THE EFFECT OF NEUROSTIMULATION ON ISCHEMIC PAIN AND METHODS OF ASSESSING PAIN

A Senior Project

presented to

the Faculty of the Biomedical Engineering Department

California Polytechnic State University,

San Luis Obispo

In Partial Fulfillment

of the Requirements for the Degree

Bachelor of Science in Biomedical Engineering

by

Kaylee Keck

December 2015
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| **ADVISOR:** | Trevor Cardinal, PHD  
Associate Professor of Biomedical Engineering |
| **ADDITIONAL ADVISOR:** | Melanie Goodman Keiser, PHD  
St. Jude Medical |
| **ADDITIONAL ADVISOR:** | Stuart Rosenberg  
St. Jude Medical |
Abstract

Peripheral arterial disease (PAD) impacts approximately eight million people in the United States [1]. Disease progression leads to chronic ischemic pain, hindering quality of life. Pharmaceuticals are a typical treatment for pain associated with PAD; but as few as 30% of patients have a significant reduction of pain (≥50%) [2].

Neurostimulation is commonly used as a treatment for various diseases and injuries, including Parkinson’s disease and sports-related back and knee injuries [2]. The objective of the study was to explore neurostimulation and its effect on pain and paresthesia for a model of acute peripheral ischemia in young college students.

Pain is highly subjective and as a result can be difficult to measure. As a result, various pain scales and questionnaires exist and are commonly used for self-reported measurement of pain. Based on literature and prior pilot work, three instruments for measuring pain were employed to determine which would provide the best signal to noise ratio. Of all the instruments tested, the McGill Pain questionnaire best showed differences in pain in this study, with the best signal to noise ratio, and is recommended for future research and clinical assessment of ischemic pain.

Neurostimulation treatment did not cause a statistically significant reduction in pain. However, different trends are seen among different patients with some patients having an apparent decrease in pain with transcutaneous electrical nerve stimulation (TENS) treatment while others have an apparent decrease in pain with interferential currents stimulation (IFC) treatment. This indicates that it would be worthwhile to further explore neurostimulation and determine what causes the differing responses. Based on the differing responses, neurostimulation should be pursued as a method of ischemic pain reduction that could be tailored to the specific patient based on what neurostimulation best helps them.

Key Words: PAD, Ischemia, Pain, Neurostimulation, McGill Pain Questionnaire, Paresthesia
Acknowledgements

Thank you to Dr. Kristen Cardinal for giving me the opportunity to be involved in this project.

Thank you to Dr. Trevor Cardinal for acting as my Senior Project advisor and as faculty advisor for this project. Thank you for your input.

Thank you to Stuart Rosenberg and Dr. Melanie Goodman Keiser for acting as project advisors for St. Jude Medical. Thank you for all of your help and input.

Thank you to Leah Schafer for selecting me to work on this project with her.

“Live as if you were to die tomorrow. Learn as if you were to live forever.”

-Mahatma Gandhi
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Chapter 1 - Introduction

1.1 PAD and Ischemia

Peripheral arterial disease (PAD), also known as peripheral arterial occlusive disease (PAOD), is the reduction of blood flow resulting from narrowed or occluded arteries, typically associated with atherosclerosis [1]. PAD often results in ischemia, or insufficient blood supply, in the limbs and is generally associated with pain [1]. PAD initially involves pain only during exercise, described as intermittent claudication, but with progression of the disease, patients develop critical limb ischemia, in which they experience pain at rest; critical limb ischemia pain associated with progressed PAD is mainly neuropathic pain [2, 3]. Neuropathic pain is a type of chronic pain that can result when nerve fibers are affected by tissue damage [2]. The nerve fibers may be injured or dysfunctional as a result of tissue damage due to lack of blood flow in the case of PAD. Unlike nociceptive pain, the intensity of the pain may change throughout the day, but it continues throughout the day regardless of activity level [3].

