation of the cardiopulmonary baroreceptors and hypoalgesia (Maixner et al., 1982; Randich, 1986; Randich & Maixner, 1984; Zamir & Maixner, 1986).

In addition to laboratory animal studies, several studies have investigated arterial baroreflex stimulation in humans to determine its role in hypertension-associated hypoalgesia. In the human population, the most commonly used noninvasive method of arterial baroreflex stimulation involves the application of negative external pressure (suction) to the neck. Via stimulating the baroreceptors located in the walls of the carotid sinuses, this procedure has been shown to increase pain thresholds in individuals exposed to cold, electrical stimulation applied to dental pulp, mechanical pressure applied to the finger, and electrical stimulation applied to the forearm (France & Ditto, 1996). Three studies, in particular, have observed reduced pain sensitivity using a neck cuff device to mechanically stimulate the carotid sinus baroreceptors (Dworkin et al., 1994; Edwards, McIntyre, Carroll, Ring, France, & Martin, 2003; Elbert, Rockstroh, Lutzenberger, Kessler, & Pietrowsky, 1988). However, results regarding the role of arterial baroreflex stimulation and the modulation of nociception have not always been straightforward, positive, and/or conclusive. In fact, negative findings from a handful of studies suggest that arterial baroreflex stimulation is unlikely to account entirely for hypertension-associated hypoalgesia (al’Absi et al., 2005; France, Ditto, & Adler, 1991; Rau et al., 1994; Schobel, Ringkamp, Behrmann, Forster, Schmieder, & Handwerker, 1996).
More recently, investigators have shifted their focus to examining the role of cardiopulmonary baroreflex stimulation and hypertension-associated hypoalgesia in humans. To date, the research is both limited and mixed; however, results from four studies have provided preliminary insight into this relationship (D’Antono, Ditto, Sita, & Miller, 2000; Ditto, Lewkowski, Rainville, & Duncan, 2009; McIntyre, Kavussanu, & Ring, 2008; Ring, Veldhuijzen van Zanten, McIntyre, & Kavussanu, 2007).

In the first study of its kind, D’Antono et al. (2000) examined 66 young adult males with differing risk of hypertension (26 with a parental history of hypertension and 40 without a parental history of hypertension. Risk for hypertension was also operationalized using resting systolic blood pressure values. D’Antono et al. (2000) found that men with elevated resting systolic blood pressure demonstrated lower ratings of mechanical finger pressure unpleasantness than men with lower resting systolic blood pressure during passive leg elevation, a classic technique that is a widely accepted means of increasing venous return to the heart and stimulating cardiopulmonary baroreceptors (D’Antono et al., 2000; Girerd, Chanudet, Larroque, Clement, London, & Safar, 1989; Grassi et al., 1988). Additionally, analyses of pain tolerance produced results that approached significance, such that men with a parental history of hypertension with relatively elevated systolic blood pressure demonstrated a slight increase ($X = + 2 s$) in pain tolerance to finger pressure pain during passive leg elevation, whereas men in all other conditions (as defined by parental history of hypertension/no parental history of hypertension, relatively elevated systolic blood pressure/relatively low systolic blood pressure, and passive leg elevation/supine) displayed a slight decrease ($X = - 4 s$) in pain.
tolerance. This accentuation of group differences in pain sensitivity via a classic
technique for cardiopulmonary baroreflex stimulation provided the best, initial support
that cardiopulmonary baroreflex stimulation may be involved in hypertension-associated
hypoalgesia in human participants (D’Antono et al., 2000).

To more clearly examine the impact of risk for hypertension on the possible pain-
reducing property of cardiopulmonary baroreceptor stimulation, Ditto et al. (2009)
studied the effects of passive leg elevation on thermal pain in 22 borderline hypertensive
and 18 normotensive males. Participants provided ratings of pain intensity and
unpleasantness on two visual analogue scales in response to each stimulus. Ditto et al.
(2009) found that passive elevation of the legs reduced ratings of thermal pain intensity
among borderline hypertensives, while leg elevation produced a slight increase in pain
intensity in normotensives.

Two studies, which specifically assessed the effects of cardiopulmonary
baroreceptor stimulation on nociceptive responding in normotensive populations, found
conflicting results. In particular, Ring et al. (2007) found that blood volume
enhancement via hyperhydration increased participants’ ratings of venipuncture and
intravenous catheterization pain in 24 healthy undergraduate men. Participants were
asked to either augment their normal fluid intake (to increase blood volume and stimulate
the cardiopulmonary baroreceptors) or restrict their fluid intake (to decrease blood
volume and inhibit the receptors) prior to having a needle and catheter inserted while
lying supine. Following catheterization, participants used the short form McGill Pain
Questionnaire to rate the pain experienced during the insertion of the needle and catheter.
Contrary to the expectation that stimulation of the cardiopulmonary baroreceptors would result in decreased pain, participants in the hypervolemic condition reported experiencing more pain ($p < .05$; Ring et al., 2007).

Finally, McIntyre et al. (2008) examined the effects of cardiopulmonary baroreceptor stimulation on the upper limb nociceptive flexion reflex (NFR) by delivering electrocutaneous stimuli to the ulnar nerve while participants lay supine with their legs raised or lowered. Participants were 16 healthy adults (7 women, 9 men) with a mean age of 22 years ($SD = 3$). NFR responses and electrocutaneous pain ratings (assessed using the short form McGill Pain Questionnaire) did not differ between legs up and legs down postures, suggesting no cardiopulmonary baroreceptor effects.

It should be noted that among the four studies that have examined cardiopulmonary baroreflex stimulation and hypoalgesia, there are certain limitations that present themselves. A limitation of all of the studies is a relatively small sample size ($N$s = 16, 24, 40, 66). Power analyses for the current study determined that a sample of $N = 136$ would be necessary to conduct the primary analyses of interest. Until results can be replicated in a larger study, findings to date should be viewed with some caution. Similarly, only one study (McIntyre et al., 2008) has examined the effects of cardiopulmonary baroreceptor stimulation on pain in both males and females. Unfortunately, this study was restricted to 16 normotensive participants. Certainly, the generalizability of all study findings in this area needs to be investigated in women as well as men. Additionally, only two studies (D’Antono et al., 2000; Ditto et al., 2009) have compared individuals at risk for hypertension and normotensive individuals with
regard to the pain experienced during conditions of cardiopulmonary baroreceptor stimulation. In these two studies, the same procedure for manipulating the cardiopulmonary baroreceptors was used (i.e., passive leg elevation). It has been suggested that the effects of other forms of cardiopulmonary baroreflex stimulation upon pain be investigated; however, Ring et al. (2007) has been the only study to date that has examined a form of cardiopulmonary baroreflex stimulation outside of passive leg elevation (i.e., hydration manipulation).

In effort to address the above-mentioned limitations of existing research, the present study examined cardiopulmonary baroreflex stimulation as a potential mechanism of decreased pain sensitivity in a large sample of both young men and women at differing risk for hypertension. Concurrent and retrospective subjective pain ratings were collected in response to both electrical and thermal stimulation of the forearm. Furthermore, a tilt table was used to provide varying conditions of baroreflex manipulation. Head-up (inhibition, or “unloading”, of the cardiopulmonary baroreflex) and head-down (stimulation, or “loading”, of the cardiopulmonary baroreflex) tilt procedures were used to elicit inhibition and stimulation of the cardiopulmonary baroreflex in a controlled manner. The present study used tilt angles that have been found to alter cardiopulmonary baroreflex activity without simultaneous arterial baroreflex activation (Goldsmith, Francis, & Cohn, 1985; Hinghofer-Szalkay, Vigas, Sauseng-Fellegger, Konig, Lichardus, & Jezova, 1996; London, Levenson, Safar, Simon, Guerin, & Payen, 1983; Mark & Kerber, 1982; Nagaya, Wada, Nakamitsu, Sagawa, & Shiraki, 1995; Tanaka, Davy, & Seals, 1999; Yamazaki, Matsumura, Nagata, Ando, & Imura, 2001; Zoller, Mark,
Abboud, Schmid, & Heistad, 1972). Cardiovascular activity was measured to provide a manipulation check.

Hypotheses included the following: (1) increased risk for hypertension, as defined by a positive parental history of hypertension and elevated resting SBP levels, would be associated with significantly higher pain thresholds, (2) across all participants, cardiopulmonary baroreflex stimulation (head-down tilt) would be associated with decreased pain ratings, whereas cardiopulmonary baroreflex inhibition (head-up tilt) would be associated with increased pain ratings, and (3) cardiopulmonary baroreflex effects would be enhanced in those at increased risk for hypertension, such that those with a positive parental history of hypertension and elevated resting SBP levels would show (a) a significantly greater decrease in pain ratings than those without risk for hypertension following cardiopulmonary baroreflex stimulation (head-down tilt), and (b) a significantly greater increase in pain ratings than those without risk for hypertension following cardiopulmonary baroreceptor inhibition (head-up tilt).

Methods

Participants

The final sample included 140 participants (76 male, 64 female) ranging in age from 18-37 years (M = 19.46 years, SD = 2.26 years). Individuals identified themselves as White (91.4%), Black or African American (4.3%), Asian (3.6%), and American Indian or Alaskan Native (.7%).

Participants were recruited through the Undergraduate Psychology Experiment Management System at Ohio University and received research credit in their
undergraduate psychology course as compensation. Major eligibility requirements for participation included: (a) 18-40 years of age, (b) good physical health as indicated by the absence of chronic or acute illness, (c) no history of cardiac problems or syncope/fainting, and (d) biological parents available to confirm parental blood pressure history. All procedures used in the current study were approved by the Ohio University Institutional Review Board.

**Measures**

*Session One Questionnaire*

This brief questionnaire collected demographic information as well as assessed adherence to the study restrictions regarding use of analgesic medications, caffeine, nicotine, alcohol, and vigorous exercise. This questionnaire also asked participants to provide brief contact information for both biological parents so that the Parental Blood Pressure History Survey could be mailed to them.

*Session Two Questionnaire*

This questionnaire assessed adherence to the study restrictions regarding use of analgesic medications, caffeine, nicotine, alcohol, and vigorous exercise.

*Parental Blood Pressure History Survey*

Each biological parent received a blood pressure history survey to assess current and past history of hypertension, antihypertensive medication use, associated conditions such as diabetes or kidney disease, other significant health problems, and their family history of hypertension. This survey has been used extensively in previous research on family history of hypertension, and has demonstrated excellent reliability and validity.
(Page & France, 2001). A positive parental history of hypertension was defined as having at least one parent with a previous diagnosis of hypertension (SBP $\geq 140$ mmHg and/or DBP $\geq 90$ mmHg) that was treated with medication. Parental reports of hypertension were corroborated by a self-reported list of antihypertensive medication(s) prescribed by their physician(s). A negative parental history of hypertension was defined as the absence of a diagnosis of hypertension in both parents.

**McGill Pain Questionnaire – Short Form**

Designed to assess the qualitative aspects of pain intensity (e.g., throbbing, aching, punishing), the short form of the MPQ allows quantitative, multidimensional pain ratings to be obtained in a brief period of time (Melzack, 1987). Following each block in the baroreflex manipulation protocol, participants used the MPQ-SF to rate 15 pain descriptors on a four point scale with anchors of 0 (none), 1 (mild), 2 (moderate), and 3 (severe). They completed separate MPQ-SFs for electrical and thermal stimulation. A reliable and well-validated measure, the MPQ-SF has been utilized frequently across a range of clinical and research applications (Melzack, 1987).

**Numerical Pain Rating Scale**

A numerical rating scale to rate the pain level of each electrical and thermal stimulation was displayed on the ceiling and walls of the participant testing room. Participants were asked to verbally rate each stimulation from 0 to 100 with the following points as anchors: 0 (no sensation perceived), 1 (just noticeable sensation), 25 (uncomfortable), 50 (painful), 75 (very painful), and 100 (maximum tolerable pain). If at
any time a participant rated a stimulation as 100, the experimental session was terminated. Participants provided pain ratings for each stimulation delivered.

Procedure

*Laboratory Testing Procedure: Session One*

The laboratory protocol for Session One lasted approximately 1 hour and 10 minutes and included the following: (1) introduction; (2) electrode and Thermode placement; (3) preparation for measurement of blood pressure and heart rate; (4) assessment of electrical and thermal subjective pain thresholds; (5) acclimatization procedure; (6) assessment of pain responses during and following cardiopulmonary baroreflex manipulation; (7) assessment of blood pressure and heart rate during baroreflex manipulation; (8) assessment of hydration status; and (9) debriefing.

