Respiratory Muscle Strength and Function in Patients With Neuromuscular Disease

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Protocol

1. Project Title

Respiratory Muscle Strength and Function in Patients with Neuromuscular Disease

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3. Abstract:

Respiratory insufficiency is the most common cause of morbidity and mortality in neuromuscular diseases. A hallmark of many neuromuscular diseases is progressive respiratory insufficiency and an eventual dependence upon assisted ventilation. Inspiratory muscle training (IMST) is a potential treatment option that has been shown to increase strength and ventilatory function in critically ill, difficult to wean adults and in patients with mild neuromuscular weakness. However, it is poorly understood whether breathing function can be modified by IMST, in patients with neuromuscular disease and symptomatic ventilatory insufficiency. The proposed study measures IMST-induced changes in ventilatory function in adults with neuromuscular disease, and whether strength gains translate to improved resting ventilation. Patients will undergo IMST exercises, 3-5 days per week for up to 3 months. Outcome variables include measures of change in pulmonary function, muscle strength and ventilatory pattern.

4. Background:

Inherited neuromuscular diseases (NMDs) include muscular dystrophies, motor neuron diseases, metabolic myopathies, or other congenital myopathies. Although the genetic etiology, pathophysiology, and disease course varies vastly between the inherited neuromuscular diseases, a commonality is a progressive loss of ventilatory muscle function. Respiratory muscle dysfunction increases the rate of pulmonary complications and death and is a major factor in respiratory failure[1, 2]. Respiratory failure is the primary cause of mortality for most INMDs [3].

Ventilation is a mechanical process, where the respiratory muscles function as a pressure pump to drive inspiratory airflow and increase the lung volume. Patients with neuromuscular diseases typically present with a restrictive pulmonary pattern, where compliance is reduced by muscle weakness and a stiffened chest wall, creating increased mechanical loads at baseline and intensifying neuroventilatory drive. When the efferent neuromuscular drive is consistently unmet by sufficient ventilatory motor output, the mismatch is perceived as dyspnea [4] and clinically appears as hypoventilation and hypercapnia. In chronic, progressive neuromuscular disease, the principal determinant of ventilatory insufficiency is weakness of the respiratory muscles.

The principal strategies to attenuate chronic ventilatory insufficiency are to reduce the load of breathing, to strengthen the capacity of the respiratory muscles, or a combination of the two approaches. Medications, positioning aids or assisted ventilation have been used to reduce breathing loads in NMDs [3, 5, 6]. With recent advances in pharmacological therapies and the use of assisted ventilation, survival to age 30 may exceed 80% in Duchenne muscular dystrophy

(DMD) [7]. Nevertheless, assisted strategies do not prevent or reverse expected declines in longer-term ventilator function that occur over the clinical course of progressive neuromuscular disorders. In fact, the preponderance of the literature has shown that MV independently facilitates diaphragm muscle atrophy and contractile dysfunction, known as ventilator-induced diaphragmatic dysfunction [8, 9].

Alternatively, respiratory muscle training may improve muscle function and delay ventilatory decline. It has been previously asserted that inspiratory muscle training (IMT) could overwork the respiratory muscles and induce fatigue in patients with neuromuscular compromise [10]. However, the literature does not support this assumption. Among the NMDs, the majority of IMT research has been conducted in children and young adults with DMD who do not require assisted ventilation. Training-induced strength gains tend to occur more slowly in patients with neuromuscular diseases [11]. IMT has shown effective for increasing muscle strength and endurance, regardless of disease severity [12]. However, patients with the greatest baseline ventilatory function make the largest gains in forced expiratory maneuvers [11, 12]. Additionally, breathing loads are perceived as lighter by patients, following ventilatory muscle training [13]. Patients with DMD make greater strength gains when training with high-pressure overloads, compared to low-modest resistive breathing, and have shown long term improvement in MIP, VC, and max ventilation for as long as two years [14].

