INDIANA UNIVERSITY INFORMED CONSENT STATEMENT FOR RESEARCH

The Effect of Cetirizine HCl on Exercise-Induced Arterial Hypoxemia in Highly-Trained Swimmers

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 the study to help you decide whether you want to participate. Please read this form, and ask any questions you have, before agreeing to be in the study.

TAKING PART IN THIS STUDY IS VOLUNTARY

You may choose not to take part in the study or may choose to leave the study at any time. Deciding not to participate, or deciding to leave the study later, will not result in any penalty or loss of benefits to which you are entitled, and will not affect your relationship with the Indiana University (IU) Bloomington, School of Public Health Bloomington, your athletic team, or the Human Performance Laboratories.

WHY IS THIS STUDY BEING DONE?

Oxygen is vital to maintaining endurance exercise performance. Some otherwise healthy individuals experience a decrease in the amount of oxygen in their blood while exercising, a phenomenon called exercise-induced arterial hypoxemia (EIAH). EIAH is marked by a widening difference between the pressure of oxygen in the lung compared to the blood and, though it has been studied for nearly 50 years, little is known about why it occurs. What is currently understood is that the type of exercise, aerobic fitness, and sex may influence whether a given individual experiences EIAH. The inflammatory effects of histamine (a molecule that signals inflammation) could explain why EIAH occurs in some individuals, as its effects in the lung would cause symptoms associated with EIAH. Previous studies have shown that drugs that stop the action of histamine can alleviate EIAH. Furthermore, while EIAH has been studied extensively in a variety of athletes, few data exist examining EIAH in swimmers, creating a knowledge gap in understanding a group of athletes whose response to exercise and chemically treated exercise environment (a chlorinated pool) is unique among exercise modes.

You were selected as a possible participant because you are a highly-trained swimmer. The study is being conducted by Dr. Robert Chapman Department of Kinesiology (Indiana University, School of Public Health – Bloomington).

HOW MANY PEOPLE WILL TAKE PART?

If you agree to participate, you will be one of 30 participants taking part in this research.

WHAT WILL HAPPEN DURING THE STUDY?

If you agree to be in the study, you will do the following things:

- You will be asked to visit the Human Performance Laboratories for Visit 1. These laboratories are located at the IU School of Public Health Building at 1025 E. 7th Street, Bloomington, IN 47405. Parking is free (with a pass obtained from the researcher) in gated parking area outside of building near the Woodlawn field and tennis courts.
- You will be asked to visit the Counsilman-Billingsley Aquatics Center for Visit 2. This facility is located at the Student Recreational Sports Center at 1601 Law Lane, Bloomington, IN 47408. Parking is free in the gated parking area on Law Lane (validated inside at the Counsilman-Billingsley Aquatics Center).
- Should you qualify for the Experimental Trials, you will be invited to visit the Human Performance Laboratories on 2 more occasions (Visits 3 and 4). During these visits, you will either be administered placebos (pills that cause no physiological effects) or cetirizine HCL (brand name: Zyrtec; an allergy medication). You will not be told (blinded) whether you are taking cetirizine HCL or placebo for each of the visits.
- For Visits 3 and 4 there will be a minimum of 5 days and a maximum of 60 days between trials.
- For female subjects, Visits 2 through 4 (if applicable) will be scheduled to take place during the first 7 days following menstruation.

This is a brief description of what will happen on each study visit. There are further details below this section explaining each study procedure as well as the risks associated with that procedure.

Screening visit (Visit 1):

- Once you arrive at the Human Performance Laboratory, an investigator will obtain written informed consent after all procedures and study risks are fully explained and all questions answered.
- You will then complete a pre-exercise health screening questionnaire (PAR-Q+) and a health history questionnaire that will assess your readiness for exercise and whether you have any medical conditions indicating a potential adverse reaction to any of the study procedures.
- You will then have your heart rate, blood pressure, height, and weight measured in a private room. You will then complete a pulmonary function test, where you will breathe through a tube so we can measure lung volumes and lung function.
- If you are determined to be ineligible for the study during this visit, you will not be allowed to participate in this study. If you are determined to be ineligible during screening, we will not use your data.
- This visit will take approximately 2 hours.

Selection exercise protocol (Visit 2):

- If you are a female, Visit 2 will be scheduled during the first 7 days of your menstrual cycle.
- You will be asked to report to the Counsilman-Billingsley Aquatics Center well hydrated and after abstaining from allergy medication for 48 hours, intense exercise for 24 hours, caffeine and alcohol for 12 hours, and food for 2 hours.
- Upon arrival at the laboratory, you will complete a health history update questionnaire to ensure no relevant changes in your health history have occurred. In the event of any changes to

your health history, you will be removed from the study if you meet any of the exclusion criteria.