*Introduction*

When a participant arrived for Session One (see Table 1 for Session One protocol), he/she was assigned credit for the session and received a complete description of the study by reviewing the informed consent form with the experimenter. After providing informed consent, the participant completed the Session One Questionnaire. Next, the participant’s height (in m) and weight (in kg) were measured using a stadiometer to determine body mass index and all eligibility requirements were confirmed. The participant was then asked to lie supine on the tilt table, which was positioned horizontally (i.e., 0 degrees head tilt). At this point, the participant was
Table 1

**Protocol for Session One**

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Task</th>
<th>Pain Measures</th>
<th>Cardiovascular Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Review informed consent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Requirements questionnaire</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Thermode and electrode placement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Prep for measurement of blood pressure and heart rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Thermal and electrical pain threshold assessment</td>
<td>0-100 pain ratings</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Acclimatization procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Tilt Testing</td>
<td>0-100 pain ratings; Blood Pressure and Heart Rate</td>
<td>MPQ</td>
</tr>
<tr>
<td>5</td>
<td>Hydration Assessment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Debriefing</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
prepared to receive electrical and thermal stimulation, and was also prepared for measurement of blood pressure and heart rate.

*Thermode and Electrode Placement*

Thermal stimulation was delivered to the ventral surface of the forearm on the nondominant arm using a computer-controlled Medoc TSA-II Neuro Sensory Analyzer (TSA-2001, Ramat Yishai, Israel). Utilizing a device called a Thermode, which was placed on the participant’s skin and secured by means of an elastic Velcro strip, the TSA-II is capable of heating the skin as needed. The Thermode is a Peltier-element-based stimulator which consists of semiconductor junctions which produce a temperature gradient between the upper and lower stimulator surfaces produced by the passage of an electric current. For safety purposes, the stimulator has a temperature limit of 50°C; if this temperature level was reached at any point during the experimental procedure, the stimulator would automatically stop and immediately return to baseline (32°C).

Electrical stimulation was delivered using a Digitimer DS7A constant current stimulator and a 40 mm concentric electrode was attached to the ventral surface of the forearm of the dominant arm.

*Preparation for Measurement of Blood Pressure and Heart Rate*

Systolic and diastolic blood pressure (in mmHg) and heart rate (bpm) were measured from the dominant arm using an automated Critikon, Dinamap (Compact T) blood pressure monitor.
Assessment of Thermal and Electrical Subjective Pain Thresholds

Following preparation, the experimenter conducted the remainder of the protocol from an adjacent room where the recording equipment and control of the stimulation equipment was located. The experimenter maintained constant visual contact with the participant through a large, one-way glass window. An intercom system allowed the participant and experimenter to maintain constant verbal interaction.

Thermal subjective pain threshold was assessed using the ascending method of limits. Specifically, thermal stimulation was increased at a .5°C/second rate of rise, starting at a baseline temperature of 32°C (an adaptation level at which a participant feels neither warmth nor cold). The participant was instructed to press a button when the stimulation became “painful,” at which point the temperature would automatically and immediately decrease to baseline. The °C at this rating level (i.e., “painful”) was recorded for a total of four trials. The resulting °C average of the final three trials was used as the thermal pain threshold. It should be noted that the °C never exceeded 50°C for safety and ethical purposes.

Electrical subjective pain threshold was assessed using the staircase method of limits. Specifically, electrical stimulation started at 0 mA and increased in 3 mA increments until the participant provided a rating of 50 or greater using the aforementioned numerical pain rating scale. Once a rating of 50 or greater was obtained, electrical stimulation was decreased in 3 mA increments until the participant provided a rating below 50. At this point, electrical stimulation was increased in 2 mA increments until a rating of 50 or greater was obtained; stimulation was then decreased in 2 mA
increments until a rating dropped below 50. Finally, electrical stimulation was increased in 1 mA increments until a rating of 50 or greater was obtained, and decreased in 1 mA increments until the participant provided a rating below 50. The average of the final four peaks and troughs was defined as the electrical pain threshold. It should be noted that the mA intensity never exceeded 40 mA for safety and ethical purposes.

Acclimatization Procedure

An acclimatization procedure was developed in order to introduce the notion of variability in stimulation intensity throughout the baroreflex manipulation protocol (when, in fact, stimulation intensity did not vary during the protocol and was set at 100% of pain threshold). The acclimatization procedure was also employed to reassure the potentially anxious participant that the highest intensity stimulations that would be used throughout the protocol would not differ significantly from his/her pain thresholds.

In order to achieve these desired effects, the participant was told that he/she would be receiving stimulations of different intensities throughout the baroreflex manipulation protocol. The participant was then given the chance to experience the “maximum intensity” electrical and thermal stimulation that would be used in the following manipulation protocol. He/she received two stimulations (an electrical and thermal stimulation at 100% of the participant’s respective subjective pain threshold). The participant was not asked to rate these stimulations. Following these two stimulations, the participant was asked for his/her approval to continue.
Assessment of Pain Responses During and Following Cardiopulmonary Baroreflex Manipulation

Figure 1 provides an illustrative overview of the procedure. In this protocol, pain responses to both electrical and thermal stimulation were first recorded while the participant was lying on the tilt table positioned at $0^\circ$ (Block 1 – 1st baseline condition). During both the 1st and 3rd block (2nd baseline condition), all participants were positioned horizontally. During the second block (tilt condition), the participant was positioned at either $24^\circ$ head-up tilt (inhibition, or “unloading,” of the cardiopulmonary baroreflex) or $14^\circ$ head-down tilt (stimulation, or “loading” of the cardiopulmonary baroreflex). Block 2 position was determined randomly across the sample.

An alternating pattern of electrical and thermal stimulations was delivered in the series of 3 blocks. During each block, the participant received a total of 8 stimulations (4 electrical and 4 thermal) at a variable interval of $20 \pm 5$ seconds. Stimulation intensities during these blocks were set to the participant’s respective electrical and thermal subjective pain thresholds determined earlier in the session. The participant was asked to verbally rate each stimulation using the numerical pain rating scale. Following each block, the participant was asked to complete the short form of the McGill Pain Questionnaire twice, once in response to the electrical stimulation and once in response to the thermal stimulation (MPQ-SF; Melzack, 1987).

Assessment of Blood Pressure and Heart Rate During Baroreflex Manipulation

An automated Critikon, Dinamap (Compact T) blood pressure monitor was used to assess blood pressure and heart rate at 4 points during the baroreflex manipulation.
Figure 1. Illustration of baroreflex manipulation protocol (E = electrical stimulation; T = thermal stimulation; BP/HR = blood pressure/heart rate).
protocol (before block 1, and at the end of blocks 1, 2, and 3). The blood pressure and heart rate measurements that were taken at the end of blocks 1, 2, and 3 occurred after the administration of the stimulations but before the angle of the table was changed.

Assessment of Hydration Status

The participant remained supine on the tilt table for an additional 5 minutes while his/her hydration status was assessed (see Appendix A for findings related to hydration assessment analyses). A multifrequency bioelectrical impedance monitor (Multiscan 5000, Bodystat Ltd, Isle of Man, UK) was used to assess each participant’s level of hydration. Specifically, the monitor was used to measure total body water (TBW), and the distribution of extracellular (ECW) and intracellular water (ICW). Bioelectrical impedance analysis measures the resistance and conductance of a weak electrical current passed through the body. Resistance was measured across 4 electrodes placed on the right side of the body near the dorsal aspect of the wrist, the finger knuckles, the anterior aspect of the ankle, and the toe knuckles. A mild electric current at multiple frequencies was sent through the body and the electrodes measured the impedance of the tissues in the body. The impedance values are added to a regression equation including height and weight in order to estimate body water. The participant’s hydration percentage was calculated using TBW divided by weight (kg).

Debriefing

Upon completion of Session One, the participant was provided with a debriefing form outlining the intended purpose of the study.
Laboratory Testing Procedure: Session Two

Participants were scheduled for Session Two approximately 1-14 days following Session One. At this session, the participant completed the Session Two Questionnaire and was then asked to sit quietly for 30 minutes while resting blood pressure and heart rate readings were obtained at 5-minute intervals. Average resting blood pressure and heart rate were defined as the mean of the last 3 readings (i.e., 20, 25, and 30 minutes). These readings were obtained in a second, separate session so that true resting values could be achieved. Following the completion of this session, the Parental Blood Pressure History Survey was mailed to the biological parents of the participant.

Results

Participants

A total of 186 young adults signed informed consent forms for the study. Eight participants \((n = 8)\) were excluded due to non-adherence to the study restrictions. One participant \((n = 1)\) rated a stimulation as “100” and the experimental session was terminated. Another participant \((n = 1)\) chose to discontinue the study following the acclimatization procedure. Finally, one participant \((n = 1)\) was excluded as a result of not completing Session Two of the study. A Parental Blood Pressure History Survey was mailed to the biological parents of participants who completed the protocol \((n = 175)\) to confirm parental hypertension and antihypertensive medication history. Complete parental information was obtained from 82% \((n = 144)\) of this sample. Participants were classified as having a positive parental history of hypertension if at least one parent indicated that they had been diagnosed with hypertension by their physician and been
treated with antihypertensive medication. Parents with hypertension were asked to provide the name of their antihypertensive medication(s) as confirmation of diagnosis and treatment. Of these 144 participants, 4 were excluded; exclusions were made after all of the dependent variables were examined using the SPSS boxplot procedure to identify extreme outliers. In this instance, the extreme outliers reflected idiosyncratic use of the pain rating scales and/or MPQ scores (n = 2) and extreme blood pressure measurements (n = 2). The final sample included 140 participants.

**Participant Characteristics**

Table 2 provides descriptive characteristics for all participants. The final sample included fifty-four healthy young adults with a confirmed parental history of hypertension (23 male, 31 female) and 86 without a parental history of hypertension (53 male, 33 female). A series of 2 Group (negative parental history of hypertension, positive parental history of hypertension) X 2 Sex (male, female) ANOVAs were conducted for each of the descriptive variables [age, BMI, average resting systolic blood pressure (SBP), average resting diastolic blood pressure (DBP), and average resting heart rate (HR), total body water (TBW), and total body water/weight (TBW/Wt)].

Results of the analysis of age revealed a significant Group by Sex interaction, \( F(1, 136) = 5.19, p < .05, \eta_p^2 = .04 \), reflecting a higher age for men \( (M = 19.8, SD = 2.0) \) versus women \( (M = 18.8, SD = 1.2) \) among those without a history of parental hypertension. Results of the analysis of BMI revealed no significant main effects or interactions.
Table 2

**Characteristics of the Participant Sample**

<table>
<thead>
<tr>
<th></th>
<th>PH+</th>
<th></th>
<th>PH-</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td></td>
<td>(n = 54)</td>
<td>(n = 86)</td>
<td>(n = 53)</td>
<td>(n = 33)</td>
</tr>
<tr>
<td>Mean</td>
<td>(SD)</td>
<td>Mean</td>
<td>(SD)</td>
<td>Mean</td>
</tr>
<tr>
<td>Age (years)</td>
<td>19.0 (0.7)</td>
<td>19.8 (3.7)</td>
<td>19.8 (2.0)</td>
<td>18.8 (1.2)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.6 (3.9)</td>
<td>25.6 (4.6)</td>
<td>25.0 (4.3)</td>
<td>24.1 (3.0)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>110.8 (11.1)</td>
<td>101.2 (7.9)</td>
<td>108.4 (8.1)</td>
<td>99.5 (7.1)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>59.4 (6.9)</td>
<td>61.6 (4.9)</td>
<td>58.3 (5.8)</td>
<td>60.7 (4.4)</td>
</tr>
<tr>
<td>HR (mmHg)</td>
<td>67.1 (11.4)</td>
<td>77.3 (11.2)</td>
<td>69.9 (11.4)</td>
<td>72.5 (8.8)</td>
</tr>
<tr>
<td>TBW (liters)</td>
<td>39.6&lt;sup&gt;a&lt;/sup&gt; (3.9)</td>
<td>30.5&lt;sup&gt;b&lt;/sup&gt; (4.0)</td>
<td>41.0&lt;sup&gt;c&lt;/sup&gt; (5.0)</td>
<td>29.2&lt;sup&gt;d&lt;/sup&gt; (3.4)</td>
</tr>
<tr>
<td>TBW/Wt (%)</td>
<td>52.6&lt;sup&gt;a&lt;/sup&gt; (2.4)</td>
<td>43.9&lt;sup&gt;b&lt;/sup&gt; (3.4)</td>
<td>52.3&lt;sup&gt;c&lt;/sup&gt; (3.8)</td>
<td>45.1&lt;sup&gt;d&lt;/sup&gt; (2.3)</td>
</tr>
</tbody>
</table>

*Note: PH+ = positive parental history of hypertension; PH- = negative parental history of hypertension; BMI = Body Mass Index; SBP = average resting systolic blood pressure; DBP = average resting diastolic blood pressure; HR = average resting heart rate; TBW = total body water; TBW/Wt = total body water/weight. A smaller N was used for TBW and TBW/Wt assessments.

