Pulmonary **F**unction using non-invasive **F**orced **O**scillometry **R**espiratory testing: A prospective observational study (PUFFOR study)

ClinicalTrials.gov number: NCT### *(when available)*

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SECTION 1. ABSTRACT

Study Aims

The aims of this study are to utilize non-invasive airway oscillometry measure pulmonary function and changes in respiratory mechanics over time in term and preterm infants with and without lung disease. We propose 4 Specific Aims:

Aim 1: To quantify differences in respiratory mechanics between term and preterm infants.
Aim 2: To utilize oscillometry to predict risk of bronchopulmonary dysplasia (BPD) in preterm infants with respiratory distress syndrome (RDS).
Aim 3: To identify change in lung function in common neonatal respiratory disease states (BPD, RDS, transient tachypnea of the newborn (TTN), and meconium aspiration syndrome (MAS)).
Aim 4: To evaluate pulmonary response to chronic therapeutic interventions.

Study Design Type

This will be a prospective observational study with pre-specified Aims and Hypotheses. Oscillometry will be performed in term and preterm infants with and without lung disease. Our study will analyze lung function measures obtained in conjunction with routine clinical care in the NICU, as well as normative comparison data obtained from healthy full-term infants in the well-baby nursery. Both cross-sectional (term vs preterm; BPD vs non-BPD) and longitudinal comparisons (disease progression and therapeutic response) will be performed.

Eligibility Criteria

Infants in the UAB NICU or well-baby nursery will be eligible for enrollment. NICU participants must be off ventilator/CPAP support for ≥ 12 hours to be included in this study. Term and preterm infants without lung disease will provide comparative normative data on respiratory mechanics during the neonatal period. Disease cohorts will include BPD, RDS, TTN, and MAS as common respiratory disease represented in a NICU population. Clinical benefit of physician-directed treatments will assess response to systemic steroids, inhaled steroids, and diuretics.

Study Intervention/Methods

Serial non-invasive oscillometry at scheduled intervals.

Outcomes

Measures of Pulmonary function quantified by oscillometry will be 1) airway resistance, 2) lung compliance, 3) reactance, 4) and inertance, in newborn infants with and without lung disease (RDS, BPD, TTN, and MAS). All measures will be obtained with the same oscillometry measure.

SECTION 2. CONFLICT OF INTEREST DISCLOSURES

Financial Conflicts of Interest of the Institutions and Investigators

Dr Travers and co-investigators have no financial relationships to disclose or conflicts of interest to resolve.

Plan for Managing Identified FCOIs

None needed.

SECTION 3. STATEMENT OF PROBLEM

3.1. PRIMARY AIM OR QUESTION

Oscillometry is a feasible tool to detect clinically meaningful changes in lung function in term and preterm infants and distinguish respiratory health from disease.

3.2. SECONDARY HYPOTHESIS OR QUESTIONS (S) (IF APPLICABLE)

1) Oscillometry can detect disease progression (e.g., BPD, RDS, TTN and MAS) and resolution in infants hospitalized in the UAB NICU.
2) Oscillometry can inform therapeutic response to common pulmonary interventions (e.g., systemic steroids, inhaled steroids, and diuretics) in infants hospitalized in the UAB NICU.
3) To determine how pulmonary function differs over time between preterm infants with RDS which resolves and preterm infants with RDS who go on to develop BPD.
4) To determine the effects on pulmonary function measurements of medications and treatments given to newborn infants to treat bronchopulmonary dysplasia including physical therapy, methylxanthines, furosemide, chlorothiazide, inhaled and systemic corticosteroids, cromolyn sodium, and albuterol.

