Consent to Participate in a Research Study

Title of Research Study

Cardiac Consequences of Excessive Exercise

Principal Investigator (Available: Monday – Friday 8:30am-5pm)
Paul Dorian, MD
Division of Cardiology, St. Michael's Hospital, Tel. 416-864-5104

Co-Investigators (Available: Monday – Friday 8:30am-5pm)
Andrew Yan, MD
Division of Cardiology, St. Michael's Hospital, Tel. 416-864-5465

Kim Connelly, MD
Division of Cardiology, St. Michael's Hospital, Tel. 416-864-6060 ext. 5201

Karen Konieczny, MD
Division of Cardiology, St. Michael's Hospital, Tel. 647-984-5252

Jack Goodman, PhD
Faculty of Kinesiology and Physical Education, University of Toronto
Division of Cardiology, Mount Sinai Hospital, Tel. 416-978-6095

Zion Sasson, MD
Division of Cardiology, Mount Sinai Hospital, Tel. 416-586-8472

Co-investigators/Study Coordinators (Available: Monday – Friday 8:30am-5pm)
Laura Banks, PhD
University of Toronto, Faculty of Kinesiology and Physical Education
Research fellow under the supervision of Dr. Jack Goodman
Tel. 416-946-5613, Email: laura.banks@mail.utoronto.ca

Ryan Sless and Marianne Skrinjar
University of Toronto, Faculty of Kinesiology and Physical Education
MSc students under the supervision of Dr. Jack Goodman
Tel. 416-946-5613, Email: marianne.skrinjar@mail.utoronto.ca

Wesseem Osman
University of Toronto, Faculty of Medicine, medical student under the supervision of Dr. Paul Dorian; Tel. 416-946-5613, email: wesseem.osman@mail.utoronto.ca

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Introduction

Before agreeing to participate in this research study, it is important that you read and understand this research consent form. This form provides all the information we think you will need to know in order to decide whether you wish to participate in the study. If you have any questions, ask your study doctor or study personnel. You should not sign this form until you are sure you understand the information. All research is voluntary. You may also wish to discuss the study with your family doctor, a family member or close friend. If you decide to take part in the study, it is important that you are as accurate as possible about your health history and any medications you are taking. This will help prevent unnecessary harm to you.

Background and Purpose of the Research

Heart function during exercise is not well understood, particularly during prolonged, intensive efforts. There is little information about the long-term effects of exercise training on heart function. We do know that moderate exercise can improve heart function, reduce cardiovascular risk and extend lifespan. However, long-term intensive and prolonged exercise training may lead to heart remodeling and heart rhythm problems in middle age. These findings are not just specific to elite athletes. These heart problems may occur in a growing number of middle-age people competing in cycling, running and triathlon events. To date, most studies describing heart function during exercise and following training is focused on young athletes. It is unclear how often heart problems may develop in middle-aged athletes.

This study aims to find out if high levels of exercise training over many years may be related to changes in heart structure, function, and rhythm. Adults with a history of what some describe as 'excessive' exercise training will be compared to adults with light-to-moderate exercise history. Advanced monitoring will be performed in all participants to determine if heart rhythm abnormalities exist in excessively active athletes versus recreationally active adults. This study also aims to understand the factors that may lead to abnormal heart function in the physically active adult.

Description of the Research

Up to 200 participants will be recruited for this study to assess heart function in exercising, middle-aged adults. There are 2 groups we wish to enroll, both involving males and females between the ages of 45-65 years. The first group (about 125 participants) includes adults with a long-standing history of competitive endurance exercise training (more than 10 years). The second group (about 75 participants) includes recreationally active individuals (meeting current physical activity recommendations of 2.5 hours of moderate activity per week, for at least 10 years), not training for or competing in endurance events greater than 10 km. A smaller sample of 30 endurance-trained participants and 20 recreationally-active participants may be asked to complete multiple visits (up to 4 visits total). You may undergo the same tests and measures regardless of which group you are in. All participants to be enrolled are those who are able to exercise, free of cardiovascular/kidney disease and sleep disorders. However, individuals with hypertension and on hypertensive medication will be able to participate in the study.

