**Project Title:** Airway Clearance for Pediatric and Adult Cystic Fibrosis Patients Using a Portable Intra-Pulmonary Percussion Device

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**Abstract:**

Airway clearance has a crucial role in the prevention of progression of lung disease in cystic fibrosis patients. Despite multiple options available for airway clearance, frequently cystic fibrosis patients have difficulties performing regular airway clearance in an at-home environment. We will compare pulmonary function testing and patient satisfaction with their current home device compared to the portable internal airway percussion device proposed (PIAPD). Our hypothesis is that there is no difference in pulmonary function testing after using PIAPD comparing to their home device. Our goal is to provide an equally effective, less expensive, alternative airway clearance technique for cystic fibrosis patients.

**Background:**

Cystic Fibrosis (CF) is an autosomal recessive disease that affects more than 30,000 people in the United States and more than 70,000 worldwide. The abnormal Cystic Fibrosis Transmembrane conductance regulator (CFTR) function leads to multiple organ manifestations. In the lungs, the dysfunctional CFTR mutation leads to abnormal thick, sticky mucus in the airways that traps microorganisms, leading to infections, inflammation and respiratory failure, which are the main causes of death in CF patients. Daily airway clearance plays a key role in preventing lung function deterioration in CF. Typically, a CF patient gets airway clearance therapy at least two times daily, each session lasting for about 30 minutes. There are different types of airway clearance therapies. Some of them are active, requiring patient cooperation and some coordination of breathing, while others are predominantly passive. In the United States, the most commonly utilized technique is high frequency chest wall oscillation, more commonly known as “the VEST”. This vibration loosens secretions in the bronchi that the patient will have to actively expel. The apparatus of vest therapy involves a wearable jacket, a hose pipe and an air compressor. This apparatus requires electric supply from the mains and is not portable.

Vibrations can also be applied internally to airways through a mouthpiece. The existing devices that apply internal airway vibration include: Positive Expiratory Pressure Therapy (PEP), Flutter Valve therapy (Flutter) & Intrapulmonary Percussive Ventilation (IPV). PEP & flutter therapy involve portable, handheld devices without the need for electrical power. However, they both need patients’ active participation and they are only active during patients’ expiration phase of breathing. IPV is a modified ventilator that delivers pulses of air under pressure into airways. The equipment requires electricity and is not portable. IPV is only used within the hospital settings.

Studies comparing different modes of airway clearance therapies have shown that they are all comparable to each other when used properly. A portable “Internal Airway Percussion” (PIAP) device that can deliver internal vibration to the airways both during inspiration and expiration and that requires patients’ minimal cooperation would in theory be superior to existing devices. High frequency oscillation (HFO) of bronchial airway surface liquid (ASL) is an experimental technique developed at UF for the transmission of high-frequency square form sound waves superimposed on normal breathing through a mouthpiece and into the airways. In this pilot study, we propose to test HFO as a means of airway clearance therapy in CF patients.

If the PIAP device is non-inferior to the SOC device, it would provide CF patients several advantages. The current VEST therapy, which is SOC for airway clearance, can cost anywhere from $5,000 to $20,000 for some of the newer models. The device under study could be made and provided to patients at a fraction of this cost. Furthermore, patients with CF are extremely vulnerable to respiratory infections and complications arising from such. In the time of COVID-19, this portable system can be used in the patient's home and carried with them wherever they go. This provides a highly portable as well as cost-effective option for airway clearance which will allow them to have greater flexibility where airway clearance is performed and allow them greater freedom to pursue activities that they enjoy.

The PIAP device,(as pictured in Figure 4) that we have developed has been previously tested in several IRB-02 approved pilot studies here at the University of Florida by Dr. Paul Davenport in a population of healthy volunteers. Published results of these studies report this device's waves produce vibrations within the airways, loosening Airway Surface Liquid (ASL), enhancing airway clearance and decreasing the sense of breathing effort. Furthermore, the IAP device was found to painlessly increase exhalation of intra airway molecules and droplets in healthy individuals.

For this study, we would like to test this unique, custom designed, inexpensive, portable IAP device (PIAPD) as a comfortable alternative for airway clearance in CF patients.