3.3. BACKGROUND AND RATIONALE

TremoFlo™ C-100 Airwave Oscillometry System™ (THORASYS Thoracic Medical Systems Inc. Montreal, Quebec, Canada) is a technology for measuring lung mechanics without patient effort. Pulmonary function testing using flow-volume and lung volumes is one of the most widely used tests to objectively measure lung function in adults. Such measurements are dependent on effort and coordination by the patient which is not possible for newborn infants. The minimum age for spirometry is typically 6 years to master the technique (ATS). Therefore, newborn infants usually require forced exhalation, flow interruption, and often sedation/anesthesia in order to obtain accurate pulmonary function measurements (Di Fiore). Infant pulmonary function testing can be time-consuming and expensive to perform in newborn infants. This has limited the utilization of this potentially informative method of studying lung function particularly during transition to extra-uterine life, and in newborn lung diseases including RDS, TTN, MAS and BPD and after the effects of treatments given to newborn infants with BPD (Di Fiore).

The TremoFlo device uses the forced oscillation technique during spontaneous infant breathing and notably does not require any sedation to perform (Calogero). The forced oscillation technique measures lung function by superimposing a gentle multi-frequency airwave onto the infant's respiratory airflow while the infant breathes spontaneously. Only a short period of breathing is required to obtain a reliable measurement of airway resistance and

reactance (Calogero). Oscillometry has been successfully utilized to quantify lung function in children (Calogero, Duiverman) and adults (Oostveen, Brown) with lung disease, but never previously in newborn infants. This proposal brings this novel technique of measuring lung function to the neonatal population to identify changes in respiratory mechanics between term and pre-term gestations and quantify fluctuations in infant lung function in response to disease progression and therapeutic intervention.

Oscillometry has detects four measures of lung function:

Lung Compliance: Compliance is a measure of the elasticity or distensibility of the lungs or respiratory system. In neonates, the chest wall is very distensible and in general does not contribute substantially to compliance. It is calculated as follows:

$$\text{Compliance} = \frac{\Delta \text{ Volume (mL)}}{\Delta \text{ Pressure (cm } H_20)}$$

Lung compliance has been measured using dynamic and static techniques (Di Fiore). Dynamic lung compliance has traditionally been measured in spontaneously breathing preterm infants using devices to measure tidal volume and esophageal pressure. The difference between end-inspiration and end-expiration serve as quasi static points of reference. However, in infants with high respiratory rates such as newborn infants and those with lung disease this technique may underestimate the true compliance. Static lung compliance is calculated between points of no flow when the respiratory muscles are relaxed by occluding the airway to allow for equilibration of pressure throughout the respiratory system. Compliance is then calculated by dividing the total exhaled volume by the pressure change during the occlusion minus the pressure at end expiration. One advantage of this technique is that it does not require esophageal pressure monitoring. However, this technique allows a single measurement of compliance to be made only. The single-interruption technique has been modified using the multiple-interruption technique during expiration. The multiple measurements obtained can demonstrate changes in compliance within a single breath as the lungs fill.

Airway Resistance: Conversely, infants with increased resistance of the respiratory system, such as those with broncopulmonary dysplasia, may compensate by using slower and larger breaths (Travers). Resistance is a measure of the ability of the gas conducting part of the respiratory system and lung tissue to impede flow and includes airway resistance (the nasopharynx, larynx, trachea, and bronchi) and viscous resistance (tissue moving against tissue). Resistance is calculated as follows:

$$\text{Resistance} = \frac{\Delta \text{ Pressure (cm } H_20)}{\Delta \text{ Flow (L/sec)}}$$

Usually the mid-volume point of the breath is used for the calculation above. Similar to compliance, measurements using the interruption and multiple-interruption techniques allow for resistance to be measured, the latter at different points during the respiratory cycle (Di

Fiore). With multiple-interruption the pressure at the point of occlusion is divided by the flow immediately preceding the occlusion. Multiple-interruption techniques allow the components of resistance from the airway and tissue to be separated out. In spontaneously breathing infants with lung disease the flow in the airways may be turbulent causing the resistance to change during the respiratory cycle. The forced oscillation technique superimposes oscillatory waves of different frequencies throughout the respiratory cycle to determine both the overall respiratory system resistance as well as changes in central and heterogeneous resistance (ATS).