1.2 Neurostimulation

Pain associated with PAD is currently treated using pharmaceuticals, which proves insufficient for decreasing pain in as many as 60% of patients [2]. Neurostimulation is a non-pharmaceutical treatment to treat pain, including neuropathic pain, which is very successful in many other diseases and injuries [2, 4]. Transcutaneous electrical nerve stimulation (TENS) is a prevalent type of neurostimulation used to treat many different conditions [5]. TENS is a biphasic pulsed current, producing a square waveform [5]. TENS changes peripheral nervous system activity causing an analgesic effect and paresthesia [4]. Paresthesia is a sensation caused by pressure on peripheral nerves, often
described as “pins and needles”, much like when one would feel when one’s foot “falls asleep” [4]. Interferential currents stimulation (IFC), is another common form of neurostimulation used for various therapeutic applications [6, 7]. IFC uses burst-modulated alternating sinusoidal currents, which may be more effective at penetrating deeper through the skin than TENS [6, 7]. The difference in waveform and penetration may result in different analgesic effects.

One of the main objectives of the study was to determine if either or both neurostimulation modalities reduce pain.

1.3 Pain Scales

To determine the efficacy of the neuromodulation approach, pain must be assessed. Pain is highly subjective, so assessing pain is challenging; not everyone interprets the same pain the same way. Given that pain is so subjective, many different metrics have been developed to capture it. There are many techniques used in clinical and research settings to assess pain, including pain scales and questionnaires. Numerical Rating Scale (NRS), Face Pain Scale (FPS), and the Short Form McGill Pain Questionnaire (MPQ) are common tools for pain assessment used in healthcare [8, 9]. The NRS is very basic, allowing subjects to rank pain from 0-10 (or in some cases 1-10), with 0 being no pain and 10 being the worst pain possible. The FPS uses seven faces to gauge an individual’s pain; the FPS used in this study was developed for healthcare professionals and parents to aid in the assessment of children’s pain intensity, Appendix D [10]. The short form MPQ (henceforward referred to as simply MPQ) was developed by Melzak in 1986 after the success of the long version of the McGill Pain Questionnaire, to be used when the longer version was not practical [11].
assessments of chronic ischemic pain associated with PAD [2, 3]. The Questionnaire includes 11 sensory descriptive words and 4 affective descriptive words, Appendix E. The individual is asked to describe their pain by ranking each word as none (0), mild (1), moderate (2), or severe (3). The rankings for each word are added up to provide the MPQ pain score.

In initial pilot work, the NRS scale was used on its own. The resulting pain data provided an unclear picture of pain. To get a better idea of what was actually happening with the pain, the FPS and MPQ were implemented in further pilot studies. For many, it was unclear what each number on the NRS pain scale meant. With the FPS, participants were able to visualize their pain, and with MPQ they were able to actually describe what they were feeling. The pilot studies including all three pain scales provided a better idea of what was happening with pain.

In pilot work implementing the MPQ, it was found that after treatments, participants would on their own describe their feeling of the pain with words commonly used to describe paresthesia. So, in order to capture this, paresthesia descriptive words were included in addition to the pain words on the MPQ in all subsequent work, Appendix F.

A secondary objective of the study was to determine the efficacy of the pain scales.
Chapter 2- Methods

2.1 Design

Several pilot studies were conducted, with 8-12 college students per study, leading up to
the small-scale pre-clinical study. The small-scale pre-clinical study included 45 college-
age students. Participants volunteered for participation. Each participant completed a
consent form and a medical-history questionnaire.

For the small-scale pre-clinical study, participants received compensation, in the form of
a $25 gift card, if they refrained from consuming caffeine for the 24 hours prior to
participation.

The study involved young healthy college students, so to study the effect on ischemia,
ischemia was induced. This was done by occluding the lower arm of the dominant hand
with a manual sphygmomanometer for treatments with occlusion.

There were six treatments: placebo without occlusion (P-), placebo with occlusion (P+),
TENS without occlusion (T-), TENS with occlusion (T+), IFC without occlusion (I-), and
IFC with occlusion (I+). A random blocked design was used, in which each participant
underwent all six treatments in a random order.

