Does Pulmonary Rehabilitation Improve Frailty in Chronic Lung Disease?

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Introduction and Specific Aims

Frailty is defined as a decreased resistance to disability and illness. The prevalence of frailty is reported to be around 14% in elderly community populations and 17% in advanced heart and lung disease patients.(1, 2) Frailty consists of a constellation of three or more of the following characteristics: wasting, exhaustion, decreased physical activity, slowness, and weakness.(3) Patient's with one or more characteristics are considered "pre-frail" and those with three or more are considered "frail." Frail and pre-frail states are associated with mortality, increased falls, nursing home placements, and hospitalizations in the geriatric general population.(3-6) Frailty is also an important predictor of disease-specific outcomes in those with certain co-morbid conditions such as heart failure and osteoporosis.(3, 4, 7)

Little is known about frailty in patients with chronic lung disease. Emerging evidence by the candidate and others suggests that frailty is important for both mortality and disease-specific outcomes in lung disease patients. Preliminary evidence demonstrates the above-referenced frailty characteristics are common in chronic obstructive pulmonary disease (COPD).(8-13). In addition, this candidate has demonstrated that frailty is associated with increased mortality and hospitalization in COPD. (see preliminary data) Less is known about other chronic lung diseases and frailty. However, this candidate demonstrated that low muscle index (wasting) pretransplant is associated with worse survival and increased primary graft dysfunction following lung transplantation. (see preliminary data)

Effective strategies to improve frailty are unknown. Although patients with moderate to severe lung disease are commonly referred to pulmonary rehabilitation, it is unknown if pulmonary rehabilitation improves frailty or frailty characteristics. The main goal of pulmonary rehabilitation is to improve quality of life in patients with chronic lung disease. Although patients may increase their exercise capacity in pulmonary rehabilitation, this candidate's preliminary data suggests that frailty persists despite pulmonary rehabilitation in some patients. Certain patient factors have been shown to be associated with successful pulmonary rehabilitation.(14) It is unknown if there are patient factors that contribute to frailty improvement following enrollment in pulmonary rehabilitation. Further study examining the benefits and limitations of pulmonary rehabilitation at effectively addressing frailty and frailty characteristics is essential to improving patient outcomes in chronic lung disease.

The long-term goal for this application is to determine effective interventions to improve frailty in patients with moderate to severe lung disease. The *overall objective* of the proposed research is to determine if pulmonary rehabilitation improves frailty characteristics in patients with moderate to severe lung disease. *Our central hypothesis* is that the current model of pulmonary rehabilitation does not optimally address frailty characteristics.

Specific Aim #1 To determine the effectiveness of pulmonary rehabilitation at improving frailty characteristics of slowness (measured gait speed), weakness (grip strength), measured activity, self-reported exhaustion, and wasting (body mass index) in a cohort of patients with moderate to severe pulmonary disease.

Specific Aim #2 To determine if patient characteristics (such as demographics, affect, and uncertainty) are associated with improvement in frailty following pulmonary rehabilitation.

The candidate is uniquely poised to perform this research. She has put together an outstanding team of experts to support her including mentorship expertise in body composition, pulmonary rehabilitation, and frailty, and support from the personnel in the Mayo Clinic Pulmonary Rehabilitation Unit. Importantly, the candidate will have access to a large pulmonary tertiary referral center population and pulmonary rehabilitation facility.

Background and significance

Frailty is defined as a decreased resistance to disability and illness. It is common (as high as 17% in advance lung disease) and associated with important patient outcomes of mortality, hospitalization, and need for nursing home.(1, 2) Frailty consists of a constellation of three or more of the following characteristics: wasting, exhaustion, decreased physical activity, slowness, and weakness.(3) Patient's with one or more characteristics are considered "pre-frail" and those with three or more are considered "frail." Wasting is defined as unexplained weight loss or decrease in lean body mass. It is typically measured by body composition. Exhaustion is typically measured by self-report via questionnaire. Physical activity can be self-reported through questionnaires or, more accurately, directly measured by physical activity monitors. Slowness is typically measured by gait speed (the time it takes an individual to walk 15 feet). Finally, weakness can be measured by respiratory muscle function or hand grip strength. Measures are typically adjusted for sex and height or weight and compared to expected normative values.