Reactance: Reactance is a measure of the energy conservation in the respiratory system and includes elastic fibers in the lung tissue which determine lung compliance and the inertive forces of acceleration and deceleration of the column of air in both the airway tree and lung tissues. Resistance is a measure of the ability of the gas conducting part of the respiratory system and lung tissue to impede air flow. This includes airway resistance (through the nasopharynx, larynx, trachea, and bronchi) and viscous resistance (tissue moving against tissue). Resistance and reactance of the lung tissues are affected in different patterns depending on the location and the type of lung disease. For example, central obstruction increases resistance without changing reactance. Homogenous peripheral obstruction increases resistance and decreases reactance. Heterogenous peripheral obstruction similarly increases resistance and decreases reactance; however, the increase in resistance is larger at higher frequency oscillations compared with lower frequency oscillations. Therefore, the forced oscillation technique may allow determination of the presence, type, severity, and location of lung disease in infants.

Inertance: Inertance is a measure of the tendency of the respiratory system to resist changes in flow. In healthy adults and children inertance is a minor component of the forces in the respiratory system. However, inertance increases with increasing respiratory rate as is commonly seen in newborn infants. The equation of motion defines the relationship between pressure, flow, volume, and the elastic, resistive, and inertial components of the respiratory system. It is calculated as follows where P is the pressure that produces lung inflation, C is the compliance, V is the volume, R is the resistance, $\dot{V}$ is flow, I is inertance, and $\ddot{V}$ is acceleration:

$$P = \frac{V}{C} + R\dot{V} + I\ddot{V}$$

While the respiratory system is often modeled as being composed of a single constant compliance and a single constant resistance, the mechanical properties vary with changes in the lung volume, even within a breath between inspiration and expiration. In addition, lung disease (such as bronchopulmonary dysplasia) can be heterogeneous, and thus, different areas of the lungs can have varying mechanical characteristics. The forced oscillation technique will allow us to differentiate between different patterns of resistance and compliance/inertance within each breath to better understand lung mechanics in both healthy newborn infants and infants with the pre-specified types of lung disease (RDS, BPD, MAS, and TTN). The forced oscillation technique may also be useful for measuring the effectiveness of interventions given to treat or prevent lung disease including bronchopulmonary dysplasia.

The respiratory rate is highest at birth and decreases through infancy and early childhood (Fleming). Several physiological reasons have been proposed to explain this difference including differences in pulmonary and chest wall compliance and resistance (Kerem). Faster respiratory rates and lower tidal volumes may be optimum in spontaneously breathing preterm and term infants on the first day after birth to decrease the work of breathing. Compared to term infants, preterm infants have markedly decreased lung compliance (0.1-1.0 mL/cm H_2O/kg versus 3-5 mL/cm H_2O/kg) and somewhat decreased resistance (22 H_2O/L/second versus 29 cm H_2O/L/second) (Avery, Di Fiore). The higher spontaneous respiratory rate of preterm infants when compared with term infants is likely due to their lower lung compliance as increasing the respiratory rate rather than the tidal volume requires less work. Minute ventilation is a product of tidal volume and respiratory rate.

The spontaneous respiratory rate for any given minute ventilation is governed by the principle of minimal work. During spontaneous breathing, the respiratory muscles must work to overcome the elastic and resistive forces of the chest wall and lungs that decreases the pulmonary system compliance (Otis). When the spontaneous respiratory rate is low, excessive work has to be generated by the respiratory muscles to overcome lung and chest wall elastic forces in order to achieve larger tidal volumes. The spontaneous respiratory rate in a cohort of 24 preterm infants during temporary disconnection from ventilators ranged from 53-114 breaths per minute (Greenough). There was a significant negative correlation between gestational age and spontaneous breathing rate ($r = 0.85$). This observation is supported from well-known animal data which show that smaller animals breathe faster than larger animals (Widdicombe). Therefore, more efficient alveolar ventilation can be achieved by increasing the respiratory rate rather than increasing the tidal volume (Davis).

Conclusion: Previous evaluation of lung function in term and preterm neonates has been limited, lessening detection of disease onset, progression, and therapeutic response. The ease of oscillometry that only requires tidal breathing eliminates the need for patient cooperation and maneuvers that previously excluded lung function testing in the NICU. This proposal will evaluate the feasibility and clinical value of oscillometry in newborns, both to detect changes in premature compared to full-term gestations as well as disease cohorts. The four Specific Aims proposed in this study offer significant potential to bring this novel measure of lung function to neonatal care and introduce functional measures of lung function to bedside care.