You are being asked to consider participating in this study examining the long-term effects of exercise on heart structure, function, and rhythm. If you choose to participate in this study, you will be asked to visit St. Michael's Hospital on 1-3 occasions – depending on your study schedule and study results. Each of the study visits (1-3) will last approximately one and a half to two hours. Those participants with an abnormal test result (i.e., an abnormal ECG and/or imaging results) will be asked to come for an additional visit (as per standard of care). In

addition, you may be asked to undergo an exercise test, physical examination and debriefing session to discuss your study results (optional – Visit 4). This last visit is completely optional, but will be made available to participants who are interested. All participants will be provided with a lay summary of study results. Those participants with an abnormal test result will be asked to undergo additional testing.

Study Visits

At your initial study visit (St. Michael's Hospital), we will ask you to do the following:

1. Complete a few questionnaires (lifetime physical activity questionnaire) and/or answer questions about your everyday activities (2-week exercise diary), physical activity (physical activity readiness question; PAR-Q), family, and medical history.
2. Complete a standard, urine pregnancy test (if you are a pre-menopausal female participant).
3. Complete a brief physical examination with a study doctor to evaluate heart health related measures, including blood pressure and body composition.
4. Complete a heart rhythm assessment with a special type of electrocardiography (ECG).
5. You will be given a special heart rhythm monitor (Holter monitor) to assess your heart rhythm continuously at home for a 24 hour time period (24 hour continuous ECG monitor). This can be returned within a 1 week period, either during an additional study visit and/or at a time that is convenient for the participant.

During a second study visit (University of Toronto), you will be asked to complete a standard maximal-intensity, exercise test on a treadmill (or bicycle, if you have a condition that prevents you from running). Before this test, you will be asked to complete a brief questionnaire about your readiness to participate in physical activity as well as validated psychological questionnaires to assess positive/negative affect, pride, optimism, and neuroticism. In this test, you will be asked to exercise for about 10-15 minute until you feel tired. This will tell us about your fitness and heart health. During a separate visit, participants will be given the option to complete a second exercise test on a bicycle. This exercise test will be completely optional and performed only in participants who have a long-standing history of cycling (e.g. cyclists and triathletes).

About 125 participants from the first group including adults with a long-standing history of competitive endurance exercise training (more than 10 years), and about 75 participants from the second group including recreationally active individuals (meeting current physical activity recommendations of 2.5 hours of moderate activity per week, for at least 10 years) will be involved in this initial study visit.

You may or may not also be randomly (i.e., like flipping a coin) assigned to attend two additional study visits for advanced heart assessment. If you are not asked to attend any additional visits, you will have completed the study at this point. However, you may also be asked to attend the following two additional study visits based on test results from your initial study visit (e.g., based on your exercise history and/or if you have clinically relevant findings, such as an abnormal ECG). These additional study visits will take place within 8 – 12 weeks of the initial study visit, and within 1-4 weeks of each other. There will be about 50 participants involved in the additional study visits (about 30 from the first group, and about 20 from the second group). The following study assessments will be performed during these additional study visits:

1. A blood sample (20 ml or 6 teaspoons) will be collected to measure blood markers. You

will be asked to arrive at Mount Sinai Hospital to have your blood drawn. Blood drawn will be done on the same day in which you will be asked to have an echocardiogram. These blood markers may tell us about your heart health and kidney function. We need to ensure that you have normal kidney function prior to having special cardiac imaging (with a contrast dye).