2.2 Experimental Setup and Procedure

The participants were instrumented to measure blood flow, blood pressure, heart rate,
respiration rate, hand grip, and skin temperature (All measurements, aside from pain are
presented in the Master’s thesis by Leah Schafer), Figure 1. A manual
sphygmomanometer was used to occlude the treatment arm, and a hand dynamometer
was used for performing exercise. During the later pilot studies and the small-scale pre-clinical study, the face pain scale and MPQ/Paresthesia questionnaire words were posted on the wall across from the participant (see Appendices D-F for scale and questionnaire).

After the participant completed the health history and consent forms, Appendices A and B, they sat in the medical chair and were instrumented to measure blood flow, blood pressure, respiration, and grip strength. The neurostimulation electrodes were placed on the participant’s back at the C7 and T4 vertebrae locations, approximately 3 cm to the left and right of the vertebral column, Figure 2. For the treatments with TENS or IFC, the frequency was set to 100 Hz and pulse duration to 200 μs. The intensity of the neurostimulation was increased by increments of one millivolt until the sensory threshold
was reached, specifically the threshold in which the participant could feel the neurostimulation but there was no pain or muscle twitching.

NRS and FPS pain (Number pain 0-10 and Face A-G) were assessed every minute throughout all phases and the McGill Pain/Paresthesia Questionnaire was performed halfway through both the exercise and occlusion phase. For the questionnaire, each word was read to the participant and the participant was asked to respond “none”, “mild”, “moderate”, or “severe” based on the pain they were feeling in their treatment arm.

Each treatment began by collecting one minute of baseline measurements, then progressed to the Exercise stage, in which the maximum strength was determined through three maximal contractions lasting 1 second each. The participant then maintained their grip on the hand dynamometer at 25±5% of their maximum grip for three minutes. After three minutes the manual sphygmomanometer was inflated to 180 mmHg to occlude
blood flow and the participant released the hand grip dynamometer. The cuff was inflated for three minutes, before a one minute recovery stage. For treatments without occlusion, the manual sphygmomanometer was not inflated.

The participant was allowed to rest roughly 10-15 minutes between each treatment to ensure that they returned to baseline. The protocol was then repeated for each treatment in random order for each participant.

2.3 Statistical Methods

For the number and face pain data, a binary logistic regression model was used to compare differences in pain between TENS, IFC, and placebo.

The responses for the MPQ/Paresthesia Questionnaire data, were converted into numerical form by assigning “none” with 0, “mild” with 1, “moderate” with 2, and “severe” with 3. The numerical questionnaire data was analyzed using an ANOVA-General Linear Model to compare the different treatments.
Chapter 3- Results

3.1 Pilot Studies Results

The initial objective of the pilot studies was to determine if the pain scale(s) being used were adequate to capture the changes in pain, and which pain scale could best do this. The follow-up objective was to determine which of the pain metrics was best.

From the initial pilot studies using only the NRS rating scale, most participants had a change of pain of either 0 or 1. The results showed no difference between the neurostimulation modalities and their ability to reduce pain compared to placebo.

Later pilot studies using the FPS and the MPQ pain scales still did not show a significant difference in change in pain for TENS or IFC compared to placebo. The MPQ pain scale, however, did result in being able to detect larger changes in pain ranging from 1 to 8.

3.2 Small-Scale Pre-Clinical Study Results

The main objective of the small-scale pre-clinical study was to determine whether TENS or IFC would have an effect on pain, especially during occlusion. A secondary objective was to determine the efficacy of the pain scales, specifically the MPQ scale, which pilot work indicated to be the best metric.
3.2.2 Numerical Rating Scale Results

