EFFECTS OF ISOMETRIC EXERCISE ON THE RELATIONSHIP BETWEEN MUSCLE PAIN AND RESTING BLOOD PRESSURE AND RESTING HEART RATE

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Master of Arts

By

Sarah K. Mobley

Dr. Pamela Hinton, Thesis Supervisor

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The undersigned, appointed by the Dean of the Graduate School,
Have examined the Thesis entitled

EFFECTS OF ISOMETRIC EXERCISE ON THE RELATIONSHIP BETWEEN MUSCLE PAIN AND RESTING BLOOD PRESSURE AND RESTING HEART RATE

Presented by Sarah K. Mobley

A candidate for the degree of Master of Arts

And hereby certify that in their opinion is worthy of acceptance.

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Professor Pamela Hinton

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Professor Erin Dannecker

_____

Professor John Thyfault

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Figure Page

INTRODUCTION

Over the past 20 years, a number of studies have examined whether analgesia occurs after exercise. These studies generally found that exercise can diminish the amount of pain perceived. This phenomenon is known as hypoalgesia. It is currently unclear how exercise alters the pain response, but research indicates there is an interaction between the pain-modulatory and cardiovascular systems (20, 22, 59). It has been reported that there is an inverse relationship between blood pressure (BP) and pain perception (5, 37). Furthermore, there is evidence to suggest that the negative association between BP and pain is not just a phenomenon observed in hypertensive individuals, but represents a continuous association that extends into normotensive individuals (9, 18, 19). A number of studies have examined the relationship between pain and BP, but very few have examined this relationship using resistance exercise to induce muscle pain.

Why is the Relationship between Pain and Cardiovascular Responses Important?

Silent myocardial ischemia is a common phenomenon in patients with coronary heart disease (CHD). Patients who do not feel pain during ischemia may delay or avoid seeking medical attention, and are at increased risk of cardiac morbidity and mortality. It has been estimated that 80% of ischemic episodes in patients with coronary artery disease are asymptomatic (13, 17). Based on routine electrocardiograms, 45% of women and 35% of men with hypertension were shown to have experienced a heart attack but could not recall any symptoms (i.e., angina) (33). This may be related to findings that high BP is associated with suppression of chest pain during episodes of myocardial ischemia. Such an effect has been observed during clinical exercise testing, as individuals with elevated resting systolic BP show a delayed onset of angina during episodes of exercise-

induced myocardial ischemia (42). Therefore, examining the relationship between pain and cardiovascular responses during and following resistance exercise may provide insight in the phenomenon of silent ischemia.

Effect of Isometric Exercise on Cardiovascular and Pain Regulatory Systems

During static exercise, heart rate (HR) and blood pressure (BP) increase more than during dynamic exercise performed at the same relative intensity (72). The sizeable increases in BP and HR during and immediately following isometric exercise make it a practical mode for examining the relationship between cardiovascular function and exercise-induced muscle pain immediately following exercise.

Cardiovascular and Exercise-Induced Muscle Pain Responses to Isometric Exercise

Ray and Carter (61) examined if exercise-induced muscle pain is modulated by the central mechanisms that affect cardiovascular control during exercise. Twenty-four subjects participated in isometric handgrip exercise at 30% of maximal voluntary contraction to fatigue, followed by two minutes of post-exercise muscle ischemia. Forearm muscle pain, blood pressure and HR were measured continuously during the isometric handgrip exercise and post-exercise muscle ischemia. Muscle pain ratings, mean arterial pressure and HR all increased significantly during the isometric handgrip exercise. The increases in muscle pain were not significantly correlated with the increases seen in systolic BP.

Cardiovascular and Exercise-Induced Analgesia Responses to Isometric Exercise

Many of the studies that have examined the relationship between pain and BP/HR have induced pain in healthy participants using stimuli, such as a pressure algometer or cycling (32, 66), before and after resistance exercise. These studies actually focused on

the pain from a different stimulus (e.g., pressure algometer) than resistance exercise. Ring et al (63) conducted a study in which subjects performed isometric handgrip exercise at 1%, 15% and 25% of maximal voluntary contraction (MVC) Pain was induced by electrocutaneous stimulation of the sural nerve during performance of the isometric contractions until a NFR (nociceptive flexion reflex) threshold was reached. The NRF (or pain) ratings were averaged for analyses. Blood pressure was assessed pre-exercise, during exercise, and post-exercise. Overall pain intensity ratings were significantly lower during 25% MVC compared with 1% and 15% MVC. Systolic and diastolic BP significantly increased during the 25% MVC trial. The results from the ANCOVA analyses indicated that diastolic BP fully accounted for, and systolic BP partially accounted for, the effects of exercise on pain. These results demonstrate that a relationship may exist between exercise-induced analgesia and cardiovascular response.

In 2000, Koltyn et al (37) completed a study in which subjects completed isometric exercise using a handgrip for two minutes. Pain thresholds and pain ratings were measured only during the pressure stimulus, which was applied to the forefinger for two minutes before and after isometric exercise. The average of the pain ratings was determined and used in the analyses. Blood pressure (systolic and diastolic) and HR were measured at rest before isometric exercise and during the pressure stimulus. Resting diastolic BP was positively and significantly correlated with pain thresholds during the pressure stimulus. In addition, there was a negative correlation between pain ratings and systolic BP during the pressure stimulus, which immediately followed the isometric exercise. However, the correlation was statistically significant only in the male participants.

In contrast to Koltyn et al (37), Umeda et al (72) conducted a study, sampling only women, in which subjects completed two exercise bouts at 25% maximum voluntary contraction for one minute and three minutes. A pressure stimulus was applied to the forefinger immediately following each isometric bout. Pain thresholds and pain ratings were measured only during the pressure stimulus. Blood pressure (systolic and diastolic) and HR were measured before isometric exercise and during the pressure stimulus. Blood pressure and HR increased significantly following the isometric exercise compared to baseline values. Pain thresholds tended to increase following isometric exercise during the pain stimulus. However, the effect size was relatively small. The results also indicated that the correlations between resting systolic or diastolic BP and pain threshold were not significant. Similar results were demonstrated in a study done by Kadetoff and Kosek (32). However, correlations between cardiovascular measures and pain were not analyzed.

Effect of Eccentric Exercise on Cardiovascular and Pain Regulatory Systems

Few investigations have examined the relationship between cardiorespiratory responses and eccentric exercise-induced muscle pain 48 hours post-exercise. Because the pain-inducing effect of eccentric exercise peaks at 48 hours post-eccentric exercise, resting BP/HR should be measured at baseline and 48 hours after eccentric exercise.

In a study executed by Gleeson et al (23), six healthy, untrained male subjects performed a cycle ergometer exercise test 48 hours following an eccentric or concentric exercise bout. Muscle pain was measured in each leg pre- and 48 hours-post eccentric/concentric exercise bout before the cycling test and during the cycle test. An average pain rating was calculated using the pain ratings from each leg. Heart rate was

measured during the cycle test only. Heart rate and muscle pain were significantly higher during the cycling test, 48 hours following eccentric exercise, as compared to concentric exercise. Correlations between muscle pain and HR were not analyzed. Hollander et al (30) found there to be a positive correlation between muscle pain and HR (BP was not examined). Increases in both muscle pain and HR were also found by Gleeson. However, muscle pain was assessed immediately following the eccentric exercise in the study done by Hollander.

Conversely, Bajaj et al (5) executed a study where young males performed eccentric exercise of the right hand. Mean arterial pressure (MAP), pain threshold and pain ratings were measured before, immediately following eccentric exercise, 24 and 48 hours post-eccentric exercise. Pain threshold and pain ratings were measured using a pressure stimulus applied to the finger. Pain ratings were measured twice a day (morning and evening) and the average of the maximal rating from the morning and evening times was used for analyses. The pain ratings measured 48 hours post-eccentric exercise indicated muscle soreness in the hand was significantly higher compared to before exercise. Mean arterial pressure (MAP) was significantly reduced at 48 hours compared to pre-exercise values. The results demonstrated that eccentric exercise caused increased muscle soreness in the exercising hand, which may relate to the reduced mean arterial pressure seen 48 hours post-eccentric exercise. This finding suggests that an inverse relationship between muscle pain and MAP may exist 48 hours post-eccentric exercise, but correlations between muscle pain and MAP were not analyzed.

Potential Physiological Mechanism Linking Pain and Cardiovascular Response

Potential Mechanisms Underlying the Relationship between BP/HR and Pain Immediately Following Isometric Exercise

Studies indicate that static exercise is associated with a reduction in pain (37, 61); however, the mechanism for this phenomenon is still unknown. It is currently unclear how exercise alters pain response, but research indicates there is an interaction between pain-modulatory and cardiovascular systems, more particularly BP and HR (20, 22, 59). Currently, there are several proposed mechanisms to explain the relationship between pain and BP/HR observed immediately following isometric exercise. These mechanisms include endogenous opioid mechanisms (6, 24, 65), noradrenergic mechanisms (28, 35, 42, 63), and activation of arterial baroreceptors (1, 2).

Mechanisms Underlying the Relationship between BP/HR and Pain Post-Eccentric Exercise

The potential physiological mechanisms that underlie the pain and cardiovascular responses to eccentric exercise involve systems that alter muscle pain over an extended period of time (4). These mechanisms are specific to eccentric exercise because eccentric exercise-induced pain, often referred to as delayed onset of muscle pain, peaks 48 hours following exercise due to the muscle damage that is created during eccentric exercise. The prolonged effects of eccentric exercise on muscle pain allow the relationship between exercise-induced pain and cardiovascular response to be examined at rest and 48 hours after eccentric exercise.

A potential mechanism underlying eccentric exercise-induced pain is exercise-induced inflammation. Muscle damage resulting from eccentric contractions attracts

several different types of white blood cells (11), which are present in the muscle from 24 hours to 14 days after stress-inducing exercise (6, 29, 48, 56). These cells contribute to the degradation of damaged muscle tissue by release of reactive oxygen species and pro-inflammatory cytokines (11). Inflammatory associated cytokines, such as interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), have been shown to be expressed within the skeletal muscle up to five days after eccentric exercise (21, 26). This local inflammatory response has been shown to increase systemic inflammation as well (21). Moreover, there is some experimental evidence that expression of cytokines and inflammation may be related to increased BP (41, 64).

Limitations of Past Studies

There are several limitations of the past studies. First, only a few studies have examined the pain and BP/HR response immediately following isometric exercise or 48 hours post eccentric exercise. Of these studies, only two have examined the correlation between exercise-induced analgesia and cardiovascular response. Also, many of the studies that have examined the relationship between pain and BP/HR have induced pain in healthy participants using stimuli, such as a pressure algometer or cycling (32, 66), before and after resistance exercise. Exercise-induced muscle pain was probably induced in these studies, but the studies actually focused on the pain from a stimulus (e.g., pressure algometer) other than resistance exercise. Therefore, the pain rating may have been in response to the pressure stimulus, not the exercise itself.

Lastly, the majority of studies that have examined the relationship between pain and cardiovascular response as a result of exercise-induced pain have used a small muscle group to perform contractions. Results from these studies may have demonstrated

a more robust change in BP and HR response if a larger muscle mass had been used. Research suggests that muscle mass may be an important determinant of the relationship between muscle pain and cardiovascular response (51, 65). Also, the responses seen with a larger muscle mass may parallel the responses seen with whole body activities, which would more closely mimic the muscle mass recruited during activities of daily living.

PURPOSE

The primary objective of this study was to examine the relationship between isometric exercise-induced muscle pain (difference between post- and pre-isometric muscle pain) and resting BP and HR. It was hypothesized that a higher resting BP and HR would be associated with a smaller increase in isometric exercise-induced muscle pain.

Four exploratory objectives related to the effects of eccentric exercise were also examined in this study. The exploratory objectives only examined the participants that completed the eccentric exercise, which was half of the total recruited population (n=16). The objectives are as follows:

1. To examine differences in the strength of the relationship between isometric exercise-induced muscle pain ratings (difference between post- and pre-isometric muscle pain) and resting BP and HR pre- and two days post-eccentric exercise. It was hypothesized that the relationship between isometric exercise-induced muscle pain and resting BP and HR would be significantly different two days post-eccentric exercise compared with pre-eccentric exercise.

2. To examine the change in resting BP, resting HR and salivary cortisol from pre- to two days post-eccentric exercise. It was hypothesized that resting BP, resting HR and salivary cortisol would be significantly increased two days post-eccentric exercise compared with pre-eccentric exercise levels.
3. To examine the differences in the strength of the relationship between non-exercising extension pain and resting BP and HR pre- and two days post-eccentric exercise. It was hypothesized that the relationship between non-exercising extension pain and resting BP and HR would be significantly different two days post-eccentric exercise compared with pre-eccentric exercise.
4. To examine if the change in resting salivary cortisol (difference between 2 days post- and pre-eccentric resting salivary cortisol) was significantly correlated to the change in non-exercising extension pain (difference between 2 days post- and pre-eccentric baseline muscle pain). It was hypothesized that the changes in salivary cortisol and non-exercising extension pain would be positively correlated.

METHODS

Participants

Thirty-four participants, ages 18-40 years were recruited for this cross-sectional study. All participants were screened prior to the session. Women were be required to have regular menstrual cycles and the eccentric exercise was performed within 4-10 days of the start of the most recent cycle. Participants had a BMI≤40 kg/m^2. Participants had

not participated in structured, regular upper body strengthening activity for the previous six months, were free from any arm, shoulder, or wrist injuries in the previous year, and were not currently possess any symptoms in arms, shoulders or wrists. All participants were clear of chronic medical conditions and medications that may effect pain perception. All participants were required to adhere to the following conditions prior to both sessions: no smoking (3 hrs), no caffeine (8 hrs), no alcohol (24 hrs), no dairy products (24 hrs), no pain relievers (48 hrs), must consume 17-20 oz of water at 2-3hr, 7-10 oz of water 10-20 min, eat within 5hr, but not 1 hr prior to each session, no illness (2 wk), no donating blood (2 wk), no piercings/tattoos (2 wk), no unusual physical activity (7 d), no illegal substance (7 d). All participants completed the Ohio Blood Pressure History Questionnaire (Page & France, 2001; al'Absi et al, 2005) and pre- and post-exercise muscle pain questionnaires prior to and post exercise.