Little is known about frailty in patients with chronic lung disease. Emerging evidence suggests that frailty is important for both mortality and disease-specific outcomes in lung disease patients. Evidence demonstrates the above-referenced frailty characteristics are common in chronic obstructive pulmonary disease (COPD). For example, patients with COPD have been noted in separate studies to have wasting(8, 9), fatigue(10), lower physical activity(11), slower gait speed(12), or decreased strength (13). In addition, wasting has been associated with COPD mortality, and increased fatigue has been associated with increased COPD hospitalizations.(8, 10). These studies suggest the possible importance of the frailty phenotype in COPD. In addition, a mixed measure of frailty with functional and sensory deficits that found the mixed measure is associated with increased shortness of breath, health care utilization and disabilities in COPD.(15) A similar constellation of deficits was associated with an increased mortality at 12 years in patients with COPD.(16) Finally, this candidate has demonstrated that frailty is associated with increased mortality and hospitalization in COPD. (see

preliminary data) Less is known about other chronic lung diseases and frailty. However, this candidate demonstrated that low muscle index (wasting) pretransplant is associated with worse survival and increased primary graft dysfunction following lung transplantation. (see preliminary data) Lung transplant candidates are typically a mixed representation of several chronic lung diseases, therefore, suggesting importance of frailty beyond COPD.

In the above mentioned preliminary data, research participants underwent pulmonary rehabilitation. Despite this frailty and frailty characteristics persisted. This suggests that pulmonary rehabilitation alone may be ***insufficient*** to address frailty in its current form. Prior studies have attempted to identify patient factors that lead to success in pulmonary rehabilitation.(14) It is unknown if such factors will be important to successful improvement in frailty characteristics.

Proposed methodology

We propose a single-center, prospective cohort study with **Aim 1**: measurements of frailty characteristics pre- and post-pulmonary rehabilitation referral and **Aim 2**: measurements of baseline affect, uncertainty, and demographics to examine associations between patient characteristics and improvements in frailty characteristics.

Outcomes

Aim 1: Outcomes will include median change in grip strength, gait speed, physical activity, and body composition and comparison of pre and post self-reported exhaustion. In addition, prevalence of frailty and pre-frailty will be compared pre and post pulmonary rehabilitation. **Aim 2:** Associations of positive or negative affect, baseline measure of uncertainty, and demographic factors and median or percent change in frailty characteristics.

Summary of background and significance:

Frailty is common in advanced lung disease and is associated with decreased time to hospitalization, increased length of hospital stay, and increased mortality. In addition, in lung transplant patients frailty is associated with increased primary graft dysfunction and mortality. There is a knowledge gap regarding effective interventions to treat frailty and frailty characteristics. Pulmonary rehabilitation is widely available and utilized in patients with moderate to severe lung disease. Whether pulmonary rehabilitation improves frailty is unknown.

Alignment with career goals:

This proposal aligns perfectly with the candidate's goal of attaining an independent career in clinical research focusing on optimization of pretransplant risks as frailty is prevalent in pretransplant populations and associated with significant transplant risks (mortality and primary graft dysfunction). This work will serve as preliminary data for a future R01 on optimizing pre-transplant risks including frailty. Furthermore, this aligns with the candidates training goals: gaining initial experience in prospective clinical trials and physiologic and psychometric measurements and increasing competitiveness for R01 funding.

Innovation: This application is innovative because:

1. Frailty is a novel risk factor for **death and hospitalization** in moderate to severe lung disease.
2. The ability of pulmonary rehabilitation to improve frailty and frailty characteristics is unknown.

