Utilization of Pulmonary Clearance Devices in Amyotrophic Lateral Sclerosis

Background:

ALS:

Amyotrophic lateral sclerosis (ALS) is a progressive degenerative neuromuscular disease with no known cause or cure. ALS causes weakness in many muscles in the body, including the muscles involved in respiration and swallowing. Weakness in these muscles can cause respiratory problems, making breathing more difficult. Respiratory problems are among the most serious symptoms of ALS and should not be ignored. Shortness of breath may be the first respiratory symptom that some patients experience. Patients may notice shortness of breath when engaged in vigorous physical activities like running, exercising, walking long distances, or climbing stairs. They may also have difficulty breathing at night which can interfere with sleep and cause fatigue or morning headaches. Patients often find themselves waking frequently throughout the night. Difficulty breathing at night occurs when the chest muscles relax too much to assist with breathing during the dreaming phase of sleep.

Problems with swallowing can also interfere with breathing. When the swallowing muscles are weakened, food and saliva are more easily inhaled (aspirated) into the windpipe which leads to choking. Aspiration of food or saliva can also introduce bacteria into the lungs, increasing the risk of respiratory infection and pneumonia.

High Frequency Chest Compression Devices (HFCC):

Disease conditions, such as cystic fibrosis (CF), chronic bronchitis, bronchiectasis, and immotile cilia syndrome, can lead to abnormal airway clearance which is a source of increased sputum production, often purulent or tenacious. The underlying pathology of the decline in mucociliary clearance varies with the given disease. Chest physical therapy (CPT), which is also referred to as percussion and postural drainage (P/PD), is the standard treatment program that attempts to compensate for abnormal airway clearance. By improving the clearance of lung secretions, which may often be tenacious, complications of infection, atelectasis, and hyperinflation are reduced, and the decline in respiratory function is slowed in these types of diseases. Depending on the severity of the disease and any presence of infection, CPT sessions can be from 1-3 times per day for 20-30 minutes. A physical therapist or another trained adult in the home, typically a parent if the affected individual is a child, may administer CPT. The need for regular therapy can be particularly burdensome for adolescents or adults who wish to lead independent lifestyles. CPT is time consuming and requires the assistance of a skilled caregiver.

Different types of airway clearance techniques and devices have been developed in an attempt to address the problem of convenience and compliance with CPT. Airway clearance techniques or systems have been most often associated and studied in the treatment of CF. Of these techniques, daily P/PD and HFCC devices, such as the Vest™ Airway Clearance System and Incourage Airway Clearance System,

are passive techniques that do not require the participation of the affected person. Although there have been a range of studies on these alternatives, there remains a lack of scientific evidence to support any secretion clearance technique over another.

HFCC devices have shown improved lung function and sputum clearance in many who are afflicted with CF with few adverse effects. However, the therapy has not been shown to be superior to conventional CPT in short-term studies, and its impact on long-term prognosis is unknown. In addition, it is not clear from the clinical studies which subjects would derive the most benefit from this therapy, or at what time during the course of the disease HFCC should be initiated. Interpretations of the data derived from the clinical trials of HFCC for CF are complicated by issues in study design, small sample sizes, inadequate length of follow-up, heterogeneity of study subjects, and lack of control for confounding variables, such as concurrent treatment, disease severity, respiratory functions variability, and age. Moreover, there remain questions of the validity and reliability of outcomes measures, such as sputum weight and respiratory function indexes for the determination of therapeutic efficacy.