Experimental Design

General Procedure

The participant completed two sessions. The first session served as a baseline session. Blood pressure, HR, cortisol and pain ratings were taken at the beginning of Session 1, prior to eccentric exercise. Tonic and phasic isometric muscle contraction tests were performed following all of the baseline measurements. Following the isometric muscle contraction tests, the participant performed three sets of 12 eccentric muscle contractions. Session 2 occurred two days following Session 1. The procedure for Session 2 paralleled Session 1, except no eccentric exercise was performed at the end of Session 2.

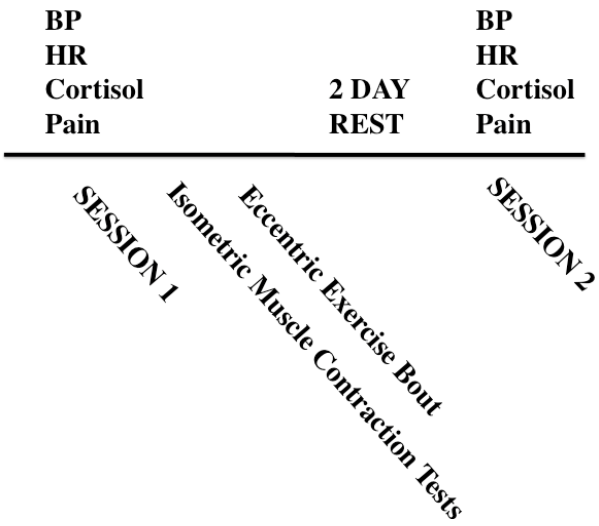


Figure 1. Overall study protocol. Timeline is not to scale. It is to show the sequence of events. BP, blood pressure; HR, heart rate.

Session 1 (baseline session)

All participants were required to read, sign and receive a copy of the informed consent and HIPAA forms. Each participant was screened at the beginning of the session (Figure 2) to ensure eligibility to participate based on the inclusion and exclusion criteria and session restrictions (see *Subjects* section). The participant was instructed on the use of the pain scale (based on the recommendations of Price and colleagues, 1994), which ranged from 0-100 (0=no pain, 100=most intense pain imaginable). Bilateral arm muscle pain at rest in a standardized position and during elbow flexion and extension movement through active range of motion was taken. The participant then completed the Ohio Blood Pressure questionnaire. After the questionnaire was completed, the subject performed a mouth rinse with water. Following the mouth rinse, the participant was moved to the Biodex machine and properly set up for upper-body testing, which took approximately 10-15 minutes. Then, a pre-eccentric exercise salivary cortisol collection was completed (ensuring ten minutes have passed since the mouth rinse), prior to any testing on the

Biodex machine. Pre-eccentric exercise blood pressure and heart rate measurements were also taken at this time. Following the pre-eccentric exercise saliva collection, blood pressure and heart rate measurements, the 3RM static strength test was performed. Following the static strength test, the isometric muscle contraction trials (tonic and phasic) were completed in random order.

The participant completed a pre-exercise, muscle-pain questionnaire at the cessation of the isometric contractions. Following completion of the pre-exercise questionnaire, the participant performed the 3RM eccentric strength test, which was used to generate a goal of 75% maximal strength at which the three sets of 12 eccentric exercises was performed. Overall ratings of pain and perceived exertion were collected for the strength test and each set of repetitions.

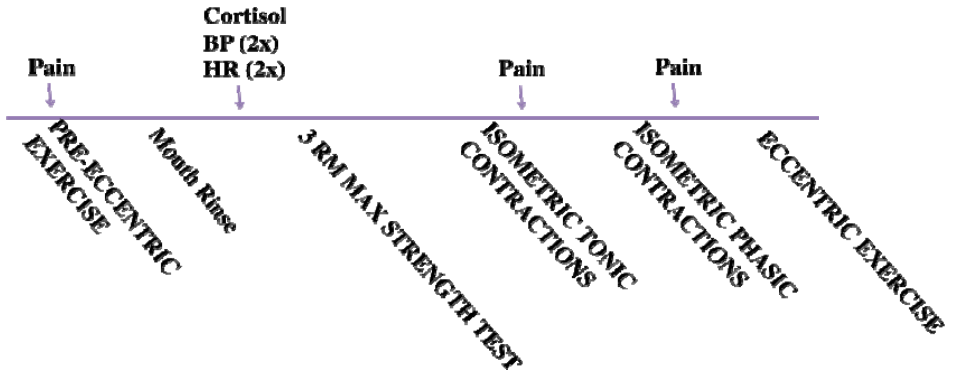


Figure 2. Session 1 (Baseline Session) Protocol. Timeline is not to scale. It is to show the sequence of events. Blood pressure, heart rate, and pain were all measured immediately following muscle contractions. Isometric tonic and phasic contractions were performed in a randomized order. BP, blood pressure; HR, heart rate.

Session 2

The second session (Figure 3) was conducted two days after Session 1. The participant was screened to ensure eligibility based on the same inclusion/exclusion

criteria as in Session 1. The participant completed a post-exercise muscle pain questionnaire. Bilateral arm muscle pain during rest, flexion and extension was obtained. The participant then completed a mouth rinse with water. Following the mouth rinse, the participant was moved to the Biodex machine and the muscle contraction trials, salivary cortisol, blood pressure and heart rate procedures were measured using the same protocol as described in *Session 1*.

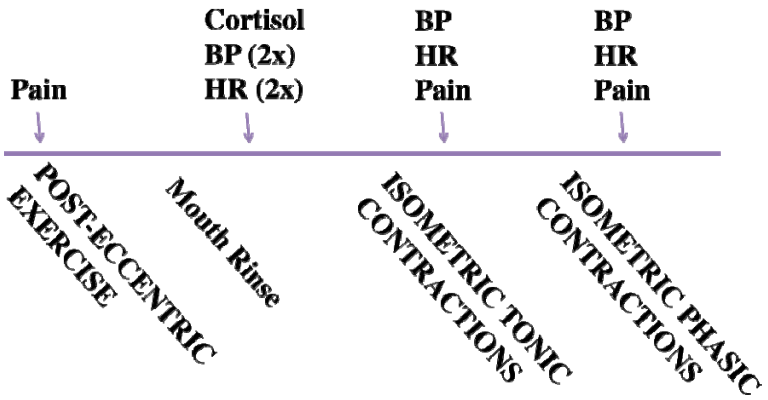


Figure 3. Session 2 Protocol. Timeline is not to scale. It is to show the sequence of events. Blood pressure, heart rate and pain were all measured immediately following muscle contractions. Isometric tonic and phasic contractions were performed in a randomized order. BP, blood pressure; HR, heart rate.

Exercise Protocols

Muscle Contraction Test Protocol

Static strength was measured by having the participant perform three maximal repetitions at both 45° and 90° of elbow flexion. The order of the static strength tests was randomized. The peak force at 45° of flexion was used as the basis for determining the goal lines, which was used as targets of intensity of the two subsequent tests: (1) two trials of 30s sustained contraction at a goal of 45% of peak force while positioned at 45° of flexion (tonic), and (2) two trials of ten contractions ramping up and down at a goal

from 26-40% of peak force for 30s while positioned at 45° of flexion (phasic). The tonic and phasic muscle contraction tests were performed in random order for each participant. During each trial, the participant gave a pain rating every 3s. An overall pain rating was also be taken at the cessation of each pain trial. All contractions were performed using the Biodex System 3 (Biodex Medical Systems). Blood pressure and heart rate were taken twice after each trial of muscle contraction was completed.

Eccentric Exercise Protocol

Each participant performed a 3-repetition eccentric strength test, which was used to determine peak eccentric strength. Three sets of 12 eccentric contractions at a goal of 75% of peak eccentric strength were then performed. All of the sets of eccentric exercise were performed at 90°/second through and active range of motion. All contractions were performed using the Biodex System 3. A one-minute rest period was provided between sets.

Salivary Cortisol

Saliva was collected and analyzed for cortisol using Salimetrics (State College, PA) cortisol kits, which included Salimetrics Oral Swabs and collection tubes. Saliva was collected at the beginning of each session (pre-eccentric exercise and two days post-eccentric exercise). Each participant was instructed on the use and procedure for saliva collection prior to muscle contraction tests. Ten to 15 minutes prior to each collection, each participant completed a mouth rinse with water to minimize the influence of acidic or high-sugar foods, which can compromise assay performance by lowering sample pH and influencing bacterial growth. For the collection, the participant was instructed to hold the oral collection swab under the tongue for two minutes to ensure complete saturation

of the swab. At the end of the two-minute period, the participant removed the swab and placed it in the collection tube and capped the tube. Date and time of each saliva collection was recorded. Each collection tube containing the oral swab was immediately placed into an -80°C freezer. All collection swabs were thawed and centrifuged at 3000 rpm for 15 minutes to extract saliva. Samples were assayed in triplicate according to the kit insert for the immunoassay kit (Salimetrics, Expanded Range High Sensitivity Salivary Cortisol Enzyme Immunoassay Kit). The average CV for the standards was 4.7%.

Blood Pressure and Heart Rate Measurements

Systemic arterial blood pressure was measured in the non-exercising arm, which was the non-dominant arm, with a sphygmomanometer and stethoscope using procedures recommended by the American Heart Association (American Heart Association, 2010). All participants were seated with the non-exercising arm elevated to the same level of the heart. Systolic BP was noted as the first sound heard and diastolic BP as the last sound heard. Two consecutive pre-eccentric exercise BP measurements were made to establish accuracy. Heart rate was measured using palpitation of the radial artery of the non-exercising arm. Heart rate was measured for one minute. The pre-eccentric exercise BP and HR measurements were taken twice and the average of the two measurements was used for analyses. Participants were seated on the Biodex machine for 10-15 minutes prior to pre-eccentric exercise blood pressure and heart rate measurements.

Pain Ratings

Pain ratings were measured on a 0 (no pain)-100 (most intense pain imaginable) scale. Baseline pain ratings, which were taken at rest, were measured at the beginning of

each session after the participant was seated for approximately 10 minutes. Baseline pain ratings included ratings of each arm while at rest and in active motion (flexion and extension). Pain ratings for overall pain felt during the test were taken at the cessation of each maximal test, each set of eccentric contractions and each isometric muscle contraction test. Pain ratings were also taken every three seconds during the isometric muscle contraction tests. A visual aid of the pain rating scale was visible at all times during all exercise tests.

Questionnaires

Ohio Blood Pressure Questionnaire

In order to evaluate familial history of hypertension, we administered the Ohio Blood Pressure History Questionnaire (Page & France, 2001). It included nine items about age, sex, recalled blood pressure, medications for hypertension, health conditions, and immediate biological relatives with hypertension. This questionnaire has been used repeatedly in studies supporting a relationship between history of hypertension and pain response (al'Absi et al, 2005; France et al, 2005). The Ohio Blood Pressure Questionnaire was filled out at the beginning of the first session, prior to any exercise testing.

Pre- and Post-Exercise Muscle Pain Questionnaires

Expected and actual muscle pain, controllability of muscle pain, predictability of muscle pain, and effects of muscle pain on daily activities and mood were assessed with a pre- and post-exercise muscle pain questionnaires. Each participant filled out the pre-exercise questionnaire directly before the eccentric maximal strength test and the post-exercise questionnaire at the beginning of the second session, two days after eccentric exercise.

Data Analysis

The data was analyzed using SPSS. All of the variables used in the analyses were checked for outliers using a z-score of ± 3.24. No outliers were found. The data analysis for each objective was as follows:

Primary Objective: Examine the relationship between isometric exercise-induced muscle pain (difference between post- and pre-isometric muscle pain) and resting BP and HR. *Analyses: Correlations between resting BP and HR and isometric exercise-induced muscle pain (i.e., difference between post- and pre-isometric exercise pain rating).*

Exploratory Objectives:

1. To examine differences in the strength of the relationship between isometric exercise-induced muscle pain ratings and resting BP and HR pre- and two days post-eccentric exercise. *Analyses: If regressions with resting BP and HR and isometric-exercise induced pain overlap in CI (95%) for R^2 values.*

2. To examine the change in resting BP, resting HR and salivary cortisol from pre- to two days post-eccentric exercise. *Analyses: Paired t-test to determine if resting BP, HR and salivary cortisol significantly changes from pre- to post-eccentric exercise.*

3. To examine the differences in the strength of the relationship between non-exercising extension pain and resting BP and HR pre- and two days post-eccentric exercise. *Analyses: If regressions between resting BP and HR and non-exercising extension muscle pain pre- and post-eccentric exercise overlap in CI (95%) for R^2 values.*

4. Examine if the change in resting salivary cortisol is significantly correlated to the change in baseline pain pre- and 2 days post-eccentric exercise. *Analyses: Correlation*

between the change in pain (pre- and post-eccentrics) and the change in salivary cortisol (pre- and post-eccentrics).

RESULTS

Thirty-three participants were recruited this single-blinded, randomized controlled trial study. Based on the exclusion criterion, one participant (male) was excluded from the study because he had begun an upper body-training program within seven days of the first session. Thirty-two participants (15 women and 17 men) were included in the analyses for the primary objective. Sixteen of the subjects (8 women and 8 men) who performed eccentric exercise (vs. concentric exercise) were included in all of the exploratory analyses. Descriptive statistics for each group of participants (n=32 and n=16) are listed in Table 1A and 1B, respectively.

