

INDIANA UNIVERSITY INFORMED CONSENT STATEMENT FOR RESEARCH

Effect of Flow-Resistive Inspiratory Muscle Training on The Severity of Exercise-Induced Bronchoconstriction and Cycling Time-Trial Performance

ABOUT THIS RESEARCH

You are being asked to participate in a research study. Scientists do research to answer important questions which might help change or improve the way we do things in the future.

This consent form will give you information about this study to help you decide whether you want to participate. It is your choice whether or not you want to be in this research study. Please read this form, and ask any questions you have, before agreeing to be in this study.

Disclaimer: It is possible that after completing the study questionnaires and the initial tests that you will not qualify for the study.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to understand the effects of inspiratory muscle training (training of the breathing muscles) on the severity of exercise related asthma in athletes and if this specific inspiratory muscle training will improve cycling performance.

This study will be conducted by Dr. Timothy D. Mickleborough (Principal Investigator), and co-investigator Abigail S. Sogard in the Department of Kinesiology at Indiana University.

This study involves the use of an investigational device, the PrO2Fit, which has not been specifically studied in asthma patients. "Investigational" means it is not approved by the Food and Drug Administration.

HOW MANY PEOPLE WILL TAKE PART?

If you agree to participate, you will be one of approximately 20 participants taking part in this study.

WHAT WILL HAPPEN DURING THIS PORTION OF THE STUDY?

If you agree to be in the study, you will be asked to complete the following:

You will be required to be a competitive recreational or college athlete with at least one to two years of cycling or biking experience, and are considered "moderately to highly active" from an approved physical activity questionnaire. Females will need to complete each visit during the early phase of their menstrual cycle (period) which is 1-5 days from the start of your period. You will be instructed to avoid caffeine, alcohol, and vigorous exercise 24 hours before each of the five visits. Instructions on food/diet recalls, medication use diary, and training logs will be given to you and will need to be completed 24 hours before each visit. You will complete a formal screening visit and four experimental visits. Before every visit, you will complete a COVID-19 Questionnaire online. Those who have tested positive for COVID-19 will be excluded. The five experimental visits will occur each day at approximately the same time, at least 24 hours apart, and more than 2 hours after eating food.

	Screening	Experimental			
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
STUDY PROCEEDURES	2 hours	3 hours	3 hours	3 hours	3 hours
COVID-19 Questionnaire	X	X	X	X	X

Medical Health Questionnaire	X				
Dyspnea-12 Questionnaire	X				
IPAQ	X				
Blood Pressure and Pulse	X	X	X	X	X
Height, Weight, BMI, USG	X	X	X	X	X
Study Consent	X				
PFTs and EIB Screening	X			X	
VO2peak		X			
Familiarization 16-km Cycling Time-Trial		X		X	
Constant Load Exercise			X		X
16-km Cycling Time-Trial			X		X
IMT Randomization			X		

Screening/Visit 1: You will be scheduled to meet with the investigator. Before the visit, you will complete a COVID-19 Online Questionnaire. Those who have tested positive for COVID-19 will be excluded. Your height and weight will be recorded to calculate BMI and an approved physical activity questionnaire will be given. A health questionnaire will be given to screen for pre-existing medical conditions and diagnoses. The questionnaire includes specific questions about any previous asthma or exercise-induced asthma diagnosis, compromised breathing with the Dyspnea-12 Questionnaire (D-12), any incidences of chest tightness, and breathing difficulties post-exercise. If you choose to participate, we will obtain informed consent for the study. If you are on any asthma or exercise-induced asthma medications (short-acting β_2 -agonist (SABA) such as salbutamol and albuterol), inhalers use must cease 24 hours before visits ; however, you will be required to bring your medication with you to each visit. You will undergo lung function testing and a breathing challenge for the purpose of diagnosing exercise-induced asthma.

Visit 2: You will complete an incremental cycle test to determine your endurance fitness. You will have a 1-hour rest period before the familiarization time-trial which is 16-km long. During the time-trial, a revised scale (1-10) will be used to indicate leg fatigue as well as breathing intensity and unpleasantness will be administered every 4-km. Muscle oxygenation level of the leg and ribs will be measured continuously during exercise, and lung function will be measured every 4-km.

