Smart Telehealth Exercise Intervention to Reduce COPD Readmissions

Study Protocol & Statistical Analysis Plan

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We have designed a prospective *randomized controlled* study comparing an early NMES and telehealth remote pulmonary rehabilitation intervention with usual care to determine the impact on respiratory morbidity and also to investigate the mechanisms of such benefit. The primary outcome is the rate of all-cause readmissions within 30 days following an index hospitalization for COPD exacerbation. Secondary outcomes will include change in dyspnea, functional capacity, COPD disease activity and respiratory quality of life, and also changes in skeletal muscle and systemic inflammation.

Sample Size Calculation and Statistical Considerations: We propose enrolling a sample size of convenience of 30 participants randomized to intervention and usual care. We will use the observed effects size for the primary outcome of 30-day readmission to design a larger clinical trial. Standard deviations of measures of secondary outcomes will aid sample size calculations for Specific Aims 2 and 3. Comparisons between groups will be made for continuous variables using independent t-test or Mann-Whitney U-test for non-parametric data, and using chi-square or Fisher's exact test for categorical variables. Comparisons will be deemed to be statistically significant at a two-tailed alpha of 0.05 or less. Multivariable regression models will be created to assess association between the intervention and change in systemic inflammation and other measures such as functional capacity and quality of life indices, as well as muscle biopsy measures. The results of this pilot study will inform sample size for each Aim for a large mechanistic multicenter randomized controlled trial.

Subjects: Consecutive patients admitted to the general medicine or pulmonary floors with a primary diagnosis of acute exacerbation of COPD will be eligible for the study. Subjects will be enrolled within the first 36 hours of admission after written informed consent from the subject. Those with a secondary diagnosis of congestive heart failure and other respiratory conditions that could confound the diagnosis such as pneumonia, bronchiectasis and lung cancer will be excluded. In addition, those on invasive or noninvasive mechanical ventilation will not be enrolled. Participants with pacemakers/defibrillators will not be enrolled due to concern for interaction with NMES.

Protocol/Intervention: Subjects with spirometry proven COPD and hospitalized for an acute exacerbation will be randomized in a 1:1 ratio to either receive remote tele pulmonary rehabilitation intervention or usual care. Usual care will consist of a protocolized regimen of 5 days of systemic steroids, unless the treating physician determines a different regimen, in which case the change will be documented. *NMES training protocol*: Bipolar self-adhesive neuromuscular stimulation electrodes will be placed over the distal-medial and proximal-lateral portion of the quadriceps femoris muscle group. Stimulation pulses (30 Hz trains of 300 μsec biphasic pulses) will be delivered using a Respond II neuromuscular electrical stimulator (Medtronic, San Diego, CA). A 5 sec on/25 sec off work/rest ratio will be used initially, progressing to 10 sec on/30 sec off, as described by Neder.[18] The patient will be fully supported while knee extensions are performed as the participant sits in a chair. Current from the stimulator will be manually increased and determined by patient tolerance. The goal for each patient will be to reach the highest tolerable amplitude (up to 100mA). Training will be performed on each quadriceps femoris muscle, 30 minutes/day, for 2 weeks including hospital stay till return to the COPD Clinic at which time participants will return the NMES equipment. *Remote Telehealth Intervention protocol:* On return to clinic for follow-up, patients will be initiated on remote telehealth pulmonary rehabilitation at home via a data enabled smart phone with video capabilities facilitating two-way conferencing, according to a standardized regimen for a total of 12 weeks. Safety will be monitored by also providing automatic sphygmomanometers to measure blood pressure before and after exercise, as well as heart rate and oxygen saturation assessments using a pulse oximeter. Exercise regimens will be prescribed thrice a week according to standard pulmonary rehabilitation guidelines.[66] Exercise sessions will include aerobic exercises, resistance training and breathing training techniques. Regimens will be individualized according to patients' baseline exercise tolerance as determined by initial six minute walk distance as well as their subjective sense of dyspnea. The study will have 3 aims as follows:

Aim 1: To determine if an NMES and remote tele pulmonary rehabilitation intervention reduces 30-day all cause readmissions in patients hospitalized for acute exacerbation of COPD. All COPD patients hospitalized for an acute exacerbation will be enrolled in an ongoing comprehensive COPD care management intervention, and will be evaluated by a nurse or nurse practitioner in addition to the treating physician, and treated using a standardized order set which includes delivering a uniform duration of five days of antibiotics and systemic steroids. All participants will receive standardized care that includes educational material that encompasses general information about COPD, medications, and red flag symptoms; tobacco cessation counseling for smokers; short interval follow-up at 2 weeks at the COPD Clinic; monthly follow-up at the COPD Clinic; and regular phone calls by a registered nurse to enquire about symptoms as well as to address compliance with inhalers, smoking cessation, physical activity, nutrition, vaccines and coping with a chronic health condition. These calls will be made daily for 2 weeks and then weekly for 3 months. Deterioration in a patient's symptoms will be relayed to physicians for appropriate action. **Measurements:** Exacerbations and hospitalizations will be recorded.

Aim 2: To evaluate the effects of an NMES and remote tele pulmonary rehabilitation intervention on muscle strength, dyspnea and respiratory quality of life in COPD post hospital discharge. Pre and post intervention measurements will be made comparing assessments at 14 days at the time of COPD Clinic visit with assessments at 12 weeks on completion of the intervention. These measurements will be made in both intervention and control arms. **Instruments of Measurement:** (a) Muscle strength of quadriceps using a dynamometer (b) The 30-Second Chair Stand Test to assess skeletal muscle dysfunction, leg strength and endurance (c) Functional capacity using the six minute walk test (d) Physical activity using the Modified Baecke Questionnaire for Older Adults (e) Dyspnea using the San Diego Shortness of Breath Questionnaire and the modified Medical Research Council scores (f) COPD related Quality of life using the COPD Assessment Test (g) Forced expiratory volume in the first second (FEV_1) and (h) Psychosocial Risk Factor Survey (PRFS) to measure the primary psychosocial risk factors of depression, anxiety, anger/hostility, emotional guardedness and social isolation.

Aim 3: To evaluate the effects of NMES and remote tele pulmonary rehabilitation intervention on systemic and muscle inflammation. Pre- and post- intervention assessments will be made of muscle and systemic inflammation at admission and at 4 weeks. **Instruments of Measurement:** (a) Muscle biopsy of the vastus lateralis muscle: Briefly, biopsies will performed under local anesthetic (1% Lidocaine) using a 5 mm Bergstrom type biopsy needle under suction. Approximately 50-70 mg of muscle for immunohistochemistry will be mounted cross-sectionally and frozen in liquid nitrogen-cooled isopentane. Remaining tissue will be snap frozen in ~30 mg portions for biochemical assays. Myofiber type distribution will be assessed using myosin heavy chain (MHC) isoform immunofluorescence microscopy, muscle bioenergetics in response to oxidative stress, and protein cell signaling of the IL-6/STAT3 and TNF-alpha/NF-KB pathways by immunoblotting of muscle tissue protein lysate; (b) Systemic inflammation as assessed by serum C-reactive protein (CRP), serum fibrinogen, plasma TNF-α and plasma interleukin 6.