Minimization of Quadriceps Dysfunction after Anterior Cruciate Ligament Injury

NCT03209531

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UNIVERSITY OF MICHIGAN

CONSENT TO BE PART OF A RESEARCH STUDY

INFORMATION ABOUT THIS FORM

You may be eligible to take part in a research study. This form gives you important information about the study. It describes the purpose of the study, and the risks and possible benefits of participating in the study.

Please take time to review this information carefully. After you have finished, you should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others (for example, your friends, family, or other doctors) about your participation in this study. If you decide to take part in the study, you will be asked to sign this form. Before you sign this form, be sure you understand what the study is about, including the risks and possible benefits to you.

1. GENERAL INFORMATION ABOUT THIS STUDY AND THE RESEARCHERS

1.1 Study title:

Minimization of Quadriceps Dysfunction after Anterior Cruciate Ligament Injury

1.2 Company or agency sponsoring the study

Funding for this Project is provided by National Center of Neuromodulation for Rehabilitation (NC NM4R) under NIH P2CHD086844

1.3 Names, degrees, and affiliations of the researchers conducting the study:

Chandramouli Krishnan, P.T., Ph.D., Department of Physical Medicine and Rehabilitation, University of Michigan

Riann Palmieri-Smith, PhD, ATC, School of Kinesiology, University of Michigan

Edward Wojtys, MD, Department of Orthopedics, University of Michigan

Edward Claflin, M.D., Department of Physical Medicine and Rehabilitation, University of Michigan

2. PURPOSE OF THIS STUDY

2.1 Study purpose:

Thigh muscle weakness and activation deficits (i.e., inability to fully contract the muscles) are common after anterior cruciate ligament (ACL) injury. Loss of thigh muscle strength reduces its ability to serve as a shock absorber during activities of daily living. This can lead to increased strain on the knee and deterioration of the joint (such as osteoarthritis). This research study is being done to learn if thigh muscle weakness and the lack of muscle activation that accompanies ACL injury can be improved by conditioning your brain responses using a form of training called as operant conditioning.

3. INFORMATION ABOUT STUDY PARTICIPANTS (SUBJECTS)

Taking part in this study is completely **voluntary**. You do not have to participate if you don't want to. You may also leave the study at any time. If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled.

It is important to note that your participation in this study does not influence the standard medical treatment that you may or may not be currently receiving.

3.1 Who can take part in this study?

A person between the ages of 18-45 who have undergone ACL-reconstruction surgery can take part in this study. They should be willing to participate in testing and training sessions as outlined in this document. Additionally, all subjects in the study may not:

1) have suffered a previous ACL injury to the contralateral knee;
2) have undergone previous major surgery to the contralateral knee;
3) have a history of recent significant knee injury (other than ACL) or lower-extremity fracture;
4) have a history of uncontrolled diabetes or hypertension;
5) be pregnant or plan to become pregnant;
6) have metal implants in the head;
7) have electronic devices in their ear or heart (e.g., cochlear implants or cardiac pacemakers);
8) have unexplained recurrent headaches;
9) have a recent history of seizures;
10) be taking drugs that reduce seizure threshold;
11) have a history of repeated fainting spells;

We will ask you, before you sign up to be part of the study, questions about your health condition/history to ensure you are able to participate. It is important that you accurately report your medical history.

3.2 How many people (subjects) are expected to take part in this study?

32 subjects are expected to participate in this study.

4. INFORMATION ABOUT STUDY PARTICIPATION

4.1 What will happen to me in this study?

If you choose to participate, you will be randomly assigned (e.g., like a flip of a coin) to one of the two groups:

- If you are in Group 1, you will receive magnetic stimulation of the brain, and will be asked to train the brain responses produced by the stimulation.
- If you are in Group 2, you will receive magnetic stimulation of the brain, but will not be required to train your brain responses.

