Testing of a new Therapeutic Vibration Device to reduce neuromuscular weakness in hospitalized patients.

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Testing of a New Therapeutic Vibration Device to Reduce Neuromuscular Weakness in Hospitalized Patients

Principal Investigator: Benjamin Bassin, University of Michigan: Department of Emergency Medicine

Objective: Test the ability of axial vibration to produce physiologic, biochemical, and anatomic changes consistent with exercise that would help mitigate the development of myopathy associated with prolonged immobilization.

Specific Aims:

1) Phase I: In healthy volunteer subjects, test the ability of low frequency vibration at various frequencies to produce muscle contraction activity, tissue oxygenation changes, oxygen consumption changes (only healthy volunteers), biochemical changes, and anatomical changes consistent with moderate physical activity and favorable effects of vibration.
2) Phase II: In critically ill patient subjects, test the ability of low frequency vibration at various frequencies to produce muscle contraction activity, tissue oxygenation, biochemical, and anatomical changes consistent with moderate physical activity and favorable effects of vibration.

Background Information:

During critical illness, patients who are immobilized for more than a few days develop neuromuscular weakness despite receiving full supportive care, which may include physical therapy. In patients requiring mechanical ventilation for longer than 7 days, the incidence of ICU-acquired (neuromuscular) weakness is reported to be between 25% and 60%. Such weakness may contribute to increased duration of mechanical ventilation, increased length of stay in the ICU and hospital, and poor quality of life among survivors. This is part of the newly recognized Post Intensive Care Syndrome (PICS). Moreover, patients who are transferred from the ICU to a high-dependency unit (HDU), intensive therapy unit (ITU), post-operative therapy or outpatient ambulatory care need to be mobile as well as awake for any physical therapy. Patients affected by sepsis, osteoarthritis, spinal cord injury, stroke, multiple sclerosis, cerebral palsy, cancer suffer muscle loss and weakness. Early mobilization (EM) has demonstrated the ability to significantly reduce the detrimental effects of prolonged immobilization such as polyneuropathy and myopathy, which in turn reduces the time patients spend on mechanical ventilation and the overall length of hospital stay. EM treatments include intense physical therapy, cycle ergometry, transcutaneous electrical muscle stimulation (TEMS) and continuous lateral rotational therapy (CLRT). However, scaling of intense physical therapy using therapists is impractical (especially at smaller hospitals) and cannot be implemented in heavily sedated patients. Evidence suggests that whole body vibration may be capable of producing adequate muscle contraction via muscle-spinal loops that may be sufficient to reduce the myopathy and neuropathy of prolonged immobilization thus serving as an effective countermeasure for muscle atrophy.

The purpose of this study is to test a prototype axial vibration device and strategy on its ability to activate large muscle groups, increase muscle blood flow, modulate tissue oxygenation, and increase circulating levels of metabolites associated with exercise/activity. The study will be used to find optimal vibration frequencies that provide maximal signatures associated with muscle and bone stimulation and activity. Eventually we envisage our vibration device to deliver a more effective therapy compared to the incremental gains derived from traditional measures of physical therapy in critically ill patients such

as TEMS, CLRT and cycle ergometry to patients. It may directly benefit the patient in terms of health, length of stay and reduced re-admission, hospital staff in terms of productivity (i.e., through reduction in nursing effort) and the hospital in terms of improved costs/margins and return on investment. Its utility is also envisioned in many other populations of immobilized acutely ill and injured patients as well as those with chronic conditions.

Muscle response and adaptation to vibrating force seems to be influenced by the characteristics of the input signal, i.e., frequency and amplitude, as well as muscle tension [4]. Experiments carried on the muscle-tendon unit have shown that muscle vibration is a strong proprioceptive stimulus that reaches both the primary somatosensory and motor cortices directly and that the frequency exerts a dependent effect on the Ia afferent firing rate that is reflected in differential frequency-dependent effects on corticospinal motor neuron excitability. Thus, the elevated muscle activity during whole body vibration, rely on the level of vibration and explain how the muscle activity in the lower extremity muscles could be dependent on the changes in the accelerations (i.e., the frequency and/or amplitude) delivered by the device [5].

The therapeutic vibration device we have created is based on a unique design, which has not been utilized by any previous commercial vibration therapy device. The device does not experience loss of vibration intensity and provides the flexibility of multi-dimensional parameter adjustments. It is capable of applying force through the axial skeletal spine, through bidirectional compression loading (or prestressing) between the shoulder and the plantar surfaces of the feet. It is placed around the body like a mobile frame so that the applied vibration can affect the whole body. The vibration actuators (drivers) are mobile and can vary in size, frequency response, and force. The design minimizes the possibility of mechanical interference for ventilated/intubated patients.