Visit 3: You will complete two, 8-minute constant intensity exercises, one at a low intensity and another at high intensity. During the exercises, a scale (1-10) measuring leg fatigue, breathing intensity, and unpleasantness will be given every two minutes. Muscle oxygen levels of the leg and ribs will be measured continuously, leg blood flow will be measured in the last 10 seconds of the final minute for each constant intensity exercises and lung function will be measured every two minutes. You will have a 1-hour rest period before the performance cycling time-trial. During the time-trial, a scale (1-10) measuring leg fatigue, breathing intensity, and unpleasantness will be given at 4 different distance points during the cycling exercise. Muscle oxygen levels of the leg and ribs will be measured continuously during exercise, and lung function will be measured at 4 different distance time points during exercise.

At the end of Visit 3, you will be randomly assigned to an IMT group with varying SMIPs (sustained maximal inspiratory pressures) and you will have an equal chance of being assigned to either group, but you will not be told which group you are in. Both groups will perform the same inspiratory muscle training (IMT) activities, but the targets will be different. You will receive the device needed to do this training as well as written instructions at this time. You will use a flow-resistive inspiratory muscle trainer (Pro2Fit, Smithfield, Rhode Island) in order to complete eight weeks of IMT, performed three times a week with 24 hours in between (for example: Monday, Wednesday, Friday or Tuesday, Thursday, Saturday), prior to any exercise training that day. After eight weeks of the IMT training, you will return to the lab to repeat tests done in visits 1 through 3 for your 4th and 5th visits.

Each of these tests are described below.

1. Height and Weight Measures

Height will be measured using a standard wall mounted, sliding height-measuring board (stadiometer) in meters. Weight will be measured by an electronic scale in kilograms (kg).

2. Body Mass Index (BMI)

BMI will be calculated using height and weight values with the following equation: $\text{mass (kg)} / \text{height (meters)}^2$.

3. Blood Pressure and Pulse

At the beginning of each visit, you will be asked to sit in a chair for 5-10 minutes to ensure your body is relaxed in a resting state. We will then fit you with a blood pressure cuff that will evaluate resting blood pressure and pulse rate.

4. Hydration

Your hydration status via a urine sample will be analyzed by a handheld device and will be measured and recorded before all exercise tests.

5. Menstrual cycle tracking

All female subjects will be tested within the first 5 days of their menstrual cycle. During your initial screening/informed consent visit, you will be instructed to alert us each time you get your period throughout the duration of enrollment. It is recommended that you communicate with us if your period is consistent if on birth control and at what point it happens in each pill pack. Applications to track period cycles will also be recommended, but as to which one you will use, this is up to your choosing.

6. Pulmonary Lung Function Tests

You will be asked to sit in a chair and rest comfortably for 10 minutes. You will be asked to put nose clips on your nose and breathe through a plastic mouthpiece. The nose clips are cleaned in detergent and an antibacterial solution after each use, and the plastic mouthpiece is new for each subject. While sitting in the chair, you will be asked to complete various breathing tests which measure the size of your lungs, how fast you can move air in and out of your lungs, the ability of your lungs to transfer gas to the blood, and the ability of your lungs to generate pressure. This will be done again after the exercise related asthma test to determine the degree of exercise-induced asthma severity. These tests will be performed in 5-minute increments lasting 30 minutes.

7. Exercise-induced Asthma Testing

This breathing challenge will be used as a replacement to an exercise challenge. You will try to maintain a determined breathing rate of inhalation and expiration for 6 minutes while breathing dry air from a special bag. This will feel like you though you are breathing heavy like you do in exercise, but you will be seated in a chair. You will breathe through a two-way valve and a metronome will be used to help you keep your breathing rate constant.

8. Cycle Tests

These exercise tests will be completed on a stationary bike (cycle ergometer). The tests are a maximal exercise test, constant-load exercise, and two time-trials. For all cycle tests, you will be allowed to warm-up on the cycle ergometer for 3 to 5 minutes at any pedaling rate and resistance you would like to select. A strap will be placed around your chest which will measure your heart rate. Another sensor will be placed on your thigh and rib cage and secured by an elastic bandage to measure muscle oxygen content. You will be asked to complete the cycle tests while breathing through a face mask which covers your nose and mouth. Air will flow into and out of your lungs as you breathe through the face mask. The face mask, forehead sensor, thigh sensor, and heart rate monitor are cleansed in a detergent and antibacterial solution following each use.