Regardless of group allocation you will be asked to report for training up to 3 times per week for up to 8 weeks. You will report for study treatments once you have undergone sufficient rehabilitation prescribed by your doctor and/or therapists after ACL surgery (approximately 4-6 months after surgery). During your initial visit, we will ask you to fill out several questionnaires about your general health, physical activity level, and any pain you may experience in your knee. You are free to skip any questions that you do not wish to answer. Then we will do some basic physical tests. For example, we may move your legs manually, measure how far you can bend your joints, check the looseness of your knee joint, and check for any swelling in your knee. It is recommended that you do not workout heavily or consume alcohol 24 hours prior to your participation in testing or training sessions as it minimizes confounding effects or any unforeseeable risks.

Study Testing Measurement Sessions

All study related measurements may be performed before, during, and immediately after 8-weeks of training.

In this part of the study, we will test

- your thigh muscle strength
- your ability to fully contract your muscles during strength testing
- your brain excitability and responses to magnetic stimulation

All testing procedures may be performed on both legs in a pre-determined order.

You may do these tests in any sequential order determined by the researchers depending on your time and availability for testing. These testing sessions will happen over a period of 1-2 weeks.

Quadriceps Strength and Activation Testing

- First, if you would like to warm-up your muscles, you will be provided with an opportunity to do some light exercise (e.g., exercise bike or stretching).
- Following which, we will clean your skin with alcohol wipes and may place electromyographic (EMG) electrodes (sensors) on the skin over your thigh and leg muscles. The electrodes are similar to EKG sensors that doctors use for heart exams. You will not feel the electrodes working.
- You will sit on a chair attached to a system that measures the strength of your leg muscles (Picture 1). Your leg will be attached to the system through a series of straps.
- We will place additional electrodes on the top and bottom of your thigh muscles. These electrodes will send electrical pulses into your muscles, causing them to contract. We will send only as much electricity as necessary to result in a complete muscle contraction.



Picture 1 – Schematic of a subject strapped onto a strength testing device

- You will then practice kicking/pulling against the device at 50-100% of your perceived maximum effort. You will rest for one or two minutes, and then you will kick/pull your leg muscles as hard as you can 3-5 times. We will send electrical pulses into your muscles during and directly after each kick. Throughout the testing, we will regularly ask about your comfort, please let us know if you are having any issues.
- After completing your testing session, we will schedule you for your next visit.
- These procedures may take about 1 hour during each testing and may be repeated for up to 5 times during the course of this study.

Measures of brain output

In our lab, we have a system that allows us to measure brain excitability in a noninvasive manner. To measure this, we will use a device called as transcranial magnetic stimulation (TMS) (Picture 2). Essentially, this device stimulates the nerves in the brain with a magnetic field. Because the device uses a magnetic field, the procedure is of minimal discomfort to you.

- First, we will place EMG sensors and have you sit on the strength testing device and firmly secured to it using several straps. We may then attach reflective markers on your head and place an apparatus on top of your head.
- Using a moderate magnetic stimulation level, we will then find the best position to stimulate the brain area that controls your muscles. During this procedure you will feel your muscle twitching but should not feel any pain.



Picture 2 – Picture of a TMS device

- Once the best stimulation area (hotspot) is found we will mark it using our camera system or a pen marker with washable ink.
- We will then stimulate your brain using different levels of magnetic stimulation while exerting a small contraction to establish stimulus-response curves (i.e., the characteristics of the link between your brain and your muscle). This will also establish your baseline brain excitability.
- You will then receive several TMS pulses while exerting constant muscle contraction, which will provide us your baseline control responses. During this procedure you will feel your leg muscles twitching, but it is not uncommon to have twitching occur in the face muscles due to stimulation. Throughout the testing, we will regularly ask about your comfort, please let us know if you are having any issues.
- After completing your testing session, we will schedule you for your next visit.
- These procedures may take about 2-3 hours and may be repeated for up to 7 times during the course of this study.

Questionnaires

We will provide you with a series of questions about how your knee feels and how you feel about performing activity. We will allow you to fill these out on your own while in the laboratory or we can read them to you and you can answer the questions verbally.