2. You will be asked to wear a special heart rhythm monitor (Holter monitor) for an additional 24 hour period (24 hour continuous ECG monitor). During this time period, you will be asked to complete an exercise bout performed at your typical intensity that is equal to the longest duration of a typical training week. This should not exceed 45 minutes if you are 'recreationally active' or 150 minutes if you are 'an endurance athlete'. This will allow us to assess your heart rhythm before, during, and after exercise.
3. You will be asked to have two advanced forms of heart imaging. Echocardiography and magnetic resonance imaging (MRI) of your heart will be done to determine its function and size. An echocardiogram and MRI are non-invasive tests that take pictures of your heart while you lie on a table. In the MRI test, the table will move you into a large round tube-like machine. You will be able to speak with the technician doing the MRI and there is a call button if you need to stop the test. Taking the MRI pictures does not require any preparation but the machine is noisy (you will be given ear plugs). You will need to try to lie as still as possible for about 45-60 minutes. The technician will give you breathing instructions throughout the test. An MRI contrast dye containing gadolinium (pronounced *gad-oh-lin-ee-um*) will be used to outline your blood vessels or heart muscle in the images. This may provide us with more information about your heart. Contrast dye is usually injected into a vein in your arm with a needle. You may feel a cool sensation during the injection, and you may feel discomfort where the needle is inserted. MRI contrast does not contain iodine so it will not create problems for people who are allergic to iodine. This MRI (gadolinium) contrast is different from the iodine-containing contrasts used in computed tomography (CT) and angiogram, and it does not damage the kidneys. However, if you are known to be allergic to MRI (gadolinium) contrast, or you do not wish us to use this dye, it will not be given to you during the MRI examination.

Please note that a few of these additional study tests may be performed nearby offsite. These off-site tests, which may include the echocardiogram (Mount Sinai Hospital), Holter monitoring (Mount Sinai Hospital), and exercise test (University of Toronto), will be performed off-site with a study doctor or co-investigator. This data will be collected and analyzed on-site at each location. After completing all study tests, you will have the chance to come to St.Michael's Hospital for additional follow-up if you have clinically relevant findings, such as an abnormal ECG and/or imaging results. A study doctor will be available to discuss your study results. Any further testing would be done per standard of care (outside of study testing).

Reminders

It is important to remember the following things during this study:

- You should not consume any caffeine or alcohol on the night before your study visits (12 hours prior to visit).
- No prolonged or intensive exercise (> 30 minutes) on the day before study visits (24 hours before your visit, unless told to do so by the study team).
- Tell study staff anything about your health that has changed.
- Tell your study team if you change your mind about being in this study.

<u>Potential Harms (Injury, Discomforts or Inconvenience)</u>

There may be a small amount of discomfort, redness or bruising at the site of the puncture associated with the collection of the blood sample, and if you complete the cardiac MRI assessment with an injected contrast agent (additional study visit). However, this is temporary and will disappear in a few days. You could develop an infection, but this is very rare. Occasionally, there is a feeling of dizziness or feeling faint or lightheaded after giving blood. If this occurs we will have you sit for a moment and drink a glass of water/fluid until the feeling passes.

ECG electrodes (e.g., heart stickers that are able to detect your heart rhythm) placed on your chest may cause a small amount of discomfort or redness.
The risks of exercise in this study are similar to those side effects you may currently experience during your training regime. As you know, exercise may lead to muscle soreness and feelings of tiredness.

A cardiac MRI examination does not involve any ionizing radiation and is not known to pose any health hazards. You will need to complete a standard 1-page screening MRI form to ensure that it is safe for you to undergo an MRI examination (e.g., you do not have a pacemaker, defibrillator, etc). All standard safety protocols (as in any MRI examination for clinical reasons) will be followed (e.g., removal of metal objects before entering the MRI scan room). If you feel uncomfortable in enclosed spaces (claustrophobic), you may receive a prescription for lorezapem (Ativan, which is a medication for sleep and to relieve anxiety) which you can take under the tongue 30 minutes before the MRI examination. You may feel dizziness or feel sleepy and should not drive after taking this medication.