The FDA cleared the original Vest Airway clearance system in 1998. The currently approved indications are "To promote airway clearance or improve bronchial drainage by enhancing mobilization of bronchial secretions where external manipulation of the thorax is the physician's choice of treatment. The indications typically follow the Clinical Practice Guideline published by the American Association for Respiratory Care (AARC) in 1991. In addition, the device is also indicated for the purpose of collecting mucus for diagnostic evaluation." Several earlier versions included the THAIRapy® Vest System and the ABI Vest® Airway Clearance System, amongst others (Advanced Respiratory, Inc. St. Paul, MN). A similar device, the Medpulse Respiratory Vest System (Electromed, Inc., Minnetonka, MN) also obtained FDA clearance through the 510(k) approval process (1999), and others have also been cleared by the FDA. In 2007, a similar device, the FREQUENCER™ (DYMEDSO, Inc., Boisbriand, Quebec Canada) obtained FDA clearance as substantially equivalent to the THAIRapy device. It produces sound wave stimulation to oscillate and loosen mucous secretions in the chest.

Cough Assist:

Normal clearance of airways rests on three (3) basic components: a patent airway, mucociliary clearance, and an adequate cough. Patients with spinal cord injuries or a variety of neuromuscular diseases or chest wall deformities may have impaired cough responses, which may lead to respiratory failure during respiratory tract infections due to the inability to clear the profuse respiratory secretions. Chest wall deformities may include kyphosis, scoliosis, or lordosis, while neuromuscular diseases include muscular dystrophy, poliomyelitis, spinal muscle atrophy, myasthenia gravis, amyotrophic lateral sclerosis, or cerebral palsy. The great majority of neuromuscular disease morbidity and mortality is related to respiratory muscle weakness, and the vast majority of episodes of respiratory failure occur during otherwise benign episodes of respiratory tract infections. Chest infections may result in repeated episodes of pneumonia, repeated hospitalizations, and finally, in tracheostomy with mechanical ventilation. The normal cough consists of 4 stages: 1) A precough inspiration to about 85% of total lung capacity; 2) Followed by closure of the glottis; 3) Development of thoracoabdominal pressure sufficient

to generate an explosive decompression of the chest at glottic opening; and 4) Opening of the glottis with exsufflation. The peak cough expiratory force typically exceeds 5L/sec, with total expiratory volume of about 2.3L. In general, an impaired ability to cough has been defined as a peak cough expiratory flow of less than 2-3L per second. A variety of techniques have been developed to enhance each of these stages. For example, manually assisted coughing is designed to enhance exsufflation and consists of abdominal pressure delivered by a caregiver timed with the glottic opening. Manual assisted coughing may be offered to patients with a peak cough expiratory flow of less than 5L/ sec, but is less effective in the presence of scoliosis or obesity or after meals. Glossopharyngeal breathing is a technique to increase inspiratory flow and is commonly used in patients with a decreased vital capacity due to inspiratory muscle paralysis. This breathing technique involves the use of the tongue and pharyngeal muscles to add to an inspiratory effort by projecting (gulping) boluses of air past the glottis. Mechanical insufflation-exsufflation is designed to deliver alternative cycles of positive and negative pressure. One such device, the CoughAssist, is a portable electric device which utilizes a blower and valve to alternately apply a positive and then a negative pressure to a patient's airway in order to assist the patient in clearing retained broncho pulmonary secretions. Air is delivered to and from the patient via a breathing circuit incorporating a flexible tube, a bacterial filter and either a facemask, a mouthpiece or an adapter to a tracheostomy or endotracheal tube. Physicians, respiratory therapists, nurses, and trained family members may administer this therapy. Mechanical insufflation (MI-E) has been used in a variety of patient populations as an adjunct to noninvasive ventilation using intermittent positive pulmonary ventilation (IPPV) delivered nasally or orally. For example, many patients with neuromuscular disease or chest wall deformities with progressive ventilator failure will use noninvasive IPPV either nocturnally or throughout the day, depending on such parameters as vital capacity and oxygenation levels. Patients managed at home with noninvasive IPPV may monitor oxygen desaturation levels. A sudden decrease in oxygen desaturation may prompt the use of MI-E to eliminate the presumed offending mucus plug. Advocates of MI-E state that even patients requiring 24 hour IPPV can be managed noninvasively for prolonged periods of time without hospitalization using this technique. In patients with tracheostomies, MI-E has been used as an alternative or complement to suctioning. In addition, it is suggested that MI-E is more comfortable to the patient than suctioning. MI-E may either be offered on a temporary basis in patients with noninvasive IPPV who are suffering from a respiratory tract illness, or may be used on a more chronic basis in an attempt to avoid the option of invasive tracheostomy and suctioning.