- A small sample of urine will be used to determine if you are well hydrated prior to participating. If you are a female, the same small sample of urine will be used to confirm a negative a pregnancy test.
- A 3-teaspoon blood sample will then be taken.
- After a waiting period, you will begin a 1000-yard warm-up swim prescribed by the researchers.
- You will then complete 6x100-yard swims, 6x50-yard swims, and 6x25-yard swims as quickly as possible with 10 seconds rest between each bout (Selection Exercise Test).
- You will then immediately exit the pool and a 3-teaspoon blood sample will be taken. You will then be free to leave the pool area.
- This visit will take approximately 1.5 hours.

Experimental trials (Visits 3 and 4, if applicable):

- Prior to Visit 3, the drug treatment conditions (placebo or cetirizine HCl) will be randomly assigned to Visits 3-4. However, you will be blinded by the research team from what condition you are being given during each of the experimental trials.
- If you are a female, Visits 3-4 will be scheduled during the first 7 days of your menstrual cycle.
- You will be asked to report to the Human Performance Laboratory well hydrated and after abstaining from allergy medication for 48 hours, intense exercise for 24 hours, caffeine and alcohol for 12 hours, and food for 2 hours.
- Upon arrival at the laboratory, you will complete a health history update questionnaire to ensure no relevant changes in your health history have occurred. In the event of any changes to your health history, you will be removed from the study if you meet any of the exclusion criteria.
- You will then receive the pill drug treatment corresponding to the visit number. The pill treatments are:
    - Placebo – sugar-free gelatin capsule
    - Cetirizine HCl – cetirizine HCl pill (Zyrtec®) encased in a sugar-free gelatin capsule
- A small sample of urine will be used to determine if you are well hydrated prior to participating. If you are a female, the same small sample of urine will be used to confirm a negative a pregnancy test.
- A 2-teaspoon blood sample will then be taken. You will then complete a pulmonary function test, where you will breathe through a tube so we can measure lung volumes and lung function.
- You will then complete a warm-up in the swimming flume consisting of up to 10 minutes of swimming at the first stage of the aerobic capacity test. Men will swim against a flow rate of approximately 1.5 meters per second (m/s) and a pulley mass of 1.2 kilograms (kg). Women will swim against a flow rate of approximately 1.31 m/s and a pulley mass of 1 kg.
- At the end of the warm-up, you will exit the swimming flume and fully dry off. Researchers will apply a small amount of a vasodilator cream (Finalgon®) to your forehead and, after a period of approximately 10 minutes, you will then be instrumented (fitted) with a device that will monitor your blood oxygen levels.

- You will then be instrumented with a device that will measure your energy expenditure. You will breathe in the water through a snorkel-like mouthpiece while wearing a nose clip.
- You will then complete a Graded Exercise Test to exhaustion in the swimming flume. You will begin this test swimming against the same flow rate and pulley mass as in the warm-up. The pulley mass will be increased by 0.2 kg every 1 minute until you cannot continue swimming.
- A 2-teaspoon blood sample will then be taken, and you will begin your first 20-minute rest period.
- During the rest period, you will complete a pulmonary function test, where you will breathe through a tube so we can measure lung volumes and lung function.
- You will then be similarly instrumented and swim at the same flow rate and a pulley mass corresponding with 70% of your maximal heart rate (the fastest rate at which your heart can beat) for 5 minutes (Constant Load Test).
- A 2-teaspoon blood sample will then be taken, and you will begin your second 20-minute rest period.
- You will then be similarly instrumented and swim at the same flow rate and a pulley mass corresponding with 85% of your maximal heart rate for 5 minutes (Constant Load Test).
- A 2-teaspoon blood sample will then be taken. Following this blood draw, all measurement devices will be removed, and you will be free to leave the lab.
- This visit will take approximately 2.5 hours.

Experimental Procedures: The procedures listed below are designed for research and are not for medical purposes.

Blood sample:

Description: A small volume of blood will be drawn from a vein in your arm. At each blood draw 2-3 teaspoons of blood will be obtained. If you only complete the Selection Exercise Protocol, we will collect a total of 6 teaspoons of blood. If you are selected for the Experimental Trials, we will collect a total of 22 teaspoons of blood. If it is not possible to obtain a blood sample from a vein in your arm prior to or following exercise a blood sample may be obtained by using a prick to your fingertip. Hematocrit (the percentage of your blood that is composed of red blood cells) and hemoglobin concentrations (how much of the oxygen-binding molecule hemoglobin is in your blood) will also be tested. These blood samples may be stored indefinitely.