TABLE 1A. Participants' characteristics (primary objective).

Characteristic	Total (n=32)	Mean ± SD
sex		
male	17	
female	15	
age (yr)		23 ± 5
BMI (kg/m^2)		26 ± 7.6
SBP (mmHg)		112 ± 12
DBP (mmHg)		69 ± 9
HR (mmHg)		65 ± 9
pre-isometric arm pain (0-100)		0
post-isometric arm pain (0-100)		29 ± 27

Values are means ± SD.
All BP and HR variables are the average of two measurements. SBP= resting systolic BP, DBP= resting diastolic BP, HR= resting heart rate. BMI, body mass index.

TABLE 1B. Participants' characteristics (exploratory objectives).

Characteristic	Total (n=16)	Mean ± SD
sex		
male	8	
female	8	
age (yr)		23 ± 5
BMI (kg/m^2)		24.5 ± 4.4
pre-eccentric		
SBP (mmHg)		111 ± 13
DBP(mmHg)		68 ± 9
HR (beats/min)		65 ± 8
cortisol (µg/dL)		0.15 ± 0.13
extension pain (0-100)		0
pre-isometric pain (0-100)		0
post-isometric pain (0-100)		26 ± 23
post-eccentric		
SBP (mmHg)		111 ± 11
DBP(mmHg)		66 ± 8
HR (beats/min)		67 ± 9
cortisol (µg/dL)		0.22 ± 0.16
extension pain (0-100)		25 ± 28
pre-isometric pain (0-100)		6 ± 7
post-isometric pain (0-100)		25 ± 20

Values are means ± SD.
All BP and HR variables are the average of two measurements. SBP= resting systolic BP, DBP= resting diastolic BP, HR= resting heart rate. BMI, body mass index.

Ohio Blood Pressure Questionnaire

Descriptive statistics were analyzed to find the frequency of participants with a family history of high blood pressure. Eleven participants possessed a family history of high blood pressure through at least one immediate family member. Twenty-two participants had no family history. In the subsample used in the exploratory objectives, five participants possessed a family history, while 11 did not.

Primary Objective

The primary objective was to examine the relationship between isometric exercise-induced muscle pain (difference between post- and pre-isometric muscle pain)

and resting BP and HR. It was hypothesized that a higher resting BP and HR would be associated with a smaller increase in isometric exercise-induced muscle pain. The descriptive statistics for the primary objective variables are listed in Table 1A. The change score for isometric exercise-induced pain was calculated by using the difference between post-isometric exercise-induced pain and pre-isometric exercise-induced pain. The average change score for isometric exercise-induced pain was 29 ± 27. The results from the correlations between isometric exercise-induced pain and SBP, DBP, and HR can be found in Table 2. The only significant relationship was between isometric exercise-induced pain and resting DBP ($R^2 = 0.355$, $p = 0.046$), but the two variables were positively related instead of negatively related.

TABLE 2. Correlations between isometric exercise-induced pain and resting blood pressure and heart rate.

	Pearson correlation
Δ iso pain and SBP	0.018
Δ iso pain and DBP	0.355*
Δ iso pain and HR	-0.024

Δ iso pain= (post-isometric pain)-(pre-isometric pain).
All BP and HR variables are the average of two measurements. SBP= resting systolic BP, DBP= resting diastolic BP, HR= resting heart rate.
* $p \leq 0.05$

Exploratory Objectives

The characteristics of the participants who completed eccentric exercise (n=16) are found in Table 1B. The change scores that were used in the exploratory objective analyses are listed in Table 3.

TABLE 3. Pain and cortisol change scores.

Δ isometric pain (pre-eccentric)	26 ± 23
Δ isometric pain (post-eccentric)	19 ± 18
Δ cortisol	0.07 ± 0.21
Δ extension pain	25 ± 28

Values are means ± SD.
Δ isometric pain= (post-isometric pain)-(pre-isometric pain), Δ cortisol= (post-eccentric resting cortisol)-(pre-eccentric resting cortisol), Δ extension pain= (post-eccentric extension pain)-(pre-eccentric extension pain).
Pain ratings were on a scale from 0-100.
Cortisol was measured in μg/dL.
All BP and HR variables are the average of two measurements. SBP= resting systolic BP, DBP= resting diastolic BP, HR= resting heart rate. Cortisol=resting cortisol, extension pain=non-exercising extension pain.

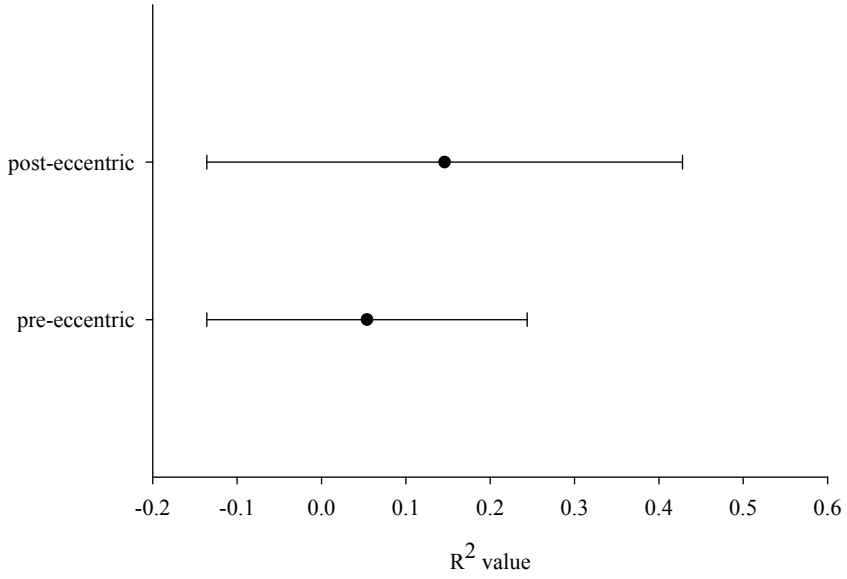
Exploratory Objective 1. The first exploratory objective was to examine differences in the strength of the relationship between isometric exercise-induced muscle pain ratings (difference between post- and pre-isometric muscle pain) and resting BP and HR pre- and two days post-eccentric exercise. It was hypothesized that the relationship between isometric exercise-induced muscle pain and resting BP and HR would be significantly different two days post-eccentric exercise compared with pre-eccentric exercise. There were no significant differences between the pre- and post-exercise R^2 values, as determined by comparing the corresponding confidence intervals (CI) for the R^2 values. The R^2 values and the corresponding confidence intervals for each of the regression analyzed for pre- and post-isometric exercise-induced pain and resting SBP, DBP and HR are summarized in Table 4 and Figures 4A-C.

Table 4. Correlations between isometric exercise-induced pain and resting blood pressure and heart rate pre- and post-eccentric exercise

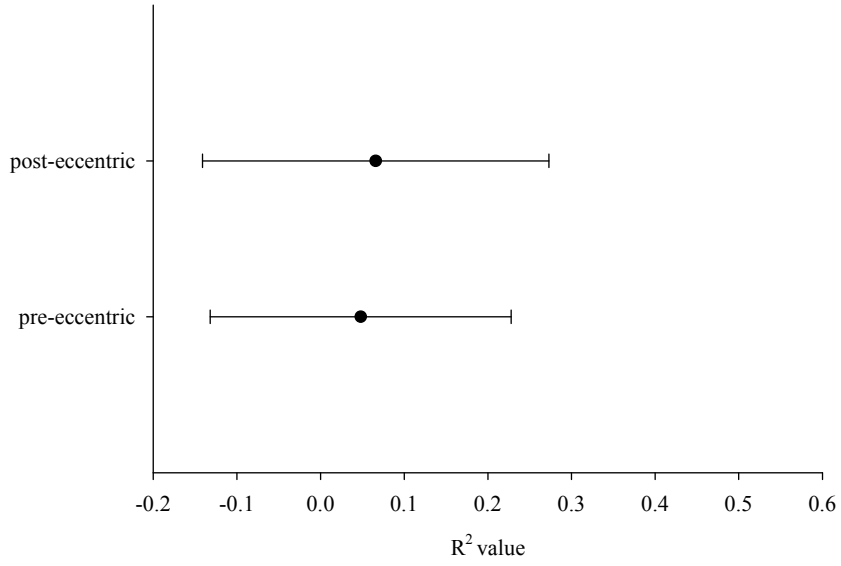
	R^2 value	p value	CI overlap *
Δ iso pain and SBP			
pre-eccentric	0.054	0.39	yes
post-eccentric	0.146	0.14	yes
Δ iso pain and DBP			
pre-eccentric	0.048	0.41	yes
post-eccentric	0.066	0.34	yes
Δ iso pain and HR			
pre-eccentric	0.101	0.23	yes
post-eccentric	0.035	0.49	yes

Δ isometric pain= (post-isometric pain)-(pre-isometric pain).
All BP and HR variables are the average of two measurements. SBP= resting systolic BP, DBP= resting diastolic BP, HR= resting heart rate.
* See Figure 4A-C for graphically representation.

A


post-eccentric
pre-eccentric
-0.2
-0.1
0.0
0.1
0.2
0.3
0.4
0.5
0.6
R^2 value

B


post-eccentric
pre-eccentric
-0.2
-0.1
0.0
0.1
0.2
0.3
0.4
0.5
0.6
R^2 value

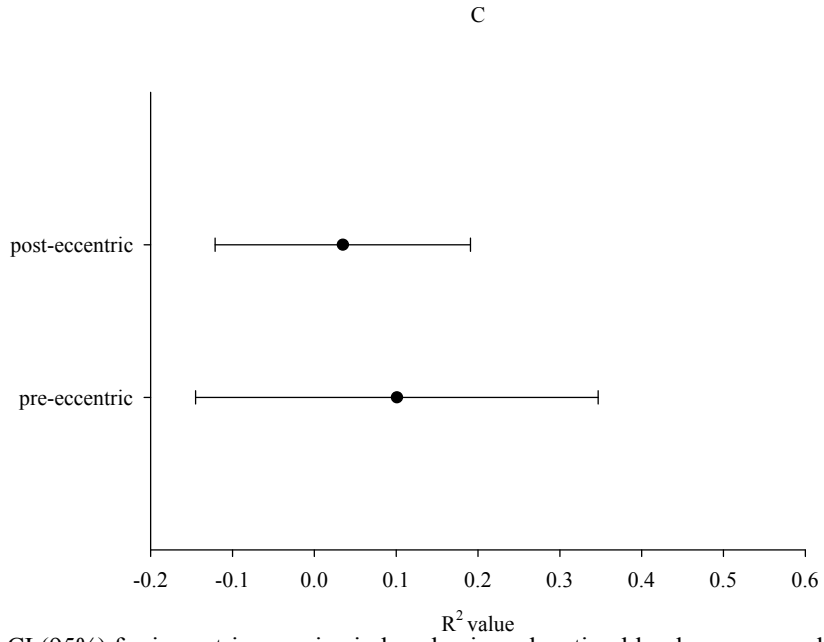


Figure 4A-C. CI (95%) for isometric exercise-induced pain and resting blood pressure and heart rate. A, isometric exercise-induced pain and resting SBP; B, isometric exercise-induced pain and resting DBP; C, isometric exercise-induced pain and resting HR. Data is presented as R^2 value ± CI.

Exploratory Objective 2. The second exploratory objective was to examine the change in resting BP, resting HR and salivary cortisol from pre- to two days post-eccentric exercise. It was hypothesized that resting BP, resting HR and salivary cortisol would be significantly increased two days post-eccentric exercise compared with pre-eccentric exercise levels. The means for the all of the pre- and post-eccentric measurements are listed in Table 1B. Resting HR significantly increased from pre- to post-eccentric exercise (p=0.01). The results from the paired t-test are summarized in Table 5.

Table 5. Pre-eccentric and post-eccentric resting blood pressure, heart rate and cortisol

	mean	SD	t	p value
SBP2-SBP1	-0.47	7.02	-0.267	0.79
DBP2-DBP1	-1.16	4.51	-1.026	0.32
HR2-HR1	2.44	3.45	2.823	0.01 *
cortisol2-cortisol1	0.07	0.208	1.425	0.17

1=pre-eccentric, 2=post-eccentric.
SBP= resting systolic BP, DBP= resting diastolic BP, HR= resting heart rate.
* indicates $p \leq 0.05$.

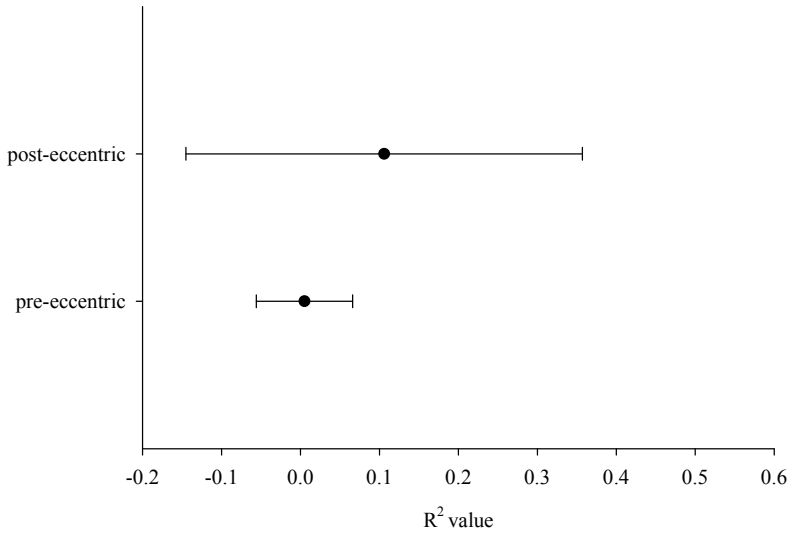
*Exploratory Objective 3.*The third exploratory objective was to examine the differences in the strength of the relationship between non-exercising extension pain and resting BP and HR pre- and two days post-eccentric exercise. It was hypothesized that the relationship between non-exercising extension pain and resting BP and HR would be significantly different two days post-eccentric exercise compared with pre-eccentric exercise. There were no significant differences between the pre- and post-exercise R^2 values, as determined by comparing the corresponding confidence intervals (CI) for the R^2 values (Table 6 and Figures 5A-C).