**Specific Aims**:

1. To determine if Portable Internal Airway Percussion Device (PIAPD) is a non-inferior at-home method of airway clearance in patients with CF, we will compare changes in pulse oximetry and forced expiratory volume in one second (FEV1) prior to and 2 hours after airway clearance performed with standard airway clearance devices vs. the PIAPD. The primary endpoint will be a comparison of results of the aforementioned pulmonary function testing between the two devices.
2. Secondary endpoints include will include comparison of patient satisfaction (tolerability and acceptability) with standard airway clearance devices and PIAPD.
3. We will measure CF patient perception of breathing effort and device use for both methods.

**Study Design:** This is a pilot study where we aim to compare initial use of the standard airway clearance device (SACD) (as pictured in Figure 2) with subsequent use of a PIAPD in patients ages 6-21 years with stable CF. Our primary hypothesis, stated as Null, is that there is no effect of on FEV1 2 hours after use and there is no effect on perception of effort and efficacy for the PIAPD device.

**General Inclusion Criteria:**

- Ages 6-21 years
- Stable CF as determined by pulmonary physician assessment
- Assents to forego additional experimental treatments during the study
- Currently using and familiar with airway clearance therapy for treatment of CF
- Participant (or parent or legal guardian if the participant is a minor) is willing to provide Informed Consent

**General Exclusion Criteria:**

- FEV1 < 40% predictive
- Pneumothorax
- Hemoptysis

- COVID-19 diagnosis within last 14 days
- Non-compliance
- Inability to obtain informed consent
- Any condition that, in the opinion of the investigator, would interfere with the study conduct or the safety of the participant

**Additional Exclusion Criteria: Outpatient Arm (in addition to general exclusion criteria above)**

- Decrease in FEV1 > 10% from baseline over last 12 months
- Antibiotic Initiation for acute CF exacerbation
- Hospitalization for CF Exacerbation

**Additional Exclusion Criteria: Inpatient Arm (in addition to general exclusion criteria above)**

- Failure to increase FEV1 $\geq$ 10 % from initial PFTs on admission by day 9 of hospitalization.

Our patients will be recruited from our CF outpatient Clinic and from our CF inpatient population. Participants will be randomly assigned to perform airway clearance with the Standard Airway Clearance device (SACD) or Portable Internal Airway Percussion device (PIAPD). A large majority of our patients will be using VEST therapy as their standard of care airway clearance. A few might be using an Intrapulmonary Percussion Device that uses a mechanism different from the device we will be testing. Based on past experience, it is unlikely that this will present a significant source of variability.

After discussing the study with a prospective participant and obtaining informed consent, participants will be randomized to either the standard of care or experimental group:

Outpatient arm:

On day 1, baseline FEV1 as measured on Smart One® portable home spirometer (Figure 1) and pulse oximetry will be obtained before and 2 hours after airway clearance, either performed with SACD method, PIAPD at 15hz. The frequency of the device will stay at 15 hz for the duration of the study as it has been previously shown to be the most effective frequency for better airway clearance (i.e., getting deeper into the airways). Participants will also be asked to give a rating of breathing effort using a Modified Borg Dyspnea Scale.

**FIGURE 1**

**Figure 1: Smart One® portable home spirometer is the standard of care for at-home measurement of FEV-1.**

For the next two weeks, airway clearance therapy, either performed with SACD method or PIAPD, will be performed by the patient daily (CF patients perform airway clearance daily as part of standard of care for their disease). Spirometry/pulmonary function testing will be collected twice per week over the two-week period with a pre and post FEV1, pulse oximetry, and rating of breathing effort. This testing will be done via telemedicine so that the PI or co-investigator can assist the patient with the PIAPD if necessary and conduct the testing in a safe and efficacious manner. At the end of the two weeks, the participant will be asked to complete a short survey regarding the ease of use and acceptability of the airway clearance device they had been using for the first part of the study.

At the end of the initial 2-week period, the patient will be crossed-over to the other arm of the study and the same procedures will be repeated as per the above procedures. At the end of the study, patients will return the PIAPD device to the study team.

