ACCELEROMETER MOTION TO MEASURE MUSCLE FATIGUE IN CRITICALLY ILL PATIENTS

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1. Full title: Accelerometer motion to measure muscle fatigue in critically ill patients

Short title: ICU Acquired Weakness

Principal Investigator: Randi N. Smith, MD, MPH

Co-Investigators: Kyle Brandenberger, PhD
Rondi Gelbard, MD

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2. Introduction and background

The primary purpose of this study is to develop a procedure to identify intensive care unit (ICU) acquired weakness. This condition occurs in a subset of people admitted into the ICU, and is associated with a 30% increased risk of death before discharge from the ICU.[1] There are currently major limitations in the ability to diagnose ICU acquired weakness, making it difficult to study.[2] The goal is to develop a non-invasive test that can be administered to both responsive and non-responsive patients. The current proposal will focus on replicating the results of previous research using motion detecting accelerometers to measure fatigue in human skeletal muscles (Willingham and McCully). This study is designed to test out the procedures in patients who have been transferred from the ICU to a lower level of care so that follow-on studies can be designed to help mitigate this condition in the ICU.

3. Objectives

Objective 1: To identify patterns of muscle fatigue that are distinct for patients with ICU acquired weakness

Objective 2: To identify differences in accelerometer data that appear only in the ICU acquired weakness group for later use as diagnostic criteria.

Objective 3: To develop a diagnostic tool for identifying ICU acquired weakness earlier in the patient's care.

The procedures outlined in this study will advance this objective by providing data that can be analyzed based on whether the subjects have ICU acquired weakness or not based on the current testing procedures.

4. Study Design and Methods

Subjects will undergo a clinical strength assessments to classify them based on whether they test positive for ICU acquired weakness. Manual muscle testing will be performed based on the medical research council (MRC) score. A score of < 48 will classify the subject was having ICU acquired weakness placing them in the "weak" group. Subjects with scores exceeding 48 will be placed into the "not weak" group.

Potential subjects will be approached regarding participation in this study. They will be provided with a written consent form, and allowed adequate time to read the form. After reading, they will

be given a chance to ask questions. If they decide to participate, they will be asked to sign the consent form.

Subjects will then be asked to fill out a health history form. The subjects will then be escorted to a clinical electrical stimulator. We plan to test a variety of skeletal muscles to ensure mastery of the technique. Conductive electrodes will be on the skin at each end of the tested muscle(s). Each subject will have two target muscle groups tested (extensor carpi radialis longus, and tibialis anterior). Each muscle will be stimulated at three separate stimulation frequencies (2 Hz, 4 Hz, and 6Hz) over 3 minutes each, for a total of 9 minutes of stimulation per muscle. The clinical electrical stimulator will then deliver mild electrical stimulations to the muscle (20-100 mA). This intensity of stimulation typically produces only mild discomfort typical of muscle contraction. The clinical stimulator has a maximum output of 110 mA, phase duration 1,000 microseconds, 250 Hz. Any stimulation delivering 25 microcoulombs or higher cannot travel through the thorax because of the risk of cardiac arrhythmias. All stimulations applied in this study will be below this threshold. The stimulation frequencies listed above will be within this safety margin.

The accelerometer used throughout the study will be an Axivity AX3 wireless accelerometer. It will be placed on the muscle belly using double sided tape between the two stimulating electrodes.

Fatigue will be defined as a drop in acceleration from peak acceleration. This will be measured using a triaxial accelerometer over 3 separate stimulation frequencies for a total of 9 minutes of testing per muscle. The device will record 2,160 individual muscle twitches. The highest acceleration over a single muscle twitch will be used as the peak acceleration. The data will then be normalized to this peak acceleration to quantify the percentage of maximal acceleration of each twitch.

The electronic stimulator is currently FDA approved for use in clinical patients so a device determination is not being requested. The accelerometer is passively recording accelerations, with no energy input to the patient. The FDA currently states the following as approved uses for clinical electrical stimulators:

INDICATIONS FOR USE
1. Relaxation of muscle spasms
2. Prevention or retardation of disuse atrophy
3. Increasing local blood circulation
4. Muscle re-education
5. Immediate post-surgical stimulation of calf muscles to prevent venous thrombosis
6. Maintaining or increasing range of motion

Powered muscle stimulators should only be used under medical supervision for adjunctive therapy for the treatment of medical diseases and conditions. Our intended use for the clinical electrical stimulator is to prevent disuse atrophy.

Risks & Discomforts: The risk of pain or discomfort associated with the use of the stimulator is very small and every effort will be made to minimize this. The electrical stimulation procedure occurs at a very low current (20-40 mili-amps) and is not typically associated with pain. There may be an unfamiliar sensation as the muscle contracts, but the majority of subjects will not find this to be uncomfortable. In the event a subject does not tolerate the stimulation, testing on that

subject will cease. Patients may decide not to continue with higher frequencies at any point during the study.

Another risk of participation in the study is a breach of confidentiality. Please refer to the 'Data and Safety Monitoring' section below for a description of how your personally identifiable health information will be protected. No personal information, including names or email addresses, will be made available to anyone outside of Grady, Emory or the GSU team.