Training for Group 1 (Operant Conditioning of Brain Responses)

If you are assigned to Group 1, you will be trained to condition your brain responses produced by magnetic stimulation.

- First, we will place EMG sensors and have you sit on the strength testing device. We will firmly secure you to the device using several straps. We may then attach reflective markers on your head and place an apparatus on top of your head.
- We will then stimulate your thigh muscles a few times.
- Following which, we will determine the hotspot and baseline brain excitability as described before. You will then be required to consistently maintain a weak force against the device during which you will receive magnetic stimulation. During this time, you will receive feedback on the magnitude of responses produced from your brain due to magnetic stimulation. You will be encouraged to use this feedback and alter the responses such that you augment the responses each time above a set criterion. This conditioning procedure will occur for all training sessions.
- Each training session will last about 1-2 hours and will be repeated up to 3 times per week for up to 8 weeks.

Training for Group 2

If you are assigned to Group 2, you will perform everything identical to Group 1, except that you will not be required to condition your brain responses (i.e., you will not be encouraged to alter the responses from your brain).

As a subject participating in this research study, you have certain responsibilities that may apply to this study, such as ensuring that you arrive at all of your scheduled appointments and report any adverse reactions you may have during the study.

At the end of this form, you will have the option of allowing us to take photographs and/or make audio or videotape recordings of you, which may be used in medical or scientific publications and presentations. We may publish and present photographs, audio recordings, and videos of you, which may include your face, depending on your decision. No other personal information about you will be included in the presentation. Consenting for taking photographs or video is optional. Even if you don't give us permission to take photographs or audio/video recordings, you can still take part in this study. You have the option to indicate your choice by placing your signatures in front of each part.

At the end of this consent form, you will also be asked whether or not you want to be contacted for future studies in our lab or by other researchers. If you decide that you would like to be contacted, please provide your consent by placing your signature in the appropriate location.

4.2 How much of my time will be needed to take part in this study?

Your participation in this study will last for approximately six months to a year and will involve up to 37 visits. These visits would include both training (about 24 visits) and testing sessions (about 13 visits). The actual number of testing and training sessions may vary depending on your availability. For e.g., the number of visits could reduce if we perform multiple evaluations during a single testing session. Each testing session will last about 2-3 hours and each training session will last about 1-2 hours.

4.3 When will my participation in the study be over?

Most subjects will complete their part of the study within 6 months to a year. The entire study is expected to last about 3 years. However, your data may be retained indefinitely for further analysis and for future purposes. We will take adequate measures to ensure that your information is secured and protected (please see section 9.0).

5. INFORMATION ABOUT RISKS AND BENEFITS

5.1 What risks will I face by taking part in the study? What will the researchers do to protect me against these risks?

The known or expected risks and the procedures that the researchers will undertake to minimize risks are listed below:

- **Allergic reactions (infrequent):** You may experience allergic reactions from the application of electrode paste and adhesive tapes necessary for attaching electrodes or markers. We will use hypoallergenic tapes to minimize allergic reactions. If redness or excessive itching occurs, the area will be monitored closely by study staff and testing will be ended at their discretion or in accordance with your wishes.
- **Skin irritation (infrequent):** You may experience some skin irritation from the tapes and sensors attached to your body, especially when removing them. This should be temporary and should usually go away by applying skin lotion. You may decide to shave your legs before the study visit.
- **Muscle or Joint Pain and Swelling (Likely):** During or following the experiment, you may feel temporary or persistent muscle aching or joint pain, swelling, or general fatigue. We will provide appropriate rest breaks during the experiment. The level of soreness should not be greater than what would be experienced following a regular exercise session.
- **Discomfort from electrical pulses (Common):** You may feel some discomfort from the electrical pulses we send into your muscles. These electrical pulses are similar to those that patients experience during rehabilitation. A researcher will be present during all study procedures, so you can tell us if you're feeling any discomfort. We will stop the electrical pulses or other procedures any time you ask us to.
- **Muscle Strain, Ligament Sprain, or patellar fracture (rare):** There is a small risk of injury during repeated muscle contractions or electrical stimulation. Current literature indicates that there is a rare chance of patellar fracture in ACL-reconstructed individuals with patellar-tendon graft during exercise and also during strength and activation testing. However, this has been reported only in individuals who are less than 2 months post reconstruction when the graft site is still healing. Since we will be testing you mostly at a time-point that is beyond 2 months (around 4-6 months post-surgery), the incidence of patellar fracture is extremely unlikely. Please let us know if you experience unusual anterior knee pain during testing.
- **Clicking noise and muscle twitching (Common):** You may feel twitches in your arms, face, and leg muscles. A loud clicking noise may be heard during the stimulus. You will have the opportunity to wear foam earplugs that can minimize this discomfort.
- **Transient headache or scalp discomfort (Likely):** There is also a small risk of temporary headaches after TMS. However, these are momentary and typically go away after the completion of the procedure.