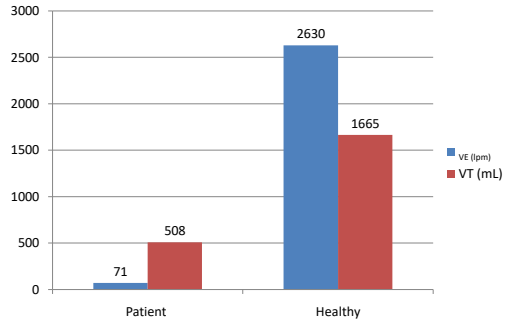
Because previous research has primarily trained adolescents and young adults, additional knowledge is needed regarding the ability of the respiratory muscles to remodel in our youngest and older patients. Therefore, we plan to include two separate age cohorts to address these gaps. Our team safely incorporated IMST into the clinical care of critically-ill, mechanically ventilated infants with and without neuromuscular disease, including a neonate who sustained a cerebrovascular accident and an infant with Pompe disease and sepsis. We report that the intervention is both feasible and safe in infants (Smith, under review, Phys Ther). Additionally, our group has reliably assessed respiratory strength and function in boys with DMD ranging from 4 through 10 years of age (Mathur, Physiother Canada, 2009). A key objective of our laboratory is to identify the stage of disease where the greatest therapeutic benefit can be achieved. The literature suggests this could occur with earlier intervention when possible (McCool, 1995, Phys Ther), but older adults with a milder disease phenotype also stand to gain from training [15].

While the findings of IMT show initial promise for patients with DMD, less is known about the ability of patients with other NMDs to respond to training. In particular, the role of IMT is virtually unknown among the rare or orphan neuromuscular diseases (i.e. metabolic and other congenital myopathies). Although a common attribute of the neuromuscular compromise is the predominance of respiratory insufficiency [16], the pathology, clinical signs, onset and response to medical management varies vastly between NMD diagnoses. For example, patients with Pompe disease may be distinguished from other NMDs by a relatively earlier involvement of ventilatory over limb muscle weakness [17]. Moreover, ventilatory muscle weakness and pulmonary function correlate poorly with ambulatory function in Pompe disease [18]. Therefore, we may not be able to apply the research in DMD directly to other progressive neuromuscular disorders.

The pattern of ventilatory muscle weakness especially differs between the NMDs. Pulmonary pressures typically decline prior to a loss of forced expiratory volumes in neuromuscular disease [19], making strength a more sensitive index of pulmonary function. While vital capacity may decline by >8% per year in DMD after the age of 12 [20], inspiratory strength remains preserved to a greater degree than expiratory strength [21, 22]. In DMD and amyotrophic lateral sclerosis, maximal inspiratory and expiratory pressures correlate equally with unassisted cough peak

flows [22, 23]. In contrast, the rate of decline in global ventilatory function varies vastly between adults with Pompe disease, but is characterized by predominant diaphragm muscle weakness[17, 18, 24]. Intercostal and diaphragm muscle involvement are differentially affected among spinal muscular atrophy variants[25] and may not occur at all in the mildest, adult-onset genotype [26].

Because the inspiratory and expiratory muscles can both be affected by neuromuscular disease, the relative roles of training either function may be examined. The expiratory muscles primarily influence the effectiveness of cough flows, which are vital for mucociliary clearance and prevention of respiratory infection. On the other hand, a functional inspiratory pump is necessary in the inspiratory phase of cough, in order to achieve an appropriate cough volume [23]. Moreover, diaphragmatic weakness results in chronic hypoventilation and pre-empts a need for ventilatory assist. Because the diaphragm is particularly weakened by assisted ventilation and disuse, we propose to conduct a pilot study of the specific role of inspiratory muscle strength training (IMST) in respiratory muscle streng ventilatory function. We have extensive experience in evaluating respiratory muscle strength and pulmonary function in the laboratory and the clinic,[27-30] and our group provides clinical post-operative IMST in difficult to wean infants and children with neuromuscular diseases [31].



ıd flows are impaired in a young adult male with late-onset Pompe disease, compared to a healthy, middle-aged adult. Light, added pressure-threshold loads further diminished flow-volume responses in the patient, but did not vary substantially in the healthy adult.

Pilot Data/Preliminary Work

We recently tested respiratory strength and sense of breathing effort, on three young adults with late-onset Pompe disease and symptom-limited respiratory function. Details from a 25 year-old male are shown in **Fig 1**. Tidal volume and peak inspiratory flow were markedly reduced during resisted breathing. In addition, the patient's maximal inspiratory pressure (MIP), a non-invasive estimate of strength, was 17 cm H_2O, which is <20% of the age-predicted value. This clinical example shows that the test procedures are feasible to perform reliably in the community or clinic settings. In addition, it illustrates the impaired baseline strength and respiratory function in patients with late-onset Pompe disease.