Inpatient arm:

Patients who are admitted to the hospital for a normal seasonal disturbance of their CF are admitted, as SOC, for a 14-day in-patient stay. When patients are admitted, they bring their VEST system, as this is the standard of care device used by over 95% of CF patients for airway clearance therapy. Following admission, patients will be informed of the study by the PI or one of the designated co-investigators. All study procedures will be explained and ample time to ask questions will be allotted. If the patient agrees to participate written informed consent will be obtained and the following procedures performed:

Hospital Stay Days 1-3: Patients will only use their SOC airway clearance therapy. This will allow for a "wash-out period" providing all the patients with good airway clearance prior to collecting data (some patients may have had poor compliance prior to hospitalization). The participant will also be asked to complete a short survey regarding the ease of use and acceptability of their SOC airway clearance device, at the end of this 3-day wash-out period. Furthermore, during this period, we will get daily spirometry with a portable spirometer once per day after first airway clearance of the day, along with pulse oximetry.

Hospital Stay Day 4: If, in the judgement of the PI, the participant has stabilized, we will randomize them to use either their SOC device or the study device. On Day 4, patients will be randomized to SOC or the new airway clearance device. We will collect the patient's ratings of breathlessness with the Modified Borg Dyspnea Scale and perform spirometry again with the Smart One® portable spirometry device before and two hours after airway clearance procedures for the first airway clearance of the day. We will also obtain pulse oximetry.

Hospital Stay Day 5: we will alternate the modality for the first airway clearance session of the day (using whichever device they were not randomized to use on Day 4), repeating the Modified Borg Dyspnea Scale and performing spirometry again before and two hours after airway clearance along with pulse oximetry. At this point, they will have used both the airway clearance devices, and they will be asked to complete a short survey regarding the ease of use and acceptability of the study airway clearance device.

**FIGURE 2**

**Figure 2: The Vest® Airway Clearance System is the standard of care for airway clearance in both adult and pediatric**

Hospital Stay Days 6-9: we will continue with daily spirometry, dyspnea measurements and pulse oximetry once per day after the first airway clearance of the day using the study device.

Hospital Stay Days 10-14: patients who have increased their FEV1 by at least 10% from admission by day 9 of hospitalization and whose symptoms have clinically improved, will be given the choice of whether to use their SOC device or the experimental study device. Whichever device they choose, they will use for two airway clearance sessions, along with dyspnea measurements, and pulse oximetry on days 10-14 of hospitalization.

At the end of the two weeks, the participant will be asked to complete a short survey regarding the ease of use and acceptability of each airway clearance device they had been using for the study. At the end of the study, we will ask that the patient return the experimental device to the study team.

Safety Endpoints:

**Outpatient:** For the outpatient population, we will cease use of the experimental device if, during any airway clearance session with the aforementioned device, the patient experiences severe shortness of breath (as measured by the Borg Scale), chest pain or any type of discomfort beyond that which would be expected from performing this type of therapy. We will also cease use of the experimental device if, for any reason, the patient decides they don't want to keep using it. Other stopping criteria would include: if there is a significant drop (>10 %) of the patient baseline FEV1 or if the patient or family changes their mind about participating in the study.

**Inpatient:** For the inpatient population, we will cease use of the experimental device If there is a significant drop ( >10 %) of the patient baseline FEV1, if the attending physician and/or PI consider it is not safe for the patient to continue participating in the study, if the patient develops a secondary infection during their hospitalization. As per the above criteria, we will also cease use of the experimental device if, during any airway clearance session with the aforementioned device, the patient experiences severe shortness of breath (as measured by the Borg Scale), chest pain or any type of discomfort beyond that which would be expected from performing this type of therapy or if the patient or family changes their mind about participating in the study.

A schematic of the experimental set-up and procedure is presented in Figure 5. The IAP apparatus was constructed from an acoustic wave controller (HPG1, Velleman_ Inc., Fort Worth, TX) connected to an amplifier (MG10, Marshall Amplification PLC, Bletchley, Milton Keynes, UK). The IAP delivered acoustic waves to the airways with adjustable waveforms, frequencies, and pressure amplitudes (Figure 4). A pressure transducer (Stoelting 50110, Stoelting Co., Wood Dale, IL) was used to measure the pressure amplitude of the IAP and to convert the measured values to the equivalent wave amplitudes.

**FIGURE 3**

**Figure 3: a snorkel-like tube connected to the amplifier was adopted for transmitting the generated waves through a mouthpiece commonly used for pulmonary function**

A snorkel-like tube connected to the amplifier was adopted for transmitting the generated waves through a mouthpiece commonly used for pulmonary function tests (Figure 3). To ensure the produced air pressure waves are transmitted down the respiratory system, the opposite end of the mouthpiece was connected to a 5 cm H2O/L/sec respiratory resistor (Model #7100R, Hans Rudolph, Inc., Shawnee, KS) throughout both the inspiration and expiration portions of the breathing cycle. Sampling bags used for aerosol sampling were 1-liter Tedlarbags (SKC Inc., Pittsburgh, PA) which had internal dimensions of 241 · 254mm2 as a deflated bag, with a wall thickness of *50 lm and single polypropylene (hose/valve and septum) fittings.