The device consists of the following parts:

1. Shoulder cups with inner layer of padding
2. Knee braces with inner layer of padding
3. Leg braces with inner layer of padding
4. Axial pre-stressing system using bands and straps from shoulders to legs
5. Vibration actuators (with amplifiers)

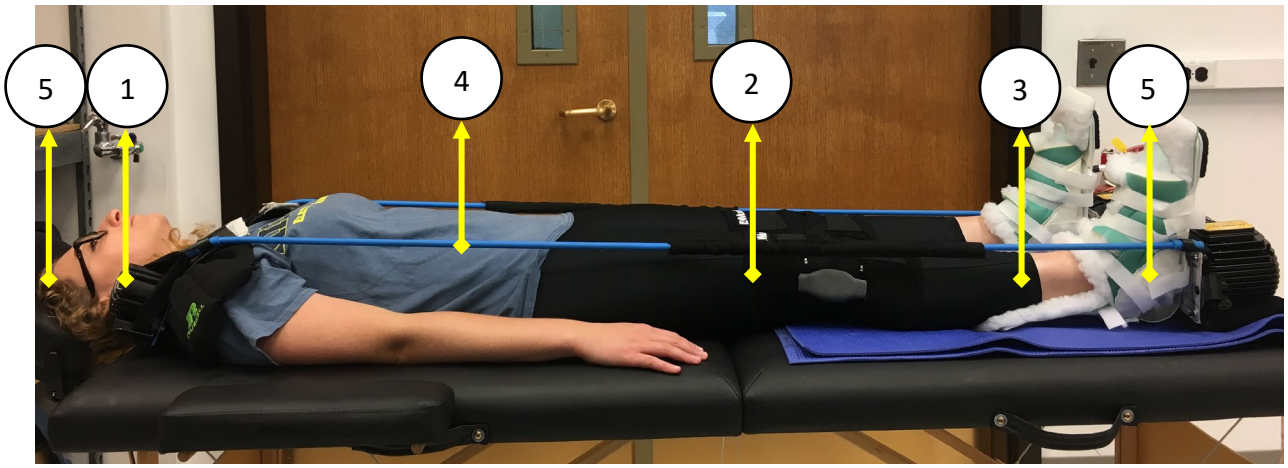

Figure 1. Therapeutic vibration device

The present prototype shoulder cups are built from Nylon 12 with stiffer inner pad lining at the shoulder interfaces. The leg braces, commercially known as PRAFO® Orthosis is a flagship product of M/s Anatomical Concepts, Inc., with a Polyurethane Foam Pad replaceable liner. The adjustable hinged knee braces are commercial off-the-shelf items, supplied by Mueller Sports Medicine, Inc. The hinges of the braces have been flipped to lock the knee joint to ensure maximum transmission of vibration through the bones axially. The resistance bands are also commercially off the shelf items and provide the necessary prestressing. Prestressing of the modular braces using resistance bands is essential to establish a proper fit and an effective vibration transmission. The actuators are driven by amplifiers, which handle all needed frequencies. The current prototype utilizes different size inertial actuators for different parts of the body. The vibration actuators, commercially known as Buttkicker have been sourced from M/s Guitammer Company. The bigger vibration actuators, mounted on the plantar side of the feet operate in the frequency range of 20 Hz – 40 Hz, as it has been identified as an optimal range for the lower part of the body [1-3]. The smaller vibration actuators mounted on the shoulders provide an excitation frequency in the range of 5 Hz -15 Hz, as the range of 7 Hz - 15 Hz for the upper part of the body is considered optimal [1-3].

Replaceable liners will be used between subjects for both knee braces and shoulder cups/leg braces.

Methodology

The modular structure allows us to target the upper, core, and body in combination. Our experiments test both single actuator applications (single frequency) and multiple actuator (multiple frequency) applications. We will test two protocols to identify the optimal frequencies and amplitudes (intensity of vibration) to achieve optimal physiologic responses consistent with moderate physical activity.

Exclusion Criteria (Phase I and II): Acute spinal cord injury, acute vertebral body fracture or injury, acute stroke or intracerebral hemorrhage, hemodynamic instability or other event/condition believed by the care team to warrant nonparticipation, known pregnancy, prisoner

Phase I (Healthy Subjects):

1) Single tone excitation (STE). STE experiments involve vibration of the axial skeleton with a single frequency. During the pilot trials, we will deliverer STE therapy to healthy volunteer subjects and measure physiologic changes.
2) Multi-Frequency Excitation (MFE). MFE experiments will utilize different frequencies at different amplitudes to upper and lower parts of the body simultaneously to healthy volunteer subjects and measure physiologic changes.

To compare MFE and STE protocols, we will collect data from same subjects for the same duration of 5 minutes over 4-5 matched episodes but will randomize (using simple computer generated randomization table generated by www.randomizer.org) the application of MFE and STE. During these times, mass loading (through adjusting the tension bands) will changed to test the effect of loading on the physiologic response to vibration. Subjects will be weighed initially and initial mass loading will match the subject's weight based mass. This loading may be increased to understand if an improved physiologic state is achieved using the measures described below.