We have also prescribed IMST exercises successfully for patients with metabolic or other congenital myopathies who require assisted ventilation, as part of routine clinical care. **Fig 2** details the progression of strength gains and reduced assisted ventilation over two weeks of IMST, in an adolescent with nemaline myopathy and postoperative ventilatory insufficiency. Her baseline strength was approximately 40% of normal for females her age (-35 cm H_2O, compared to normal values of -80-90 cm H_2O). After two weeks of IMST, she made significant gains in strength and achieved her baseline ventilatory function of BiPAP

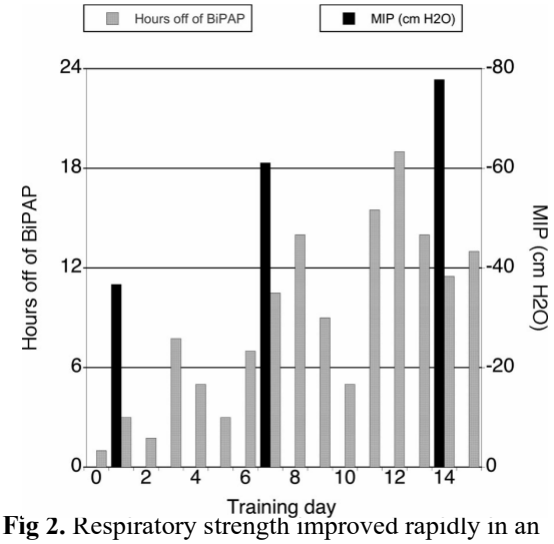


Fig 2. Respiratory strength improved rapidly in an adolescent with nemaline myopathy and post-operative ventilator failure. She initially required 24-hour BiPAP, but progressed to night-time only use, her baseline breathing status.

only during sleep. Importantly, her clinical IMST regime was nearly identical to the proposed training, and she experienced no safety events throughout the training period.

5. Specific Aims:

- To identify the effect of IMST on the strength of inspiratory and expiratory muscles, in patients with neuromuscular disease and ventilatory insufficiency.
- To determine whether IMST-associated changes in strength are associated with differences in tidal and forced pulmonary function.
- To compare the rate and extent of training response, based upon disease diagnosis and baseline function.

6. IMST Research Plan:

Hypothesis
Inspiratory muscle strength training (IMST) will significantly improve maximal inspiratory pressure and pulmonary function in patients with neuromuscular disease and respiratory muscle contractile dysfunction.

Design
Patients will be considered eligible for IMST if they have been diagnosed with an inherited neuromuscular disease and show clinical evidence of impaired pulmonary function. Subjects will undergo RMST for up to 12 weeks. Pulmonary function and strength testing and a symptom questionnaire will be administered before and after IMST.

Study Sample
This study will consist of two groups of male and female patients aged 6 months-65 years with a confirmed diagnosis of a neuromuscular disease. Group 1 will consist of children with earlier-onset disease, aged 6 months through 11 years of age upon inclusion. Group 2 will consist of patients aged 12 through 65 years, which will include both patients with later-stage, early onset disease, and those with late-onset, milder disease. The inherited neuromuscular disease classifications include: muscular dystrophies, motor neuron diseases, neuromuscular junction diseases, peripheral nerve diseases, metabolic myopathies, or other congenital myopathies that fall into the NIH classification of a rare/orphan disease. In addition, patients will demonstrate evidence of at least one of the following signs of respiratory insufficiency: (1) decreased FVC <80% of age and gender-predicted, (2) decreased maximal inspiratory pressure <80% of age and gender-predicted, (3) decreased maximal expiratory pressure <80% of age and gender-predicted, (4) any routine use of supplemental oxygen or mechanically-assisted ventilation, or (5) patient report of functionally-limiting dyspnea.

We plan to enroll up to thirty subjects and analyze the data according to baseline disease severity (age-predicted pulmonary function). No power calculation is feasible for this pilot trial; however, similar studies have found significant training differences in strength with 20-30 patient cohorts. Patients will be ineligible to participate if they have required acute antibiotic therapy for an acute respiratory infection within 15 days prior to baseline screening, were prescribed systemic corticosteroids or neuromuscular blocking agents within 15 days of the baseline screening, show laboratory evidence of hepatic or hematologic failure, are currently participating in other research studies involving investigational drugs, have a diagnosis of a primary

pulmonary disease, use tobacco products, or have any other concurrent medical condition which, in the opinion of the investigators, would make the subject inappropriate to participate in the respiratory exercises.

Subjects will be recruited from other research studies conducted by the PI and Sub-Is, the neuromuscular clinic run by the study team, or by self-referral. The study will be listed on ClinicalTrials.gov and the research team's website.

Study Procedures
Complete respiratory testing will occur before and after IMST. In conjunction with respiratory testing, baseline and exertional blood pressure, heart and respiratory rate, end-tidal CO_2 and pulse oximetry will be monitored. The following tests will be completed on all subjects.