During exercise, neurostimulation had a varying effect on change in pain in different participants, Figure 3. Overall, TENS and IFC were both slightly more likely to have an increase in NRS pain during exercise as compared to Placebo (Placebo:IFC-odds ratio 0.7889; IFC:Placebo- odds ratio 1.2905). TENS was very slightly more likely than IFC to cause an increase in pain during exercise (TENS:IFC-odds ratio 1.2905). Though none of these trends were statistically significant (Figure 4).
During the next phase of the experiment, occlusion, the trends change in NRS pain varied widely by participant, as it did in the exercise phase, Figure 5. Placebo treatment is slightly more likely than the IFC treatment to have an increase in pain during occlusion.
(odds ratio of 1.1438). TENS is slightly less likely to have an increase in pain during occlusion than both IFC and Placebo (odds ratios T:I 0.7294 and T:P 0.6377, Figure 6. Treatments with ischemia are much more likely to have an increase in pain than treatments without ischemia (odds ratio with occlusion (+): without occlusion (-) is 9.1261), Figure 6. The difference between with and without ischemia was significant. The differences between neurostimulation were not significant.

![Main Effects Plot for Change in NRS Pain](image.png)

**Figure 6 Main Effects Plot for Change in NRS Pain during the Occlusion Phase**

3.2.3 Face Pain Scale Results

The Face Pain Scale data varies greatly by participant, Figure 7. Placebo is slightly more likely than both IFC and TENS to have an increase in FPS score during exercise (odds ratios P:I 1.2286 and T:P 0.8617). TENS is slightly more likely than IFC to have an
increase in FPS pain during exercise (odds ratio T:I 1.0587). These relationships between neurostimulation, Figure 8, are not statistically significant.

![Figure 7 Line Plot of Mean Change in Face Pain during the Exercise Phase](image)
Similarly to the exercise phase, the occlusion phase shows great variability between participant changes in pain with different neurostimulation, Figure 9. Placebo is slightly less likely than both TENS and IFC to have an increase in FPS Pain during the occlusion phase.
phase (odds ratios P:I 0.7275 and T:P 1.3158). TENS is very slightly less likely to have an increase in FPS during occlusion than IFC (odds ratio T:I 1.9572). These trends in neurostimulation were not statistically significant, Figure 10. Treatments with ischemia are considerably more likely to have an increase in pain than treatments without ischemia (odds ratio 8.5105). The significant difference between with and without ischemia is illustrated by the steep slope in the ischemia panel of the Main Effects Plot, Figure 10.

Main Effects Plot for Change in Face Pain

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<td>Probability of Change in Face Pain</td>
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<td>I</td>
<td>0.15</td>
<td>0.35</td>
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<td>P</td>
<td>0.10</td>
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Figure 8 Main Effects Plot for Change in Face Pain during the Occlusion Phase

3.2.4 McGill Pain Questionnaire plus Paresthesia Questionnaire

The results of McGill Pain and Paresthesia Questionnaires scores together during the exercise phase showed that participant change in pain varied significantly (p-value 0.000). Neither ischemia nor neurostimulation affected reported pain during the exercise phase (p-values of 0.288 and 0.539 respectively). These results are illustrated by the Main Effects plot, Figure 11, which shows that the points for the different participants vary a great deal, whereas the points for IFC, TENS, and Placebo for neurostimulation in the upper right panel, and with and without ischemia in the lower left panel are relatively the
same. The interaction between ischemia and neurostimulation was also not statistically significant (p-value of 0.078), Figure 12.

![Main Effects Plot for MPQ + Parasthesia](image1)

*Figure 10 Main Effects Plot for MPQ plus Paresthesia during the Exercise Phase*

![Interaction Plot for MPQ + Parasthesia](image2)