<sup>a</sup>n = 19.  <sup>b</sup>n = 31.  <sup>c</sup>n = 51.  <sup>d</sup>n = 31.
Upon analyzing participant cardiovascular characteristics, there was a significant main effect of Sex on all three variables (SBP: $F(1, 136) = 38.14, p < .01, \eta^2 = .22$; DBP: $F(1, 136) = 5.80, p < .05, \eta^2 = .04$; HR: $F(1, 136) = 11.30, p < .01, \eta^2 = .08$), such that men exhibited a higher SBP ($M = 109.1, SD = 9.1$ versus $M = 100.3, SD = 7.5$), a lower DBP ($M = 58.6, SD = 6.1$ versus $M = 61.2, SD = 4.6$), and a lower HR ($M = 69.1, SD = 11.4$ versus $M = 74.9, SD = 10.3$) than women. Additionally, the analysis of HR revealed a significant Group by Sex interaction, $F(1, 136) = 3.90, p = .05, \eta^2 = .03$, reflecting a higher HR for women ($M = 77.3, SD = 11.2$) versus men ($M = 67.1, SD = 11.4$), specifically among those with a parental history of hypertension.

Finally, examination of the hydration status variables indicated a significant main effect of Sex on both variables (TBW: $F(1, 128) = 174.3, p < .01, \eta^2 = .58$; TBW/Wt: $F(1, 128) = 172.6, p < .01, \eta^2 = .57$), such that men exhibited a higher TBW ($M = 40.6, SD = 4.8$ versus $M = 29.9, SD = 3.7$), and a higher TBW/Wt ($M = 52.4, SD = 3.5$ versus $M = 44.5, SD = 2.9$) than women.

**Analysis of Pain Thresholds**

We hypothesized that individuals with an increased risk for hypertension, as defined by a positive parental history of hypertension and elevated resting SBP levels, would be associated with significantly higher pain thresholds (see Table 3 for descriptive statistics of pain thresholds among study participants). To examine the proposed hypothesis, a 2 Group (negative parental history of hypertension, positive parental history of hypertension) x SBP (entered as a continuous variable) x 2 Sex (male, female)
Table 3

Descriptive Statistics for Electrical and Thermal Stimulation Pain Thresholds

<table>
<thead>
<tr>
<th></th>
<th>PH+</th>
<th></th>
<th>PH-</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(n = 54)</td>
<td></td>
<td>(n = 86)</td>
</tr>
<tr>
<td>Male</td>
<td>Mean</td>
<td>(SD)</td>
<td>Mean</td>
<td>(SD)</td>
</tr>
<tr>
<td>Female</td>
<td>Mean</td>
<td>(SD)</td>
<td>Mean</td>
<td>(SD)</td>
</tr>
<tr>
<td>Male</td>
<td>Mean</td>
<td>(SD)</td>
<td>Mean</td>
<td>(SD)</td>
</tr>
<tr>
<td>Female</td>
<td>Mean</td>
<td>(SD)</td>
<td>Mean</td>
<td>(SD)</td>
</tr>
<tr>
<td>Electrical Stimulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain Threshold (in mA)</td>
<td>27.0</td>
<td>(11.9)</td>
<td>19.7</td>
<td>(11.0)</td>
</tr>
<tr>
<td>Thermal Stimulation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain Threshold (in °C)</td>
<td>48.3</td>
<td>(1.4)</td>
<td>47.3</td>
<td>(2.3)</td>
</tr>
</tbody>
</table>

Note: PH+ = positive parental history of hypertension; PH- = negative parental history of hypertension
ANOVA was conducted for (a) electrical stimulation pain threshold (in mA) and (b) thermal stimulation pain threshold (in °C).

**Electrical Stimulation Pain Threshold**

Table 4 summarizes the main effects and interactions observed for participants’ electrical stimulation pain thresholds. Evidence of higher pain thresholds in individuals at risk for hypertension would be supported by a significant interaction involving Group and SBP, such that individuals with a parental history of hypertension and higher average resting SBP would demonstrate the highest electrical stimulation pain thresholds. In partial support of this hypothesis, a significant main effect of SBP on electrical stimulation pain threshold was observed, $F(1, 132) = 7.37, p < .01, \eta^2_p = .05$. To follow-up on this significant main effect, a correlation was conducted between SBP and electrical stimulation pain threshold, revealing a positive relationship ($r = .33, p < .01$) between the two variables (see Figure 2). Consistent with the lack of interaction between SBP and Sex, correlations conducted separately for each sex found that the relationship between SBP and electrical stimulation pain threshold was similar for both men ($r = .25$) and women ($r = .23$). There were no other significant main effects or interactions.

**Thermal Stimulation Pain Threshold**

Table 5 summarizes the main effects and interactions observed for participants’ thermal stimulation pain thresholds. Similarly, evidence of higher pain thresholds in individuals at risk for hypertension would be supported by a significant interaction involving Group and SBP, such that individuals with a parental history of hypertension
Table 4

Results of a 2 Group (Negative Parental History of Hypertension, Positive Parental History of Hypertension) x SBP (Entered as a Continuous Variable) x 2 Sex (Male, Female) ANOVA for Electrical Stimulation Pain Thresholds

<table>
<thead>
<tr>
<th>Source</th>
<th>F value</th>
<th>p value</th>
<th>ηp²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>1.23</td>
<td>.27</td>
<td>.01</td>
</tr>
<tr>
<td>Sex</td>
<td>.08</td>
<td>.78</td>
<td>.00</td>
</tr>
<tr>
<td>SBP</td>
<td>7.37</td>
<td>.01</td>
<td>.05</td>
</tr>
<tr>
<td>Group x Sex</td>
<td>.24</td>
<td>.62</td>
<td>.00</td>
</tr>
<tr>
<td>SBP x Sex</td>
<td>.02</td>
<td>.90</td>
<td>.00</td>
</tr>
<tr>
<td>Group x SBP</td>
<td>1.20</td>
<td>.27</td>
<td>.01</td>
</tr>
<tr>
<td>Group x Sex x SBP</td>
<td>.31</td>
<td>.58</td>
<td>.00</td>
</tr>
</tbody>
</table>
Figure 2. Correlation between electrical stimulation pain threshold and average resting systolic blood pressure (SBP).
Table 5

Results of a 2 Group (Negative Parental History of Hypertension, Positive Parental History of Hypertension) x SBP (Entered as a Continuous Variable) x 2 Sex (Male, Female) ANOVA for Thermal Stimulation Pain Thresholds

<table>
<thead>
<tr>
<th>Source</th>
<th>F value</th>
<th>p value</th>
<th>ηp²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group</strong></td>
<td>4.34</td>
<td>.04</td>
<td>.03</td>
</tr>
<tr>
<td>Sex</td>
<td>1.24</td>
<td>.27</td>
<td>.01</td>
</tr>
<tr>
<td>SBP</td>
<td>3.20</td>
<td>.08</td>
<td>.02</td>
</tr>
<tr>
<td>Group x Sex</td>
<td>2.74</td>
<td>.10</td>
<td>.02</td>
</tr>
<tr>
<td>SBP x Sex</td>
<td>1.05</td>
<td>.31</td>
<td>.01</td>
</tr>
<tr>
<td><strong>Group x SBP</strong></td>
<td>4.71</td>
<td>.03</td>
<td>.03</td>
</tr>
<tr>
<td>Group x Sex x SBP</td>
<td>2.76</td>
<td>.10</td>
<td>.02</td>
</tr>
</tbody>
</table>
and higher average resting SBP would demonstrate the highest thermal stimulation pain thresholds. A significant main effect of Group on thermal stimulation pain threshold was revealed, $F(1, 132) = 4.34, p < .05, \eta^2_p = .03$. While this main effect should be interpreted with caution due to a significant higher-order interaction, it nevertheless demonstrates that individuals with a parental history of hypertension exhibited a higher thermal stimulation pain threshold ($M = 47.8, SD = 2.0$) than individuals without a parental history of hypertension ($M = 47.7, SD = 2.2$). A significant main effect of SBP on thermal stimulation pain threshold was not observed. Interpretation of the significant Group x SBP interaction (see Figure 3 for an illustration of the significant Group x SBP interaction), $F(1, 132) = 4.71, p < .05, \eta^2_p = .03$, suggests that SBP is positively correlated ($r = .43, p < .01$) with thermal stimulation pain threshold in individuals with a parental history of hypertension. SBP was not significantly correlated with thermal stimulation pain threshold in individuals without a parental history of hypertension ($r = .03$). These results indicate that individuals at highest risk for hypertension (both a parental history of hypertension and elevated resting SBP) exhibited the highest thermal stimulation pain thresholds.

Analysis of Pain Ratings and MPQ Scores during Cardiopulmonary Baroreflex Stimulation and Inhibition

We hypothesized that, across all participants, cardiopulmonary baroreflex stimulation (head-down tilt) would be associated with decreased pain ratings, whereas cardiopulmonary baroreflex inhibition (head-up tilt) would be associated with increased pain ratings. To examine the proposed hypothesis, a 2 Tilt Condition (baroreflex
Figure 3. Correlation between thermal stimulation pain threshold and average resting systolic blood pressure (SBP) in individuals with (PH+) and without (PH-) a parental history of hypertension.
stimulation, baroreflex inhibition) x 3 Time Interval (1\textsuperscript{st} baseline, tilt, 2\textsuperscript{nd} baseline) x 2 Sex (male, female) repeated measures MANOVA was conducted for (a) mean electrical stimulation pain ratings, (b) electrical stimulation MPQ scores, (c) mean thermal stimulation pain ratings, and (d) thermal stimulation MPQ scores. Table 6 summarizes the main effects and interactions for the repeated measures MANOVA. Figures 4a, 4b, 5a, and 5b illustrate the pattern of responses across time intervals for electrical and thermal stimulation pain ratings and electrical and thermal stimulation MPQ scores, respectively.

\textit{Mean Electrical Stimulation Pain Ratings}

Evidence of decreased pain ratings as a result of cardiopulmonary baroreflex stimulation (head-down tilt) and/or increased pain ratings as a result of cardiopulmonary baroreflex inhibition (head-up tilt) would be supported by a significant interaction involving Tilt Condition and Time Interval. However, as can be seen in Table 6, a significant Tilt Condition x Time Interval interaction was not observed.

A significant Time Interval x Sex interaction, $F(2, 135) = 3.35, p < .05, \eta^2_p = .05$, was observed, and follow-up analyses for this interaction indicated a significant main effect of Time Interval for females ($p = .04$) but not males ($p = .25$; see Figure 4a). Subsequent comparisons of Time Intervals within female participants indicated that Time Interval 1 (first baseline) differed significantly from Time Interval 2 (tilt condition; $p < .05$), Time Interval 2 (tilt condition) marginally differed from Time Interval 3 (second baseline; $p = .052$), and Time Interval 1 did not differ significantly from Time Interval 3 ($p = .59$). This pattern of responses, as illustrated in Figure 4a, indicates that electrical
Table 6

*Results of a 2 Tilt Condition (Baroreflex Stimulation, Baroreflex Inhibition) x 3 Time Interval (Baseline, Tilt, Baseline) x 2 Sex (Male, Female) Repeated Measures MANOVA for Mean Electrical Stimulation Pain Ratings, Electrical Stimulation MPQ Scores, Mean Thermal Stimulation Pain Ratings, and Thermal Stimulation MPQ Scores*

### Mean Electrical Stimulation Pain Ratings

<table>
<thead>
<tr>
<th>Source</th>
<th>F value</th>
<th>p value</th>
<th>η_p²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time Interval</td>
<td>2.55</td>
<td>.08</td>
<td>.04</td>
</tr>
<tr>
<td>Time Interval x Tilt Condition</td>
<td>2.64</td>
<td>.07</td>
<td>.04</td>
</tr>
<tr>
<td><strong>Time Interval x Sex</strong></td>
<td><strong>3.35</strong></td>
<td><strong>.04</strong></td>
<td><strong>.05</strong></td>
</tr>
<tr>
<td>Time Interval x Tilt Condition x Sex</td>
<td>1.37</td>
<td>.26</td>
<td>.02</td>
</tr>
</tbody>
</table>