**Study Device:**

High Frequency Oscillator (HFO): The device involves 1) A mouthpiece commonly used in performing pulmonary function tests, or delivering nebulized medications and 2) A High-Frequency Oscillator (HFO) that will be connected via a side port to the mouth piece. This device transmits high frequency square form audio waves through a mouthpiece or mask interface to airways. HFO device vibrates the airways thereby lifting micro molecules of airway linings in to aerosols. During quiet tidal breathing, these aerosols escape the lungs through exhaled breath. Exhaled breath passes through a special filter that traps these aerosols and micro molecules of airway linings.

**FIGURE 4**

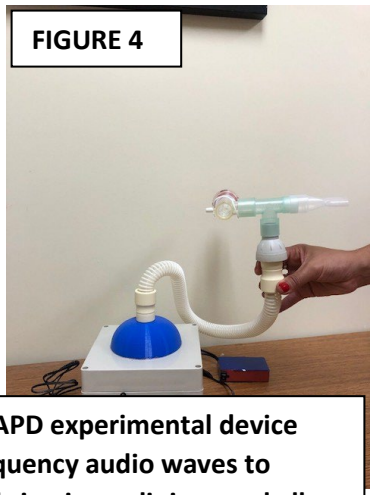
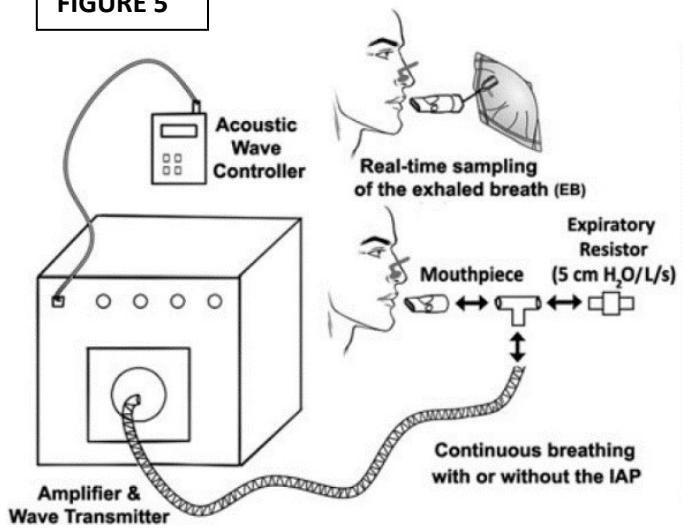


**Figure 4: The PIAPD experimental device utilizes high frequency audio waves to oscillate aerosols in airway linings and allow the to escape through exhaled breath**

**Study Procedures and the Device Interaction:**

**FIGURE 5**




The study involves subjects breathing through a mouthpiece. The mouthpiece may be connected to HFO, or R tube exhaled breath condensate (EBC) device, other forms of commercially available EBC devices that collects exhaled breath or to an Aerosol Particle Counter (APC). The study procedure causes no discomfort and requires minimal patient cooperation.

The exhalation port of the mouthpiece of HFO will have a special filter that traps aerosolized airway surface liquid (ASL) as well as microparticles present in exhaled breath.

**Figure 5: this High Frequency Oscillator (HFO) has been designed to filter ASL as well as microparticles present in exhaled breath.**

**Statistical Analysis**

We shall cross-tabulate the pre- and post-treatment spirometry measures for study condition and group. Significance for association will be obtained by repeated measures ANOVA. The false positive and false negative rates will be estimated by exact binomial confidence limits. This is a pilot study that is seeking a promising outcome as opposed to a definitive one. We shall consider the result as promising if (a) no false positives occur and (b) the false negative rate is below 50%.

Power/Sample Size: The study will have a goal to recruit 50 CF (10 inpatient and 40 outpatient) patients. Initial data analysis to be completed after the first 25 patients have completed each test condition.