- **Lightheadedness/dizziness (Infrequent):** Although not common, you may experience lightheadedness, dizziness or fainting. In the event of such symptoms, the experiment will be stopped. You will have the ability to stop the study at any time by asking the study team to either give you rest or if necessary, remove the device. . If willing, we will resume at a later time. Please let us know if you are prone to get fainting spells as that would exclude you from the study.
- **For women of child-bearing potential:** It is unknown if transcranial magnetic stimulation can pose a risk to fetuses. *To minimize this risk:* You will be asked during screening whether you are pregnant or are trying to become pregnant; you should not take part in this study if you are. Sexually-active women of child-bearing potential are asked to use a reliable birth control method for the duration of this study.
- **Seizures (Rare):** Rare cases have reported the development of seizures during or immediately after magnetic brain stimulation, but these are particularly for repetitive transcranial magnetic stimulation protocols (where burst of TMS pulses are used to modulate cortical excitability). To be extra-cautious, if you have had a recent history of seizures (< 6 months), you will be evaluated for the study participation in consultation with the physician on this study and would be excluded from this research study if recommended.
- **Unforeseeable Risks:** As with any research study, there may be additional risks that are unknown or unexpected. If you have any questions or are unsure about anything outlined below please do not hesitate to ask Dr. Krishnan or his associates.

5.2 What happens if I get hurt, become sick, or have other problems as a result of this research?

The researchers have taken steps to minimize the risks of this study. Even so, you may still have problems or side effects, even when the researchers are careful to avoid them. Please tell the researchers listed in Section 10 about any injuries, side effects, or other problems that you have during this study. You should also tell your regular doctors**.**

5.3 If I take part in this study, can I also participate in other studies?

Being in more than one research study at the same time, or even at different times, may increase the risks to you. It may also affect the results of the studies. You should not take part in more than one study without approval from the researchers involved in each study.

5.4 How could I benefit if I take part in this study? How could others benefit?

You may not receive any personal benefits from being in this study. Your participation will be of benefit to medical science and the knowledge generated may have important implications for designing therapeutic interventions to decrease quadriceps dysfunction after ACL injury.

5.5 Will the researchers tell me if they learn of new information that could change my willingness to stay in this study?

Yes, the researchers will tell you if they learn of important new information that may change your willingness to stay in this study. If new information is provided to you after you have joined the study, it is possible that you may be asked to sign a new consent form that includes the new information.

6. OTHER OPTIONS

6.1 If I decide not to take part in this study, what other options do I have?

Since your participation is voluntary, you may decide not to take part in the study at any time without penalty. Your other option is not to participate. If you choose not to participate, this will not negatively affect your relationship with your doctor or your physical therapists/athletic trainers in any way. Standard ACL rehabilitation (e.g., standard of care rehabilitation) will take place regardless of your participation in this research.

7. ENDING THE STUDY

7.1 If I want to stop participating in the study, what should I do?

You are free to leave the study at any time. If you leave the study before it is finished, there will be no penalty to you. You will not lose any benefits to which you may otherwise be entitled. If you choose to tell the researchers why you are leaving the study, your reasons for leaving may be kept as part of the study record. If you decide to leave the study before it is finished, please tell one of the persons listed in Section 10 "Contact Information" (below).