For the maximal exercise test, the initial workload will be set at 100 Watts (W) for males and 50W for females. Every minute, the workload will increase by 30W for men and 25W for women until you become so tired that you need to stop. The goal is to pedal for as long as you can, with a typical test lasting between 10 and 15 minutes.

For the constant load exercise test, the workload for the two, eight-minute tests will be calculated based on your maximal exercise test. Prior to the first 8-minute constant load exercise, a short 2-minute low load cycling bout will occur which will follow right into the beginning of the predetermined load. The first eight minutes will be a lighter workload compared to the second eight-minutes, where the workload will be harder. During the start and end exercise, ultrasound imaging will be done on your leg. This will be done in the upper thigh and hip region.

For the 16-km time trials, you can pedal at any pedaling rate you like and set the resistance/gearing at any level you like. The goal is for you to complete a 16-km ride in as short of a time as possible. You will be given real time feedback of the distance you have completed on a video monitor.

9. Inspiratory Muscle Training

You will be randomly assigned to an IMT group with varying SMIPs (sustained maximal inspiratory pressures), using a random number generation system. You will use a flow-resistive inspiratory muscle trainer device from the third-party company called PrO2Fit (Smithfield, Rhode Island) in order to complete eight weeks of IMT, performed three times a week, prior to any exercise training that day. The training device is hand-held and will be connected to a tablet or smartphone via a wireless Bluetooth connection. The test of incremental respiratory endurance (TIRE) requires you to exhale forcefully until there is no air in your lungs and immediately inhale maximally and sustain inhalation until you can't keep going. You will be required to complete 3 of these maximal inhalation tests with each training session. The best of the three for that day's training will be used that day. You must match or exceed the template with each increasing level of the work and decreasing amount of rest. Work at each level consists of 6 breaths (36 breaths total). If six breaths are completed, the next level starts. Rest intervals will progressively shorten as training continues from 40-seconds to 30-, 20-, 15-, 10-, and 5-seconds. Your training will stop if you cannot complete six breaths matching or exceeding a certain percentage of that day's maximum inhalation test or have completed all 36 breaths. You will be given written instructions on how to use the PrO2Fit device.

10. Training Log, Dietary Recall, Medication Use Diary

You will be using the automated dietary recall system to record all food and beverages consumed during 24 hours on five occasions before each visit. Using this system allows for real-time food intake/diet analysis. Training logs will be complete before all testing visits and on each IMT training day. You will keep a medication use diary throughout the duration of the study. Entries will be sent to investigator weekly reporting medication use, time taken and circumstance, and amount (number of puffs) to monitor inhaler use.

WHAT ARE THE RISKS OF TAKING PART OF THIS STUDY?

While participating in the study, the risks include the following:

- Submaximal (low and moderate effort) and maximal (all-out effort) exercise tests of healthy individuals, as described by the American College of Sports Medicine, present little risk to the subject and do not require medical clearance for subjects under the age of 40. Potential risks and/or discomforts can include episodes of temporary light-headedness, chest discomfort, leg cramps, occasional irregular heartbeats, and abnormal blood pressure responses.
 - The risk of heart attack, although minor, (approximately 1 to 2 in 10,000) does exist. One death occurs for roughly every 880,000-man hours of submaximal exercise in apparently healthy individuals. During the test you will be closely monitored for any abnormal changes in heart rate or breathing. You are free to indicate any discomfort and discontinue participation at any time.

- All face masks will be cleaned in detergent and antibacterial solution after each use, minimizing the risk of virus transmission between subjects.
- When breathing the dry gas mixture or completing a breathing challenge, you may feel lightheaded, which can be quickly reversed by removing the face mask and breathing room air. The gas mixture does not have substantial moisture and may dry out and irritate your throat.
- There is a possibility of lightheadedness and discomfort from fatigue you may feel during or after training with the IMT device. Otherwise, there are no known risks of completing inspiratory muscle training using the IMT device.
- Chances of any asthma exacerbation are possible during or after time-trial, constant-load exercise, and peak oxygen consumption exercise. There is a risk of bronchospasm. Bronchospasms can be mild and controlled with inhalers. However, they may be severe and require more than the use of a fast-acting rescue inhaler.
- It is required that you have your fast acting rescue inhaler with you at each visit in case of an asthma attack. If you do not bring your inhaler, your session will need to be rescheduled. The study team will need to check your inhaler medication for the number of puffs left indicated by the counter on the back of the inhaler and ask how current your last medication refill is.
- Dehydration can lead to performance decrements such as dizziness and overheating. The study team will provide water or Pedialyte to you to ensure adequate hydration, and ice bags will be on hand in case of overheating.
- There is a potential risk of loss of confidentiality.
- There are no known risks during other procedures such as leg blood flow, muscle oxygenation levels, rating scales, training logs, medications diaries, food/diet logs, and lung function tests.