SECTION 4. METHODS

4.1. STUDY POPULATION

This study will investigate lung function in term (≥ 37 weeks) and preterm (22-36 weeks) infants with and without newborn lung diseases (BPD, RDS, TTN, MAS).

4.1.1. Inclusion Criteria

Infants must meet all of the following criteria to be eligible:
Infants ≥ 22+0/7 weeks' gestation at birth.
Infants whose parents/legal guardians have provided consent for enrollment.
Infants admitted to the regional neonatal intensive care unit (RNICU) or the newborn nursery (NBN) at UAB.
Off ventilator/CPAP support for ≥ 12 hours before study entry.

4.1.2. Exclusion Criteria

Infants will be excluded from this study if they have any of the following:
A major congenital malformation (e.g., cardiac disease or diaphragmatic hernia).
A neuromuscular condition that affects respiration (e.g., spinal muscular atrophy or myopathy).
A terminal illness or decision to withhold or limit support (e.g., chromosomal abnormality or neoplasm)

4.2. DETAILED STUDY PROCEDURES

4.2.1. Screening

The study coordinator will maintain a log of all potentially eligible patients admitted to UAB RNICU and NBN. Infants will be recruited by approaching one or both parents/legal guardians post-natally.

4.2.2. Consent Procedures

Parents/legal guardians of eligible infants will be approached upon admission to the RNICU or NBN at UAB. Parents will be provided with a copy of the informed consent containing written information about the study and participation in the study as part of the consent process.

4.2.3. Study Intervention and Comparison

Term and preterm infants with and without newborn lung disease will have serial oscillometry to evaluate neonatal lung function. Infants will have pulmonary function testing performed using the forced oscillation technique at baseline after enrollment in the study. This will be repeated after 24 hours, 48 hours and once per week thereafter among infants who remain hospitalized.

Infants with lung disease who are receiving pulmonary medications or treatments for lung disease, as per physician order, will have additional measurements of pulmonary function before and after these treatments are given.

4.2.4. Control or Monitoring of Co-interventions

Aim 1 control: baseline oscillometry measurements will be compared over time between preterm infants and term infants without lung disease as defined by need for respiratory support.
Aim 2 control: preterm infants with RDS who go on to develop BPD will be compared with preterm infants with RDS who do not go on to develop BPD. Preterm infants who do not develop BPD will serve as controls for RDS infants who develop BPD.
Aim 3 control: baseline pulmonary function tests and serial changes over time will be compared between infants with and without lung disease. Preterm infants without lung disease will act as controls for preterm infants with lung disease. Term infants without lung disease will act as controls for term infants with lung disease.
Aim 4 control: The timing of pulmonary function testing among infants with lung disease will be recorded in relation to the timing of interventions, as ordered by the treating physician, which may affect pulmonary function including bronchodilators, steroids, diuretics, methylxanthines, different forms of physical therapy, and nebulized/inhaled medications, to determine the effects of these treatments on pulmonary function pairing the pre-treatment pulmonary function values (control) for an individual patient with the post-treatment values (intervention) for the same individual patient.

4.2.5. Primary Outcome

The primary outcome will be change in lung reactance at 7 Hz (X_7) quantified by oscillometry in each comparison group.

In Aim 1, we will compare lung function between term and preterm infants without lung disease at baseline, 24 hours, 48 hours, 72 hours, 7 days, and weekly thereafter until discharge.
In Aim 2, we will compare lung function between preterm infants with RDS who develop BPD and those who do not develop BPD.
In Aim 3, we will longitudinally evaluate change in lung function in NICU patients with lung disease (BPD, RDS, TTN, MAS) at diagnosis, 24 hours, 48 hours, 72 hours, 7 days, and weekly thereafter until resolution of disease state or NICU discharge.
In Aim 4, we will longitudinally evaluate lung function response to therapeutic intervention.