### Electrical Stimulation MPQ Scores

<table>
<thead>
<tr>
<th>Source</th>
<th>F value</th>
<th>p value</th>
<th>η_p²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time Interval</strong></td>
<td><strong>12.96</strong></td>
<td><strong>.00</strong></td>
<td><strong>.16</strong></td>
</tr>
<tr>
<td>Time Interval x Tilt Condition</td>
<td>2.30</td>
<td>.10</td>
<td>.03</td>
</tr>
<tr>
<td>Time Interval x Sex</td>
<td>1.22</td>
<td>.30</td>
<td>.02</td>
</tr>
<tr>
<td>Time Interval x Tilt Condition x Sex</td>
<td>.61</td>
<td>.55</td>
<td>.01</td>
</tr>
</tbody>
</table>

### Mean Thermal Stimulation Pain Ratings

<table>
<thead>
<tr>
<th>Source</th>
<th>F value</th>
<th>p value</th>
<th>η_p²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time Interval</strong></td>
<td><strong>7.07</strong></td>
<td><strong>.00</strong></td>
<td><strong>.09</strong></td>
</tr>
<tr>
<td>Time Interval x Tilt Condition</td>
<td>.99</td>
<td>.37</td>
<td>.01</td>
</tr>
<tr>
<td>Time Interval x Sex</td>
<td>2.07</td>
<td>.13</td>
<td>.03</td>
</tr>
<tr>
<td>Time Interval x Tilt Condition x Sex</td>
<td>.22</td>
<td>.80</td>
<td>.00</td>
</tr>
</tbody>
</table>

### Thermal Stimulation MPQ Scores

<table>
<thead>
<tr>
<th>Source</th>
<th>F value</th>
<th>p value</th>
<th>η_p²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time Interval</strong></td>
<td><strong>4.49</strong></td>
<td><strong>.01</strong></td>
<td><strong>.06</strong></td>
</tr>
<tr>
<td>Time Interval x Tilt Condition</td>
<td>.88</td>
<td>.42</td>
<td>.01</td>
</tr>
<tr>
<td>Time Interval x Sex</td>
<td>.18</td>
<td>.83</td>
<td>.00</td>
</tr>
<tr>
<td>Time Interval x Tilt Condition x Sex</td>
<td>1.12</td>
<td>.33</td>
<td>.02</td>
</tr>
</tbody>
</table>
Figure 4a. Mean electrical stimulation pain ratings for males and females across 1st baseline, tilt, and 2nd baseline time intervals.

Figure 4b. Mean thermal stimulation pain ratings for participants across 1st baseline, tilt, and 2nd baseline time intervals.
Figure 5a. Electrical stimulation MPQ scores for participants across 1st baseline, tilt, and 2nd baseline time intervals.

Figure 5b. Thermal stimulation MPQ scores for participants across 1st baseline, tilt, and 2nd baseline time intervals.
stimulation pain ratings for females were higher during both head-up and head-down tilt relative to the initial baseline.

**Electrical Stimulation MPQ Scores**

Once again, evidence of decreased MPQ scores as a result of cardiopulmonary baroreflex stimulation (head-down tilt) and/or increased MPQ scores as a result of cardiopulmonary baroreflex inhibition (head-up tilt) would be supported by a significant interaction involving Tilt Condition and Time Interval. As indicated in Table 6, no significant interactions were observed to support the above-stated hypothesis. Rather, a significant main effect of Time Interval on electrical stimulation MPQ scores was observed, $F(2, 134) = 12.96, p < .01, \eta^2_p = .16$ (see Figure 5a). Follow-up analyses revealed that Time Interval 1 differed significantly from Time Interval 2 ($p < .01$) and Time Interval 3 ($p < .01$); Time Interval 2 did not differ significantly from Time Interval 3 ($p = .42$). Figure 5a illustrates this effect as a decrease in electrical stimulation MPQ scores from initial baseline to the subsequent tilt and post-tilt baseline conditions.

**Mean Thermal Stimulation Pain Ratings**

Results of the analysis (see Table 6) revealed a significant main effect of Time Interval on mean thermal stimulation pain ratings, $F(2, 135) = 7.07, p < .01, \eta^2_p = .09$ (see Figure 4b). Subsequent comparisons of time intervals indicated that Time Interval 1 differed significantly from Time Interval 2 ($p < .01$); significant differences were not found between Time Interval 1 and Time Interval 3 ($p = .07$) or Time Interval 2 and Time Interval 3 ($p = .07$). As depicted in Figure 4b, thermal stimulation pain ratings increased significantly from the initial baseline to the tilt condition.
Thermal Stimulation MPQ Scores

Similar to the above analyses, the only significant finding (see Table 6) was a significant main effect of Time Interval on thermal stimulation MPQ scores, $F(2, 134) = 4.49, p < .05, \eta_p^2 = .06$ (see Figure 5b). Follow-up analyses revealed that Time Interval 1 differed significantly from Time Interval 2 ($p < .05$) and Time Interval 3 ($p < .01$); Time Interval 2 did not differ significantly from Time Interval 3 ($p = .25$). Figure 5b illustrates the trend in which the time intervals differed, reflecting a decrease in thermal stimulation MPQ scores across time.

Analysis of Cardiopulmonary Baroreflex Effects in those at Increased Risk for Hypertension

We hypothesized that cardiopulmonary baroreflex effects would be enhanced in those at increased risk for hypertension, such that those individuals with a parental history of hypertension and elevated resting SBP levels would show (a) a significantly greater decrease in pain ratings than those without risk for hypertension following cardiopulmonary baroreflex stimulation (head-down tilt) and (b) a significantly greater increase in pain ratings than those without risk for hypertension following cardiopulmonary baroreflex inhibition (head-up tilt). To examine the proposed hypothesis, a 2 Group (negative parental history of hypertension, positive parental history of hypertension) x 2 Tilt Condition (baroreflex stimulation, baroreflex inhibition) x 2 Sex (male, female) x SBP (entered as a continuous variable) ANOVA was conducted on change scores for (a) changes in electrical stimulation pain ratings, (b) changes in electrical stimulation MPQ scores, (c) changes in thermal stimulation pain ratings, and
(d) changes in thermal stimulation MPQ scores. Change scores were defined as mean value during the initial baseline interval minus the mean value during the tilt interval.

Changes in Electrical Stimulation Pain Ratings

Table 7 summarizes the main effects and interactions observed for participants’ changes in electrical stimulation pain ratings. Evidence of enhanced cardiopulmonary baroreflex effects in individuals with an increased risk of hypertension would be supported by a significant interaction involving Group, SBP, and Tilt Condition. As can be seen in Table 7, this hypothesis was not upheld as no significant main effects nor interactions were observed.

Changes in Electrical Stimulation MPQ Scores

Table 8 summarizes the main effects and interactions observed for participants’ changes in electrical stimulation MPQ scores. A significant main effect of Group on electrical stimulation MPQ change scores was observed, $F(1, 124) = 9.69, p < .01, \eta_p^2 = .07$. Follow-up analyses on this main effect revealed that individuals without a parental history of hypertension had higher change scores ($M = 1.55, SD = 2.97$) than individuals with a parental history of hypertension ($M = 1.06, SD = 3.77$). Again, a significant interaction involving Group, SBP, and Tilt Condition was expected in order to support the hypotheses. In this instance, a significant Group x SBP x Tilt Condition interaction was observed, $F(1, 124) = 9.08, p < .01, \eta_p^2 = .07$; however, a significant higher-order interaction was also observed, thus leading to an interpretation first and foremost of the significant Group x SBP x Tilt Condition x Sex interaction, $F(1, 124) = 7.49, p < .01, \eta_p^2 = .06$. 
Table 7

Results of a 2 Group (Negative Parental History of Hypertension, Positive Parental History of Hypertension) x 2 Tilt Condition (Baroreflex Stimulation, Baroreflex Inhibition) x 2 Sex (Male, Female) x SBP (Entered as a Continuous Variable) ANOVA for Changes in Electrical Stimulation Pain Ratings

<table>
<thead>
<tr>
<th>Source</th>
<th>F value</th>
<th>p value</th>
<th>ηp²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>.07</td>
<td>.79</td>
<td>.00</td>
</tr>
<tr>
<td>Tilt Condition</td>
<td>.54</td>
<td>.46</td>
<td>.00</td>
</tr>
<tr>
<td>Sex</td>
<td>1.74</td>
<td>.19</td>
<td>.01</td>
</tr>
<tr>
<td>SBP</td>
<td>.10</td>
<td>.75</td>
<td>.00</td>
</tr>
<tr>
<td>Group x Tilt Condition</td>
<td>.13</td>
<td>.71</td>
<td>.00</td>
</tr>
<tr>
<td>Group x Sex</td>
<td>.33</td>
<td>.56</td>
<td>.00</td>
</tr>
<tr>
<td>Group x SBP</td>
<td>.07</td>
<td>.79</td>
<td>.00</td>
</tr>
<tr>
<td>Tilt Condition x Sex</td>
<td>.65</td>
<td>.42</td>
<td>.00</td>
</tr>
<tr>
<td>Tilt Condition x SBP</td>
<td>.70</td>
<td>.40</td>
<td>.01</td>
</tr>
<tr>
<td>Sex x SBP</td>
<td>1.47</td>
<td>.23</td>
<td>.01</td>
</tr>
<tr>
<td>Group x Tilt Condition x Sex</td>
<td>.90</td>
<td>.34</td>
<td>.01</td>
</tr>
<tr>
<td>Group x Tilt Condition x SBP</td>
<td>.11</td>
<td>.74</td>
<td>.00</td>
</tr>
<tr>
<td>Group x Sex x SBP</td>
<td>.38</td>
<td>.54</td>
<td>.00</td>
</tr>
<tr>
<td>Tilt Condition x Sex x SBP</td>
<td>.42</td>
<td>.52</td>
<td>.00</td>
</tr>
<tr>
<td>Group x Tilt Condition x Sex x SBP</td>
<td>.84</td>
<td>.36</td>
<td>.01</td>
</tr>
</tbody>
</table>
Table 8

Results of a 2 Group (Negative Parental History of Hypertension, Positive Parental History of Hypertension) x 2 Tilt Condition (Baroreflex Stimulation, Baroreflex Inhibition) x 2 Sex (Male, Female) x SBP (Entered as a Continuous Variable) ANOVA for Changes in Electrical Stimulation MPQ Scores

<table>
<thead>
<tr>
<th>Source</th>
<th>F value</th>
<th>p value</th>
<th>η²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>9.69</td>
<td>.00</td>
<td>.07</td>
</tr>
<tr>
<td>Tilt Condition</td>
<td>.00</td>
<td>.98</td>
<td>.00</td>
</tr>
<tr>
<td>Sex</td>
<td>.09</td>
<td>.76</td>
<td>.00</td>
</tr>
<tr>
<td>SBP</td>
<td>.00</td>
<td>.95</td>
<td>.00</td>
</tr>
<tr>
<td>Group x Tilt Condition</td>
<td>8.28</td>
<td>.00</td>
<td>.06</td>
</tr>
<tr>
<td>Group x Sex</td>
<td>11.42</td>
<td>.00</td>
<td>.08</td>
</tr>
<tr>
<td>Group x SBP</td>
<td>9.95</td>
<td>.00</td>
<td>.07</td>
</tr>
<tr>
<td>Tilt Condition x Sex</td>
<td>.29</td>
<td>.59</td>
<td>.00</td>
</tr>
<tr>
<td>Tilt Condition x SBP</td>
<td>.01</td>
<td>.94</td>
<td>.00</td>
</tr>
<tr>
<td>Sex x SBP</td>
<td>.14</td>
<td>.71</td>
<td>.00</td>
</tr>
<tr>
<td>Group x Tilt Condition x Sex</td>
<td>6.96</td>
<td>.01</td>
<td>.05</td>
</tr>
<tr>
<td>Group x Tilt Condition x SBP</td>
<td>9.08</td>
<td>.00</td>
<td>.07</td>
</tr>
<tr>
<td>Group x Sex x SBP</td>
<td>12.91</td>
<td>.00</td>
<td>.09</td>
</tr>
<tr>
<td>Tilt Condition x Sex x SBP</td>
<td>.27</td>
<td>.60</td>
<td>.00</td>
</tr>
<tr>
<td>Group x Tilt Condition x Sex x SBP</td>
<td>7.49</td>
<td>.01</td>
<td>.06</td>
</tr>
</tbody>
</table>
Follow-up analyses on this four-way interaction revealed a significant Group x SBP x Tilt Condition interaction for females ($p < .01$) but not males ($p = .77$). Follow-up on this three-way interaction revealed a significant SBP x Tilt Condition interaction for females without a parental history of hypertension ($p < .05$) but not for females with a parental history of hypertension ($p = .09$). Subsequent comparison of tilt conditions indicated a significant main effect of SBP on changes in electrical stimulation MPQ scores for cardiopulmonary baroreflex inhibition (head-up tilt; $p < .01$) but not cardiopulmonary baroreflex stimulation (head-down tilt; $p = .97$). Consequently, a significant negative correlation ($r = -.657, p < .01$) between SBP and electrical stimulation MPQ change scores was revealed in females without a parental history of hypertension in the cardiopulmonary baroreflex inhibition (head-up tilt) condition (see Figure 6). As illustrated in Figure 6, in females without a parental history of hypertension, cardiopulmonary baroreflex inhibition (head-up tilt) had less of an effect (i.e., change scores approaching zero) on electrical stimulation MPQ scores in those with higher SBP levels than those with lower SBP levels. This finding is not consistent with any of the above-stated hypotheses and should be interpreted with caution given the limited sample size ($n = 16$).