*Figure 9 Interaction Plot for MPQ plus Paresthesia during the Exercise Phase*

Again, during the occlusion phase, the MPQ and Paresthesia data show participant to be significant with a great deal of variability (p-value of 0.000). Ischemia does have a significant effect on change in pain during the occlusion phase, with treatments with ischemia having an increase in pain compared to without (p-value of 0.000). Neurostimulation does not have a significant effect on the change in MPQ and
Paresthesia score during occlusion (p-value of 0.630). These results are illustrated by the main effects plot, Figure 13. Participant varies in an irregular manner and ischemia has a steeply sloped line with (+) ischemia higher than (-) ischemia. Neurostimulation again has values that are relatively unchanged. The interaction between neurostimulation and ischemia is again not significant (p-value of 0.126), illustrated by the similarly sloped lines in the interaction plot in Figure 14.
3.2.5 McGill Pain Questionnaire Pain Score
The MPQ score data on its own shows variability by participant during the exercise phase as well (p-value of 0.000). **Figure 15.** Neither ischemia nor neurostimulation significantly affect the change in MPQ pain only during the exercise phase (p-values 0.063 and 0.897 respectively), **Figure 16.** Tukey confidence intervals illustrate this as
well in Figures 17 and 18, since all intervals include 0 the factor levels are not significantly different.

Figure 13 Line Plot of Mean for MPQ Pain Scores during the Exercise Phase

Figure 14 Main Effects Plot for MPQ Pain Only during the Exercise Phase
Figure 15 Tukey Confidence Intervals for Difference of Means between with and without Ischemia for MPQ Pain Scores during the Exercise Phase

Figure 16 Tukey Confidence intervals for the Difference of Means between Neurostimulation modalities for MPQ Pain Scores during the Exercise Phase
The interaction between ischemia and neurostimulation is not statistically significant, **Figure 19.** The MPQ score data during occlusion ranges by participant as well, **Figure 20.** Both participant and ischemia have a significant effect on change in MPQ pain score during occlusion (p-values of 0.000). Neurostimulation does not significantly change the
MPQ-assessed pain during occlusion (p-value 0.918), Figure 21. The interaction between ischemia and neurostimulation is also not significant during occlusion (p-value 0.104), Figure 22.

![Main Effects Plot for MPQ Pain Only](image1)

*Figure 20 Main Effects Plot for MPQ Pain Score during the Occlusion Phase*

![Interaction Plot for MPQ Pain Only](image2)

*Figure 19 Interaction Plot for MPQ Pain Score during the Occlusion Phase*

### 3.2.6 Paresthesia Questionnaire Score

Like the MPQ pain scores, paresthesia score varied by participant, Figure 23.
Paresthesia Questionnaire scores during the exercise phase are significantly affected by participant and neurostimulation (p-values 0.000 and 0.022 respectively), Figures 24 and 25. TENS increases paresthesia more than placebo during exercise, Figure 25.

**Figure 22** Line Plot of Mean Paresthesia Score during the Exercise Phase, for each participant

**Figure 21** Main Effects Plot for Paresthesia during the Exercise Phase
The interaction between neurostimulation and ischemia is not statistically significant (p-value of 0.075), Figure 26.

Participant also causes variation in Paresthesia during the occlusion phase (p-value 0.000), Figure 27. During occlusion, ischemia significantly affects the change in paresthesia (p-values of 0.000), Figure 28. Neurostimulation does not significantly affect Paresthesia during occlusion (p-value 0.238). The interaction between ischemia and
neurostimulation is not significant during occlusion as with exercise, (p-value of 0.080), Figure 29.

Figure 25 Line Plot of Mean Paresthesia Score during the Occlusion Phase, for each participant

Figure 26 Main Effects Plot for Paresthesia during the Occlusion Phase
Figure 27 Interaction Plot for Paresthesia score during the Occlusion Phase
Chapter 4- Discussion

The objectives of this study were to determine the best way of assessing pain and to determine if either TENS or IFC neurostimulation modalities affect acute ischemic pain.

The MPQ appears to be a better way of assessing the pain caused in this study. A larger difference in pain can be seen, whereas with the NRS and Face pain scales the differences in pain detected were small, typically between 0 and 1. For future work, the MPQ would be recommended for the assessment of pain.

The results of the data provided by the pain scales indicate that neither TENS nor IFC induce analgesia during either the exercise or occlusion. This may result from the study being done with all young, healthy participants, in which there was not enough pain to be able to detect significant changes in pain.

TENS did increase paresthesia during the exercise phase. This may be due to the way in which TENS interacts with the nervous system. Future research could explore this effect.