Table 6. Correlations between non-exercising extension pain and resting blood pressure and heart rate pre- and post-eccentric exercise.

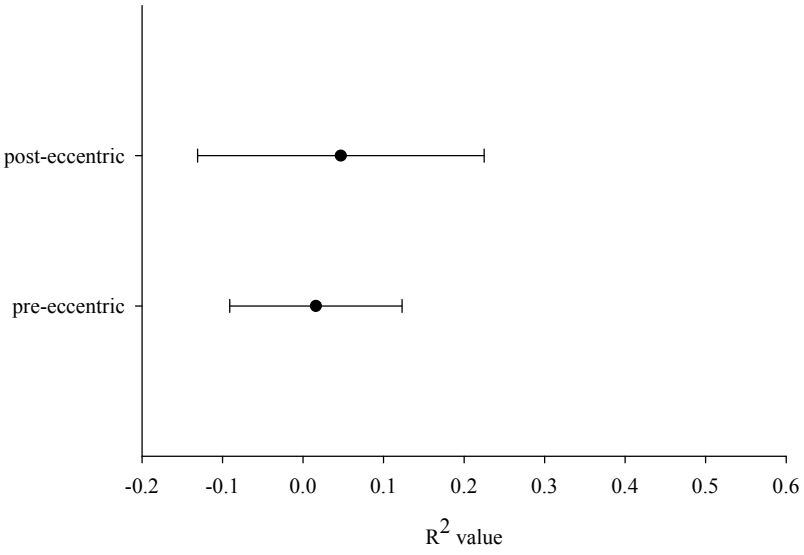
	R^2 value	p value	CI overlap *
Δ iso pain and SBP			
pre-eccentric	0.005	0.79	yes
post-eccentric	0.106	0.22	yes
Δ iso pain and DBP			
pre-eccentric	0.016	0.65	yes
post-eccentric	0.047	0.42	yes
Δ iso pain and HR			
pre-eccentric	0.195	0.09	yes
post-eccentric	0.002	0.89	yes

Δ ext pain= (post-eccentric non-exercising extension pain)-(pre-eccentric non-exercising extension pain).
All BP and HR variables are the average of two measurements. SBP= resting systolic BP, DBP= resting diastolic BP, HR= resting heart rate.
* See Figure 5A-C for graphical representation.

A


post-eccentric
pre-eccentric
-0.2
-0.1
0.0
0.1
0.2
0.3
0.4
0.5
0.6
R2 value

B


post-eccentric
pre-eccentric
-0.2
-0.1
0.0
0.1
0.2
0.3
0.4
0.5
0.6
R2 value

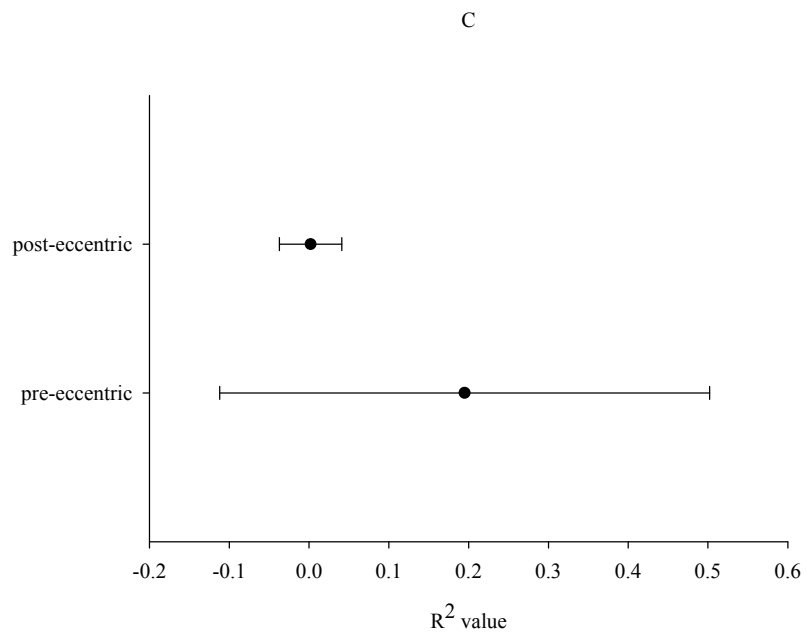


Figure 5A-C. CI (95%) for non-exercising extension pain and resting blood pressure and heart rate. A, non-exercising extension pain and resting SBP; B, non-exercising extension pain and resting DBP; C, non-exercising extension pain and resting HR. Data is presented as R^2 value ± CI.

Exploratory Objective 4. The last exploratory objective was to examine if the change in resting salivary cortisol (difference between 2 days post- and pre-eccentric resting salivary cortisol) was significantly correlated to the change in non-exercising extension pain (difference between 2 days post- and pre-eccentric baseline muscle pain). It was hypothesized that the changes in salivary cortisol and non-exercising extension pain would be positively correlated. The correlation between the change in non-exercising extension pain and salivary cortisol pre- and post-eccentric exercise was not significant (Table 7).

Table 7. Change in resting cortisol and non-exercising extension pain.

	Pearson correlation	p value
Δ cortisol and Δ ext pain	-0.178	0.51

Δ cortisol= (post-eccentric cortisol)-(pre-cortisol); Δ ext pain= (post-eccentric non-exercising extension pain)-(pre-eccentric non-exercising extension pain). N=16.

DISCUSSION

A number of studies have indicated that hypoalgesia occurs during and following exercise (5, 37). There is evidence indicating an interaction between pain modulatory and cardiovascular systems. For example, elevated resting BP has been associated with reduced sensitivity to noxious stimulation (8, 20, 22). In addition, acute elevations in BP have also been associated with alterations in pain perception (60). Exercise elevates BP due to physical demands of the activity but only a limited amount of research has been conducted examining the relationship between exercise pain and BP. Moreover, the interaction between exercise, pain and BP has been primarily examined indirectly. Therefore, the present study was designed to examine the relationship between isometric and eccentric-induced muscle pain and BP and HR.

The primary objective of this study was to examine the relationship between isometric exercise-induced muscle pain (difference between post- and pre-isometric muscle pain) and resting BP and HR. It was hypothesized that a higher resting BP and HR would be associated with a smaller increase in isometric exercise-induced muscle pain. The present results indicate that a significant negative relationship did not exist between isometric exercise-induced muscle pain and resting BP (systolic or diastolic) or HR. Resting DBP and the change in isometric exercise-induced pain were positively correlated. However, the direction of this correlation was in opposite direction of the predicted hypothesis.

The first and third exploratory objectives also examined the relationship between resting BP/HR and exercise-induced pain (isometric in the first objective, eccentric in the third objective). For both objectives, it was hypothesized that the relationship between

isometric exercise-induced muscle pain and resting BP and HR would be significantly different two days post-eccentric exercise compared with pre-eccentric exercise. A significant increase from pre- to post-eccentric exercise resting HR was found ($p = 0.01$). However, the increase was not significantly correlated with either pain rating. Neither of the relationships between exercise-induced muscle pain and resting BP or HR was found to be significantly different pre- and post-eccentric exercise. There are several potential reasons that the predicted hypotheses for examining the relationship between exercise-induced muscle pain and resting BP and HR were not supported in this study.

Timing of Blood Pressure and Heart Rate Measurements

The methodology in studies examining the relationship between cardiovascular and pain responses to resistance exercise have varied in several ways. For example, Ray and Carter (61) used BP and pain ratings during the isometric exercise, while Koltyn et al (37), Umeda et al (72) and Bajaj et al (5) used resting BP and pain ratings during a pressure stimulus. Ring et al (63) used both resting BP and HR during electrical stimulation, which occurred during the exercise bout. These studies varied in the timing of the BP and/or HR measurement used for analyses, which may have contributed to the variation in the results. Changes in resting BP and/or HR associated with eccentric exercise may be caused by different mechanisms, as compared to changes in BP and/or HR that are associated with isometric exercise and seen immediately following exercise. An increase in resting BP and/or HR associated with eccentric exercise may be a result of increases in inflammation (41, 64), while an increase in BP and/or HR immediately following isometric exercise may be due to a different mechanism, such as a baroreceptors reflex (1, 2) or an endogenous opioid mechanism (6, 24, 65). There is a

body of evidence that suggests the existence of an inverse relationship between pain response to a non-exercise stimulus, such as a pressure or cutaneous stimulus, and resting BP (1, 20). However, whether this inverse relationship also exists between resting BP and/or HR and exercise-induced pain alone still remains unclear.

Resting BP and/or HR were used in the current study to examine the relationship between resistance exercise and cardiovascular response. None of the relationships examined in the current study between pain and resting BP or HR were found to be negatively correlated. Only a couple of studies (5, 37) examining the effect of resistance exercise on the relationship between BP and pain found a significant negative relationship between resting BP and pain response. This may mean that the timing of the BP and/or HR measurement is not the variable responsible for dictating the relationship between pain and cardiovascular response.

Type of Pain Stimulus

Many of the studies that have examined the relationship between pain and BP/HR have induced pain in healthy participants using stimuli, such as a pressure algometer or cycling (30, 61), before and after resistance exercise. Exercise-induced muscle pain was most likely induced in these studies; however, these studies actually focused on the pain from a different stimulus (i.e. pressure algometer) than resistance exercise. In the study conducted by Koltyn et al (35), participants were requested to rate pain from a pressure stimulus before and after isometric exercise. Therefore, the pain rating was in response to the pressure stimulus, not just the exercise itself. The studies that have found a negative association between pain and BP and/or HR have not used exercise as the pain stimulus. Instead, stimuli such as electrical (20) and thermal (56) stimulation were used instead.

This suggests that the type of pain being induced may be an important factor when examining the relationship between pain and BP. To our knowledge, only one study exists that has examined the relationship between exercise-induced muscle pain and cardiovascular response. In the study conducted by Ray et al (61), BP, HR and exercise-induced muscle pain all increased during exercise. In the present study, a significant change in the strength of the relationship between resting BP and HR and exercise-induced muscle pain from pre- to post-exercise was not observed. Therefore, it could be possible that the type of pain that is induced during exercise differs from that created when using a noxious stimulus.

It has been suggested that pain is part of a homeostatic mechanism that signals the presence of tissue damage and encourages humans to alter their behavior (17). The sensory attributes of pain depend on the tissue of origin (10). Superficial pain, such as that originating in skin, is perceived as sharp and/or burning and is limited to a small well defined area, whereas deep pain, such as that originating in muscle, is dull and aching and difficult to localize (29). In a study conducted by Svensson (71), which measured cutaneous pain from a high energy CO_2 laser and muscle pain from an electrical stimulus, it was concluded that similar cerebral activation patterns suggested that the perceived differences between skin and muscle pain are mediated by differences in the intensity and pattern of neuronal activity. However, it should be recognized that a superficial stimulus, such as the pressure stimulus used by Koltyn et al (35) and Umeda (73), may also involve the muscle, and maybe bone, depending upon the location and methodology used, not just the skin. Therefore, overlap between the types of tissue activated by two different stimuli may exist.

In addition to these differences in the perception of superficial and deep pain, it has been observed that pain originating in deep structures evokes very different behavioral and cardiovascular responses to pain originating in superficial structures (10). Lewis (44) observed that pain originating in skin evokes a rise in pulse rate and a sense of invigoration, whereas deep pain evokes a slowing of pulse and falling of the blood pressure.

Moreover, different types of pain may also elicit different emotional and cognitive responses, which then influence pain response. Psychological factors, such as situational and emotional factors that exist when a person experiences pain, can alter the strength of these perceptions (48). More specifically, attention, understanding, control, expectations and the aversive significance can affect pain perception (48). Because the pain created as a result of exercise may be associated with a more positive outcome, such as gains in strength and fitness, it may be that the pain associated with exercise is perceived in a different manner than those types of pain associated with non-exercising stimuli. For example, a study conducted by Dannecker et al (16), found that delayed-onset of muscle pain was appraised as more predictable and controllable and less threatening in comparison to ischemic and heat pain stimuli. Therefore, the way a person rates exercise-induced pain, as compared to other pain stimuli, may also be different.

Type of Pain Rating

Another difference between studies of this nature is the type of pain rating that is used in the data analyses. The muscle pain ratings used in the correlations conducted in the study by Ray and Carter (61) were the highest muscle pain ratings reported during the exercise bout, while the present study used an overall pain rating from the isometric

contraction bout. However, by using the highest pain rating, or even an overall or average rating, the pain measure does not demonstrate the variance of the pain ratings across time. In our study, we found a significant positive correlation between resting DBP and isometric exercise-induced pain ($R^2 = 0.355$, $p = 0.046$). By using an overall pain rating, the trend in the pain felt during the isometric exercise may not be fully examined. For example, a person could have a sensation of pain that is lower than the peak pain at the beginning of the isometric contraction. When the person rates the overall pain felt during the contraction, he/she might recall the more intense pain felt at the end of the contraction and may rate the pain higher. Kahneman et al (33) suggests that retrospective evaluations of pain are often dominated by the discomfort at the worst and at the final moments of stimulation. In the present study, the isometric contractions lasted only 30 seconds, so the trend in pain may not have been a significant contributing factor. However, if the pain-inducing stimulus is tested for an extended period of time, it may be that the trend of the pain experienced throughout the entire exercise bout should be analyzed to fully examine the relationship between exercise-induced pain and BP/HR response.