7.2 Could there be any harm to me if I decide to leave the study before it is finished?

No, there is no harm associated with leaving the study before it is finished. You may choose to leave the study at any time.

7.3 Could the researchers take me out of the study even if I want to continue to participate?

Yes. There are many reasons why the researchers may need to end your participation in the study. Some examples are:

- ✓ The researcher believes that it is not in your best interest to stay in the study.
- ✓ You become ineligible to participate.
- ✓ Your condition changes and you need treatment that is not allowed while you are taking part in the study.
- ✓ You do not follow instructions from the researchers.
- ✓ The study is suspended or canceled.

8. FINANCIAL INFORMATION

8.1 Who will pay for the costs of the study? Will I or my health plan be billed for any costs of the study?

The study will pay for research-related items or services that are provided only because you are in the study. If you are not sure what these are, see Section 4.1 above or ask the researchers for a list. If you get a bill you think is wrong, call the researchers' number listed in section 10.1.

You or your health plan will pay for all the things you would have paid for even if you were not in the study, like:

- Health care given during the study as part of your regular care
- Items or services needed to give you study drugs or devices
- Monitoring for side effects or other problems
- Deductibles or co-pays for these items or services.

By signing this form, you do not give up your right to seek payment if you are harmed as a result of being in this study.

8.2 Will I be paid or given anything for taking part in this study?

You will receive $10 per hour for each session in which you participate. You will receive the payment upon the completion of study participation.

8.3 Who could profit or financially benefit from the study results?

No person or organization has a financial interest in the outcome of the study.

9. CONFIDENTIALITY OF SUBJECT RECORDS AND AUTHORIZATION TO RELEASE YOUR PROTECTED HEALTH INFORMATION

The information below describes how your privacy and the confidentiality of your research records will be protected in this study.

9.1 How will the researchers protect my privacy?

- In any publications that result from this research report, neither your name, nor any information from which you may be identified will be published without your consent.

- Research records will be kept in a separate research file that does not include names, registration numbers, or other information that is likely to allow someone other than the researchers to link the information to you.
- Personal identifiers will be removed from the data before we share any of this information with anyone else.
- Only the research investigators of this study will have access to the list that connects identifying information with your information. This will be kept in a locked cabinet in the PI's office or lab.

9.2 What information about me could be seen by the researchers or by other people? Why? Who might see it?

Signing this form gives the researchers your permission to obtain, use, and share information about you for this study, and is required in order for you to take part in the study. Information about you may be obtained from any hospital, doctor, and other health care provider involved in your care, including:

- Hospital/doctor's office records, including test results (X-rays, blood tests, urine tests, etc.)
- All records relating to your condition, the treatment you have received, and your response to the treatment.
- Demographic information
- Personal identifiers

There are many reasons why information about you may be used or seen by the researchers or others during or after this study. Examples include:

- The researchers may need the information to make sure you can take part in the study.
- The researchers may need the information to check your test results or look for side effects.
- University, Food and Drug Administration (FDA) and/or other government officials, auditors, and/or the IRB may need the information to make sure that the study is done in a safe and proper manner.
- Study sponsors or funders, or safety monitors or committees, may need the information to:
  - Make sure the study is done safely and properly
  - Learn more about side effects
  - Analyze the results of the study
- Insurance companies or other organizations may need the information in order to pay your medical bills or other costs of your participation in the study.
- The researchers may need to use the information to create a databank of information about your condition or its treatment.
- Information about your study participation may be included in your regular UMHS medical record.
- If you receive any payments for taking part in this study, the University of Michigan accounting department may need your name, address, social security number, payment amount, and related information for tax reporting purposes.
- Federal or State law may require the study team to give information to government agencies. For example, to prevent harm to you or others, or for public health reasons.

The results of this study could be published in an article, but would not include any information that would let others know who you are. If your name or other information that might identify you will be used in the publications or presentations, the researchers will ask for your separate written permission.