Although TENS or IFC neurostimulation did not generally induce analgesia, the variability between participants suggests that TENS may be efficacious in some patients, while IFC may be better for others. This may be due to differences between participants, whether due to individual physiology, gender, athleticism, or other unknown factors. Further work would include additional replicates and an emphasis on examining different factors to explore what causes the differing trends between participants.

Due to many participants never reporting any pain, likely due to the use of young, healthy participants, further studies should be conducted with individuals who actually suffer from PAD or other diseases causing ischemic pain, and on people from varying age
groups. In a study with participants who have the disease, there would be a higher amount of pain and thus differences in pain would be more easily detected. With differences in pain more easily detected, a trend may become clearer.
**Conclusion**

The results indicated that the MPQ makes it easier to view changes in pain for this type of simulated pain study than NRS or FPS; the large difference in the pain detected by this study lead to the recommendation that MPQ be used either in place of or in addition to the other scales in the assessment for self-reporting pain.

This study did not show neurostimulation to be statistically significant, therefore, evidence was not found to show that neurostimulation significantly reduces ischemic pain in young college students. However, different trends were shown in different participants, which indicate trends toward neurostimulation affecting pain, though differently in different participants. This leads to the desire for future work to explore the differences in participants that lead to the differences in effects of neurostimulation. In addition, neurostimulation may be further explored as a treatment for ischemic pain reduction, which would need to be personalized for the individual.
References


Appendices

Appendix A: Informed Consent Form

INFORMED CONSENT TO PARTICIPATE IN A RESEARCH PROJECT:
"Determining Limb Blood Flow Changes in Response to Electrical Neurostimulation"

A research project on peripheral blood flow and ischemic pain is being conducted by
Leah Schaefer and Kaylee Keck in the Department of Biomedical Engineering at Cal Poly, San Luis
Obispo. The purpose of the study is to measure changes in blood flow, heart rate, and blood pressure
due to the application of electrical neurostimulation.

You are being asked to take part in this study by first filling out a short medical history
questionnaire. Questions marked with an asterisk (*) are required, but any others you do not wish to
answer may be omitted. These questions are directly related to your safety. During each treatment
session, you will be hooked up to a neurostimulation device that will be attached to your upper back
with electrodes, a blood flow measurement system using skin probes on the upper arms, a respiration belt
wrapped around your midsection, and a blood pressure cuff applied to each arm. Appropriate clothing
should be worn to ensure proper placement of the electrodes on your upper back.

You will be asked to squeeze a handgrip force measurement device for a short period of time.
You will experience electrical stimulation from the attached electrodes, which you may feel as a warm,
tingling sensation on your back. Your participation will take approximately 1.5 hours in two separate
sessions on two different days, which includes a 30-minute break in-between each session, for a total of
approximately 3 hours. In some of these sessions, the neurostimulation device will be hooked up to you,
but no current will be applied, as in you will not feel any sensation on your back. This will be randomized.
Please be aware that you are not required to participate in this research and you may discontinue your
participation at any time without penalty.

The possible risks associated with participation in this study include pain due to temporarily
induced ischemia i.e. insufficient blood flow to the tissue, skin irritation from the application of skin probes
and electrodes, and possible discomfort and/or stress from gripping the hand force measurement device.
If your personal pain tolerance threshold is reached at any point, you may discontinue your participation
immediately. If you should experience residual pain or tingling after the duration of the experiment or an
allergic reaction at the site of the probes or electrodes, please be aware that you may contact Cal Poly
Health and Counseling Services, located in building 27, at (805) 756-1211 for assistance.

Your confidentiality will be protected by recording your medical history, age, gender, height and
weight on a document with a corresponding code. This document will be kept as a hard copy only
and separate from the corresponding list of codes. Your information will only be accessible to the researchers
in this study. If the results of the study are published, any identifying information will be omitted. There are
no direct benefits to you associated with this study. Depending on the outcome of the study, this could
become an additional treatment method for individuals with ischemic pain.