Changes in Thermal Stimulation Pain Ratings

Table 9 summarizes the main effects and interactions observed for participants’ changes in thermal stimulation pain ratings. Similar to the above findings regarding changes in electrical stimulation MPQ scores, a significant Group x SBP x Tilt Condition
Figure 6. Correlation between SBP and electrical stimulation MPQ change scores in females without a parental history of hypertension in the cardiopulmonary baroreflex inhibition (head-up tilt) condition.
Table 9

Results of a 2 Group (Negative Parental History of Hypertension, Positive Parental History of Hypertension) x 2 Tilt Condition (Baroreflex Stimulation, Baroreflex Inhibition) x 2 Sex (Male, Female) x SBP (Entered as a Continuous Variable) ANOVA for Changes in Thermal Stimulation Pain Ratings

<table>
<thead>
<tr>
<th>Source</th>
<th>F value</th>
<th>p value</th>
<th>ηp²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>1.27</td>
<td>.26</td>
<td>.01</td>
</tr>
<tr>
<td>Tilt Condition</td>
<td>.98</td>
<td>.32</td>
<td>.01</td>
</tr>
<tr>
<td>Sex</td>
<td>.00</td>
<td>.98</td>
<td>.00</td>
</tr>
<tr>
<td>SBP</td>
<td>.00</td>
<td>.96</td>
<td>.00</td>
</tr>
<tr>
<td><strong>Group x Tilt Condition</strong></td>
<td><strong>13.05</strong></td>
<td><strong>.00</strong></td>
<td><strong>.09</strong></td>
</tr>
<tr>
<td>Group x Sex</td>
<td>.64</td>
<td>.43</td>
<td>.00</td>
</tr>
<tr>
<td>Group x SBP</td>
<td>1.16</td>
<td>.28</td>
<td>.01</td>
</tr>
<tr>
<td>Tilt Condition x Sex</td>
<td>1.13</td>
<td>.29</td>
<td>.01</td>
</tr>
<tr>
<td>Tilt Condition x SBP</td>
<td>.84</td>
<td>.36</td>
<td>.01</td>
</tr>
<tr>
<td>Sex x SBP</td>
<td>.01</td>
<td>.93</td>
<td>.00</td>
</tr>
<tr>
<td><strong>Group x Tilt Condition x Sex</strong></td>
<td><strong>7.65</strong></td>
<td><strong>.01</strong></td>
<td><strong>.06</strong></td>
</tr>
<tr>
<td><strong>Group x Tilt Condition x SBP</strong></td>
<td><strong>14.41</strong></td>
<td><strong>.00</strong></td>
<td><strong>.10</strong></td>
</tr>
<tr>
<td>Group x Sex x SBP</td>
<td>.76</td>
<td>.38</td>
<td>.01</td>
</tr>
<tr>
<td>Tilt Condition x Sex x SBP</td>
<td>1.06</td>
<td>.31</td>
<td>.01</td>
</tr>
<tr>
<td><strong>Group x Tilt Condition x Sex x SBP</strong></td>
<td><strong>7.90</strong></td>
<td><strong>.01</strong></td>
<td><strong>.06</strong></td>
</tr>
</tbody>
</table>
x Sex interaction was observed, $F(1, 124) = 7.90, p < .01, \eta^2_p = .06$. As can be seen in Table 9, there were no significant main effects.

Similar to the electrical stimulation MPQ score findings, follow-up analyses on the four-way interaction revealed a significant Group x SBP x Tilt Condition interaction for females ($p < .01$) but not males ($p = .38$). Follow-up on this three-way interaction revealed a significant SBP x Tilt Condition interaction for females with a parental history of hypertension ($p < .01$) but not for females without a parental history of hypertension ($p = .08$). Subsequent comparison of tilt conditions indicated a significant main effect of SBP on changes in thermal stimulation pain ratings for cardiopulmonary baroreflex inhibition (head-up tilt; $p < .01$) but not cardiopulmonary baroreflex stimulation (head-down tilt; $p = .10$). Consequently, a significant negative correlation ($r = -.660, p < .01$) between SBP and thermal stimulation pain rating change scores was revealed in females with a parental history of hypertension in the cardiopulmonary baroreflex inhibition (head-up tilt) condition (see Figure 7).

As illustrated in Figure 7, in females with a parental history of hypertension in the cardiopulmonary baroreflex inhibition (head-up tilt) condition, thermal stimulation pain ratings increased relative to baseline (i.e., change scores decreased below zero) in those with higher SBP levels than those with lower SBP levels. This finding is consistent with the hypothesis that individuals with a parental history of hypertension and elevated resting SBP levels would experience a greater increase in pain ratings than those without risk for hypertension following cardiopulmonary baroreflex inhibition (head-up tilt).
Figure 7. Correlation between SBP and thermal stimulation pain rating change scores in females with a parental history of hypertension in the cardiopulmonary baroreflex inhibition (head-up tilt) condition.
However, this finding was restricted to female participants and should be interpreted with caution given the limited sample size ($n = 18$).

**Changes in Thermal Stimulation MPQ Scores**

Table 10 summarizes the main effects and interactions observed for participants’ changes in thermal stimulation MPQ scores. There were no significant main effects or interactions.

**Analysis of Cardiovascular Responses to Changes in Tilt**

In addition to the analyses that were performed on the study hypotheses, a 2 Tilt Condition (baroreflex stimulation, baroreflex inhibition) x 3 Time Interval (post-1st baseline, post-tilt, post-2nd baseline) repeated measures MANOVA was conducted for the cardiovascular measurements taken throughout the cardiopulmonary baroreflex manipulation protocol. These analyses were conducted to confirm that changes in tilt were not associated with blood pressure and/or heart rate responses that would suggest stimulation of arterial baroreceptors. A significant finding would provide evidence for arterial baroreceptor involvement. Table 11 summarizes the main effects and interactions observed for participants’ blood pressure and heart rate responses.

Upon examining whether changes in tilt affected SBP levels, no significant main effects or interactions were observed. These findings provide support that changes in tilt did not affect systolic blood pressure responses.

Examination of diastolic blood pressure revealed a significant main effect of Time Interval on DBP levels, $F(2, 135) = 28.29, p < .01, \eta^2 = .29$, as well as a significant Tilt Condition x Time Interval interaction, $F(2, 135) = 3.23, p < .05, \eta^2 = .05$. While the
Table 10

Results of a 2 Group (Negative Parental History of Hypertension, Positive Parental History of Hypertension) x 2 Tilt Condition (Baroreflex Stimulation, Baroreflex Inhibition) x 2 Sex (Male, Female) x SBP (Entered as a Continuous Variable) ANOVA for Changes in Thermal Stimulation MPQ Scores

<table>
<thead>
<tr>
<th>Source</th>
<th>$F$ value</th>
<th>$p$ value</th>
<th>$\eta^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>1.29</td>
<td>.26</td>
<td>.01</td>
</tr>
<tr>
<td>Tilt Condition</td>
<td>1.29</td>
<td>.26</td>
<td>.01</td>
</tr>
<tr>
<td>Sex</td>
<td>.13</td>
<td>.72</td>
<td>.00</td>
</tr>
<tr>
<td>SBP</td>
<td>.32</td>
<td>.57</td>
<td>.00</td>
</tr>
<tr>
<td>Group x Tilt Condition</td>
<td>.02</td>
<td>.90</td>
<td>.00</td>
</tr>
<tr>
<td>Group x Sex</td>
<td>.01</td>
<td>.93</td>
<td>.00</td>
</tr>
<tr>
<td>Group x SBP</td>
<td>1.08</td>
<td>.30</td>
<td>.01</td>
</tr>
<tr>
<td>Tilt Condition x Sex</td>
<td>2.07</td>
<td>.15</td>
<td>.02</td>
</tr>
<tr>
<td>Tilt Condition x SBP</td>
<td>1.20</td>
<td>.27</td>
<td>.01</td>
</tr>
<tr>
<td>Sex x SBP</td>
<td>.13</td>
<td>.72</td>
<td>.00</td>
</tr>
<tr>
<td>Group x Tilt Condition x Sex</td>
<td>.28</td>
<td>.60</td>
<td>.00</td>
</tr>
<tr>
<td>Group x Tilt Condition x SBP</td>
<td>.04</td>
<td>.84</td>
<td>.00</td>
</tr>
<tr>
<td>Group x Sex x SBP</td>
<td>.02</td>
<td>.88</td>
<td>.00</td>
</tr>
<tr>
<td>Tilt Condition x Sex x SBP</td>
<td>1.91</td>
<td>.17</td>
<td>.01</td>
</tr>
<tr>
<td>Group x Tilt Condition x Sex x SBP</td>
<td>.20</td>
<td>.66</td>
<td>.00</td>
</tr>
</tbody>
</table>
Table 11

Results of a 2 Tilt Condition (Baroreflex Stimulation, Baroreflex Inhibition) x 3 Time Interval (Post-1\textsuperscript{st} Baseline, Post-Tilt, Post-2\textsuperscript{nd} Baseline) Repeated Measures MANOVA for the Cardiovascular Measurements Taken Throughout the Cardiopulmonary Baroreflex Manipulation Protocol

<table>
<thead>
<tr>
<th>Source</th>
<th>F value</th>
<th>p value</th>
<th>ηp(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic Blood Pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time Interval</td>
<td>1.10</td>
<td>.34</td>
<td>.02</td>
</tr>
<tr>
<td>Time Interval x Tilt Condition</td>
<td>.35</td>
<td>.70</td>
<td>.00</td>
</tr>
<tr>
<td>Diastolic Blood Pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time Interval</td>
<td>28.29</td>
<td>.00</td>
<td>.29</td>
</tr>
<tr>
<td>Time Interval x Tilt Condition</td>
<td>3.23</td>
<td>.04</td>
<td>.05</td>
</tr>
<tr>
<td>Heart Rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time Interval</td>
<td>27.67</td>
<td>.00</td>
<td>.29</td>
</tr>
<tr>
<td>Time Interval x Tilt Condition</td>
<td>36.31</td>
<td>.00</td>
<td>.35</td>
</tr>
</tbody>
</table>
main effect should be interpreted with caution due to a significant higher-order interaction, it nevertheless reveals that Time Interval 1 differed significantly from Time Interval 2 ($p < .01$), and Time Interval 2 differed significantly from Time Interval 3 ($p < .01$); Time Interval 1 did not differ significantly from Time Interval 3 ($p = .18$). The trend in which the time intervals differed reflects an increase in DBP in the tilt conditions.

Follow-up analyses on the Tilt Condition x Time Interval interaction (see Figure 8) indicated a significant main effect of Time Interval on DBP levels in both the baroreflex stimulation (head-down tilt), $F(2, 64) = 7.88, p < .01, \eta_p^2 = .20,$ and inhibition (head-up tilt), $F(2, 70) = 21.65, p < .01, \eta_p^2 = .38,$ conditions. Results are consistent with the main effect findings, such that DBP was significantly increased in both tilt conditions and greater in the baroreflex inhibition condition (head-up tilt; $M = 62.9$) than the baroreflex stimulation condition (head-down tilt; $M = 60.5$). Consequently, these results suggest that changes in tilt were associated with a diastolic blood pressure response, therefore suggesting stimulation of arterial baroreceptors.

