Study Title: Impulse Oscillometry and the Bronchoprotective Effects of Deep Inspiration
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Short title: The DITO Study (Effects of Deep Inspiration on Tremoflo Oscillometry)

1. PURPOSE OF STUDY

- To gain experience using Impulse Oscillometry to measure lung function in human subjects.
- To determine if airway impedance, measured by Impulse Oscillometry, is impacted by a deep inspiration maneuver in a small cohort of healthy human subjects.

2. BACKGROUND AND RATIONALE

Impulse Oscillometry (IO) is a noninvasive method of measuring respiratory mechanics and is quickly being adopted as an adjunctive test in the diagnosis and monitoring of lung disease (1). During IO, pressure oscillations are applied at the mouth during tidal breathing across a range of frequencies to measure variables of resistance and reactance (2). Unlike conventional pulmonary function testing that require modified breathing maneuvers like forced exhalation or sustained breath holding, IO is analyzed during normal tidal breathing, requires minimal cooperation by the test subject, and may be advantageous in patients who perform poorly with traditional lung function testing. IO also has the potential of detecting small changes in the periphery of the lung (3), which has generated particular interest in its clinical utility in obstructive lung disease. Resistance and reactance variables measured by IO seem to have greater sensitivity than traditional spirometry in measuring bronchodilatory response (4), which has strong implications for its use in the monitoring and treatment of airways diseases like asthma. Although IO has been investigated for decades in pulmonary physiology labs, recent improvements in technology have led to the development of handheld devices that can obtain accurate and reproducible measurements during a few minutes of tidal breathing. Consequently, there is renewed interest in incorporating IO into routine pulmonary function testing, and in fact IO is currently covered under certain CPT codes. Co-investigator Dr. Georas is the Medical Director of Pulmonary Function Labs at the URMC, and we are considering incorporating IO into our clinical testing protocols. We recently purchased a Tremoflo C-100 Oscillometer from Thorasys, Inc., and one goal of this RSRB proposal is to gain preliminary experience with this procedure and device in healthy subjects. We considered conducting pilot testing in healthy subjects as a Quality Improvement / Quality Control project, without a full proposal to the RSRB. However, we realized that we could simultaneously conduct a small scale research project, where we address an unknown question in the field: what is the effect of deep inspiration on respiratory impedance as measured by IO?

Deep inspiration (DI) has been demonstrated to have beneficial effects on the lungs of healthy subjects (5). In particular, DI performed by healthy individuals before bronchoprovocation testing results in less bronchoconstriction (6). This bronchoprotective effect of DI was not observed in patients with asthma (7), suggesting that an inability to modulate small airway smooth muscle is an important aspect of asthma pathophysiology. The bronchoprotective effect of DI has been mostly evaluated using bronchoprovocation testing with spirometry and there is limited data on the effect of deep inspiration on the oscillometry variables of resistance and reactance (8). If the bronchoprotective effect of DI

can be reliably demonstrated in healthy subjects using oscillometry, then there is potential for oscillometry to detect the absence of bronchoprotection with DI in individuals with asthma. The capability of detecting these small airway changes has strong implications in future asthma pathophysiology research. The secondary aim of this study is to evaluate whether there is a detectable difference in oscillometry variables before and after DI in healthy subjects. Thus this RSRB proposal aims to "kill two birds with one stone", namely to: (1) gain experience with a new device to measure lung function, and (2) to determine if DI influences respiratory function as measured by IO.

3. ADMINISTRATIVE ORGANIZATION

- The participating UR research locations for this study are:
  - Mary Parkes Center for Asthma, Allergy, and Pulmonary Care
  - Pulmonary Clinic at Strong Memorial Hospital

4. STUDY DESIGN

- This is a single-center study that will enroll healthy subjects from a convenient study population.
- The aims of the study are to:
  - Gain experience with performing impedance oscillometry using a Tremoflo C-100 in healthy subjects.
  - Determine if there is a detectable difference in oscillometry variables before and after deep inspiration in healthy human subjects.
- Study outcomes:
  - Oscillometry measurements before and after deep inspiration to include respiratory system resistance (Rrs), respiratory system reactance (Xrs), and resonant frequency (Fres).

4.1. SUBJECT POPULATION

- Up to fifty (50) healthy subjects will be recruited from Mary Parkes Asthma and Allergy Center and the outpatient pulmonary clinics at the University of Rochester Medical Center, and from the Pulmonary and Critical Care Division at the University of Rochester.

4.2. STUDY INTERVENTIONS

- Measurement of airway impedance using the Forced Oscillation Technique
  - THORASYS® tremoFlo® C-100 Airwave Oscillometry System™ (AOS)
    - This is a 510(k) FDA approved, non-significant risk device, and will be used according to FDA indication, which states: "*The tremoFlo C-100 Airwave Oscillometry System is intended to measure respiratory system impedance using the Forced Oscillation Technique (FOT). tremoFlo C-100 Airwave Oscillometry System is intended for use with pediatric and adult patients 4 years of age or older. The device is designed to be used by pulmonologists, general practitioners, nurses, respiratory therapists, laboratory technologists, medical researchers and similarly trained personnel in hospitals, clinics, and private physician offices*".
    - This is a non-significant risk device because it does not require any

instrumentation or other procedures, and the subjects simply breathes normally for a few minutes into a mouthpiece while the device measures pressure at the mouth piece.