If you have questions regarding this study or would like to be informed of the results when the
study is completed, please feel free to contact Leah Schaefer at (530) 354-5061 or Dr. Trevor Cardinal at
(805) 756-6244. If you have concerns regarding the manner in which the study is conducted, you may
contact Dr. Steve Davis, Chair of the Cal Poly Human Subjects Committee, at (805) 756-2754,
sdavis@calpoly.edu, or Dr. Dean Wendt, Interim Dean of Research, at (805) 756-1508,
dwendt@calpoly.edu.

If you agree to voluntarily participate in this research project as described, please indicate your
agreement by signing below. Please keep one copy of this form for your reference, and thank you for your
participation in this research.

__________________________________________________________
Signature of Volunteer

__________________________________________________________
Date

__________________________________________________________
Signature of Researcher

__________________________________________________________
Date

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Appendix B: Medical History Questionnaire

MEDICAL HISTORY

*= Required

General Information

Participant:

Name: ___________________________________________________________________________

Contact phone number(s): __________________________________________________________

Age: _________________________________
Height: _______________________________
Weight: _______________________________
Dominant Hand: □ Right □ Left

Sex:
□ Male □ Female

Women only answer the following:

Yes  No
□ □  *Are you currently pregnant?
□ □  Are you currently breast-feeding?

Men and women answer the following:

Have you consumed caffeine in the last 12 hours? □ Yes  □ No

Have you exercised to 50% of your maximum heart rate (moderate exercise) in the last:

48 hours?  □ Yes  □ No
12 hours? □ Yes  □ No

List any prescription medications you are currently taking:
_________________________________________________________________________________

Do you have any implantable electrical devices (pacemaker, implantable cardioverter defibrillator, etc.)?

□ Yes  □ No  If yes, please list:
In the past two months, have you experienced any major injury or significant trauma to your arms or upper back?  □ Yes  □ No  If yes, please describe:

---

**Past Medical History**

Have you ever experienced any of the following:

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>
| ☐   |     | Heart attack
| ☐   |     | High blood pressure (hypertension)
| ☐   |     | Rheumatic Fever
| ☐   |     | Heart murmur (abnormal heart sound)
| ☐   |     | Arrhythmia (irregular heartbeat)
| ☐   |     | Diseases of the arteries (peripheral artery disease, coronary artery disease, etc.)
| ☐   |     | *Epilepsy or seizures
| ☐   |     | Varicose veins (twisted, enlarged veins)
| ☐   |     | Diabetes or abnormal blood sugar
| ☐   |     | Phlebitis (inflammation of the veins)
| ☐   |     | Stroke
| ☐   |     | Anemia (low red blood cell count)
| ☐   |     | *Dermatitis/eczema (inflammation of the skin)
| ☐   |     | *Pain or tingling sensations in your limbs
| ☐   |     | *Syncope (fainting)

**Smoking**

Have you ever smoked tobacco?  □ Yes  □ No

If yes, how long did you smoke *OR* how long have you been smoking? ____________________________

How frequently did/do you smoke? ____________________________

**Drinking**

On average, do you drink more than 1 alcoholic beverage per day?  □ Yes  □ No

Do you have a past history of heavy drinking?  □ Yes  □ No
Appendix C: Protocol

PROTOCOL FOR STUDY

I. Setup
1. Turn on the laptop.
2. Connect the power supply to PowerLab.
3. Connect the USB cable from PowerLab to the laptop.
4. Connect the respiration belt to Input 1 on the front panel of PowerLab.
5. Connect the Hand Dynamometer to Input 2 on the front panel of PowerLab.
6. Connect the power supply to the Laser Doppler Flow (LDF) system and turn it on.
7. Connect the skin probes to Channels 1 and 2 on the LDF system.
8. Connect the BNC cables from the LDF system to Inputs 3 and 4 on the front panel of PowerLab.
9. Turn on the PowerLab system.
10. Open LabChart on the laptop and open the customized settings file.
   i. The raw breath signal in millivolts (mV), the respiratory rate in breaths per minute (BPM), the handgrip force in Newtons (N), CBF 1 in perfusion units (PU), and CBF 2 in PU should all be displayed in LabChart at this point.