Approach:

Preliminary data

The candidate's preliminary work informs the proposed research approach. The candidate's previous work has been devoted to the study of body composition and frailty in patients with advanced lung disease. The candidate sought to determine if muscle index (a measurement of body composition and therefore wasting) correlated to important outcomes in lung transplant. We conducted a retrospective cohort study of adult lung transplant recipients at Mayo Clinic Rochester with computed tomography images of the lumbar L2-L3 level within six months of transplant. We analyzed these images using Slice-o-matic software, version 4.2 (TomoVision, Magog, Canada) to determine the skeletal muscle index (cm^2/m^2) (a measurement of body composition). Higher skeletal muscle index was beneficial with a hazard ratio (HR) of 0.89 (95% CI 0.81-0.97) and was protective against primary graft dysfunction at 72 hours. In follow-up the candidate sought to determine if frailty was important in advance lung disease patients who do not undergo transplant. Data from the National Emphysema Treatment Trial (NETT) were therefore retrospectively analyzed. 902 patients were included. Frail patients had a worse survival with an adjusted Hazard Ratio (aHR) of 1.57; (CI) 1.08-2.29; p=0.018), decreased time to hospitalization aHR of 1.70 (CI 1.11-2.59; p=0.014) and increased hospital days (adjusted increase of 8 days; CI 5.3-10.7; p<0.0001). Interestingly, both our lung transplant program and the NETT trial required pulmonary rehabilitation as a condition of participation. This suggests that frailty persists in some patient despite pulmonary rehabilitation.

Based on the preliminary data, lowering the risks of frailty in patients with advanced lung disease is an unmet need and further information regarding the efficacy of pulmonary rehabilitation in treating frailty is needed.

Specific Aim #1

Participants and Criteria: Patients will be identified from the Mayo Clinic Rochester, MN Pulmonary Division. Patients who either are referred to enroll in pulmonary rehabilitation at Mayo Clinic in Rochester or who are referred for nursing education regarding pulmonary rehabilitation enrollment will be approached. **Recruitment:** A study referral reminder will be incorporated into the pulmonary rehabilitation referral and pulmonary rehabilitation nursing education referrals. **Inclusion/Exclusion criteria**: Eligible patients will be aged 18 years or older, referred for pulmonary rehabilitation, and consenting to research. **Retention strategy:** Patients will be given remuneration for completing the 3 to 6 month follow-up appointment. **Methods:** This is a single-center, prospective trial examining the effects of pulmonary rehabilitation on frailty and frailty characteristics and associations between patient characteristics and improvement in frailty characteristics. Patient will be approached for recruitment in a private setting regarding willingness to participate in the study by the principal investigator or other authorized study personnel and consented with IRB-approved consent procedure and written consent form. Patients will receive a full explanation of all procedures, risks, benefits, and alternatives and all questions will be answered. Once consented patient will undergo physiologic testing and complete questionnaires. Activity monitors will be sent with patients (including a return addressed envelope with postage) to assess one week of measured activity. At three to six months physiologic testing and activity monitor recordings will be repeated. Patients will also be asked to specify the number of completed pulmonary rehabilitation sessions. **Data: Medical Record Abstraction** Patient demographics, pulmonary diagnoses, weight, height, and pulmonary function tests will be recorded. **Physiologic Measurements and Testing: Grip strength** will be measured using a Jamar Digital Hand Held Dynamometer. Three serial measurements will be taken (using the dominant hand), averaged, and adjusted by gender and BMI using normative table. **Gait Speed** will be measured using a wireless infrared timing system. Self-selected walking speed over a distance of 15 feet will be averaged over 3 trials and then adjusted for gender and height. **Dual Energy X-ray Absorptiometry (DEXA) scan** will determine body composition (body mass, fat mass and fat-free mass) at baseline and at 3-6 months following initiation of pulmonary rehabilitation. **State-of-the-art activity monitors (Sensewear Armband, Body media, Pittsburgh,PA)** will quantify kcals burned, active and sleep time, as well as quality of sleep (baseline and 3 to 6 months following initiation of pulmonary rehabilitation).