Salivary Cortisol

The second exploratory objective was to examine the change in salivary cortisol from pre- to two days post-eccentric exercise. It was hypothesized that salivary cortisol would be significantly increased two days post-eccentric exercise. The results from the paired t-test demonstrated that salivary cortisol did not increase significantly post-eccentric exercise. Gleeson et al (23) demonstrated a significant increase in cortisol concentration post-eccentric exercise, compared to the concentric exercise group. However, in the study conducted by Gleeson, cortisol was measured immediately

following the cycling bout, which was conducted pre- and post-eccentric exercise. In our study, resting salivary cortisol was measured and analyzed. Peak cortisol concentration usually peaks about 30 minutes following the cessation of high-intensity exercise (39). Therefore, it may be that significant increases in cortisol may not last 48 hours post-exercise.

There are several factors that can affect cortisol levels, such as menstrual cycle and time of day (39). However, both of these factors were controlled in the current study. The size of the muscle performing the exercise may also be a variable that influences change in cortisol (52). Some research suggests that increases in cortisol seem to be the largest with intense exercise of a long duration (72, 74) Therefore, the largest effect of an exercise associated hormone-induced upregulation of cortisol may be expected when performing high-intensity exercise engaging in large muscle mass for a substantial duration. In the present study, the biceps brachii of the nondominant arm was used to perform the contractions. Therefore, it may be that the bicep is not large enough to elicit significant increases in cortisol.

Limitations

The population that was recruited for this study was a healthy (mean BMI = 24.5 ± 4.4), young population (mean age = 23 ± 5). The majority of the studies that have examined the relationship between exercise-induced analgesia and BP/HR have used a hypertensive population (20) or a population with a familial history of hypertension (18). Moreover, those with hypertension and/or a familial history of hypertension are more susceptible to coronary heart disease (CHD) and experiencing a silent myocardial attack (41). Therefore, it may be advantageous to examine the relationship between exercise-

induced muscle pain and BP/HR using a hypertensive population or a population with a familial history of hypertension. Also, the average population recruited in this study was young. It may be helpful to examine the relationship between exercise-induced muscle pain and BP/HR in an older population since that population is at a greater risk of developing hypertension (31) and possibly experiencing silent myocardial ischemia (46). Lastly, the sample size was relatively small (primary objective, n=32; exploratory objectives, n=16). A larger sample size may more closely represent the larger population.

Another limitation involves the protocol for the isometric muscle contraction tests. In this study, both tonic and phasic isometric muscle contraction tests were performed. The order was randomized; therefore, some of the participants performed phasic contractions before the tonic contractions. The phasic contractions may have influenced the results, either in pain response and/or BP and HR response, during the subsequent tonic contraction tests.

Also, all of the muscle contractions were performed with the biceps brachii of the non-dominant arm. As previously discussed, the size of the muscle mass may affect both cardiovascular response (65) and change in cortisol level (52). Therefore, different results may be seen if a larger muscle mass was used to perform the resistance exercise. Moreover, increases in pain, cardiovascular response and cortisol all seem to be affected by the exercise intensity (63, 72) and duration (72, 74). Different results may have been seen if the exercise intensity and duration were increased.

CONCLUSION

There is evidence indicating an interaction between pain and cardiovascular systems. Several studies have examined this relationship using isometric exercise (35, 59,

61, 68), while others have used eccentric exercise (5, 21). The purpose of this study was to investigate the relationship between isometric and eccentric exercise-induced muscle pain and cardiovascular response. Our study indicated that a significant negative relationship does not exist between exercise-induced muscle pain and BP or HR. These results contradict some of the previously conducted research in this area. However, there are several methodological differences (timing of BP/HR measurements, type of pain rating) between studies that have been conducted, which make it difficult to construct a substantial conclusion on the relationship between exercise-induced muscle pain and cardiovascular response. Moreover, the majority of studies that have found a negative relationship between pain and cardiovascular response have not used exercise as the pain stimulus. It may be that exercise-induced muscle pain is perceived differently from superficial stimulation; therefore, it does not produce the same inverse relationship with BP/HR. The results from this study do not support the hypothesis that a negative relationship exists between exercise-induced muscle pain and resting BP/HR. However, a lack of research in this area still exists.

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APPENDIX A

EXTENDED LITERATURE REVIEW

INTRODUCTION

Over the past 20 years, there have been a number of studies conducted examining whether analgesia occurs after exercise. These studies generally found that exercise can diminish the amount of pain perceived, known as hypoalgesia. It is currently unclear how exercise alters pain response, but research indicates there is an interaction between pain-modulatory and cardiovascular systems (20, 22, 59). It has been reported that there is an inverse relationship between blood pressure (BP) and pain perception. Furthermore, there is evidence to suggest that the negative association between BP and pain is not just a phenomenon observed in those with hypertension, but represents a continuous association that extends into the normotensive range as well (9, 18, 19). There are a number of studies that have examined the relationship between pain and BP, but very few that have examined this relationship using resistance exercise to induce muscle pain.

The few studies that have examined pain and cardiovascular responses to resistance exercise vary in methodology. More specifically, these studies have used different pain measurements (thresholds or ratings) and measured different types of pain (pain produced by exercise or by another stimulus, such as a pressure algometer). The timing of BP and HR measurements also differ between studies. Some studies examine resting BP/HR, while others measure BP/HR during resistance exercise or immediately following. Also many of the studies measured either BP or HR, but not together. This is important because changes in HR account for only 25% of the change in BP (52). These methodological differences have resulted in inconsistent results in the literature. Therefore, the direct effect of resistance exercise on the cardiovascular and pain

regulatory systems is still unknown. Insight into this area of research may be beneficial in assessing the symptoms associated with silent ischemia.

Effect of Isometric Exercise on Cardiovascular and Pain Regulatory Systems

During static exercise, heart rate (HR) and blood pressure (BP) increase more than during dynamic exercise performed at the same relative intensity (72). The sizeable increases in BP and HR during and immediately following isometric exercise make it a practical mode for examining the relationship between cardiovascular function and exercise-induced muscle pain immediately following exercise. The majority of studies that have measured both BP and HR have not tested isometric exercised-induced muscle pain (31, 36, 72). Instead, other types of pain stimuli have been administered to a healthy population before and after isometrics to examine the effect of the exercise-induced analgesia in relation to cardiovascular responses. Therefore, gaps in the literature still exist.

Cardiovascular and Exercise-Induced Muscle Pain Responses to Isometric Exercise

Ray and Carter (61) examined if exercise-induced muscle pain is modulated by the central mechanisms that affect cardiovascular control during exercise. Twenty-four subjects participated in two bouts of isometric exercise, a control trial and a trial with administration of endogenous opioids. During both trials, the subjects performed isometric handgrip exercise at 30% of maximal voluntary contraction to fatigue, followed by two minutes of post-exercise muscle ischemia. Forearm muscle pain was assessed using a 0-10 scale every 15 seconds during the isometric handgrip exercise and post-exercise muscle ischemia. Blood pressure and HR were measured continuously during the isometric handgrip exercise and post-exercise muscle ischemia. Muscle pain ratings,

mean arterial pressure and HR all increased significantly during the isometric handgrip exercise. Correlations were used to examine the relationship between systolic BP and muscle pain during the isometric exercise. The increases in muscle pain were not significantly correlated with the increases seen in systolic BP. The muscle pain ratings used in the correlations were the highest muscle pain ratings reported during the exercise bout, but this does not demonstrate the variance of the pain ratings across time. Overall, studies that examined the relationship between pain induced by a single bout of isometric exercise and BP and HR response to isometric exercise are lacking.

Cardiovascular and Exercise-Induced Analgesia Responses to Isometric Exercise

Ring et al (63) examined the effects of graded isometric exercise on both pain ratings and nociceptive flexion reflex (a spinal reflex promoting withdrawal from a potential noxious stimuli, NFR) and determined the extent to which any exercise-induced hypoalgesia was mediated by increases in arterial BP. Twenty-four subjects performed isometric handgrip exercise at 1%, 15% and 25% of maximal voluntary contraction (MVC) until a NFR threshold was reached (mean=4.5 minutes). Pain induced by electrocutaneous stimulation of the sural nerve, which was administered concurrent with performance of the isometric contractions, was assessed. Stimulation of the sural nerve was administered in a staircase manner until the first NRF was detected (mean=13 stimulations). The pain ratings were averaged to produce an overall pain intensity rating. Blood pressure was assessed pre-exercise (1, 3, and 5 minutes prior), during exercise (30, 90, 150 and 210 s into each exercise bout) and post-exercise (1, 3, and 5 minutes post). The BP measurements taken in each exercise condition were averaged to produce mean systolic and diastolic BP. Overall pain intensity ratings were significantly lower during

25% MVC compared with 1% and 15% MVC. Systolic and diastolic BP significantly increased during the 25% MVC trial. Although correlations were not analyzed in this study, ANCOVA's were conducted to determine whether statistically removing the variance in pain ratings associated with BP would reduce the effect of exercise on pain. The results indicated that diastolic BP fully accounted for, and systolic BP partially accounted for, the effects of exercise on pain. These results demonstrate that a relationship may exist between exercise-induced analgesia and cardiovascular response; however, because correlations were not analyzed, that conclusion cannot be made based on the results from this study.

In 2000, Koltyn et al (37) examined the relationship between exercise-induced analgesia and BP using isometric handgrip exercise in men and women. The subjects completed isometric exercise using a handgrip for two minutes. A pressure stimulus was applied to the forefinger for two minutes before and after isometric exercise. Pain thresholds and pain ratings were measured only during the pressure stimulus. The average of the pain ratings was determined and used in the analyses. Blood pressure (systolic and diastolic) and HR were measured at rest before isometric exercise and during the pressure stimulus. Correlations were analyzed for pain perception (threshold and rating) and BP at rest before exercise and during the pressure stimulus following the exercise; however, correlations between HR and pain were not analyzed. Resting diastolic BP was positively and significantly correlated with pain thresholds during the pressure stimulus. Correlation analyses using BP during the pressure stimulus demonstrated that as systolic BP increased, the corresponding pain ratings decreased significantly. This result indicates that a negative correlation between pain ratings and

systolic BP during the pressure stimulus, which immediately followed isometric exercise, exists. However, the statistically significant findings were present in the men only.

In contrast to Koltyn et al (37), Umeda et al (72) conducted a study, sampling only women, to determine if pain from a noxious stimulus and BP are altered immediately after brief isometric contractions. Subjects completed two exercise bouts at 25% maximum voluntary contraction for one minute and three minutes, the order of which was randomized. A pressure stimulus was applied to the forefinger immediately following each isometric bout. Pain thresholds and pain ratings were measured only during the pressure stimulus. Blood pressure (systolic and diastolic) and HR were measured before isometric exercise to serve as a baseline and during the pressure stimulus. Blood pressure and HR increased significantly following the isometric exercise compared to baseline values. Pain thresholds tended to increase following isometric exercise during the pain stimulus. However, the effect size was relatively small. Correlation analyses were performed to examine the relationship between pain thresholds during the pressure stimulus following the exercise and resting BP only. The results indicated that the correlations between resting systolic and diastolic BP were not significantly correlated with pain thresholds. Heart rate and pain thresholds were not analyzed in the correlations. Parallel results were demonstrated in a study done by Kadetoff and Kosek (32). However, correlations between cardiovascular measures and pain were not analyzed.

The results from Umeda et al are not consistent with the findings from Koltyn et al. This may be due to differences in BP measurements used in the correlation analyses. Umeda et al ran correlations using only resting BP whereas, Koltyn et al measured BP at

rest and during the pressure stimulus, immediately following the exercise. Both studies used pain measurements (thresholds or ratings) during the pressure stimulus, immediately following the exercise. However, the different time points used to analyze BP may have contributed to the variation in results seen between the two studies. Also, while pain thresholds were analyzed in both studies, pain ratings were analyzed by Koltyn et al only. More research is necessary to elucidate the correlation between pain and BP and HR response immediately following isometric exercise.

Effect of Eccentric Exercise on Cardiovascular and Pain Regulatory Systems

More than 200 published experiments have examined muscle pain resulting from eccentric exercise in humans (59). Few investigations have sought to examine the relationship between cardiorespiratory responses and eccentric exercise-induced muscle pain. Because the pain-inducing effect of eccentric exercise peaks at 48 hours post-eccentric exercise, resting BP/HR should be measured at baseline and 48 hours after eccentric exercise. Therefore, measuring pain and BP/HR immediately following eccentric exercise would not adequately assess the pain and cardiovascular responses associated with the eccentric exercise.

While studies have examined pain and BP/HR responses post-eccentric exercise, the cardiovascular responses were a secondary variable of interest, so the correlation between pain and non-exercising BP/HR responses 48 hours after eccentric exercise has not been examined. None of the studies have measured both resting BP and HR in conjunction with pain, which may provide a more complete understanding of the relationship between pain and cardiovascular response.