Pulmonary Function Tests: Subjects will complete tidal flow-volume assessments and forced expiratory maneuvers according to American Thoracic Society guidelines.[32] Three to five trials will be administered, separated by at least 2 minutes of rest.

Repeated Inspiratory Load Compensation: Subjects will undergo 4 sets of 10 maximal-effort breaths against standardized resistances (one set each at 0, 5, 10, and 15 cm H_2O). If a patient cannot generate at least 20% of resting tidal volume with one of the lower standardized resistances, we will forego testing with any higher loads. Trials will be separated by at least three minutes of rest.

Maximal Respiratory Pressures: Subjects will perform maximal inspiratory and expiratory pressure maneuvers, in accordance with American Thoracic Society testing guidelines.[32] Trials will be administered until 5% variability is achieved between three trials (typically achieved within 5 trials), and separated by at least 2 minutes of rest.

Every attempt will be made to assist participants and their families to travel to University of Florida for respiratory testing. If the study team determines that it is not in the best interest of the eligible participant to travel for a test session, the study team will consider the option of conducting the requisite tests at a site local to the subject.

Training
IMST Training: All subjects will receive IMST for up to 3 months, using a commercially-available respiratory training device (depending upon initial strength: Threshold PEP or IMT devices, Philips-Respironics). Patients and their families will be instructed in the use of the assigned training device. Subjects will complete loaded breaths, at an intensity of up to 50% of maximal pressure. In the unlikely event that the subject cannot initially exercise at this intensity, the subject will exercise at the highest load that is well-tolerated (determined by full opening of the training valve, absence of dyspnea or fatigue, and stable vital signs).

The subject will be instructed to take 8-15 deep, forceful breaths through the Threshold device, followed by at least 3 minutes of rest. The process will be repeated 3 more times for a total of 4 sets of 8-15 breaths. IMST will be completed three to five days per week, based upon the subject's daily baseline level of fatigue.

Subjects and their families will be directly monitored by telephone during every IMST session for the first two weeks and receive real-time feedback to ensure proper technique and provide instruction on progression of the training. IMST will routinely occur at home, yet an investigator will continue to participate in IMST at least once per week remotely by telephone or video

conference. We have experience in remote monitoring of IMST in ventilator-dependent children, and remotely-supervised sessions enable investigators to monitor compliance, progress the IMST load, and provide feedback.

Statistical Methods
The primary endpoints for inspiratory muscle training efficacy will include respiratory muscle strength. Secondary outcome measures include be respiratory function and breathing pattern during loaded breathing.

Changes in strength and respiratory function will be analyzed by repeated measures ANOVA.

7. Possible Discomforts and Risks:

Brief periods of loading (<30 seconds) have not been shown to cause clinically significant or sustained changes in cardiac function [37].Also, the incidence of blood gas dysfunction is extremely rare, due to the limited duration of the testing and training sets. Nevertheless, the protocol includes strict limits on baseline and exertional vital signs, end-tidal CO_2 and SpO_2, in order to minimize cardiorespiratory work.

Inspiratory muscle strength training has been associated with a very low risk of adverse events, even in hospitalized patients with cardiovascular impairment, heart failure and ventilator dependence. A recent randomized, controlled trial of pre-operative home-based IMST in high-risk cardiac surgery patients yielded 0 adverse events among 276 participants [38], while an additional 20 pre-operative patients awaiting elective aneurysm repair experienced no IMST complications [39]. Moreover, a similar protocol has been used clinically in the Shands surgical ICU to facilitate ventilator weaning in well over 100 pediatric and adult patients without any complications attributable to IMST. The inspiratory muscle strength training protocol used by our research team has been designed to minimize excessive physiological stress, primarily by employing moderate intensities, brief training sets, and prolonged rest periods.

Respiratory testing or training may elicit transient fatigue or shortness of breath that resolves within several seconds of completion. Each training set typically lasts less than 15 seconds, and at least two to three minutes of rest will be provided between trials to minimize feelings of exertion, and perceived exertion will be monitored during training sessions.

8. Possible Benefits:

The potential benefit to participants is to determine the feasibility and efficacy of IMST exercises that have shown to be effective to increase strength and aid weaning in adults with ventilator dependence or to improve strength in mild-severity neuromuscular disease. The training regime could provide an adjuvant treatment for symptomatic patients with neuromuscular disease.

9. Conflict of Interest:

No conflicts of interest have been identified for any of the investigators in this study.

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