Results of the heart rate analyses revealed a significant main effect of Time Interval on HR levels, $F(2, 135) = 27.67, p < .01, \eta_p^2 = .29,$ as well as a significant Tilt Condition x Time Interval interaction, $F(2, 135) = 36.31, p < .01, \eta_p^2 = .35.$ While the main effect should be interpreted with caution due to a significant higher-order interaction, it nevertheless reveals that Time Interval 1 differed significantly from Time Interval 2 ($p < .01$) and Time Interval 3 ($p < .01$), and Time Interval 2 differed significantly from Time Interval 3 ($p < .01$).
Figure 8. Diastolic blood pressure responses to changes in tilt (Tilt Condition x Time Interval interaction).
Follow-up analyses on the Tilt Condition x Time Interval interaction (see Figure 9) indicated a significant main effect of Time Interval on HR levels in both the baroreflex stimulation (head-down tilt), $F(2, 64) = 3.47, p < .05, \eta^2 = .10$, and inhibition (head-up tilt), $F(2, 70) = 47.56, p < .01, \eta^2 = .58$, conditions. In the cardiopulmonary baroreflex inhibition (head-up tilt) condition, Time Interval 1 differed significantly from Time Interval 2 ($p < .01$) and Time Interval 3 ($p < .01$), and Time Interval 2 differed significantly from Time Interval 3 ($p < .01$). In the cardiopulmonary baroreflex stimulation (head-down tilt) condition, Time Interval 1 differed significantly from Time Interval 2 ($p < .05$) and Time Interval 3 ($p < .05$); Time Interval 2 did not differ significantly from Time Interval 3 ($p = .60$). These results suggest the stimulation of arterial baroreceptors given that, once again, both tilt conditions were associated with a heart rate response. However, given that the cardiopulmonary baroreflex inhibition (head-up tilt) condition produced greater DBP and HR changes than the cardiopulmonary baroreflex stimulation (head-down tilt) condition (based upon Figures 8 and 9 as well as the associated effect sizes from the analyses), it is possible that the cardiopulmonary baroreflex inhibition (head-up tilt) condition is more likely to be associated with arterial baroreceptor stimulation.
Figure 9. Heart rate responses to changes in tilt (Tilt Condition x Time Interval interaction).
Discussion

The present study examined cardiopulmonary baroreflex stimulation as a potential mechanism of decreased pain sensitivity in both young men and women at differing risk for hypertension (see Table 12 for a summary of significant findings related to the study hypotheses). Partially consistent with our initial hypothesis and the previous literature, individuals with higher average resting SBP demonstrated the highest electrical stimulation pain thresholds. Further, individuals at highest risk for hypertension (both a parental history of hypertension and elevated resting SBP) exhibited the highest thermal stimulation pain thresholds. Contrary to our hypothesis, however, cardiopulmonary baroreflex manipulation did not impact pain perception in the expected manner. Across all participants, concurrent numerical pain ratings increased in both of the tilt conditions, whereas retrospective pain ratings decreased over time. Consequently, except for a small subsample of females responding to thermal stimulation in the cardiopulmonary baroreflex inhibition (head-up tilt) condition, cardiopulmonary baroreflex effects were not enhanced in those at increased risk for hypertension. To our knowledge this is the first study that has examined cardiopulmonary baroreflex stimulation as a potential mechanism of decreased pain sensitivity in a large sample of both men and women at differing risks of hypertension. Similarly, it is the first known study examining this phenomenon to use a tilt table to load and unload the cardiopulmonary baroreceptors as well as to use two different noxious stimuli (electrical and thermal stimulation).
Table 12

*A Summary of the Significant Findings related to the Study Hypotheses*

<table>
<thead>
<tr>
<th>Analyses Related to Study Hypotheses</th>
<th>Source</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Analysis of Pain Thresholds</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Electrical Stimulation Pain Threshold</td>
<td>SBP</td>
<td>.01</td>
</tr>
<tr>
<td>b. Thermal Stimulation Pain Threshold</td>
<td>Group x SBP</td>
<td>.03</td>
</tr>
<tr>
<td>2. Analysis of Pain Ratings and MPQ Scores during Cardiopulmonary Baroreflex Stimulation and Inhibition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Mean Electrical Stimulation Pain Ratings</td>
<td>Time Interval x Sex</td>
<td>.04</td>
</tr>
<tr>
<td>b. Electrical Stimulation MPQ Scores</td>
<td>Time Interval</td>
<td>.00</td>
</tr>
<tr>
<td>c. Mean Thermal Stimulation Pain Ratings</td>
<td>Time Interval</td>
<td>.00</td>
</tr>
<tr>
<td>d. Thermal Stimulation MPQ Scores</td>
<td>Time Interval</td>
<td>.01</td>
</tr>
<tr>
<td>3. Analysis of Cardiopulmonary Baroreflex Effects in those at Increased Risk for Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Changes in Electrical Stimulation Pain Ratings</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>b. Changes in Electrical Stimulation MPQ Scores</td>
<td>Group x Tilt Condition x Sex x SBP</td>
<td>.01</td>
</tr>
<tr>
<td>c. Changes in Thermal Stimulation Pain Ratings</td>
<td>Group x Tilt Condition x Sex x SBP</td>
<td>.01</td>
</tr>
<tr>
<td>d. Changes in Thermal Stimulation MPQ Scores</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Electrical and Thermal Stimulation Pain Thresholds

Consistent with the literature, our results indicated that individuals with an increased risk for hypertension demonstrated significantly higher electrical and thermal stimulation pain thresholds. However, it has been suggested that a combination of risk factors for hypertension may be most reliably associated with differences in pain perception (France & Ditto, 1996). In fact, studies that have examined multiple risk factors have demonstrated that hypertension risk factors combine both additively and interactively to determine sensitivity to pain (D’Antono et al., 1999; Ditto et al., 1997; Ditto et al., 1998; France & Stewart, 1995; Page & France, 1997). Consequently, it was expected that individuals at highest risk for hypertension (both a parental history of hypertension and elevated resting SBP) would exhibit the highest pain thresholds. While this was the case with regard to thermal stimulation pain thresholds, only elevated resting SBP was associated with higher electrical stimulation pain thresholds.

As has been found in previous studies, results may vary depending on the type of noxious stimulation employed. One hypothesis is that the differing nature of the stimuli used in the present study contributed to the discrepancy in findings. For instance, thermal stimulation is a more “natural” pain stimulus that activates specific nociceptors responsive to heat. In contrast, electrical stimulation is an unnatural sensation that activates wide dynamic range (WDR) receptors rather than any specific nociceptor. Unfortunately, in consulting the previous literature with regard to the consistency of findings from thermal versus electrical stimulation, no trends emerged to suggest that it may be more common to obtain effects for thermal versus electrical stimulation. In prior
studies that have utilized thermal stimulation and subjective pain threshold to examine pain perception in individuals with a parental history of hypertension and/or elevated resting blood pressure (Bragdon, Light, Girdler, & Maixner, 1997; Fillingim & Maixner, 1996; Fillingim, Maixner, Bunting, & Silva, 1998; Maixner, Fillingim, Kincaid, Sigurdsson, & Harris, 1997; Rau et al., 1994), evidence of decreased pain perception (i.e., higher subjective pain thresholds) in individuals at risk for hypertension was found in all but one of the studies (Fillingim et al., 1998). Similarly, in those studies that utilized electrical stimulation and subjective pain threshold to examine pain perception in individuals with a parental history of hypertension and/or elevated resting blood pressure (Elbert et al., 1988; France, Froese, & Stewart, 2002; France et al., 2005; Page & France, 1997), all but one study (France et al., 2002) reported decreased pain perception (i.e., higher subjective pain thresholds) in individuals at risk for hypertension. In sum, it remains unclear as to why the noxious stimuli in the present study generated different findings with regard to subjective pain thresholds.

The Effects of Cardiopulmonary Baroreflex Stimulation and Inhibition on Pain Ratings

Based upon the inhibitory influence of baroreceptor stimulation on the central nervous system, it was expected that, across all participants, cardiopulmonary baroreflex stimulation (head-down tilt) would be associated with decreased pain ratings, whereas cardiopulmonary baroreflex inhibition (head-up tilt) would be associated with increased pain ratings. Contrary to expectation, this pattern of responding was not observed. However, the pattern of responding that did occur sheds some interesting light on the manipulation protocol. For instance, electrical and thermal stimulation numerical pain
ratings tended to increase in the tilt condition, regardless of the tilt direction. Females, in particular, provided significantly higher numerical pain ratings for the electrical stimulation in the tilt condition. All participants provided higher numerical pain ratings for the thermal stimulation upon tilting. It is certainly plausible that the tilt conditions were not psychologically equivalent to the supine position, and therefore the tilting in and of itself had a confounding influence on the numerical pain reports.

In the D’Antono et al. (2000) study, participants were asked to indicate their preferred position (i.e., supine versus legs elevated) after the experiment; the majority reported that they preferred lying with their legs flat. The fact that most subjects found lying with their legs elevated to be less comfortable led D’Antono et al. (2000) to conclude that this may have dampened the pain-reducing qualities of cardiopulmonary baroreflex stimulation. With regard to the present study, it is possible that the numerical pain ratings reported in both tilt conditions were higher compared to baseline as a result of the distress associated with the tilting experience. Future studies that utilize a tilt table to manipulate the cardiopulmonary baroreceptors may wish to employ a design in which the participants are first acclimatized to the tilting procedure. An acclimatization procedure would hypothetically remove the novelty or aversive quality of the tilting, thus allowing researchers to obtain pain ratings that are less contaminated. Another option would be to utilize milder tilt angles, which potentially could reduce both participant distress as well as the tendency to activate the arterial baroreflex.

Of additional interest, while MPQ scores similarly did not confirm our hypotheses, they also did not mirror the pattern of responding observed for the numerical
pain ratings. Rather, MPQ scores appeared to decrease over time in response to both electrical and thermal stimulation. While the numerical pain ratings reflected distress during the tilt condition, the retrospective MPQ scores suggested that participants were acclimating to the noxious stimuli over time.

In trying to determine which pain ratings (concurrent versus retrospective) most accurately reflect the pain experience as a result of the baroreflex manipulation, it is important to recognize their inherent differences. For instance, MPQ scores, given their retrospective nature, are less likely to be influenced by affect and/or anxiety than concurrent numerical pain ratings. Whereas the concurrent numerical pain ratings are thread together with anticipatory anxiety (i.e. the participant is continually preparing to receive, and perhaps worry about, future stimulations of unknown intensities), the retrospective MPQ scores may reflect the participant’s sense of relief. Interestingly, previous research suggests that individuals at increased risk for hypertension not only demonstrate decreased perception of pain, but they also exhibit attenuated affective reactions (Wilkinson & France, 2009). This would imply that the strongest Group x SBP effect in the present study would be found when looking at affective responses to pain. Consequently, concurrent numerical pain ratings, which capture the affective response to pain, may be best-suited (versus the retrospective MPQ scores) for examining the results of the present study.

However, since it is still not clear as to why and/or how differences in pain perception occur between those at risk and not at risk for hypertension, it is important for future studies to continue to assess both concurrent and retrospective pain ratings. For
instance, with both types of ratings available, researchers would be able to examine whether differences existed only in the affective-laden ratings or only in those ratings where anxiety had been reduced. Together, the results of both concurrent and retrospective pain ratings would provide the most comprehensive insight into this phenomenon than either rating alone.

*Cardiopulmonary Baroreflex Effects in those at Increased Risk for Hypertension*

Finally, it was expected that cardiopulmonary baroreflex effects would be enhanced in those at increased risk for hypertension. Given that our initial hypotheses on the effects of cardiopulmonary stimulation and inhibition were not upheld, the expectation that these effects would be enhanced in those at increased risk for hypertension was somewhat moot. However, the findings did underscore a potential gender distinction, which will be important for future investigators to expand upon given the limited research in this area on females to date. In particular, females with a parental history of hypertension and elevated resting SBP levels experienced a greater increase in thermal stimulation numerical pain ratings than those without risk for hypertension following cardiopulmonary baroreflex inhibition (head-up tilt). Although consistent with our hypothesis, this finding was restricted to a sample of 18 females. The only other study in this area to enroll female participants to date (McIntyre et al., 2008) did not provide results that were differentiated by sex.

*Limitations*

Despite addressing several of the limitations present in previous studies (i.e., small sample sizes, lack of female participants, limited procedures for manipulating the
cardiopulmonary baroreceptors), certain limitations inherent in the present study must be acknowledged. Perhaps the limitation of primary importance involves the means by which the cardiopulmonary baroreceptors were manipulated in the present study. Specifically, the present study did not have a direct manipulation check of cardiopulmonary baroreceptor stimulation/inhibition (i.e. stimulation of cardiopulmonary baroreceptors was not documented with forearm blood flow). However, previous studies have assessed cardiovascular activity alone as a way in which to validate their postural manipulations (Ditto et al., 2009; McIntyre et al., 2008; Ring et al., 2007).

Unfortunately, in the present study, a similar manipulation check found that cardiovascular activity differed among the manipulation conditions, indicating an arterial baroreceptor influence. Granted, those studies that have not used direct manipulation checks in the past have been limited to producing only relatively specific stimulation of cardiopulmonary as opposed to arterial baroreceptors. The present study makes obvious the potential contributing role of the arterial baroreceptors under postural manipulation and substantiates the difficulty inherent in stimulating the cardiopulmonary baroreceptors with the same degree of precision as arterial baroreceptors. Consequently, results of the present study cannot speak specifically to any isolative effect that the cardiopulmonary baroreceptors may have on decreased pain perception in individuals at increased risk for hypertension. In fact, even when the cardiopulmonary baroreceptors are limited to a contributory role given the presence of stimulated arterial baroreceptors, the current findings would appear to suggest that baroreflex manipulation via tilting has little, if any, influence on electrical and/or thermal pain. Rather, the tilting conditions appeared to
cause enough distress (e.g., increased concurrent pain ratings in both head-up and head-down tilt conditions) that any pain-dampening effects of baroreceptor stimulation that may have been detected were negated.