Gadolinium (a contrast agent) may be injected into your vein before the last set of images in order to view your heart more clearly. This dye will be eliminated by your body within 24 hours. Serious reactions to the special contrast dyes used for MRI are very rare. However, side effects are possible and include: headache, dizziness, faintness, a decrease in blood pressure, injection site reaction, nausea and/or vomiting, sweating, skin rash and taste disturbance. Very rarely (less than one in a thousand), patients are allergic to gadolinium. If you have experienced any of these symptoms previously with a contrast agent, please inform your study doctor. Rarely (four in a thousand cases), the contrast dye can be harmful in patients with severe kidney disease. If there is any concern that you may have undiagnosed kidney disease, you will not receive gadolinium contrast for your MRI examination.

Women as Research Participants

If you are female, you may participate in this study if you are certain you are not pregnant. All pre-menopausal women wishing to participate will be asked to undergo a standard, urine pregnancy testing prior to entry into the study.

Potential Benefits

There are no direct benefits to you from participating in this study. You may find out information about your heart health. The results from this study may further medical or scientific knowledge.

Confidentiality and Privacy

All persons involved in the study, including the study investigators, study coordinators and delegates (hereby referred to as ‘study personnel’) are committed to respecting your privacy. No other persons will have access to your personal health information or identifying information without your consent, unless required by law. The study personnel will make every effort to keep

your personal health information private and confidential in accordance with all applicable privacy legislations, including the Personal Health Information Protection Act (PHIPA) of Ontario. Any personal health information or personal information collected about you will be 'de-identified' (coded) by replacing your personal identifying information with a 'study number'. The study coordinator and principal investigator are in control of the study code key, which is needed to connect our personal health information to you. The link between the study number and your personal identity will be safeguarded by the study personnel.

All information that identifies you, both paper copy and electronic information, will be kept confidential and stored and locked in a secure place, at St. Michael's Hospital and/or at the University of Toronto, that only the study personnel will be able to access. Electronic files will be stored securely on hospital or institutional networks or securely on any portable electronic devices. No information identifying you will be allowed to be sent elsewhere without your explicit consent for this (e.g., to allow your study results to be sent to your family doctor).

It is important to understand that despite these protections being in place, there continues to be the risk of unintentional release of information. The study coordinator and principal investigator will protect your records and keep all the information in your study file (including your name, address and telephone number) confidential to the greatest extent possible. The chance that this information will accidentally be given to someone else is small.

By signing this form, you are authorizing access to your personal health information by the study personnel, the Research Ethics Boards (Mount Sinai Hospital, St. Michael's Hospital, and the University of Toronto) and by government regulatory authorities (e.g., Health Canada). Such access will be used only for the purpose of verifying the authenticity and accuracy of the information collected for the study, without violating your confidentiality to the extent permitted by applicable laws and regulations.

Federal and Provincial Data Protection regulations, including the Personal Information Protection and Electronic Documents Act (PIPEDA 2000) and the Personal Health Information Protection Act (PHIPA 2004) of Ontario, protect your personal information. They also give you the right to control the use of your personal information (including personal health information) and require your written permission for this personal information to be collected, used, or disclosed for the purposes of this study, as described in this consent form. You have the right to review and copy your personal information collected in this study.

The study investigators will keep your study records securely stored for up to 5 years after the study has been completed, and then the study records will be securely destroyed.

Study Results

The results of this study will be presented at conferences and published in graduate student theses and medical journals. Your identity will remain confidential (i.e., you will not be personally identified in any presentation or publication of the study results). If you are interested in obtaining a copy of the published study results, you should contact Dr. Laura Banks, co-investigator.

Communication with Primary Care Doctor

You may wish to have your study results sent to your primary care/family doctor. This is optional and you may indicate your consent for this on the signature page of this document. If

you agree to this, the study doctor will send a letter to your physician describing your study results. It is important to know that your personal information (specifically your name and date of birth) will be on this letter. There is the risk of the unintentional release of information should the letter be intercepted. The decision of notifying your family physician about your study results is entirely up to you.