When using the PrO2Fit device, you will feel the sensation similar to lifting weights at high repetitions or holding a plank for a period of time. You will be training your respiratory muscles like you would in the gym lifting weights. You will be inhaling through the device as hard and as long as you can until you quit, and you will try to complete a certain number of respirations and sets with shortened rest time.

If any further complications happen, researchers who are Adult CPR/AED/First Aid certified will be on hand. If the situation escalates, 911 emergency services will be called for medical assistance. If an adverse event happens outside of the lab, please call 911 emergency services for medical assistance

WHO WILL PAY FOR MY TREATMENT IF I AM INJURED?

If you are injured as a result of participating in this study, costs not covered by your health care insurer will be your responsibility. Also, it is your responsibility to determine the extent of your health care coverage. No money or funds are set aside to pay for these types of injuries. However, you are not giving up any legal rights or benefits to which you are otherwise entitled by signing this Informed Consent form.

WHAT ARE THE BENEFITS OF TAKING PART IN THE STUDY?

The benefits to participation that are reasonable to expect are information regarding your overall level of fitness. Other than this information, you will gain little benefit. All subjects will be provided with feedback concerning their own results and the general findings of the study upon request.

WILL I BE PAID FOR PARTICIPATION?

You will be paid \$15 for each experimental visit and receive \$15 every 3 weeks (2 times) during training period for a possible total of \$105. Payment will be made via a gift card and will be given to you at the end of each completed testing session.

A description of this clinical trial will be available on ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of results. You can search this website at any time.

HOW WILL MY INFORMATION BE PROTECTED?

Every effort will be made to keep your personal information confidential, but we cannot guarantee absolute confidentiality. No information which could identify you will be shared in publications about this study. Your personal information may be shared outside the research study if required by law and/or to individuals or organizations that oversee the conduct of research studies, and these individuals or organizations may not be held to the same legal privacy standards as are doctors and hospitals.

Researchers may release information about you when you say it is okay. For example, you may still give them permission to release information to insurers, medical providers, or others not connected with the research.

WHO SHOULD I CALL WITH QUESTIONS OR PROBLEMS?

For questions about the study, contact the researcher, Timothy Mickleborough, Ph.D. at (812) 855-0753.

In the event of an emergency, you may contact the researcher, as well as your first listed emergency contact documented in the completed medical history paperwork. If further assistance is needed, please call the nearest hospital, IU Health Center, or physician.

For questions about your rights as a research participant, to discuss problems, complaints, or concerns about a research study, or to obtain information or to offer input, please contact the IU Human Research Protection Program office at 800-696-2949 or at irb@iu.edu.

WHAT IF I DO NOT PARTICIPATE OR CHANGE MY MIND?

After reviewing this form and having your questions answered, you may decide to sign this form and participate in the study. Or you may choose not to participate in the study. This decision is up to you. If you choose not to participate in this study or change your mind after signing this document, it will not affect your usual medical care or treatment or relationship with the researcher and the university.

If you change your mind and decide to leave the study in the future, the study team will help you withdraw from the study safely. If you decide to withdraw, please contact the researcher as soon as possible. The researcher may stop your participation in the study, even if you do not want to stop, if there is concern that you could injure yourself by performing one of the exercise tasks in the study, fail at any time to meet the inclusion criteria for the study, have an abnormal response to exercise, are unable to complete the exercise tests, or are unable to complete any study tasks properly to obtain valid measures, etc. You will be told about new information that may affect your health, welfare, or willingness to stay in the study.

PARTICIPANT CONSENT

In consideration of all the above, I agree to participate in this study. I will be given a copy of this document to keep for my records.

Participant's Printed Name: _____

Participant's Signature: _____ Date: _____

Printed Name of Person Obtaining Consent: _____

Signature of Person Obtaining Consent: _____ Date: _____