Specific Recommendations for Future Studies

Given the findings and limitations of the present study, as well as the limited and mixed findings from the previous literature, continued investigation into the role of cardiopulmonary baroreceptors in pain seems warranted. Recommendations for future research include: (1) examining the effects of other types of cardiopulmonary baroreflex stimulation, including lower body negative pressure and plasma volume expansion, upon pain, (2) implementing an acclimatization procedure for cardiopulmonary baroreflex manipulation procedures that may seem novel and/or averse, (3) utilizing direct manipulation checks, such as forearm blood flow, to document appropriate manipulation of the cardiopulmonary baroreceptors, (4) assessing the effects of different levels of cardiopulmonary baroreceptor stimulation on pain given the possibility that the nature of the effect depends on the intensity of the stimulation, (5) enrolling female participants in studies in order to improve generalizability of findings to women, (6) investigating the effects of cardiopulmonary baroreceptor stimulation on pain associated with different types of noxious stimuli, and (7) administering both concurrent and retrospective pain measures. With additional investigation into this phenomenon based upon the above recommendations, it is hopeful that a clearer picture will be unveiled regarding the hypertensive process and its association with altered pain sensitivity.
Conclusions/Clinical Implications

The research regarding cardiopulmonary baroreflex stimulation and its role in decreased pain sensitivity has been varied; so much so that findings thus far have suggested that cardiopulmonary baroreceptors may have hyperalgesic, hypoalgesic, and/or no effects in humans. While the findings of the present study provide additional confirmation that the hypertensive process is associated with decreased pain perception, they did not support the notion that cardiopulmonary baroreflex stimulation is the mechanism responsible for this association. Rather, the current findings lend credibility to the notion that baroreflex stimulation is not invariably involved in hypertensive hypoalgesia, and this phenomenon is likely the result of multiple overlapping systems. For instance, it has been suggested that endogenous opioid and descending pain modulation mechanisms may also play a role in hypertensive hypoalgesia (France, 1999). Most likely, a complex physiological interaction between all of these mechanisms is responsible for decreased pain perception in individuals at risk for hypertension.

Despite the null findings associated with the present study, the impetus to uncover the mechanism(s) responsible for this phenomenon continues to prevail given the significant clinical implications associated with hypertension-associated hypoalgesia. For instance, research has revealed a number of clinically relevant consequences associated with a decreased perception of pain in individuals with hypertension. Specifically, research has examined the way in which this relationship may play a role in silent myocardial ischemia, unrecognized myocardial infarction, undiagnosed hypertension, and non-adherence to hypertension treatment recommendations (Asmar et al., 1996; Ditto,

Given the argument that hypoalgesia and hypertension are correlated phenomena that may share a common pathophysiology, continued investigation into the apparent overlap of pain and cardiovascular regulatory mechanisms may lead to useful insights into the development of problems such as hypertension and silent ischemia, as well as innovative pharmacological and behavioral treatment approaches (France & Ditto, 2000). With additional information about the processes involved in the development of hypertension, practitioners may be able to target specific patients for closer blood pressure monitoring as well as possible dietary and lifestyle modifications (France & Ditto, 2000). Ultimately, given that a reduced sensitivity to painful stimuli may reflect pathophysiological processes that are associated with the development of hypertension, a continued examination of such processes could yield promising findings relevant to future clinical and treatment implications.
References


Appendix A

Exploratory Analyses for the Hydration Data
To date, only one study (Ring et al., 2007) has examined the relationship between hydration status and experimental pain in human participants. In particular, Ring et al. (2007) found that blood volume enhancement via fluid loading increased participants’ ratings of venipuncture and intravenous catheterization pain in 24 healthy undergraduate men. Participants were asked to either augment their normal fluid intake (to increase blood volume and activate the cardiopulmonary baroreceptors) or restrict their fluid intake (to decrease blood volume and unload the receptors) prior to having a needle and catheter inserted while lying supine. Following catheterization, participants used the short form McGill Pain Questionnaire to rate the pain experienced during the insertion of the needle and catheter. The hydration manipulation had the expected physiological effects, increasing both blood volume and total body water (as determined using a Bioelectrical Body Composition Analyzer); total body water was higher in the hypervolemic condition ($M = 46.9$, $SD = 4.3$) versus the euvoletic condition ($M = 46.6$, $SD = 4.5$), and approached significance, $F = 3.71$, $p < .10$, $\eta^2 = .14$. Contrary to the expectation that stimulation of the cardiopulmonary baroreceptors would result in decreased pain, participants in the hypervolemic condition reported experiencing more pain ($p < .05$; Ring et al., 2007).

In order to examine this potential relationship in the present study, a series of correlations were conducted between total body water measures and each of the thermal and electrical stimulation pain ratings/thresholds. In addition, because gender differences in body weight may influence total body water estimates, a weight-adjusted estimate of total body water was used to examine these correlations. As can be seen in Table 1, there
Table 1

Correlations Among Weight-Adjusted Total Body Water (TBW/Wt), Pain Thresholds, Average Pain Ratings, and Average MPQ Scores

<table>
<thead>
<tr>
<th>Pain Variables</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrical Stimulation Pain Threshold</td>
<td>.15</td>
<td>.08</td>
</tr>
<tr>
<td>Average Electrical Stimulation Pain Ratings</td>
<td>.13</td>
<td>.13</td>
</tr>
<tr>
<td>Average Electrical Stimulation MPQ Scores</td>
<td>.07</td>
<td>.42</td>
</tr>
<tr>
<td>Thermal Stimulation Pain Threshold</td>
<td>.07</td>
<td>.40</td>
</tr>
<tr>
<td>Average Thermal Stimulation Pain Ratings</td>
<td>.13</td>
<td>.12</td>
</tr>
<tr>
<td>Average Thermal Stimulation MPQ Scores</td>
<td>-.03</td>
<td>.69</td>
</tr>
</tbody>
</table>

Note: TBW/Wt = total body water/weight (percentage)
were no significant relationships observed between any of the pain measures and weight-adjusted total body water (TBW/Wt). Similar exploratory analyses were conducted with intracellular and extracellular water concentrations, but none of these correlations ($r = -0.23$ to $0.22$) achieved statistical significance after correcting for multiple comparisons.
Appendix B

Measures and Forms Used in the Current Study
Human Participants Informed Consent Form

Title of Research: Responses to Electrical and Thermal Stimulation During Head-Up and Head-Down Tilt-Table Testing

Principal Investigator: Erin Hockman, M.S., Dept. of Psychology, Ohio University

Federal and university regulations require signed consent for participation in research involving human subjects. After reading the statements below, please indicate your consent by signing this form.

Explanation of Study

Purpose of the research

The purpose of this study is to examine physiological and psychological responses to noxious stimuli (brief electrical shock and thermal stimulation), and to evaluate individual differences in pain perception at rest and during head-up and head-down tilt. If you agree to be in this study, you will be asked to complete two laboratory sessions (the first session lasting no more than two hours and the second session lasting no more than one hour). You will receive two research credits for the first session and one research credit for the second session.

Procedures to be followed

Session 1: In this session you will review the informed consent form and ask any questions which you may have about the study. If you decide to participate, we will ensure that you meet all the study requirements. Major eligibility requirements for participation include (a) 18-30 years of age, (b) good physical health as indicated by the absence of chronic or acute illness, (c) no history of cardiac problems or syncope/fainting, and (d) biological parents available to confirm parental blood pressure history. At this session we will record contact information regarding your biological parents so that we can mail them a blood pressure questionnaire. Then stimulating devices will be attached to your right and left forearms. The device on your dominant forearm will be used to deliver brief electrical pulses, and the device on your dominant forearm will be used to deliver brief thermal stimulation. Next we will have you lie flat on a tilt-table and we will attach a blood pressure cuff to your middle dominant arm to monitor your heart rate and blood pressure. Another blood pressure monitor will be
attached to the middle finger of your nondominant arm to continuously monitor your heart rate and blood pressure.

At this point we will determine your pain thresholds for both electrical and thermal stimulation. After each stimulation you will be asked to rate the stimulation intensity using a scale with anchors of 0 (no sensation), 25 (uncomfortable), 50 (painful), 75 (very painful), and 100 (maximum tolerable). When determining your electrical pain threshold, we will ask you to receive a series of stimulations until you give a rating of 50 or greater. This will be repeated three times. Similarly, we will assess your thermal pain threshold by asking you to press a button when the thermal stimulation becomes “painful.” We will repeat this process three times as well. The intensity of electrical and thermal stimulation will be increased slowly. At the upper range of stimulation intensities you may experience discomfort or pain for each stimulation. However, the stimulation is extremely brief and leaves no residual discomfort. If you find the stimulation to be too uncomfortable, you can discontinue at any time simply by asking the experimenter to stop.

After your electrical and thermal pain thresholds are determined, the tilt-table procedure will begin. It will include three blocks that are approximately 3 minutes each in length. In the first and third block you will remain horizontal. In the second block you will be tilted either 24 degrees head-up or 14 degrees head-down. During each 3-minute block you will receive 8 stimulations (1 every 20 ±5 seconds) and will rate each stimulation on the 0-100 scale. The stimulations will alternate between electrical and thermal. You will also fill out a brief questionnaire following each block.

After the tilt-table procedure, we will ask you to remain supine on the tilt table while we measure your hydration status for 5 minutes using a bioelectrical impedance monitor. All bioelectrical impedance measurements will be obtained non-invasively using electrodes attached to the skin.

Session 2: You will sit quietly for 30 minutes while a blood pressure reading is taken from your left arm at 5-minute intervals. During this time you will also be asked to fill out 4 brief questionnaires.

**Duration of subject's participation**

The first session will last no more than 2 hours; the second session will last no more than 1 hour. You may choose to discontinue the study at any time without penalty.
Identification of specific procedures that are experimental

The procedures in use in this project are well studied and have been used extensively in prior research.

Risks and Discomforts

The electrical and thermal stimulations are likely to elicit temporary increases in heart rate and blood pressure as well as sensations of discomfort or pain. Further, to apply the electrode for electrical stimulation, it is necessary to slightly abrade the skin using a commonly used application gel. Like an exfoliation cream, it takes off the dead skin. In some cases, you might experience redness of the skin in the days following the experiment; however, this redness should go away by itself. If you experience anything more than mild redness or irritation, please contact the experimenter. A potential short-term side effect of tilting can be lightheadedness, low blood pressure, and under rare circumstances loss of consciousness. You may discontinue the procedure at any time for any reason.

Benefits

The main benefit to you is the opportunity to increase your knowledge and understanding of psychological research methods. In addition, you will receive information regarding your heart rate, blood pressure, and hydration status.

The wider societal benefit is the opportunity to extend previous findings obtained in this laboratory regarding potential differences in pain sensitivity in individuals with and without a genetic risk for hypertension. This information is important in that there may be overlap between the mechanisms responsible for decreased pain sensitivity and risk for blood pressure elevation in at-risk populations. This study will provide a test of the potential role of the cardiopulmonary baroreflex as a mechanism for this reduced pain sensitivity.

Confidentiality and Records

All information obtained from you will be kept strictly confidential. This information will be identified according to a code number known only to those directly involved with this research project. The key that relates your name to the code number will be destroyed (leaving only code numbers) at the conclusion of the study. Further, any information collected from you will be stored in a locked filing cabinet available only to the research personnel. In the event of publication of the research findings, data from this study will be reported only as an aggregate and therefore no individually identifying information will be published.
**Compensation**
You will receive 2 research credits for participation in the first session and 1 research credit for participation in the second session, for a total of 3 credits.

**Contact Information**
If you have any questions regarding this study, please contact Erin Hockman, M.S. at (216) 316-1903 or via email at eh248002@ohio.edu. You may also contact the supervisor of the study, Christopher France, Ph.D., at (740) 593-1079 or via email at france@ohio.edu.

If you have any questions regarding your rights as a research participant, please contact Jo Ellen Sherow, Director of Research Compliance, Ohio University, (740) 593-0664.