Potential Costs and Reimbursement

If you choose to participate in this study, you will be provided with $25 for recognition of your time and study-related expenses (i.e., meals, transit). If you complete the additional study visits (to have heart imaging done via MRI and echocardiogram), you will be provided with an additional $25 per study visit for recognition of extra involvement in this study.

Compensation for Injury

If you suffer an injury as a direct result of the study, medical care will be provided to you in the same manner as you would ordinarily obtain any other medical treatment. In no way does signing this form waive your legal rights nor release the investigators or involved institutions from their legal and professional responsibilities.

Participation and Withdrawal

Your participation in this study is completely voluntary. By signing this form, you are agreeing to participate in the study. If you choose not to participate, you and your family will continue to have access to customary care at St. Michael's Hospital. If you choose to participate, you can withdraw at any time without any effect on the care that you or your family will receive at St. Michael's Hospital. The study doctor may discontinue your participation in the study for various reasons, including:

1. It is not in your best interest to continue in the study.
2. You need treatment which is not allowed in this study or do not meet eligibility for study participation.
3. You fail to follow study instructions.
4. The study is cancelled.

If you withdraw or are withdrawn from the study, data collected by the study investigators up until your withdrawal may be included in the research results.

New Findings or Information

We may learn new things during the study that you may need to know. We can also learn about things that might make you want to stop participating in the study. If so, you will be notified about any new information in a timely manner. You may also be asked to sign a new consent form discussing these new findings if you decide to continue in the research study.

Research Ethics Board Contact

- If you have questions regarding your rights as a research participant, you may contact the Chair, Research Ethics Board, St. Michael's Hospital at 416-864-6060 ext. 2557, or the Office of Research Ethics at the University of Toronto at 416-946-3273 during business hours. The Research Ethics Board is also required to do periodic review of ongoing research studies. As part of this review, someone may contact you from the Research Ethics Board to discuss your experience in the research study.

Study Contacts

If you have any questions regarding the study or study procedures, you should contact Dr. Paul Dorian, Principal Investigator, at 416-864-5104, or contact Dr. Jack Goodman, Co-Investigator, at 416-978-6095 or contact Dr. Laura Banks, Co-Investigator/Study Coordinator, at 416-978-0762 during business hours.

Statement of Consent

The research study has been explained to me, and my questions have been answered to my satisfaction. I have the right not to participate in this study and the right to withdraw without compromising the quality of medical care at St. Michael's Hospital for me and for other members of my family. As well, the potential harms and benefits (if any) of participating in the research study have been explained to me.

I have been told that I have not waived my legal rights nor released the investigators or involved institutions from their legal and professional responsibilities. I know that I may ask now, or in the future, any questions I have about the study or the research procedures. I have been assured that records relating to me will be kept confidential and that no information will be released or printed that would disclose my personal identity without my permission unless required by law. I have been given sufficient time to read and understand the above information. *Check the appropriate box and initial below to indicate your decision:*

I would like the study doctor to share the results of all of the tests done for this study with my family doctor.

□ _____ (Initials) I agree; □ _____ (Initials) I do not agree

I consent to participate in this study. I will be given a signed copy of this consent form.

_____	_____	_____
Name of Participant (Printed)	Signature of Participant	Date

Information in the consent form was accurately explained to, and apparently understood by, the above-named participant, and consent was freely given.

_____	_____	_____
Name of Witness (Printed)	Signature of Witness	Date

_____	_____	_____
Name of Person Obtaining Consent (Printed)	Signature of Person Obtaining Consent	Date

I_____ (printed name of investigator) am the investigator responsible for the conduct of this study at St. Michael's Hospital, and I have delegated the explanation of this study to this participant to _____ (name of person obtaining consent).

_____	_____
Signature of Investigator	Date