Cardiovascular and Pain Responses Two-Days Post Eccentric Exercise

In 1995, Gleeson et al (23) compared the effects of prolonged eccentric versus concentric exercise on exercise-induced analgesia and HR responses. Six healthy, untrained male subjects performed a cycle ergometer exercise test 48 hours following an eccentric and concentric exercise bout. All subjects completed both an eccentric and concentric exercise bout, which were randomized and performed two weeks apart. Muscle pain was measured in each leg pre- and 48 hours-post eccentric/concentric exercise bout before the cycling test and during the cycle test. An average pain rating was calculated using the pain ratings from each leg. Heart rate was measured during the cycle test only. Heart rate and muscle pain were significantly higher during the cycling test, 48 hours following eccentric exercise, as compared to concentric exercise. Correlations between muscle pain and HR were not analyzed. Hollander et al (30) found there to be a positive correlation between muscle pain and HR (BP was not examined). Increases in both muscle pain and HR were also found by Gleeson. However, muscle pain was assessed immediately following the eccentric exercise in the study done by Hollander.

Conversely, Bajaj et al (5) examined the time course of changes in pain threshold, pain ratings, and mean arterial pressure 48 hours post eccentric exercise. Eleven young males performed eccentric exercise of the right hand. Mean arterial pressure (MAP), pain threshold and pain ratings were measured before, immediately following eccentric exercise, 24 and 48 hours post-eccentric exercise. Pain threshold and pain ratings were measured using a pressure stimulus applied to the finger. Pain ratings were measured twice a day (morning and evening) and the average of the maximal rating from the morning and evening times was used for analyses. The pain ratings measured 48 hours post-eccentric exercise indicated muscle soreness in the hand was significantly higher

compared to before exercise. Mean arterial pressure (MAP) was significantly reduced at 48 hours compared to pre-exercise values. The results demonstrated that eccentric exercise caused increased muscle soreness in the exercising hand, which may relate to the reduced mean arterial pressure seen 48 hours post-eccentric exercise. This finding suggests that an inverse relationship between muscle pain and MAP may exist 48 hours post-eccentric exercise, but correlations between muscle pain and MAP were not analyzed. Therefore, that conclusion cannot be made from the results from this study.

Potential Physiological Mechanism Linking Pain and Cardiovascular Response

Potential Mechanisms Underlying the Relationship between BP/HR and Pain Immediately Following Isometric Exercise

Studies indicate that static exercise is associated with a reduction in pain (37, 61); however, the mechanism for this phenomenon is still unknown. It is currently unclear how exercise alters pain response, but research indicates there is an interaction between pain-modulatory and cardiovascular systems, more particularly BP and HR (20, 22, 59). There are currently several different proposed mechanisms to explain the relationship seen between pain and BP/HR immediately following isometric exercise. All of the proposed mechanisms discussed below involve systems that respond immediately to a painful stimulus, such as isometric exercise.

Endogenous opioid mechanisms. Opioid receptors belong to a large superfamily of G protein-coupled receptors (GPCRs) (73). These receptors are physiologically important because they mediate the actions of the majority of neurotransmitters and hormones. Opioid receptors, which are activated by endogenously produced opioids, are an important part of pain inhibitory pathway activity (8, 46). Several studies have

reported that elevated BP and lower levels of pain sensitivity are related to increased levels of plasma opioids (24, 66). However, research by Bragdon et al (7), who examined plasma levels of beta-endorphin, a potent, pain-relieving endogenous opioid, failed to support opioid mediation of the BP and pain relationship. Therefore, other mechanisms to explicate the relationship between cardiovascular and pain responses during exercise have also been examined.

Noradrenergic mechanisms. Noradrenergic activity is a primary non-opioid mechanism that is associated with the relationship between cardiovascular and pain responses to isometric exercise. The noradrenergic pathway is a system of neurons that is responsible for the synthesis, storage, and release of the neurotransmitter norepinephrine. The central noradrenergic pathway is a crucial component of the pain inhibitory system (29, 36, 40) and is known to be important in cardiovascular regulation (43, 68). The relationship between the pain inhibitory system and cardiovascular regulation has been suggested by research indicating that normotensive subjects with higher BP exhibited both increased pain tolerance and elevated circulating levels of norepinephrine, which can decrease pain responses (66).

Activation of arterial baroreceptors. Increased BP causes an increase in the activation of the stretch receptors called arterial baroreceptors (63). The increased activation of arterial baroreceptors triggers pain inhibitory activity in the entire body (22, 75). Because increased activation of the baroreceptors occurs as a result of increased stretch, the effect on the pain and cardiovascular systems is immediate and ceases shortly after the cessation of the stimulus (75). Experimental data in normotensive subjects support a role for baroreceptors mediating the relationship between BP and pain

sensitivity by demonstrating that direct stimulation of baroreceptors produces diminished pain sensitivity immediately following stimulation (1, 3).

Mechanisms Underlying the Relationship between BP/HR and Pain Post-Eccentric Exercise

The potential physiological mechanisms that underlie the pain and cardiovascular responses to eccentric exercise involve systems that alter muscle pain over an extended period of time (5). These mechanisms are specific to eccentric exercise because eccentric exercise-induced pain peaks 48 hours following exercise. Therefore, the proposed mechanisms for a potential relationship between BP/HR and eccentric-exercise induced pain must produce responses that will peak 48-hours following the eccentric exercise. The prolonged effects of eccentric exercise on muscle pain allow the relationship between exercise-induced pain and cardiovascular response to be examined at rest and 48 hours after eccentric exercise.

Inflammatory response and reactive oxygen species resulting from eccentric-exercise. A potential mechanism underlying eccentric exercise-induced pain is exercise-induced inflammation. Muscle damage resulting from eccentric contractions attracts several different types of white blood cells, including leukocytes, neutrophils and macrophages (11). Neutrophils and macrophages are present in the muscle from 24 hours to 14 days after stress-inducing exercise (6, 27, 47, 53). These cells contribute to the degradation of damaged muscle tissue by release of reactive oxygen species and pro-inflammatory cytokines (11).

Inflammatory associated cytokines, such as interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), have been shown to be expressed within the

skeletal muscle up to five days after eccentric exercise (21, 27). This local inflammatory response has been shown to increase systemic inflammation as well (21). Plasma levels of IL-6 were shown to remain elevated for several days following eccentric contractions of the elbow flexors (13, 57). MacIntyre et al (50) examined the relationship between IL-6, neutrophils, and delayed onset of muscle soreness following eccentric exercise. Delayed onset of muscle soreness was increased from 0-48 hours post exercise, as were IL-6 and neutrophil number.

Research has shown IL-6 release in response to exercise may also be partially responsible for increases in anti-inflammatory substances, such as cortisol (54). Therefore, cortisol production, which is secreted in response to stress-inducing exercise (23), has also been established as a method to quantify stress and inflammation resulting from stressful exercise (27). Gleeson et al (23) found cortisol levels to be significantly elevated 48 hours post-eccentric exercise, which supports the data showing increased levels of inflammation at the corresponding time point.

There is some experimental evidence that expression of cytokines and inflammation may be related to increased BP (39, 61). Chae et al (12) examined the relationship between BP and levels of IL-6 at baseline in healthy men. The results demonstrated a significant positive relationship between BP and levels of IL-6, which suggests inflammation may be a mechanism underlying hypertension. These results have been matched in other studies examining the relationship between inflammation and BP (28, 69). Inflammation has also been shown to impair endothelium-dependent dilation (28), which would result in an increase in BP, 36 hours post-exercise.

The effect of eccentric exercise-induced inflammation on BP/HR 48 hours post-eccentric exercise has not been examined (50). Eccentric exercise induces pain that peaks 48 hours post-exercise, which results in a prolonged state of inflammation following the exercise bout, lasting at least 48 hours. Although this chronic inflammation caused by eccentric exercise has not been studied in relation to BP/HR response, chronic inflammation has been shown to result in increased BP in other areas of research, such as obesity. Obesity-related research shows that inflammation from excess adipose tissue can lead to a chronic state of inflammation (24, 44, 61), which is associated with increased blood pressure.

Cortisol as an Indicator of Exercise-Induced Stress

The effect of exercise on neural function has long been recognized. It is well established that the stress resulting from acute anaerobic exercise increases glucocorticoid production from the adrenal cortex (39). Of these glucocorticoids, cortisol accounts for approximately 95% of all glucocorticoid activity (40). Moreover, the significant elevations in cortisol seen during acute exercise do not seem to be dependent on either gender or training status. Although hormonal elevations are often attributed to plasma volume changes, when corrected for plasma volume change, cortisol concentrations still remain elevated. Recently, salivary cortisol has emerged as an alternative method to measure cortisol levels because it evades the error that can be seen when measuring plasma cortisol, which can be altered by the changes in plasma volume, especially during exercise. Recent research shows that, during exercise, salivary and serum levels of cortisol are very similar (44, 71).

Gleeson et al (23) compared the effects of prolonged eccentric versus concentric exercise on exercise-induced analgesia. Plasma cortisol was measured before and immediately following a cycle ergometer test, which was performed pre- and two days post-concentric and eccentric exercise. In the post-concentric condition, plasma cortisol concentration did not increase before or immediately following the cycle ergometer test, but a significant increase was observed at both time points in the post-eccentric condition. Gleeson et al concluded that the higher plasma cortisol concentration prior to the cycle ergometer test, two days post-eccentric exercise, compared with the concentric exercise bout, may be due to the stress associated with normal ambulatory movements with sore muscles. Moreover, the higher plasma concentration of cortisol immediately following the cycling in the post-eccentric condition also indicated that the exercise was more stressful when the subjects exercised with sore muscles.

Limitations of Past Studies

Lack of Relevant Research

Only a few studies have examined the pain and BP/HR response immediately following isometric exercise or 48 hours post eccentric exercise. Of these studies, only two have examined the correlation between exercise-induced analgesia and cardiovascular response. Only a few studies, which were executed by Umeda et al (72), Koltyn et al (37), and Ring et al (63), looked at the effect of isometric exercise on exercise-induced analgesia and cardiovascular responses. There are currently no studies that have examined the correlation between exercise-induced muscle pain and cardiovascular response 48 hours post-eccentric exercise. Gleeson et al (23) and Bajaj et

al (5) examined the pain and cardiovascular responses independent of each other and made inferences to the relationship between pain and BP/HR response.

Type of Stimulus Used to Examine the Pain and BP/HR Relationship

Many of the studies that have examined the relationship between pain and BP/HR have induced pain in healthy participants using stimuli, such as a pressure algometer or cycling (32, 64), before and after resistance exercise. Exercise-induced muscle pain was probably induced in these studies, but the studies actually focused on the pain from a different stimulus (i.e. pressure algometer) than resistance exercise. In the study conducted by Koltyn et al (37), participants were requested to rate pain from a pressure stimulus before and after isometric exercise. Therefore, the pain rating was in response to the pressure stimulus, not the exercise itself. We are aware of only one study in the literature that specifically tested the relationship between resistance exercise-induced muscle pain and cardiovascular response (61).

Effect of Muscle Mass on Cardiovascular Response

The majority of studies that have examined the relationship between pain and cardiovascular response as a result of exercise have used a small muscle mass to perform contractions. Results from these studies may have demonstrated a more robust change in BP and HR response if a larger muscle mass had been used. Mitchell (51) examined the pain, BP and HR responses to isometric contractions performed at 40% maximal voluntary contraction by the fingers, forearm, knee extension and handgrip with simultaneous knee extension. A significant effect of the muscle mass was found on the increase in HR and BP. These findings were supported by Seals et al (65), who demonstrated that the increase in the muscle sympathetic nerve activity produced during

isometric handgrip exercise was greater (by 40-70%) during two-handed exercise at 30% maximal voluntary contraction than with either arm exercising alone. This research suggests that muscle mass may be an important determinant of the relationship between muscle pain and cardiovascular response. Also, the responses seen with a larger muscle mass may parallel the responses seen with whole body activities, which would more closely mimic the muscle mass recruited during activities of daily living.

Pain, Cardiovascular Responses and Application to Silent Myocardial Ischemia

Silent myocardial ischemia is a common phenomenon in patients with coronary heart disease (CHD). Patients who do not feel pain during ischemia may delay or avoid seeking medical attention, and are at increased risk of cardiac morbidity and mortality. It has been estimated that 80% of ischemic episodes in patients with coronary artery disease are asymptomatic (14, 17). Even very serious and severe episodes of ischemia may be asymptomatic, with an estimated 10-15% of myocardial infarctions being silent (33). There is emerging evidence that decreased pain in association with hypertension may complicate accurate and early detection of cardiac disease (21). Data from the Framingham Heart Study indicated that men and women with hypertension are almost twice as likely to suffer an unrecognized myocardial infarction (33). Based on routine electrocardiograms, 45% of women and 35% of men with hypertension were shown to have experienced a heart attack but could not recall any symptoms (i.e., angina) (32). This may be related to findings that high BP is associated with suppression of chest pain during episodes of myocardial ischemia. Such an effect has been observed during clinical exercise testing, as individuals with elevated resting systolic BP show a delayed onset of angina during episodes of exercise-induced myocardial ischemia (42). Hypertension may

be associated with a significant attenuation of clinical pain perception, which may lead to serious adverse health consequences.

APPENDIX B

INFORMED CONSENT

CONSENT FORM TO PARTICIPATE IN A RESEARCH STUDY

INVESTIGATOR'S NAME: ERIN ALICE DANNECKER, PHD, ATC

PROJECT # 1134037

DATE OF PROJECT APPROVAL: MARCH 17, 2009

FOR HS IRB USE ONLY
APPROVED _____ HS IRB Authorized Representative Date **EXPIRATION DATE:** _____

STUDY TITLE: SENSORY INTEGRATION BEFORE AND AFTER AN EXERCISE BOUT

INTRODUCTION

This consent may contain words that you do not understand. Please ask the investigator or the study staff to explain any words or information that you do not clearly understand.

This is a research study. Research studies include only people who choose to participate. As a study participant you have the right to know about the procedures that will be used in this research study so that you can make the decision whether or not to participate. The information presented here is simply an effort to make you better informed so that you may give or withhold your consent to participate in this research study.