There are no psychosocial risks anticipated from this study. If the patient is uncomfortable or wishes to terminate their participation in the study at any time, they may do so. This will not affect their health care treatment. Formal removal from the study can be done by contacting any of the individuals overseeing the study or members of the individual's normal care team at Grady.

Potential Benefits: The patient may or may not receive a direct benefit from participating in this study. The anticipated benefits involve helping patients better manage their condition and follow treatment plans. The information gained from the study may help improve care for future patients.

Data storage: Strict patient confidentiality will be maintained. Data other than the health history forms will be collected via a triaxial accelerometer and downloaded directly to a Georgia State University computer. This data will be stored on the computer and backed up to a digital storage device that is locked inside filing cabinet inside a locked office. Only the researchers listed on this application will have access to the data. Following the completion of this study, data will be maintained on a university computer. Any paper records will be stored in the manner listed above. All patient information will be de-identified prior to post-study analysis.

5. Participant selection

Requested Sample Size: 150 (extra 50 to account for subject drop outs)

Inclusion criteria:
1. Patients ≥18 years of age
2. Patients transferred from the ICU to a lower level of care within the past 7 days
3. Mechanical ventilation for greater than 7 days while in the ICU
4. Ability to understand English and provide written consent

Exclusion criteria:
1. Vulnerable populations including: patients who are pregnant or prisoners
2. Patients who are unable to understand English or provide written consent

Subject recruitment plan:
Screening for eligibility: Targeted patients will include those recently transferred from the ICU to a lower level of care within the hospital. Following routine care, patient records will be reviewed and patients will be asked if they are interested in joining this study and if they meet the aforementioned inclusion and exclusion criteria.

Withdrawal from study: Formal removal from the study can be done by contacting any of the individuals overseeing the study or members of the individual's normal care team at Grady. This

can be done at any time without affecting the patient's ability to obtain routine follow-up care from the post-op clinic or care staff.

Informed consent: Consent will be obtained from patients by a trained research assistant or trained member of the study staff. As mentioned above, patients will be identified as meeting inclusion criteria at the time of transfer from the ICU. If they are eligible, the research assistant will approach them with the opportunity of enrolling in the study. At the time, all potential risks, benefits, and procedures related to participating in the study will be explained as described on the informed consent form. The patients will be given the attached informed consent form and, in the case that they sign it, will begin the on-boarding process for enrollment. All patients have the option to avoid enrollment into the study and can end participation in the study at any time, as described above. Patients will be randomly selected and enrolled by research assistants, rather than directly by the principal investigator, minimizing the risk of coercion.

6. Statistical Analysis

Data will be split into 2 groups (weak vs non-weak) based on clinical strength assessment scores. A 2 factor ANOVA will be used to compare peak acceleration, time to peak acceleration, end acceleration, and fatigue ratio based on group (weak vs non-weak) and stimulation frequency (2 Hz, 4 Hz, 6 Hz). We are collecting 9 minutes of accelerometer data for each muscle, and MRC scores for each subject. A post-hoc analysis with Bonferroni correction will be used to identify where differences occur.

7. Adverse event reporting

The probability of adverse events remains extremely low given the nature of this intervention, but patients can report all events directly to the study staff. Depending on the nature of the event, the individual's participation in the study may be terminated. In the case of a data leak or HIPAA violation, the study staff will jointly address the nature of the leak and determine if any PHI has been leaked. Beyond this, standard HIPAA reporting guidelines will be followed.

8. Data and Safety Monitoring Plan

No personally identifiable (PI) information will be shared with anyone outside of the research team or patient's care team. Any data shared following completion of the study will be de-identified prior to use, protecting the patients' PHI and abiding by the HIPAA Privacy Rules. The only foreseeable disclosure of data beyond the study is in the case of publication of data.

If any breaches in confidentiality or identifying information are identified, the PI will notify the IRB using the eIRB adverse event reporting system within 48 hours. All protected health information will be destroyed within five years after study publication. All HIPAA-mandated federal regulations will be followed accordingly.

Adherence to the IRB-approved protocol will be assured by restricting participant enrollment to trained research staff. Research assistants and staff trained in IRB protocol for study enrollment will participate in enrollment. Additionally, study staff and corresponding research assistants will be briefed on study protocol prior to the beginning of the study to assure that the correct procedure and guidelines are followed.

9. References

1. Hermans, G., Van Mechelen, H., Clerckx, B., Vanhullebusch, T., Mesotten, D., Wilmer, A., Van Cromphaut, S. (2014). Acute outcomes and 1-year mortality of intensive care unit–acquired weakness. A cohort study and propensity-matched analysis. *American journal of respiratory and critical care medicine, 190*(4), 410-420.

2. Jolley, S. E., Bunnell, A. E., & Hough, C. L. (2016). ICU-acquired weakness. *Chest, 150*(5), 1129-1140.

3. Willingham TB, McCully KK, Raeder C, Wiewelhove T, Schneider C, Döweling A, Kellmann M, Meyer T, Pfeiffer M, Ferrauti A, Gravestock HJ. Assessment of skeletal muscle endurance using twitch electrical stimulation and accelerometer-based mechanomyography. Advances in Skeletal Muscle Function Assessment. 2017.1;1(2):9.