- We are not seeking approval for a new indication or new patient population for the device. Rather, in this study we are testing its effectiveness to detect differences in oscillometry before and after deep inspiration in healthy subjects.
- The device will be stored in the Department of Pulmonary and Critical Care Medicine Department Office. Only the co-investigators in this study will have access to the device. The device is portable so will be moved to the clinic locations mentioned in section 3 where testing will be performed.
- The device is handheld with a removable mouthpiece/filter attachment that is disposable. The subject places his/her mouth over the mouthpiece and breathes normally. A button is pressed on the side of the device that begins the test. Sound waves are generated at the mouth and measurements are made over several seconds. After about 20-30 seconds, the first collection of data is complete. This process is repeated at least 3 times to ensure repeatability. Once the test is complete, the removable filter is disposed.
- Data will be collected and stored using a password-protected standard laptop used only for this research project.

5. INCLUSION AND EXCLUSION CRITERIA

- Inclusion Criteria:
  - Age $\geq$ 18
  - Vaccinated against COVID-19
  - Ability to provide informed consent
  - Willingness to perform breathing test
  - Willingness to provide basic demographic data (outlined in section 8)
  - Must be able to speak and understand English.

- Exclusion Criteria:
  - Unable to or unwilling to provide consent, perform test, or provide basic demographic data.

6. RECRUITMENT METHODS

- Subjects will be recruited from the outpatient clinics at the University of Rochester Medical Center and the Mary Parkes Asthma Center. Recruitment flyers will be posted at multiple locations in these sites. The study will also be advertised to faculty and staff of the Pulmonary & Critical Care Medicine Division by group email and announcements at Divisional conferences. There are no plans to email individual subjects directly. Our outreach to faculty and staff of the Pulmonary & Critical Care Medicine Division is justified, because they have experience in the ordering, conduct and interpretation of pulmonary function tests, and we think many of them will be interested in participating in

the study and learning about this new way of measuring pulmonary function. We will avoid coercion by using neutral phrasing and making it clear that participation is strictly voluntary, and that there is no penalty for deciding not to participate.

- Interested participants will be asked to contact the study team members directly.
- We currently do not have the resources or infrastructure to enroll non-English speaking patients. We will re-evaluate if this changes at a future date.

7. CONSENT PROCESS

- The investigator will review the details of the study with the subject in person or by phone call.
- The subject will have the opportunity to read the consent form fully and ask questions. The subject may wish to consider the study further and can be given a copy of the informed consent to take home for review.
- The investigator will review with the patient that participation in the study is entirely voluntary. The subject will be informed that the decision to not participate in the study will not affect the subject's personal or professional relationship with the investigator.
- The consent process is as follows: the consent will be distributed only as a paper copy for simplicity. The subject will be presented a paper copy of the consent at the time of testing. The consent will be reviewed in its entirety with the subject. If the subject agrees to proceed, he or she may sign two copies. One copy will be sent home with the subject and the other copy will be locked in the Pulmonary & Critical Care Fellow's Office.

8. STUDY PROCEDURES

- Consent and testing procedure:
    - The investigator performing the test will discuss the protocol with the subject, answer all questions and obtain written consent prior to study enrollment.
    - Subjects will be instructed to refrain from taking deep breaths, sighs, or yawns, for at least 10 minutes prior to testing.
    - Data collected will include oscillometry impedance data (detailed below) and basic demographic information. Demographic information includes age, biological sex, self-reported race, and history of lung disease. All data collected will be stored on the research laptop which will be password protected. Data collected will be deidentified.

      <u>February 2022 revision</u>:
    - In addition to basic demographic information, subjects will be asked to fill out the following validated questionnaires: The Pittsburgh Vocal Cord Dysfunction Index, Asthma Control Test (ACT), the STOP-BANG Score (for obstructive sleep apnea), and the Newcastle Laryngeal Hypersensitivity Questionnaire (a measure of laryngeal symptoms).
    - Mallampati score will be calculated by looking into the subject's mouth and neck circumference will be measured by using a disposable paper measuring tape.

- No data will be obtained or accessed from the medical record.

- Oscillometry will be performed as follows:

    - A new disposable mouthpiece/filter will be attached to the device.
    - A noseclip will be provided and can be self-applied by the subject.
    - The subject will then place mouth over the mouthpiece.
    - The subject will place hands over cheeks to limit upper airway artifact.
    - The subject is asked to breath normally.
    - The investigator will then press the button on the side of the device to begin data collection.
    - One run of the test is about 20-30 seconds of tidal breathing. The test will be repeated at least 3 times to ensure repeatability.
    - The subject will then be instructed to rest off of the mouthpiece and nose clips will be removed.
    - Next, the subject will be instructed to take five sequential deep breaths to maximal lung inflation (TLC) and maximal lung deflation (RV). Subjects will be encouraged to achieve maximal values (e.g. "keep going!" during inhalation, and "blow, blow blow!" during exhalation).
    - Then oscillometry will be repeated as above.
    - Once testing has concluded, the removable mouthpiece/filter will be discarded into a biohazard bin. The device and all surfaces will be wiped down with a Cavi Wipe or a Hydrogen Peroxide Wipe.