Potential Risks: You may experience discomfort and in rare circumstances you may feel lightheaded or faint. There is also a rare risk of infection. Having trained individuals draw your blood using clean techniques will minimize this risk.

Duration: Visits 2, 3, and 4. There will be 2 blood draws during Visit 2, and 4 blood draws in Visits 3-4 (if applicable). Approximately 30 seconds in duration.

Heart rate:

Description: Heart rate will be measured by fitting a waterproof brassiere-like harness with two electrodes.

Potential Risks: None.

Duration: Visits 3 and 4, measured continually.

Blood pressure:

Description: Your blood pressure will be monitored using a cuff placed on your upper arm that is inflated and deflated periodically.

Potential Risks: You may feel slightly uncomfortable due to inflation of the cuff around your arm or fingertip.

Duration: Visit 1, measured once.

Blood oxygen levels:

Description: How much oxygen is in your blood will be measure using a light-based sensor placed on your forehead.

Potential Risks: None.

Duration: Visits 3 and 4, measured continually.

Energy expenditure:

Description: The air you breathe out will be analyzed by a computer.

Potential Risks: None.

Duration: Visits 3 and 4, measured continually.

Lung function:

Description: Following 10 minutes seated rest, you will be asked to breathe on a mouthpiece. Following 30 seconds of normal breathing you will be instructed to breathe in as far as possible and to breathe out as fast as possible. A computer will analyze the volume of air that you breathed in and out. This will be repeated three times.

Potential Risks: None.

Duration: Visit 1. This measurement will take approximately 20 minutes.

Body weight:

Description: You will be asked to measure your body weight on a scale in a private room.

Potential Risks: None.

Duration: Visit 1**.**

Body height:

Description: Your body height will be measured using a stadiometer.

Potential Risks: None.

Duration: Visit 1.

Questionnaires:

Description: You will take short surveys to assess your current health and physical activity levels, and whether there have been any changes in your health history.

Potential Risks: None.

Duration: Visit 1, this measurement will take approximately 15 min. On Visits 2 & 3, this measurement will take approximately 3 minutes.

Urine Specific Gravity:

Description: Your hydration status will be measured use a urine refractometer.

Potential Risks: None.

Duration: Visits 2-4.

Timeline of study procedures:

Table 1: Description of study procedures that will take place on each visit to the laboratory.

STUDY PROCEDURES	Screening (Visit 1)	Selection Exercise Test (Visit 2)	Experimental Trials – Randomized Crossover (Visits 3-4)	
			Placebo	Cetirizine HCl
Height	X		X	X
Weight	X		X	X
Heart rate	X		X	X
Urine specific gravity		X	X	X
Blood pressure	X			
Health history questionnaire	X			
Health history update questionnaire		X	X	X
Lung function	X		X	X
Blood sample		X	X	X
Selection exercise test		X		
Blood oxygen levels			X	X
Energy expenditure			X	X
Graded exercise test			X	X
Constant load tests			X	X
Placebo pill			X	
Cetirizine HCl pill				X

WHAT ARE THE RISKS OF TAKING PART IN THE STUDY?

Bacterial/Viral Transmission: There is a risk of germ transmission through shared face masks, despite cleaning and treatment in an anti-bacterial solution following each use. Researchers will thoroughly scrub all shared equipment with anti-bacterial detergent and warm water immediately following use.

Exercise: 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 and do not require medical clearance for individuals 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.

Drowning: There is a risk of drowning during swimming exercise. During the Selection Exercise Protocol, lifeguards from Campus Recreational Sports will be present. During the Experimental Trials, you will be closely monitored by researchers, at least one of whom has completed safety training in accordance with USA Swimming coaching standard.

Drug administration:

- Cetirizine HCl: Serious side effects of cetirizine HCl ingestion are exceedingly rare, and in very rare cases subjects can experience anaphylaxis. Cetirizine HCl can have adverse reactions with midodrine (low blood pressure medication), ritonavir (an HIV treatment), and could exacerbate symptoms of any medication that can cause drowsiness, dry mouth, or infrequent urination. Mild side effects of cetirizine HCl include drowsiness, headaches, dry mouth, nausea, dizziness, stomach pain, diarrhea, sore throat, cold-like symptoms of the nose, itching, paresthesia (tingling) in the hands or feet, and feeling agitated.