4.2.6. Secondary Outcomes

Secondary measures of lung function will be comparison of resistance data at available frequencies including r7, r13, and r19; reactance at other available frequencies including 13 and 19 Hz, impedance data including resistance as a function of frequency R(f), reactance as a function of frequency X(f), and coherence at each frequency Coh(f); resonance frequency (fres); reactance area AX7; reactance difference DeltaX7; tidal volume and respiratory rate. In addition measures over time will allow us to create normative data curves of changes in these measurements over time in the given populations.

4.2.7. Compliance Monitoring

All participants are hospitalized in the UAB RNICU or newborn nursery, so clinical history including medication adherence will be recorded.

Oscillometry will be administered by physicians and nurses trained in the care of newborn infants and in the use of the forced oscillation technique device. Measurements will be repeated until a stable consistent measurement is obtained as recommended by the manufacturer of the device. The coefficient of variation between three valid measurements with the device should not exceed 15%.

4.3. POTENTIAL RISKS AND BENEFITS TO SUBJECTS

Infants enrolled in this study are not expected to have risks above routine care. Measurements are taken by placing a new disposable mask over the baby's mouth and nose and allowing them to breathe normally. It is possible that some infants will find having a mask on their face for 5-10 seconds uncomfortable but this is immediately reversible by removal of the mask.

SECTION 5. ANALYTICAL PLAN

5.1. STATISTICAL ANALYSIS PLAN

Results will be analyzed by the Student's t test, as appropriate for parametric data, and by Mann-Whitney U rank sum test for nonparametric data. A *p* value of <0.05 will be considered statistically significant.
Non-independent parametric data will be analyzed by the paired Student's t test, and Wilcoxon signed rank test for non-independent non-parametric data.
Chi-square or Fisher's exact test will be used as appropriate to analyze categorical data.
Analysis of covariance and multiple regression models will be used to examine the interaction between, and the independent effects of factors including birth weight, gestational age, gender, ethnicity, socioeconomic group, maternal smoking, type and severity of lung disease, treatment with surfactant (including number of doses), days of mechanical ventilation before study entry, days of respiratory support before study entry, treatment with antenatal steroids, and treatment with postnatal steroids upon primary and secondary outcomes.

5.2. SAMPLE SIZE

This observational study will include all eligible infants enrolled at UAB RNICU and NBN.
Aim 1 (Comparison of lung compliance in term and pre-term infants)
Assuming lung reactance at 7 Hz (X_7) initial measurements will have an absolute 20% difference (more negative) in preterm infants without RDS compared to term controls will need to recruit 264 infants (132 term and 132 preterm infants) assuming power of 90%, type I error rate of 5% and standard deviation of 0.5 of the mean.

Aim 2 (Comparison of BPD and non-BPD lung compliance)
Assuming lung reactance at 7 Hz (X_7) initial measurements will have an absolute 20% difference (more negative initially) in preterm infants with RDS who go on to develop BPD (including O2 requirement at 28 days –mild BPD) compared to preterm controls with RDS who do not develop BPD will need to recruit 264 infants (132 BPD, 132 non-BPD) assuming power of 90%, type I error rate of 5% and standard deviation of 0.5 of the mean.
It will not be possible to know in advance which infants with RDS will go on to develop BPD so we plan to enroll as many preterm infants with RDS as possible until the sample size for infants with RDS who develop BPD is reached.
Aim 2 (

Aim 3 (Comparison of common neonatal respiratory disorders)
RDS - Assuming lung reactance at 7 Hz (X_7) initial measurements will have an absolute 20% difference (more negative) in preterm infants with RDS compared to preterm controls will need

to recruit 264 infants (132 per arm) assuming power of 90%, type I error rate of 5% and standard deviation of 0.5.
BPD - Assuming lung reactance at 7 Hz (X_7) initial measurements will have an absolute 20% difference (more negative) in preterm infants with BPD compared to preterm controls will need to recruit 264 infants (132 per arm) assuming power of 90%, type I error rate of 5% and standard deviation of 0.5 of the mean.
TTN - Assuming lung reactance at 5 Hz (X_5) initial measurements will have an absolute 20% difference (more negative) in term infants with TTN compared to term controls will need to recruit 264 infants (132 per arm) assuming power of 90%, type I error rate of 5% and standard deviation of 0.5 of the mean.
MAS - Assuming lung reactance at 7 Hz (X_7) initial measurements will have an absolute 50% difference (more negative) in term infants with MAS compared to term controls will need to recruit 42 infants (21 per arm) assuming power of 90%, type I error rate of 5% and standard deviation of 0.5 of the mean.