II. Application
1. Seat the participant in a chair with both arms supinated and gently resting on the tray. Ensure that they are comfortable and properly positioned before continuing.
2. Apply the electrodes to the C7 and T4 vertebrae locations, approximately 3 cm to the left and right of the vertebral column (Figure 1).†
3. Wrap the respiration belt around the participant’s chest, just below the xiphoid process.
4. Attach the skin probe connected to Channel 1 of the LDF system to the left arm, 2 cm below the crease of the wrist.
5. Attach the skin probe connected to Channel 2 of the LDF system to the right arm, 2 cm below the crease of the wrist.
6. Wrap the cuff connected to the manual sphygmomanometer around the participant’s left forearm, 2 cm below the crease of the elbow.
7. Wrap the cuff connected to the blood pressure monitor around the participant’s right arm.
8. Instruct the participant to loosely grip the Hand Dynamometer in their dominant hand.
9. Instruct the participant to squeeze the Hand Dynamometer as hard as possible for a second or two, and then relax their grip.*
10. Determine Maximum Voluntary Contraction (MVC) by recording the average of three handgrip trials and calculate 25% of MVC.
III. Treatment

1. Begin treatment according to assigned group code.†
2. Every minute, assess the intensity of the participant’s pain via the NPRS. In addition, halfway through each interval of the treatment i.e. “baseline”, “exercise”, “occlusion”, and “recovery”, record the participant’s blood pressure and heart rate from the monitor.
3. Set the stimulation frequency to 100 Hz, pulse duration to 200 μs, and slowly adjust the intensity to just above sensory threshold (no pain or muscle contraction) by asking the participant when he/she begins to feel a strong, but comfortable tingling sensation.
4. Begin 1 min metronome and instruct participant to verbalize his or her pain level every min.
5. Begin 1.5 min metronome and collect BP & HR data every 1.5 min.
6. Begin recording baseline blood flow for 3 minutes at resting heart rate.
7. Place the hand dynamometer in the participant’s left hand. Instruct the participant to perform a static handgrip exercise for 3 minutes at 25% MVC.
8. Five seconds before exercise completion, inflate the sphygmomanometer cuff to 180 mmHg.¹
9. Maintain cuff inflation at 180 mmHg for 3 minutes, while still recording blood flow.
10. Deflate the cuff immediately and record for 3 minutes.
11. Stop recording.
12. Insert comments for “baseline”, “exercise”, “occlusion”, and “recovery” at the end of each interval.
13. Detach all equipment from the participant and wait at least 10 minutes before beginning the next treatment.

* Adapted from "Effect of transcutaneous electrical nerve stimulation on muscle metaboreflex in healthy young and older subjects." by Vieira, et. al.
† Group codes: Placebo/PECO (P-), Placebo/PECO+ (P+), TENS/PECO (T-), TENS/PECO+ (T+), IFC/PECO (I-), IFC/PECO+ (I+)

† Only if PECO+ group
Appendix D: Face Pain Scale [14]

"Determining Limb Blood Flow Changes in Response to Electrical Stimulation"
SF Questionnaire

Participant: _____________________________  Date: ____________

Ask: “How would you describe your pain based on the following words?” Check one of the columns for each descriptor:

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Throbbing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shooting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stabbing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sharp</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cramping</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gnawing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot-burning</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aching</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Splitting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tiring-exhausting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sickening</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fearful</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Punishing-cruel</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
Appendix F: Paresthesia Questionnaire

"Determining Limb Blood Flow Changes in Response to Electrical Stimulation"
Paresthesia Questionnaire

Participant: ___________________________  Date: ___________

Ask: "How would you describe your feeling based on the following words?" Check one of the columns for each descriptor:

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>None</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tingling</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Tickling</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Pricking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itching</td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>