Please take your time to make your decision and discuss it with your family and friends.

You are being asked to take part in this study because you are a healthy volunteer between the ages of 18 and 40 years old.

This study is being sponsored by the National Institutes for Arthritis and Musculoskeletal and Skin Diseases.

In order to participate in this study, it will be necessary to give your written consent.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to evaluate healthy people's responses to muscle contractions, heat, light, and sound before and after exercise. This research is being done because there is some evidence that responses to multiple senses are altered in certain medical conditions such as headaches, but the little is known about the senses of pain, hearing, and vision may relate to one another.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 40 people will take part in this study at this institution.

WHAT IS INVOLVED IN THE STUDY?

You will be asked to complete two laboratory sessions with two days in between them. In the first session, the investigator will collect demographic and personal information (e.g., age, sex, race, ethnicity, height, weight, health history, medication consumption, menstrual cycle, and previous experience with and perceptions of muscle pain) about you and you will be screened to ensure that you are eligible to participate based on specific criteria. Next, you will be asked to complete several written forms that ask questions about your typical activity level; your blood pressure history; your performance of specific tasks with your arm, shoulder, and hand; and your beliefs about how you typically respond to common events that may be painful.

After the forms are completed, the investigator will ask you about any pain that you may have in your body and any muscle pain that you may have in your arms. Then, locations for the application of adhesive electrodes and a handheld device will be marked on the skin of non-dominant arm. After those locations are marked,10mL of blood will be

collected from your dominant arm by a trained phlebotomist or nurse. Next, you will be asked to rinse your mouth with water and your sensory responses to muscle contractions, heat, light, and sound will be completed in a random order. You can stop any of the sensory tests at any time.

Muscle contractions – Before the muscle contractions, your blood pressure and heart rate will be measured two times. Also you will be asked to chew on a cotton swab in order for us to collect your saliva. Then your skin will be prepared for the application of adhesive electrodes, which may require abrading the skin by applying a gel or sandpaper. The muscle contraction sensory test will begin by measuring the strength of your nondominant arm while it is held in place. You will be asked to pull on a handle as hard as you can for three to five repetitions with your arm held in two different positions. During these two strength tests, adhesive electrodes on your upper arm will be sending information about your muscle function to a computer. Next, you will be asked to complete a task where you hold a constant contraction for 30 seconds two times and another task where you contract and relax your arm over 30 seconds two times. So you will be asked to contract your nondominant arm for 30 seconds four times. The investigator will ask you for ratings to describe how the strength tests and muscle contraction tasks felt to you. Also, your blood pressure and heart rate will be measured twice after each of the two muscle contraction tasks. In addition, you will be asked to chew on a cotton roll after each of the two muscle contraction tasks in order for us to collect your saliva.

Heat stimulus – This sensory test involves a heated surface being applied to the skin of your nondominant arm by the investigator. The heated surface is controlled by a computer. On four occasions, the investigator will hold the heated surface on your arm for 30 seconds. Again, the investigator will ask you for ratings to describe how the heated surface felt to you.

Light stimulus – This sensory test involves having you look at a light that is computer controlled by a computer. On four occasions, you will be asked to focus on the light for 30 seconds. Again, the investigator will ask you for ratings to describe how looking at the light felt to you.

Sound stimulus – This sensory test involves having you listen to a sound over headphones that is controlled by a computer. On four occasions, you will be asked to listen to the sound for 30 seconds. Again, the investigator will ask you for ratings to describe how looking at the light felt to you.

After the sensory testing, a second investigator will begin to work with you and the first investigator will leave the room. The second investigator will describe some arm exercise that you will be asked to complete with your nondominant arm. Next, you will be asked to complete a written form that asks you how you expect to be feeling and about completing normal tasks two days after the exercise that you are about to complete. Then,

the arm exercise will begin with another strength test where your arm is moving instead of being held in specific locations. You will be asked to pull on a handle as hard as you can for three to five repetitions with your arm held in two different positions. Then, you will finish the session by completing three sets of twelve repetitions of arm exercise at a specific intensity level. This session will last about 3 hours.

The second session will be conducted two days after the first. You will be asked to fill out one form to make sure that you can still participate in the study and forms that asks questions about how you are currently feeling and functioning and your beliefs about how you typically respond to pain. Next, the investigator will ask you about any pain that you may have in your body and any muscle pain that you may have in your arms. Then, locations for the application of adhesive electrodes and a handheld device will be marked on the skin of non-dominant arm. After those locations are marked,10mL of blood will be collected from your dominant arm by a trained phlebotomist or nurse. As you near the end of the session, you will be asked to rinse your mouth with water and your sensory responses to muscle contractions, heat, light, and sound will be completed in a random order just as was done in the first session. To finish the session, adhesive electrodes will be placed on different spots on your nondominant arm and electrical current will be applied to the electrodes while you hold your arm in one position and bend and straighten it. The investigator will ask you for ratings of how your arm feels as the current is applied. This session will last about two hours.

HOW LONG WILL I BE IN THE STUDY?

We think you will be in the study for four days, but the investigator and/or your doctor may decide to take you off this study if you (1) do not follow the criteria for staying in the study, (2) an event occurs which may increase the risk of injury to you, or (3) you have an unexpected and/or serious response to any of the procedures.

You can stop participating at any time. Your decision to withdraw from the study will not affect in any way your medical care and/or benefits.

WHAT ARE THE RISKS OF THE STUDY?

While on the study, you are at risk for the side effects described below. You should discuss these with the investigator and/or your doctor. There may also be other side effects that we cannot predict.

- Brief pain from heat is likely to occur
- Brief pain from blood draws is likely to occur
- Brief pain from arm muscle contractions is likely to occur

- Muscle soreness, weakness, loss of flexibility, and swelling from the exercise contractions may persist for several days depending upon the type of exercise. In about 3% of people, these effects can be unusually large and last longer. If you end up being one of the high risk responders, you should avoid activities that require use of that arm, ex driving, lifting objects, riding a bike, etc.
- Temporary redness and irritation of your skin from heat is likely to occur.
- Minor skin damage (i.e., burn) from heat is possible, but rare
- Temporary redness and irritation of your skin will occur if it is necessary to abrade your skin before adhesive electrodes are applied
- Infection from the blood draws is possible, but rare.
- Bruising from the blood draws happens occasionally.
- Dizziness and/or fainting from the blood draws is possible, but rare.

There is a low risk that large amounts of swelling in the upper arm could cause permanent damage to your muscles and/or nerves. Only one report of such damage from exercise in the upper arm was found and no reports of such damage from exercise in an experiment were found. Regardless, it is very important that you quickly report swelling and ANY loss of feeling in your arms or hands to the investigator or program staff.

There is a very low risk that exertional rhabdomyolysis, which is significant damage of muscle tissue, and myoglobinuria, which is a large amount of muscle proteins in the urine, may occur. These conditions have been associated with decreased kidney function and/or kidney failure in some circumstances, but not with the type of arm exercise you will be asked to complete. However, due to the seriousness of these conditions, it is very important for you to discuss any unusual things you notice about your arms and/or urine color with the investigator during the study and for several weeks after you have finished the study.

The tasks within this study should not be a risk for pregnant women. However, the investigators want to minimize risk as much as possible so it is necessary for women in this study to avoid getting pregnant while they are in this study. If you are female and sexually active, the investigators will ask if you are using some form of contraception according to your doctor's or a manufacturer's advice. If you have any questions about the reproductive issues or about preventing pregnancy, please discuss them with your doctor before continuing with this study.

For the reasons stated above, the investigator will observe you closely and encourage you to report any worrisome symptoms. If you have any worrisome symptoms, notify an investigator immediately.

The principal investigator's office telephone number is 573-882-8698 and cellular telephone number is 573-881-1176.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. You may expect to benefit from taking part in this research to the extent that you are contributing to medical knowledge. We hope the information learned from this study will benefit patients with heightened responses to pain in the future.

WHAT OTHER OPTIONS ARE THERE?

Instead of being in this study, you have the option to not participate in this research study. Please discuss this option with the investigator.

WHAT ABOUT CONFIDENTIALITY?

Information produced by this study will be stored in the investigator's file and identified by a code number only. The code key connecting your name to specific information about you will be kept in a separate, secure location. Information contained in your records may not be given to anyone unaffiliated with the study in a form that could identify you without your written consent, except as required by law. If the investigator conducting this study is not your primary, or regular doctor, she must obtain your permission before contacting your regular doctor for information about your past medical history or to inform them that you are in this trial.

It is possible that your medical and/or research record, including sensitive information and/or identifying information, may be inspected and/or copied by the study sponsor (and/or its agent), the Food and Drug Administration (FDA), federal or state government agencies, or hospital accrediting agencies, in the course of carrying out their duties. If your record is inspected or copied by the study sponsor (and/or its agents), or by any of these agencies, the University of Missouri will use reasonable efforts to protect your privacy and the confidentiality of your medical information.

The results of this study may be published in a medical book or journal or used for teaching purposes. However, your name or other identifying information will not be used in any publication or teaching materials without your specific permission.

WHAT ARE THE COSTS?

There are no costs associated with participation in this study unless you experience an unexpected and/or serious response to a procedure and seek medical care.

WILL I BE PAID FOR PARTICIPATING IN THE STUDY?

If you participate in the study as scheduled, you will be paid $12/hour up to a total of $72.

WHAT IF I AM INJURED?

It is not the policy of the University of Missouri to compensate human subjects in the event the research results in injury. The University of Missouri, in fulfilling its public responsibility, has provided medical, professional and general liability insurance coverage for any injury in the event such injury is caused by the negligence of the University of Missouri, its faculty and staff. The University of Missouri also will provide, within the limitations of the laws of the State of Missouri, facilities and medical attention to subjects who suffer injuries while participating in the research projects of the University of Missouri. In the event you have suffered injury as the result of participation in this research program, you are to contact the Risk Management Officer, telephone number (573) 882-1181, at the Health Sciences Center, who can review the matter and provide further information. This statement is not to be construed as an admission of liability.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Participation in this study is voluntary. You do not have to participate in this study. Your present or future care will not be affected should you choose not to participate. If you decide to participate, you can change your mind and drop out of the study at any time without affecting your present or future care in the University of Missouri. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. In addition, the investigator of this study may decide to end your participation in this study at any time after she has explained the reasons for doing so and has helped arrange for your continued care by your own doctor, if needed.

You will be informed of any significant new findings discovered during the course of this study that might influence your health, welfare, or willingness to continue participation in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

If you have any questions regarding your rights as a participant in this research and/or concerns about the study, or if you feel under any pressure to enroll or to continue to participate in this study, you may contact the University of Missouri Health Sciences Institutional Review Board (which is a group of people who review the research studies to protect participants' rights) at (573) 882-3181.

You may ask more questions about the study at any time. For questions about the study or a research-related injury, contact the principal investigator's office telephone number is 573-882-8698 or cellular telephone number is 573-881-1176.

A copy of this consent form will be given to you to keep.

SIGNATURE

I confirm that the purpose of the research, the study procedures, the possible risks and discomforts as well as potential benefits that I may experience have been explained to me. Alternatives to my participation in the study also have been discussed. I have read this consent form and my questions have been answered. My signature below indicates my willingness to participate in this study.

_____ _____

Subject/Patient* Date

_____ _____

Legal Guardian/Advocate/Witness (if required)** Date

_____ _____

Additional Signature (if required) (identify relationship to subject)*** Date

*A minor's signature on this line indicates his/her assent to participate in this study. A minor's signature is not required if he/she is under 7 years old. Use the "Legal Guardian/Advocate/Witness" line for the parent's signature, and you may use the "Additional Signature" line for the second parent's signature, if required.

**The presence and signature of an impartial witness is required during the entire informed consent discussion if the patient or patient's legally authorized representative is unable to read.

***The "Additional Signature" line may be used for the second parent's signature, if required. This line may also be used for any other signature which is required as per federal, state, local, sponsor and/or any other entity requirements.

"If required" means that the signature line is signed only if it is required as per federal, state, local, sponsor and/or any other entity requirements.

SIGNATURE OF STUDY REPRESENTATIVE

I have explained the purpose of the research, the study procedures, identifying those that are investigational, the possible risks and discomforts as well as potential benefits and have answered questions regarding the study to the best of my ability.

_____ _____

Study Representative**** Date

****Study Representative is a person authorized to obtain consent. Per the policies of the University of Missouri Health Care, for any 'significant risk/treatment' study, the Study Representative must be a physician who is either the Principal or Co-Investigator. If the study is deemed either 'significant risk/non-treatment' or 'minimal risk,' the Study Representative may be a non-physician study investigator.