Venous blood sample: You may experience discomfort during venous blood draws and may feel lightheaded or faint. This risk will be minimized by the venipuncture always occurring in the semi-recumbent or supine position. There is a rare risk of infection following venous blood draws. This risk will be minimized by blood draws only being conducted by trained laboratory personnel.

Electricity and Water: There is a risk of operating electrical equipment in proximity to water. All equipment that is connected to an electrical outlet will never be suspended above the pool and will be secured with safety straps in a fashion that will not allow their entry into the pool. A battery-powered device will be the only device suspended above the water (during Experimental Trials only). The device will be connected by multiple metal components to a steel guide wire connected to a steel frame over the pool.

Loss of Confidentiality

Any time information is collected, there is a potential risk for loss of confidentiality. Every effort will be made to keep your information confidential. However, this cannot be guaranteed.

Other Risks

There also may be other side effects that we cannot predict.

WHAT ARE THE POTENTIAL BENEFITS OF TAKING PART IN THE STUDY?

By completing Visit 2, you will receive information regarding your inflammatory response to intense exercise. By completing Visits 3-4 (if applicable), you will receive information regarding your aerobic fitness and your ability to maintain arterial blood oxygenation during exercise.

WILL I RECEIVE MY RESULTS?

We may learn things about you from the study activities which could be important to your health or to your treatment. If this happens, this information will be provided to you. Some of this information relates to your health history, blood pressure, or lung function. You may need to meet with professionals with expertise to help you learn more about your research results. The study team/study will not cover the costs of any follow-up consultations or actions.

HOW WILL MY INFORMATION BE PROTECTED?

Your personal information will remain confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. No information which could identify you will be shared in publications about this study.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the study investigator and his/her research associates, the Indiana University Institutional Review Board or its designees, and any state or federal agencies who may need to access your medical and/or research records (as allowed by law). Federal agencies may include the Food and Drug Administration (FDA).

WILL MY INFORMATION BE USED FOR RESEARCH IN THE FUTURE?

Information or specimens collected from you for this study may be used for future research studies or shared with other researchers for future research. If this happens, information which could identify you will be removed before any information or specimens are shared. Since identifying information will be removed, we will not ask for your additional consent.

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 the results. You can search this website at any time.

Specimens collected from you for this research may be used to develop products which could be sold in the future. The investigator does not plan to share any profits or losses from the sale of those products with you.

WHAT WILL YOU DO WITH MY GENETIC INFORMATION?

We will not use the specimens collected as a part of this study for whole genome sequencing, which involves mapping all of your DNA.

WILL I BE PAID FOR PARTICIPATION?

You will be compensated with $100 for completing Visit 2. If you are selected for the experimental trials, you will receive $100 for each trial (Visits 3 and 4) that you complete, for a total of $300. Compensation will be paid by VISA gift card.

WILL IT COST ME ANYTHING TO PARTICIPATE?

There is no cost to you for taking part in this study.

WHO WILL PAY FOR MY TREATMENT IF I AM INJURED?

In the event of physical injury resulting from your participation in this study, necessary medical treatment will be provided to you and billed as part of your medical expenses. 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. There is no program in place for other monetary compensation for such injuries. However, you are not giving up any legal rights or benefits to which you are otherwise entitled. Because you are participating in research that is not conducted at a medical facility, you will be responsible for seeking medical care and for the expenses associated with any care received.

WHO SHOULD I CALL WITH QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, contact the researcher, Dr. Robert Chapman, at 812-856-2452. After business hours or in the event of an emergency, please call Dr. Chapman at 812-340-0691.

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 Subjects Office at 800-696-2949 or at irb@iu.edu.

CAN I WITHDRAW FROM THE STUDY?

If you decide to participate in this study, you can change your mind and decide to leave the study at any time in the future. The study team will help you withdraw from the study safely. If you decide to withdraw, please tell Dr. Chapman of your decision.

Your participation may be terminated by the investigator without regard to your consent in the following circumstances: your inability to follow direction, if you cannot attend your scheduled appointments, or if a change in your health history between any of the visits to the laboratory meet any of the exclusion criteria.

PARTICIPANT'S CONSENT

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

Participant's Printed Name:_____

Participant's Signature: _____ **Date**:_____

Printed Name of Person Obtaining Consent: _____

Signature of Person Obtaining Consent: _____ **Date**:_____