______________________________

I certify that I have read and understand this consent form and agree to participate as a subject in the research described. I agree that known risks to me have been explained to my satisfaction and I understand that no compensation is available from Ohio University and its employees for any injury resulting from my participation in this research. I certify that I am 18 years of age or older. My participation in this research is given voluntarily. I understand that I may discontinue participation at any time without penalty or loss of any benefits to which I may otherwise be entitled. I certify that I have been given a copy of this consent form to take with me.

Signature__________________________________________Date__________________

Printed Name__________________________________________
Session One Questionnaire

First Name: _________________________  Last Name: _______________________

Local Phone Number: ________________________

Age: _____  Sex: Male / Female

Race: _____ American Indian or Alaskan native
_____ Asian
_____ Native Hawaiian or Other Pacific Islander
_____ Black or African American
_____ White

Ethnicity: _____ Hispanic or Latino
_____ Not Hispanic or Latino

Do you have *any* significant health problem(s)?
YES NO
If yes, please describe ____________________________________

Have you ever been diagnosed with low blood pressure or syncope (fainting)?
YES NO
If yes, please describe: ____________________________________

Are you currently taking *any* prescription or non-prescription medication?
YES NO
If yes, please describe: ____________________________________

Have you consumed any caffeine or alcohol today?
YES NO
If yes, please describe: _________________________________

Have you had any nicotine (e.g., smoking, chewing tobacco, etc.) today?
YES NO
If yes, please describe: _________________________________

Have you engaged in any vigorous exercise today?
YES NO
If yes, please describe: _________________________________

**PARENTAL HEALTH HISTORY**

1. Was your biological FATHER ever told by his doctor that he:
   a) had high blood pressure? yes no don't know
   b) should take blood pressure medication? yes no don't know

2. Was your biological MOTHER ever told by her doctor that she:
   a) had high blood pressure? yes no don't know
   b) should take blood pressure medication? yes no don't know

So that we may contact your parents to ask about their blood pressure history, please fill in your parents' address(es) below. We will send them a one-page questionnaire that asks about their blood pressure history. We do not reveal any of your personal health information to your parents.

<table>
<thead>
<tr>
<th>Father’s Name</th>
<th>Mother’s Name</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>City</th>
<th>State</th>
<th>ZIP</th>
<th>City</th>
<th>State</th>
<th>ZIP</th>
</tr>
</thead>
</table>
Session Two Questionnaire

First Name: _________________________  Last Name: _______________________

Do you have *any* significant health problem(s)?  YES  NO
If yes, please describe: ________________________________________________

Have you ever been diagnosed with low blood pressure or syncope (fainting)?  YES  NO
If yes, please describe: ________________________________________________

Are you currently taking *any* prescription or non-prescription medication?  YES  NO
If yes, please describe: ________________________________________________

Have you consumed any caffeine or alcohol today?  YES  NO
If yes, please describe: ________________________________________________

Have you had any nicotine (e.g., smoking, chewing tobacco, etc.) today?  YES  NO
If yes, please describe: ________________________________________________

Have you engaged in any vigorous exercise today?  YES  NO
If yes, please describe: ________________________________________________
Parent Letter and Blood Pressure History Surveys

Date

XXXXX
XXXXX
XXXXX

Dear XXXXX,

Your (daughter or son), has participated in our study concerning individual differences in stimulation responses in healthy young adults with and without a family history of high blood pressure. This study has been approved by Ohio University’s Institutional Review Board. The goal of our research is to learn more about potential mechanisms in the development of hypertension (high blood pressure). Since our main focus is family blood pressure history, we must contact the parents of all participants to request additional information to complete the study.

Your help in completing our investigation would be greatly appreciated. We ask that you take a few minutes to complete the attached questionnaire and return it in the enclosed postage-paid envelope. All responses to the questionnaire remain strictly confidential. To help ensure confidentiality, each questionnaire is identified with a numerical code only. This number is used to combine your responses with the information provided by your child. The key that relates your name to the code number will be destroyed (leaving only code numbers) at the conclusion of the study. Further, any information collected from you will be stored in a locked filing cabinet available only to the research personnel. In the event of publication of the research findings, data from this study will be reported only as an aggregate and therefore no individually identifying information will be published.

By completing the enclosed questionnaire it is understood that you are consenting to the use of this information in our research project. You are, of course, under no obligation to complete this questionnaire. Further, if your child attends Ohio University, his/her grades are in no way related to this decision.

I would like to thank you for your kind attention to this letter. If you require further information, please do not hesitate to email (eh248002@ohio.edu) or telephone (216-316-1903). My supervisor, Chris France, Ph.D., is also available to contact by email (france@ohio.edu) or telephone (740-593-1079).

Sincerely,

Erin Hockman, M.S.
Graduate Student
Clinical Health Psychology
Because this study is concerned with the effects of a genetic history of hypertension (high blood pressure), this form should be completed by the biological father only.

<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. What is your age?</td>
<td>_______</td>
</tr>
<tr>
<td>2. How long has it been since you last had your blood pressure checked by your doctor?</td>
<td>___ 0 to 6 months ___ 6 to 12 months ___ 1 to 5 years ___ more than 5 years ___ never</td>
</tr>
<tr>
<td>3. If you know, what is your typical blood pressure now?</td>
<td>_____</td>
</tr>
<tr>
<td>systolic</td>
<td>diastolic</td>
</tr>
<tr>
<td>4. Have you ever been told by a doctor that you had hypertension (high blood pressure)?</td>
<td>Yes No Don't Know</td>
</tr>
<tr>
<td>If yes, how old were you when you received this diagnosis?</td>
<td>_______</td>
</tr>
<tr>
<td>5. Has a doctor ever prescribed medication for you to treat hypertension (high blood pressure)?</td>
<td>Yes No Don't Know</td>
</tr>
<tr>
<td>If yes, please list the medication(s):</td>
<td>__________</td>
</tr>
<tr>
<td>6. Do you suffer from diabetes or kidney disease?</td>
<td>Yes No Don't Know</td>
</tr>
<tr>
<td>If yes, please describe:</td>
<td>__________</td>
</tr>
<tr>
<td>7. Do you suffer from any other significant health problems?</td>
<td>Yes No Don't Know</td>
</tr>
<tr>
<td>If yes, please describe:</td>
<td>__________</td>
</tr>
<tr>
<td>8. From the list below, please circle any of your biological relatives who were told by a doctor that they had hypertension (high blood pressure) before age 55:</td>
<td>Your Mother Your Father Your Sister(s) Your Brother(s)</td>
</tr>
</tbody>
</table>
**MOTHER’S FORM**

Because this study is concerned with the effects of a genetic history of hypertension (high blood pressure), this form should be completed by the biological mother only.

1. What is your age? _______

2. How long has it been since you last had your blood pressure checked by your doctor?
   - ___ 0 to 6 months
   - ___ 6 to 12 months
   - ___ 1 to 5 years
   - ___ more than 5 years
   - ___ never

3. If you know, what is your typical blood pressure now? ______ _______
   systolic     diastolic

4. Have you *ever* been told by a doctor that you had hypertension (high blood pressure)?
   Yes  No  Don't Know
   If yes, how old were you when you received this diagnosis? ______
   If yes, was your high blood pressure related to pregnancy? ______

5. Has a doctor *ever* prescribed medication for you to treat hypertension (high blood pressure)?
   Yes  No  Don't Know
   If yes, please list the medication(s):
   __________________________________________

6. Do you suffer from diabetes or kidney disease?  Yes  No  Don't Know
   If yes, please describe:
   __________________________________________

7. Do you suffer from any other significant health problems?  Yes  No  Don't Know
   If yes, please describe:
   __________________________________________

8. From the list below, please circle any of your biological relatives who were told by a doctor that they had hypertension (high blood pressure) before age 55:
   - Your Mother
   - Your Father
   - Your Sister(s)
   - Your Brother(s)
100

McGill Pain Questionnaire – Short-Form (MPQ-SF): Response to Electrical Stimulation

1) Make a mark along the line that corresponds to the pain you experienced from the last 4 electrical stimulations you received:

No pain | Worst possible pain

2) Which word best describes the pain you experienced from the last 4 electrical stimulations you received (choose one)?

______ No pain
______ Mild
______ Discomforting
______ Distressing
______ Horrible
______ Excruciating

3) Indicate the degree to which each of the 15 words applies to the pain you experienced from the last 4 electrical stimulations you received:

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>THROBBING</td>
<td>①</td>
<td>②</td>
<td>③</td>
</tr>
<tr>
<td>2.</td>
<td>SHOOTING</td>
<td>①</td>
<td>②</td>
<td>③</td>
</tr>
<tr>
<td>3.</td>
<td>STABBING</td>
<td>①</td>
<td>②</td>
<td>③</td>
</tr>
<tr>
<td>4.</td>
<td>SHARP</td>
<td>①</td>
<td>②</td>
<td>③</td>
</tr>
<tr>
<td>5.</td>
<td>CRAMPING</td>
<td>①</td>
<td>②</td>
<td>③</td>
</tr>
<tr>
<td>6.</td>
<td>GNAWING</td>
<td>①</td>
<td>②</td>
<td>③</td>
</tr>
<tr>
<td>7.</td>
<td>HOT-BURNING</td>
<td>①</td>
<td>②</td>
<td>③</td>
</tr>
<tr>
<td>8.</td>
<td>ACHING</td>
<td>①</td>
<td>②</td>
<td>③</td>
</tr>
<tr>
<td>9.</td>
<td>HEAVY</td>
<td>①</td>
<td>②</td>
<td>③</td>
</tr>
<tr>
<td>10.</td>
<td>TENDER</td>
<td>①</td>
<td>②</td>
<td>③</td>
</tr>
<tr>
<td>11.</td>
<td>SPLITTING</td>
<td>①</td>
<td>②</td>
<td>③</td>
</tr>
<tr>
<td>12.</td>
<td>TIRING-EXHAUSTING</td>
<td>①</td>
<td>②</td>
<td>③</td>
</tr>
<tr>
<td>13.</td>
<td>SICKENING</td>
<td>①</td>
<td>②</td>
<td>③</td>
</tr>
<tr>
<td>14.</td>
<td>FEARFUL</td>
<td>①</td>
<td>②</td>
<td>③</td>
</tr>
<tr>
<td>15.</td>
<td>PUNISHING-CRUEL</td>
<td>①</td>
<td>②</td>
<td>③</td>
</tr>
</tbody>
</table>
McGill Pain Questionnaire – Short-Form (MPQ-SF): Response to Thermal Stimulation

1) Make a mark along the line that corresponds to the pain you experienced from the last 4 thermal stimulations you received:

No pain  [ ]  Worst possible pain

2) Which word best describes the pain you experienced from the last 4 thermal stimulations you received (choose one)?

[ ] No pain
[ ] Mild
[ ] Discomforting
[ ] Distressing
[ ] Horrible
[ ] Excruciating

3) Indicate the degree to which each of the 15 words applies to the pain you experienced from the last 4 thermal stimulations you received:

<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. THROBBING</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. SHOOTING</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3. STABBING</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4. SHARP</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5. CRAMPING</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6. GNAWING</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7. HOT-BURNING</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>8. ACHING</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>9. HEAVY</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>10. TENDER</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>11. SPLITTING</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>12. TIRING-EXHAUSTING</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>13. SICKENING</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>14. FEARFUL</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>15. PUNISHING-CRUEL</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
Debriefing Form

Title of Research: Responses to Electrical and Thermal Stimulation During Head-Up and Head-Down Tilt-Table Testing

Principal Investigator: Erin Hockman, M.S., Dept. of Psychology, Ohio University

Thank you for participating in this study!

The objective of this study is to assess the effects of manipulating the cardiopulmonary baroreflex (by head-up and head-down tilt) on response to noxious (painful) stimuli in individuals at varying degrees of risk for hypertension. We determine risk for hypertension on the basis of parental history of the disorder and resting systolic blood pressure.

Previous studies have demonstrated that people with high blood pressure are less sensitive to pain. Further, these studies suggest that there may be some overlap between the mechanisms responsible for decreased pain sensitivity and elevated blood pressure. Therefore, we are investigating potential differences in pain sensitivity in at-risk populations (e.g., individuals with and without a family history of hypertension, individuals with and without elevated resting blood pressure) under different conditions of baroreflex manipulation.

Based on previous research conducted at Ohio University as well as other laboratories, we expect that, as a group, individuals at risk for hypertension will show decreased pain sensitivity. We also expect that pain sensitivity will be reduced during the head-down tilt due to increased activation of the cardiopulmonary baroreflex.

You may wish to ask the experimenter to give you a summary of your physiological responses during the study. Feel free to ask any questions you might have.

If you wish to contact the principal investigator for any reason, Erin Hockman can be reached at (216) 316-1903 or via email (eh248002@ohio.edu). If you wish to contact her supervisor, Dr. Christopher France can be reached at (740) 593-1079 or via email (france@ohio.edu).