Questionnaires

Name of questionnaire	*abbrev*	Purpose of questionnaire	N of items	Cronbach's alpha
Mischel Uncertainty in Illness Scale	*MUIS*	Uncertainty in illness measure	33	0.65-0.90
Positive Affect Negative Affect Schedule	*PANAS*	Positive and negative affect	20	0.84-0.90
Chronic Respiratory Questionnaire	*CRQ*	Disease-specific quality of life measure in lung disease	20	0.84
Short form Health Survey-26	*SF-36*	Exhaustion question only	1	0.82-0.95

Sample size A convenience sample of consecutive prospective consenting patients will be enrolled. This is a pilot study and therefore sample size calculations are not required. However, in order to inform our enrollment we have made the following calculations: **Change in grip strength.** A sample size of 40 per sample will have 80% power to detect a difference in means of 20%, assuming a baseline mean of 28 in women and a standard deviation of 6.3 (as reported for females age range 50-59), using a paired t-test with a 0.05 two-sided significance level.(17) However, given an estimated prevalence of frailty of 17% we would like to recruit at least 100 patients to further study frailty in a larger sample. Based on annual pulmonary rehabilitation participants at Mayo Clinic in Rochester (~150 patients), annual referrals for nursing pulmonary education (~250-300 patients), and a recruitment rate of 80% for similar studies, we feel this is realistic.

Quality Assurance / Quality Controls:

Data abstraction Spreadsheet will be standardized (for definitions and protocol) and audited by PI weekly to ensure selection criteria and protocol compliance and monthly for completion and accuracy.

Personnel training All personnel will be trained to perform the hand grip and gait speed assessments.

Analysis plan:

Patient demographic characteristics will be summarized by mean, median and standard deviation and range (continuous variables) and counts and percents (categorical variables). A two–tailed $p < 0.05$ will be considered statistically significant. Frail performance will be defined as a performance of <20% predicted on physiologic tests. Pre- and post- intervention

tests will be compared using Wilcoxon Signed Rank or paired t-test as appropriate. Subgroup analysis will be performed for frail patients and those completing > 6 and > 12 pulmonary rehabilitation sessions.

Budget

Primary expenses of this project include personnel time, statistical support, and participant remuneration. Dr. Benzo's lab will provide use of the activity monitors. Dr. Kennedy has necessary equipment for gait speed and grip strength determinations. Funding is provided by the Nelson Benefactor Career Development Award.

Timeline: The proposed study enrollment will be completed in the 9 months with most follow-up assessments completed in the one-year time frame.

Protection of human subjects:

Recruitment Procedures will be approved by the Mayo Institutional Review Board.

Data and materials A potential risk is loss of confidentiality. Data will be transferred into a password-protected database in a password-protected computer. Questionnaires will be coded without identifying features and will be stored in a locked cabinet. All data will be reported in composite form.

Physiologic Testing Another potential risk is discomfort, desaturation, or tachycardia during physiologic testing. Subjects will be monitored for adverse symptoms. Supplemental oxygen at the patient's usual settings will be allowed during testing. Clinical emergency response teams provide emergency medical coverage for the CRU and clinical area of Gonda 18. We estimate the risk to patient to be equivalent to daily activities.

Potential benefits Potential benefits of this study include improved knowledge of the benefits of pulmonary rehabilitation and knowledge of frailty performance characteristics.

Inclusion of women, minorities and children: Children will not be represented as frailty risks and pulmonary rehabilitation interventions differ. Our study will include women and minorities. No vulnerable group will be specifically targeted. We expect the minority population to mirror census data. Due to the demographics of the Southeast Minnesota area our targets are 2% black, 2% Asian, 4.5% Hispanic and 4.5% 'other' for an ideal target of 13% minority participation. Of course, health disparities occur in minority use of healthcare services so discrepancies may occur. In order to ensure that women and minorities will be appropriately represented and that the study population will be representative of all eligible patients, the PI will ensure that patients being considered meet criteria and no additional exclusions are applied.

Resources, environment, and personnel

Office space

Dr. Kennedy has a 100 ft^2 private office with access to all necessary standard office equipment, office supplies, computer software and hardware.

Personnel

Dr. Cassie Kennedy M.D. is the principal investigator. She is a clinical expert in lung disease and lung transplantation and has completed the CTSA certificate in clinical research.

Dr. Roberto Benzo M.D. is the senior investigator and mentor. He is an NIH-funded expert in lung disease and pulmonary rehabilitation.

Dr. Nathan LeBrasseur Ph.D is a coinvestigator and co-mentor and an NIH-funded expert in frailty measures and serves as the Director of the CRU Muscle Performance and Physical Function Laboratory.

Jim Garrett, R.R.T is a member of the Mayo Clinic Pulmonary rehabilitation staff.

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