    - Only individuals vaccinated against the COVID-19 virus will be included in this study. This study will follow all University of Rochester Medical Center guidelines in regards to Universal Precautions for individuals vaccinated against the COVID-19 virus.

    - Note that the IO procedure is not considered aerosol-generating, and no special procedures are needed to perform the maneuver in COVID vaccinated subjects (personal communication from Dr. Brenda Tessini, UR Infection Prevention, 6/24/21).

- **Data storage:** All oscillometry data will be deidentified and downloaded to the research laptop. All demographic data will be deidentified and entered into the research laptop. At the conclusion of the data collection phase of the study, the deidentified data will be analyzed on the laptop using Microsoft Excel.
- **Medical Record**: Since this study is exploratory in nature, we do not plan to record subject's participation in this study, or any IO results, in the subject's electronic health record.

9. RISKS TO SUBJECTS

9.1. Potential Risks: the potential risks include possible breach of confidentiality, risk of

infection, and discomfort from wearing the nose clip or breathing into the mouthpiece.

9.2. Protection Against Risks: The risk of the breach of confidentiality will be reduced by deidentifying data and restricting data access. The risk of infection will be reduced by using a disposable mouthpiece/filter attachment, cleaning the device with a disinfectant between uses, screening subjects for a transmissible respiratory infection, and limiting the testing to individuals vaccinated against COVID-19. Note that IO has been performed in tens of thousands of patients worldwide without adverse effects including infection. The risk of discomfort from wearing the nose clip or breathing into the mouthpiece will be mitigated by allowing subjects to stop testing if they find the brief procedure too uncomfortable.

9.3. Alternatives to participation: non-participation.

10. POTENTIAL BENEFITS TO SUBJECTS

There are no anticipated benefits from participating in this study.

11. COSTS FOR PARTICIPATION

None.

12. PAYMENT FOR PARTICIPATION

- None.

13. SUBJECT WITHDRAWALS

- Subjects can withdraw from study participation at any time and no reason is needed.
- The investigators will otherwise include all data collected from subjects who undergo the proper consent process and who are able to perform the test.

14. PRIVACY AND CONFIDENTIALITY OF SUBJECTS AND RESEARCH DATA

- Each subject will be assigned a unique identifying number (subject ID number). Demographic data and oscillometry data collected will be listed under this unique identifying number on the Excel Sheet saved to the password protected research laptop.
- The subject ID number is otherwise deidentified and will not be linked to the subject in any way. For the purposes of this study, there is no reason to link any patient identifiers to the deidentified subject ID number.
- Consent forms will be maintained in the locked Pulmonary & Critical Care Fellow's Office. Access will be restricted to the co-investigators of this study.

15. DATA / SAMPLE STORAGE FOR FUTURE USE

- Raw oscillometry data will be stored on the device under password protection. Raw oscillometry data on the device and deidentified data saved to the research laptop will be maintained for a maximum of 3 years.
- Once data has been analyzed, the results (which will be deidentified) may be shared at future research conferences.

16. DATA AND SAFETY MONITORING PLAN

The risks from participation in this study are low. Risks are mainly related to breach of confidentiality and infection. The following steps will be taken to ensure data and safety monitoring.

- Definitions:
  - Adverse Event: any untoward medical occurrence related to the study procedure.
  - Serious Adverse Event: Any adverse event resulting in an ED visit, inpatient hospitalization, significant incapacity or death or may require medical or surgical intervention to prevent one of the above outcomes.
- Participants will be asked to contact the investigator if they experience any adverse event that could be related to the study in the days to weeks following the visit.
- If a serious adverse event is identified or reported, a physician who is not a member of the study team will be asked to perform an independent review.
- Adverse events will be reported as required by institutional IRB.

- **DATA ANALYSIS PLAN**
  - Oscillometry measurements before and after deep inspiration will include respiratory system resistance (Rrs), respiratory system reactance (Xrs), and resonant frequency (Fres).
  - We will calculate mean and standard deviation for values obtained before DI (Pre) and after DI (Post). Data will be tested for normal distribution and outlier effects. Differences between Pre and Post will be determined using t-test or ANOVA. Statistical significance will be determined as $p<0.05$
  - Differences between Pre and Post values will be analyzed after the first twenty (20) subjects have completed testing. If promising trends appear with borderline significance (e.g. $0.05<p<0.10$) or if there are a subset of apparent responders, then an additional twenty subjects will be enrolled and analyzed.
  - A formal power and sample size calculation was not performed for this study, which is exploratory in nature.

17. REFERENCES

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