Aim 4 (Comparison of lung compliance response to therapeutic intervention)
Methylxanthines - Assuming lung reactance at 7 Hz (X_7) measurements will have an absolute 15% difference (more positive) lung compliance following this therapy we plan to recruit 120 infants (60 per arm) assuming power of 90%, type I error rate of 5% and standard deviation of 0.5 of the mean.
Physical therapy - Assuming lung reactance at 7 Hz (X_7) measurements will have no significant difference with a non-inferiority margin of 15% following this therapy we plan to recruit 120 (60 per arm) infants assuming power of 90%, type I error rate of 5% and standard deviation of 0.5 of the mean.
Nebulized cromolyn sodium - Assuming lung reactance at 7 Hz (X_7) measurements will have no significant difference with a non-inferiority margin of 15% following this therapy we plan to recruit 120 infants (60 per arm) assuming power of 80%, type I error rate of 5% and standard deviation of 0.5 of the mean.
Albuterol - Assuming lung reactance at 7 Hz (X_7) measurements will have an absolute 15% difference (more positive) following this therapy we plan to recruit 120 infants assuming power of 90%, type I error rate of 5% and standard deviation of 0.5 of the mean.
Furosemide - Assuming lung reactance at 7 Hz (X_7) measurements will have an absolute 20% difference (more positive) following this therapy we plan to recruit 70 infants assuming power of 90%, type I error rate of 5% and standard deviation of 0.5 of the mean.
Chlorothiazide - Assuming lung reactance at 7 Hz (X_7) measurements will have an absolute 20% difference (more positive) following this therapy we plan to recruit 70 infants assuming power of 90%, type I error rate of 5% and standard deviation of 0.5 of the mean.
Systemic postnatal steroids for BPD - Assuming lung reactance at 7 Hz (X_7) measurements will have an absolute 30% difference (more positive) following this therapy, we plan to recruit 30 infants assuming power of 90%, type I error rate of 5% and standard deviation of 0.5 of the mean.
Inhaled postnatal steroids for BPD - Assuming lung reactance at 7 Hz (X_7) measurements will have an absolute 30% difference (more positive) following this therapy we plan to recruit 30

infants assuming power of 90%, type I error rate of 5% and standard deviation of 0.5 of the mean.

5.3. AVAILABLE POPULATION

This will be a single center study at University of Alabama at Birmingham. There are approximately 4000 infants born at UAB each year and approximately 1200 admissions to the RNICU. Thus, achieving enrollment goals is not anticipated to be a difficulty for the research team.

5.4. PROJECTED RECRUITMENT TIME

It is estimated that recruitment will continue for two years.

5.5. STUDY MONITORING PLAN

5.5.1. Reporting Adverse Events

Serious and unanticipated adverse events are unlikely in this observational study using a non-invasive device to measure pulmonary function. Data on the following potential adverse events that could possibly be related to the pulmonary function testing will be recorded and evaluated as part of continuous safety monitoring during the trial:
1. Apnea or bradycardia < 80 bpm for more than 1 minute/requiring IPPV during measurement.
2. Hypoxemia with SpO2 < 60% for more than 1 minute/requiring IPPV during measurement.

5.5.2. Data Monitoring Plan and Stopping Rules

The Data Safety Monitoring Committee will review the progress of the study. Serious and unanticipated outcomes will be evaluated on a biannual basis by the chair of the Data Safety Monitoring Committee, and if the incidence of any of these outcomes is determined to be 20% greater in any arm of the study higher in studied infants when compared with expected baseline, this information will be provided to the Study PI and committee and the Data Safety Monitoring Committee for immediate consideration, and evaluated for consideration of termination of the study.

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