Objectives:

Primary Aim

The primary objective of this pilot study is to determine the potential clinical effect of airway clearance devices in patients with ALS over a period of 180 days (25.7 weeks).

Secondary Aim

The secondary aim is to determine the potential effectiveness of HFCC as a stand-alone airway clearance therapy as compared to HFCC in conjunction with a Cough Assist Device over a period of 180 days (25.7 weeks).

Study Design:

This 180 day (25.7 weeks) pilot study is designed to evaluate the effectiveness of airway clearance devices in adults with ALS. Subjects will be randomized in a 1:1 ratio to one of two treatment groups: treatment with an HCFF device alone or treatment with both an HFCC device and a cough assist device.

This outpatient study includes a screening/baseline visit followed by a 180 day (25.7 weeks) treatment period with three scheduled clinic visits (day 30, day 90, day 180). Pulmonary assessments and ALS outcome measures will be collected at each visit in addition to quality of life assessments and device usage diaries.

Informed consent will be obtained from all subjects prior to any study procedures, including screening and baseline assessments. Institutional standard of care for ALS will be maintained for each subject.

Study Population:

Inclusion criteria

1. Suspected, possible, probable, Probable (Lab-Supported), or Definite ALS according to El Escorial Criteria
2. Males and females age 18 and above
3. Novel to airway clearance device use
4. Forced vital capacity ≤ 75% of predicted

Exclusion criteria

1. Any contraindication for pulmonary ventilation or perfusion scan including allergy to radioisotopes
2. Any contraindication for use of a pulmonary clearance device
    a. Susceptibility to pneumothorax
    b. Recent (within 30 days) barotrauma
    c. Unstable head or neck injury
    d. Active hemorrhage with hemodynamic instability

Sample size

20 male and female subjects aged 18 and older will be randomized into one of two treatment groups in a 1:1 randomization ratio (10 subjects per group).

Intervention

After completing the screening and baseline assessments subjects will be randomized.

Treatment group A –Subjects randomized to group A will be fitted for and issued a HFCC device for home use. Subjects will be instructed to use the HFCC device 2-3 times per day for 15-30 minutes each. Subjects will be instructed to keep a device usage, concomitant medication, and adverse event diary.

Treatment group B – Subjects randomized to group B will be fitted for and issued a HFCC device and will also be issued a cough assist device. Subjects will be instructed in the use of both devices. The HFCC device should be utilized 2-3 times per day for 15-30 minutes each followed by sessions with the cough assist until secretions have been cleared. Subjects will be instructed to keep a device usage, concomitant medication, and adverse event diary.

Outcome Measures

Pulmonary Function Testing - Spirometry is the most common of the pulmonary function tests and measures lung function, specifically the measurement of the amount (volume) and/or speed (flow) of air that can be inhaled and exhaled.

FVC – Forced Vital Capacity: the determination of the vital capacity from a maximally forced expiratory effort

FEV-1 – Volume of air that has been exhaled at the end of the first second of forced expiration

MIP/MEP – Maximum Inspiratory Pressure/Maximum Expiratory Pressure: MIP is the pressure generated during maximal inspiratory effort against a closed system. MEP is the pressure generated during maximal expiratory effort against a closed system

Diffusion capacity – measures the transfer of gas from the air in the lung to the lung blood vessels.