APPENDIX C

DATA RECORDING SHEETS

DATA RECORDING SHEET_baseline

Participant # _____

Session1

Date _____

Start Time_____

Randomization Sensory: Heat ____ Tonic ____ Pain ____ Light ____ Phasic____ Unp ____ Sound ____ Biodex____

Dominant Arm: Right Left Height _____ (cm) Upper arm length_____ (cm) 25% _____

Weight _____ (kg) Lower arm length_____ (cm) 20%_____

Baseline 0-100 ratings **@ REST** Right arm - pain_____unpleasantness _____

Left arm - pain _____unpleasantness _____

Flex / Ext Flex / Ext

w/active FULL ROM Right arm - pain _____unpleasantness _____

Left arm - pain _____unpleasantness _____

[collect blood & rinse mouth]

Sensory Tests:

Heat: _____ Light: _____

Tonic		Phasic		Tonic		Phasic	
Pain	Unp	Pain	Unp	Pain	Unp	Pain	Unp
____3	____3	____3	____3	____3	____3	____3	____3
____6	____6	____6	____6	____6	____6	____6	____6
____9	____9	____9	____9	____9	____9	____9	____9
____12	____12	____12	____12	____12	____12	____12	____12
____15	____15	____15	____15	____15	____15	____15	____15

____18____18	____18____18	____18____18	____18___18
____21____21	____21____21	____21____21	____21___21
____24____24	____24____24	____24____24	____24___24
____27____27	____27____27	____27____27	____27 ___27
____30____30	____30____30	____30____30	____30 ___30
Overall:	Overall:	Overall:	Overall:
_____ _____	_____ _____	_____ _____	_____ _____

Sound: _____

Tonic		Phasic	
Pain	Unp	Pain	Unp
____3	____3	____3	____3
____6	____6	____6	____6
____9	____9	____9	____9
____12	____12	____12	____12
____15	____15	____15	____15
____18	____18	____18	____18
____21	____21	____21	____21
____24	____24	____24	____24
____27	____27	____27	____27
____30	____30	____30	____30
Overall:		Overall:	
_____	_____	_____	_____

[collect cortisol]

Pre-muscle contraction blood pressure and heart rate:

BP (1)_____ HR (1)_____

(2)_____ (2)_____

3RM Tests: **Randomization isometric 3RM tests:** 45° or 90° [collect sEMG w/90°]

45/90 Overall ratings: RPE_____

Pain_____

Unp_____

45/90 Overall ratings: RPE_____

Pain_____

Unp_____

Peak Torque for 45 3RM:

Max. Torque: _____

Biodex Settings	Right Arm	Left Arm
Dynamometer height		
Dynamometer orientation	30°	30°
Seat horizontal translation		
Seat tilt	85°	85°
Chair horizontal translation	0°	0°
Chair height		
Limb support pad height and direction		
Elbow/shoulder attachment length		

Biodex : _____

Tonic		Phasic	
Pain	Unp	Pain	Unp
____3	____3	____3	____3
____6	____6	____6	____6
____9	____9	____9	____9
____12	____12	____12	____12
____15	____15	____15	____15

____18	____18	____18	____18
____21	____21	____21	____21
____24	____24	____24	____24
____27	____27	____27	____27
____30	____30	____30	____30
Overall:		Overall:	
_____	_____	_____	_____
RPE:		RPE:	
_____	_____	_____	_____

End Time_____ Investigator's initials _____

DATA RECORDING SHEET_second session

Participant # _____

Session 2

Date _____

Start Time_____

Current 0-100 ratings **@ REST** Right arm - pain _____unpleasantness _____

Left arm - pain _____unpleasantness _____

Flex / Ext Flex / Ext

w/active FULL ROM Right arm - pain _____unpleasantness _____

Left arm - pain _____unpleasantness _____

[collect blood & rinse mouth]

Sensory Tests:

Heat: _____ Light: _____

Tonic		Phasic		Tonic		Phasic	
Pain	Unp	Pain	Unp	Pain	Unp	Pain	Unp
____3	____3	____3	____3	____3	____3	____3	____3
____6	____6	____6	____6	____6	____6	____6	____6
____9	____9	____9	____9	____9	____9	____9	____9
____12	____12	____12	____12	____12	____12	____12	____12
____15	____15	____15	____15	____15	____15	____15	____15
____18	____18	____18	____18	____18	____18	____18	____18
____21	____21	____21	____21	____21	____21	____21	____21
____24	____24	____24	____24	____24	____24	____24	____24
____27	____27	____27	____27	____27	____27	____27	____27
____30	____30	____30	____30	____30	____30	____30	____30

Overall: Overall: Overall: Overall:

_____ _____ _____ _____ _____ _____ _____ _____

Sound: _____

Tonic		Phasic	
Pain	Unp	Pain	Unp
____3	____3	____3	____3
____6	____6	____6	____6
____9	____9	____9	____9
____12	____12	____12	____12
____15	____15	____15	____15
____18	____18	____18	____18
____21	____21	____21	____21
____24	____24	____24	____24
____27	____27	____27	____27
____30	____30	____30	____30
Overall:		Overall:	
_____	_____	_____	_____
RPE:		RPE:	
_____	_____	_____	_____

[collect cortisol & rinse mouth]

Pre-muscle contraction blood pressure and heart rate: BP (1)____HR (1)____

(2)____ (2)____

3RM Test: **Isometric 3RM tests:** 90° [collect sEMG w/90°]

90 Overall ratings: RPE_____

Pain_____

Unp_____

Biodex : _____

Tonic		Phasic	
Pain	Unp	Pain	Unp
____3	____3	____3	____3
____6	____6	____6	____6
____9	____9	____9	____9
____12	____12	____12	____12
____15	____15	____15	____15
____18	____18	____18	____18
____21	____21	____21	____21
____24	____24	____24	____24
____27	____27	____27	____27
____30	____30	____30	____30
Overall:		Overall:	
_____	_____	_____	_____
RPE:		RPE:	
_____	_____	_____	_____

Post Muscle Contraction Blood Pressure/Heart Rate:

Tonic: Pain [collect cortisol & rinse mouth] BP_____ HR_____

BP_____ HR_____

Phasic: Pain [collect cortisol & rinse mouth] BP_____ HR_____

BP_____ HR_____

Nondom 0-100 ratings **@ REST** pain _____ unpleasantness _____

Flex / Ext Flex / Ext

w/active FULL ROM pain _____ unpleasantness _____

TENS Nondom 0-100 ratings:

@ REST pain _____ unpleasantness _____

Flex / Ext Flex / Ext

w/active FULL ROM pain _____ unpleasantness _____

End Time_____ Investigator's initials _____

DATA RECORDING SHEET_isokinetic CON or ECC

Participant # _____

Session 1

Date _____

Start Time_____

Biodex Strength/Exercise Tests: **Randomization isokinetic:** Concentric or Eccentric

Strength Test (Overall rating): RPE_____

Pain_____

Unp_____

Peak Torque for CON or ECC 3RM:

Max. Torque: _____

Exercise Test:

Set 1: RPE____ Pain____ Unp____

Set 2: RPE____ Pain____ Unp____

Set 3: RPE____ Pain____ Unp____

Restrictions –

- no brushing teeth within previous 1 hour
- no eating anything (including candy) or chewing gum within previous 1 hour
- no drinking anything other than water within previous 1 hour
- no smoking of a cigarette within previous 3 hours
- no caffeine within previous 8 hours
- no alcohol within previous 24 hours
- no dairy products within previous 24 hours
- no pain relievers within previous 48 hours before Session 1 or three days

☐ discussed research design
☐ confirmed schedule (w/reminder card)
☐ reminded restrictions
☐ obtained borrowed clothing from participant

End Time_____ Investigator's initials _____

APPENDIX D

MUSCLE PAIN QUESTIONNAIRES

ID# _____

Date _____

Pre-Exercise Questionnaire

Using the following definitions, please answer questions 1 and 2.

There are two aspects of pain that we are interested in measuring: the intensity; how strong the pain feels and the unpleasantness; how disturbing the pain is for you. The distinction between these two aspects of pain might be made clearer if you think of listening to a sound, such as a radio. As the volume of the sound increases, I can ask you how loud it sounds, or how unpleasant it is to you. The intensity of the pain is like loudness; the unpleasantness of the pain is how much the sound bothers you and it depends not only on intensity, but also on other factors that may affect you. Although some pain sensations may be equally intense and unpleasant, we would like you to judge these two aspects of your pain independently.

_____ 1. Please rate the highest intensity of the muscle pain in your nondominant arm from the exercise that you expect to feel using a scale of 0 (no pain sensation) to 100 (most intense pain sensation imaginable).

_____ 2. Please rate the highest unpleasantness of the muscle pain in your nondominant arm from the exercise that you expect to feel using a scale of 0 (not at all unpleasant) to 100 (most unpleasant imaginable).

_____ 3. Please rate the frequency that you expect to feel muscle pain in your nondominant arm during your normal daily activities over 48 hours after you leave the laboratory using a scale of 0 (never) to 100 (constantly).

_____ 4. Please rate the frequency that you expect the muscle pain in your nondominant arm to interfere with your normal daily activities over 48 hours after you leave the laboratory using a scale of 0 (never) to 100 (constantly).

Using the following definitions, please answer questions 5 and 6.

Threat - anticipated or actual physical or psychological harm, loss, injury, or damage.

Challenge - a test of one's strength, endurance, or abilities with the potential for growth, mastery, or gain

_____ 5. Please rate how threatened you feel by the expected muscle pain in your nondominant arm from the exercise using a scale of 0 (no threat) to 100 (most threatening pain imaginable).

_____ 6. Please rate how challenged you feel by the expected muscle pain in your nondominant arm from the exercise using a scale of 0 (no challenge) to 100 (most challenging pain imaginable).

PLEASE BE SURE TO COMPLETE THE NEXT PAGE

_____ 7. Please rate how predictable you expect the muscle pain in your nondominant arm from the exercise to be using a scale of 0 (not at all predictable) to 100 (completely predictable).

_____ 8. Please rate how controllable you expect the muscle pain in your nondominant arm from the exercise to be using a scale of 0 (not at all controllable) to 100 (completely controllable).

9. Please rate the likelihood that the following behaviors would decrease muscle pain from exercise using a scale of 0 (not likely) to 100 (definitely). Please rate each behavior listed.

_____ apply heat to the arm
_____ apply cold to the arm
_____ stretch the arm
_____ massage the arm
_____ rest the arm
_____ exercise the arm
_____ take a pain relieving medication

_____ apply a pain relieving cream to the arm

Please draw vertical lines perpendicularly across each of the horizontal lines at the location that best describes the level that you currently feel of each of the following negative feelings as it relates to your current pain.

11. depression: none _____ most severe imaginable

12. anxiety: none _____ most severe imaginable

13. frustration: none _____ most severe imaginable

14. anger: none _____ most severe imaginable

15. fear: none _____ most severe imaginable

ID# _____

Date _____

Post-Exercise Questionnaire

Using the following definitions, please answer the next two questions.

Threat - anticipated or actual physical or psychological harm, loss, injury, or damage.

Challenge - a test of one's strength, endurance, or abilities with the potential for growth, mastery, or gain

_____ 1. Please rate how threatened you have felt over the previous 24 hours by the muscle pain in your nondominant arm from the exercise using a scale of 0 (no threat) to 100 (most threatening pain imaginable).

_____ 2. Please rate how challenged you have felt over the previous 24 hours by the muscle pain in your nondominant arm from the exercise using a scale of 0 (no challenge) to 100 (most challenging pain imaginable).

_____ 3. Please rate how predictable the muscle pain in your nondominant arm from the exercise has been over the previous 48 hours using a scale of 0 (not at all predictable) to 100 (completely predictable).

_____ 4. Please rate how controllable the muscle pain in your nondominant arm from the exercise has been over the previous 48 hours using a scale of 0 (not at all controllable) to 100 (completely controllable).

_____ 5. Please rate the frequency that you have felt muscle pain in your nondominant arm during your normal daily activities over the previous 48 hours using a scale of 0 (never) to 100 (constantly).

_____ 6. Please rate the frequency that the muscle pain in your nondominant arm has interfered with your normal daily activities over the previous 48 hours using a scale of 0 (never) to 100 (constantly).

7. Please rate the likelihood that you would do the following behaviors to <u>decrease the current muscle pain</u> in your <u>nondominant arm</u> from exercise using a scale of 0 (not likely) to 100 (definitely). Please rate each behavior listed.

_____ apply heat to the arm
_____ apply cold to the arm
_____ stretch the arm
_____ massage the arm
_____ rest the arm
_____ exercise the arm
_____ take a pain relieving medication

_____ apply a pain relieving cream to the arm

PLEASE BE SURE TO COMPLETE THE NEXT PAGE

Please draw vertical lines perpendicularly across each of the horizontal lines at the location that best describes the level that you currently feel of each of the following negative feelings as it relates to your current pain.

8. depression: none _____ most severe imaginable

9. anxiety: none _____ most severe imaginable

10. frustration: none _____ most severe imaginable

11. anger: none _____ most severe imaginable

12. fear: none _____ most severe imaginable

Please draw vertical lines perpendicularly across each of the horizontal lines at the location that best describes the amount of impact from the muscle pain in your nondominant arm from exercise.

14. How much has the nondominant arm pain prevented you from doing what you wanted to do over

the previous 48 hours?

_____

no interference complete interference

15. How difficult was it to endure the nondominant arm pain over the previous 48 hours?

_____

not at all difficult — most difficult imaginable

16. With regard to future harm or impaired health, how concerned are you currently about the nondominant arm pain?

_____

not at all concerned — most intensely concerned imaginable

APPENDIX E

OHIO BLOOD PRESSURE QUESTIONNAIRE

Ohio Blood Pressure History Survey

Directions: This survey is designed to assess your blood pressure history as well as any potentially associated medical conditions. Please fill in the blanks or circle the appropriate response to indicate your answer to each question.

1. What is your age? _____
2. Are you male or female? _____ Male _____ Female
3. How long has it been since you last had your blood pressure checked by a doctor? _____ 0 to 6 mos _____ 6 to 12 mos _____ 1 to 5 yrs _____ more than 5 yrs _____ never

4. If you know, what is your typical blood pressure now? _____ first/upper number (systolic) _____ second/lower number (diastolic)
5. Have you ever been told by a doctor that you have hypertension (high blood pressure)? _____ Yes _____ No
6. Has a doctor ever prescribed medication for you to treat hypertension? _____ Yes _____ No
   If yes, please list the medications.
   _____
   _____
   _____
   _____
7. Do you suffer from any significant health problems? _____ Yes _____ No
   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 before age 55.

Mother Father Sister(s) Brother(s)