Measurable outcomes and expected timeline: We expect the PIAPD is equal to standard airway clearance in CF patients. We expect PIAPD will decrease the sense of breathing effort and increase patient sense of efficacy.

**Compliance/Accountability/Regulatory**

Statement of Compliance

This study will be conducted in compliance with the protocol and will be generally consistent with current Good Clinical Practices (GCP), adopting the principles of the Declaration of Helsinki and all applicable regulatory requirements (ICH E6, 45CFR46, and FDA 21CFR sections 11, 50, 56, 312).

Prior to study initiation, the protocol and the informed consent documents will be reviewed and approved by UF's Institutional Review Board (IRB). Any amendments to the protocol or consent materials will be approved before they are implemented.

**Adverse Event Reporting and Safety Monitoring**

In the event of an adverse event the following definitions and processes will be used/followed:

Adverse Event Definitions

In this clinical research study, an adverse event (AE) is any occurrence or worsening of an undesirable or unintended sign, symptom or disease that is associated with study procedures. As an observational study, AEs occurring between study visits will not be reported unless deemed associated with study procedures. Throughout the study, the investigator must record AEs related to study procedures on source documents regardless of severity.

Unexpected Adverse Event

An AE is considered unexpected when the nature (specificity) or severity of the event is not consistent with the risks described in the protocol or informed consent document for specific protocol-required interventions.

Grading Adverse Event Severity

This study will utilize the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE Version 3.0) to classify AE severity.

All AEs Grade 2 or greater pertaining to study procedures will be recorded on the UF IRB adverse event log, which will be review by the IRB annually at continuing review. The investigator will make a determination as to the relation to participation in the study. Events will be assessed and reported in accordance with the ICH Guidelines for Good Clinical Practice and per the guidance of the DHHS Office for Human Research Protections (OHRP). Should there be an adverse event or unanticipated problem that is both serious and unexpected it will be evaluated by the PI and reported to the IRB as appropriate per current regulatory guidelines.

**Informed Consent**

Participants will sign their own informed consent form (or in the case of parents, they will consent for their child). This study will require written assent from minors. This study does not allow for use of legally authorized representatives or LARs. Each participant will receive a signed copy of their informed consent for their records. Participants will have the opportunity to ask questions before they sign the consent form and when a study coordinator calls them to confirm their information.

**Risks and Benefits**

Aside from the normal shortness of breath, which is expected as part of doing standard of care airway clearance and pulmonary function testing, there are no discomforts or risks associated with study that we know of. This research study may also include risks that are unknown at this time.
If the portable airway device works as well as the standard airway clearance device, it will potentially provide a less expensive, portable alternative for patients with CF that they can use in their homes without coming to clinic and during telemedicine visits with their physician.

It is also possible, that patients may not see an improvement and may even see a worsening of their airway clearance as measured by FEV-1 while using the experimental device.

**Confidentiality**

Investigators and staff will maintain the highest degree of confidentiality permitted for the clinical and research information obtained from subjects participating in this study. When a participant signs a consent they will be assigned a study ID which will be attached to their surveys and data. All study records will be locked in secure filing cabinets in locked offices in UF research space.

**Conflicts of Interest**

The investigators have no financial interests in any entity which could potentially benefit from the outcomes of this research. This study is internally funded by the Department of Medicine and the investigational device being used was created by Dr. Paul Davenport who has previously used the device in several UF IRB approved research protocols. This device has been reviewed by the UF Office of Technology and Licensing, who determined that the invention was not eligible for a patent or other licensing as it was too “similar” to currently approved/marketed products. The justification for the use of this device in the clinical space, is that it is much cheaper than the current airway clearance devices currently on the market making it ideal for patients with no insurance or lower incomes. Additionally, with the advent of COVID-19 patients with CF are at increased risk when leaving their house and coming to the clinic in order to perform pulmonary function testing and airway clearance. The device under investigation is portable and can be utilized in the home environment and monitored by the provider with telemedicine.

**Protocol deviations**

Any deviations from the protocol will be filed, as appropriate, on our deviation log and reported at the annual continuing review. Any deviations which have the potential to impact participant safety will be reported per UF guidelines.

**Data handling and record keeping**

Data collection will comply with all applicable guidelines regarding patient confidentiality and data integrity. REDCap data security protocols provide private, secure, and encrypted transmission of data between server and client computers over the public Internet network. All data systems are HIPAA compliant.