The following will be measured:

1) Tissue hemoglobin oxygen saturation (StO2) using near infrared spectroscopy of the thighs, biceps, and brain. This measure will at baseline (prior to each vibration episode), continuously during vibration, and then for 30 minutes after vibration.
2) Oxygen consumption (VO2) using a VO2 monitor and mask. This measure will at baseline (prior to each vibration episode), continuously during vibration, and then for 30 minutes after vibration.
3) Muscle contraction using a noninvasive electromyography (EMG). This measure will at baseline (prior to each vibration episode), continuously during vibration, and then for 30 minutes after vibration.
4) Self-selected walking test for recording walking data. The measure will be at baseline. The time required for a subject to walk 10 meters will be recorded and that speed will be selected on the treadmill. The subject will walk for 3 minutes. EMG data will be collected.
5) Blood sampling before and after vibration (10 cc's each) may occur to examine markers that are believed to be associated with serum glucose, lipids, inflammatory cytokines (e.g., IL-6, TNFα, IL-1β), growth hormone, cortisol and bone turnover markers (e.g., C-terminal telopeptide of type I collagen (CTX-I) *and* tartrate-resistant acid phosphatase 5b.

Measures 1-4 above will be made with commercially available devices. Blood assays will be performed in our research laboratories using standard assaying methods.

We anticipated enrolling approximately 50 healthy volunteers.

<u>Phase II (Critically Ill Subjects):</u>

Phase II may begin prior to Phase I completion.

Phase II will consist of trialing optimal loading and frequencies developed in phase I on a targeted population of critically ill or injured subjects who are expected to experience prolonged immobilization in the intensive care unit. Patient subjects may or may not be mechanically ventilated.

These patient subjects will be subjected to a similar series of vibration tuning protocols to maximize physiologic response.

The following will be measured:

1) Tissue hemoglobin oxygen saturation (StO2) using near infrared spectroscopy of the thighs, biceps, and brain. This measure will at baseline (prior to each vibration episode), continuously during vibration, and then for 30 minutes after vibration.
2) Muscle contraction using a noninvasive electromyography (EMG). This measure will at baseline (prior to each vibration episode), continuously during vibration, and then for 30 minutes after vibration.
   Rectus femoris muscle geometry using Ultrasound as a measure of muscle mass preservation. This measure will be made prior to the first vibration episode and then at the end of the enrollment (5 days later).Blood sampling before and after vibration (10 cc samples) to examine markers that are believed to be associated with serum glucose, lipids, inflammatory cytokines (e.g., IL-6, TNFα, IL-1β), growth hormone, cortisol and bone turnover markers (e.g., C-terminal telopeptide of type I collagen (CTX-I) *and* tartrate-resistant acid phosphatase 5b.

Measures 1-3 above will be made with commercially available devices. Blood assays will be performed in our research laboratories using standard assaying methods. We will not measure VO2 on patient subjects due to the complexity of the measure and need for integration into the ventilator circuit.

Patient subjects will be recruited to undergo up to three vibration sessions per day for up to 5 days. Each vibration session is expected to last 5-10 minutes. Blood will be taken prior to the very first vibration session. A second sample of blood will be taken at the end of the last vibration session of the day for each day. A pre-vibration sample will only be obtained on the first day. Thus each patient subject will have a maximum of 5 samples taken during the course of their enrollment.

We anticipated enrolling approximately 50 patient subjects.

Potential Risk and Potential Benefit to the Subjects:

This study is believed to represent minimal risk since whole body vibration platforms are ubiquitous in the their use in the fitness industry and there are several that are FDA approved. None, however are adapted for use for patients immobilized in bed and none have the ability to have their frequencies adjusted.

The potential risks identified with the above project may include the following:

1) Transient muscle soreness
2) Bruising and discomfort from venipuncture (health volunteers). Blood from patient subjects will be taken from pre-existing intravenous catheters.
3) Anemia (patient subjects). We will not obtain blood from patients whose last recorded hemoglobin level is less than 8 mg/dl.
4) Breach of confidentiality

The potential benefits identified to the subjects include:

1) Knowledge that they are contributing to increasing medical knowledge and to a potential technology that will help mitigate the myopathy associated with prolonged immobility.
2) Potential improvement in muscle strength and reduced myopathy (patient subjects).

Statistical Analysis:

Continuous data will be presented as mean (SD) or median (IQR), while categorical data will be presented as percentages. An effect-response analysis will be conducted to describe the effect of changing frequency on the different physiologic responses using a single tone excitation as well as the multi frequency excitation. Effect-response curves will be constructed with the frequencies on the x-axis and the physiologic response on the y-axis. The threshold-effect (desired frequency) will be determined for individual physiologic changes as well as at different combinations.

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