If your name and pictures will be used in any publications or presentations, the researchers will ask for your separate written permission.

A description of this clinical trial will be available on http://www.clinicaltrials.gov/, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this website at any time.

9.3 What happens to information about me after the study is over or if I cancel my permission?

As a rule, the researchers will not continue to use or disclose information about you, but will keep it secure until it is destroyed. Sometimes, it may be necessary for information about you to continue to be used or disclosed, even after you have canceled your permission or the study is over.

Examples of reasons for this include:

- To avoid losing study results that have already included your information
- To provide limited information for research, education, or other activities (This information would not include your name, social security number, or anything else that could let others know who you are.)
- To help University and government officials make sure that the study was conducted properly

As long as your information is kept within the University of Michigan Health System, it is protected by the Health System's privacy policies. For more information about these policies, ask for a copy of the University of Michigan "Notice of Privacy Practices". This information is also available on the web at http://www.uofmhealth.org/patient+and+visitor+guide/hipaa. Note that once your information has been shared with others as described under Question 9.2, it may no longer be protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA).

9.4 When does my permission expire?

Your permission will not expire unless you cancel it. You may cancel your permission at any time by writing to the researchers listed in Section 10 "Contact Information" (below).

10. CONTACT INFORMATION

10.1 Who can I contact about this study?

Please contact the researchers listed below to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Talk about study-related costs to you or your health plan
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal Investigator: Dr. Chandramouli Krishnan, P.T., Ph.D.
Mailing Address: 325 E. Eisenhower Parkway, Suite 3013, Ann Arbor, MI - 48108
Telephone (Cell): 734.936.4031

You may also express a concern about a study by contacting the Institutional Review Board listed below.

University of Michigan Medical School Institutional Review Board (IRBMED)
2800 Plymouth Road
Building 520, Room 3214
Ann Arbor, MI 48109-2800
Telephone: 734-763-4768 (For International Studies: US Country Code: 001)
Fax: 734-763-1234
e-mail: irbmed@umich.edu

If you are concerned about a possible violation of your privacy or concerned about a study you may contact the University of Michigan Health System Compliance Help Line at 1-866-990-0111.

When you call or write about a concern, please provide as much information as possible, including the name of the researcher, the IRBMED number (at the top of this form), and details about the problem. This will help University officials to look into your concern. When reporting a concern, you do not have to give your name unless you want to.

11. RECORD OF INFORMATION PROVIDED

11.1 What documents will be given to me?

Your signature in the next section means that you have received copies of all of the following documents:

- This "Consent to be Part of a Research Study" document. (*Note: In addition to the copy you receive, copies of this document will be stored in a separate confidential research file and may be entered into your regular University of Michigan medical record.)*

12. SIGNATURES

Consent to Participate in the Research Study

I understand the information printed on this form. I have discussed this study, its risks and potential benefits, and my other choices with _____ (Study Team Member). My questions so far have been answered. I understand that if I have more questions or concerns about the study or my participation as a research subject, I may contact one of the people listed in Section 10 (above). I understand that I will receive a copy of this form at the time I sign it and later upon request. I understand that if my ability to consent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Consent to be contacted for future/other ongoing studies

I understand that I may be eligible for other ongoing or future studies in the lab. I would like to be contacted for any other ongoing or future studies.

Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Consent for using photographs/videos to be used in presentations/publications

I consent for using my photographs/videos to be used in presentations or publications, including medical journals, textbooks, and electronic publications. I understand that the image may be seen by members of the general public, in addition to scientists and medical researchers that regularly use these publications in their professional education. I also agree for my photographs or videos to be shown for teaching purposes.

Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Principal Investigator or Designee

I have provided this participant and/or his/her legally authorized representative(s) with information about this study that I believe to be accurate and complete. The participant and/or his/her legally authorized representative(s) indicated that he or she understands the nature of the study, including risks and benefits of participating.

Legal Name: _____

Title: _____

Signature: _____

Date of Signature (mm/dd/yy): _____