Chest X-Ray – a projection radiograph of the chest used to diagnose conditions affecting the chest

Lung Ventilation Scan – a nuclear scanning test commonly used to detect abnormalities in air flow. A radioactive tracer gas or mist is inhaled into the lungs. Pictures from the scan indicate areas of the lungs that are not receiving enough air or that retain too much air. Areas of the lung that retain too much air are brighter spots on the film and areas not receiving enough air are dark.

Lung Perfusion Scan— a nuclear scanning test commonly used to detect abnormalities in blood flows. A radioactive tracer is injected into a vein. Pictures from the scan indicate areas of the lungs that are not receiving enough blood or that retain too much blood. Areas of the lung that retain too much blood are brighter spots on the film and areas not receiving enough blood are dark.

McGill Single item quality of life question – Assess the improvement of/ rate of deterioration of the subject's quality of life.

Follow-up Schedule

All subjects regardless of treatment group will undergo the following:

Screening/Baseline (all procedures to be completed within + 7 days of screening/baseline visit)
Informed consent
Physical/Pulmonary Examination
Medical history review/ Demographics
Vital signs
Pulmonary Function Testing
- FVC
- FEV-1
- MIP/MEP
- Diffusion capacity

Chest X-ray
Lung Ventilation Scan
Lung Perfusion Scan
McGill single item QOL question
Adverse event review
Concomitant medication review
Post use survey
Review usage diary
Randomization

Equipment Delivery and Instruction visit – After subject has been randomized, the appropriate equipment will be ordered and delivered to the patient's home. Equipment representatives will instruct subjects in appropriate use of the equipment.

Visit 1 (30 days ±7 days after baseline- all procedures to be completed within this window)
Vital signs
Pulmonary Function Testing
- FVC
- FEV-1
- MIP/MEP
- Diffusion capacity

Chest X-ray
Lung Ventilation Scan
Lung Perfusion Scan
McGill single item QOL question
Adverse event review
Concomitant medication review
Diary usage review
Post use survey

Visit 2 (90 days ±7 days after baseline- all procedures to be completed within this window)
Vital signs
Pulmonary Function Testing
- FVC
- FEV-1
- MIP/MEP
- Diffusion capacity

Chest X-ray
Lung Ventilation Scan
Lung Perfusion Scan
McGill single item QOL question
Adverse event review
Concomitant medication review
Diary usage review
Post use survey

Visit 3 (180 days ±7 days after baseline- all procedures to be completed within this window)/Early Termination
Physical/Pulmonary examination
Vital signs
Pulmonary Function Testing
- FVC
- FEV-1
- MIP/MEP
- Diffusion capacity

Chest X-ray
Lung Ventilation Scan
Lung Perfusion Scan
McGill single item QOL question
Adverse event review
Concomitant medication review
Diary usage review
Post use survey

Risks:

As with any electronic device, there is a rare risk for both the vest and cough assist of electrocution, fire, personal injury or equipment damage. However, these risks are minimized when following all instructions in the user manuals.

Data Analysis

Changes in Pulmonary function testing results, lung ventilation scan results, and lung perfusion scan results will be compared across the two treatment groups for each time point. Changes from baseline measurements to the study endpoint will also be analyzed. Descriptive statistics will be utilized for analysis of adverse events and quality of life assessments.

Stopping Rules

All research activities are completely voluntary. Subjects may discontinue their participation in the study at any time. The Investigator may stop a subject's participation secondary to safety issues, intolerance of the airway clearance devices, and/or noncompliance with study protocol including airway clearance device usage.

Study Organization:

Cedars Sinai Medical Center

127 South San Vicente Blvd.

LA, CA 90048

Investigators

Principle Investigator:	Ashraf Elsayegh MD
Co-Investigators:	Robert Baloh, MD PhD
	Richard Lewis, MD
	Abirami Muthukumaran, MD
	Peggy Allred, PT DPT
Collaborating Departments	Pulmonary Medicine
	Nuclear Medicine

Sponsor:

RespirTech

2896 Centre Pointe Drive

St. Paul, MN 55113 800-793-1261