

**Atrial electromechanical function in middle-aged endurance athletes
with and without Atrial Fibrillation**

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1.0 RESEARCH OBJECTIVES

1.1 Study Rationale

Despite extensive literature characterizing cardiac structure, function and electrical conduction in sedentary patients with AF, no data exists in athletic populations with AF. Measurement of these parameters would provide insight into the mechanisms and pathophysiology of exercise-induced AF, as well as the functional consequences of paroxysmal AF in this cohort. These data may inform the management of AF in athletes who continue to train and provide the basis for developing prognostic indicators in a population at greater risk for AF development, particularly in middle-age. Accordingly, this study will examine cardiac function, specifically left ventricular and left atrial phasic function in the presence of paroxysmal AF in endurance trained athletes. Secondly, atrial electromechanical function will be assessed in athletes to further explore functional parameters that may provide prognostic value.

1.2 Objectives

1) to assess and compare left atrial phasic volumes and function (as measured by ejection fraction and strain) at rest and during submaximal exercise in middle-aged endurance trained athletes with AF and age-matched healthy endurance trained athletes without AF.

2) to compare atrial electromechanical delay (AEMD) in middle aged endurance-trained athletes with AF to age-matched healthy non-AF endurance trained athletes. An exploratory objective will be to determine whether there is a correlation between P-wave duration and AEMD.

1.3 Hypotheses

1) It is expected that left atrial strain will be impaired in athletes with AF compared to athletes without AF at both rest and during submaximal exercise- though impairments will be more pronounced during submaximal exercise. Specifically, it is hypothesized that left atrial (LA) reservoir function will be reduced in athletes with AF, as it is a strong predictor for AF.

2) It is expected that despite similar left atrial size, athletes with AF will have significantly prolonged AEMD compared to age-matched athletes without AF.

Additionally, it is hypothesized that P wave duration and AEMD will be correlated, suggesting AEMD may be a sensitive and precise measure for atrial fibrosis.

2.0 STUDY POPULATION

This will be a cross-sectional cohort study involving: Male endurance trained athletes who have been diagnosed with paroxysmal AF (AF-ET) and 2) and male endurance trained athletes without diagnosis or history of AF or AF symptoms (H-ET). The study will be limited to male participants given the higher prevalence of AF compared to females.

Global Inclusion Criteria: Participants eligible will be male endurance athletes (between ages of 45 and 65). Subjects will be life-long participants (20 years +) of prolonged, intensive endurance running, cycling, rowing or triathlons. Athletes must be involved in year-round training and competition (in at least one or more events per year). Unrestricted participation history of light-intensity activity (eg. golf, walking etc) will be allowed.

Inclusion Criteria for H-ET: This group will be a referent population that is recruited from an existing cohort from our previously conducted study ‘Cardiac Consequences of

Endurance Exercise.’ Participants who have had prescreening, completed a resting signal averaged ECG, cMRI and Holter monitoring will be eligible.

Inclusion Criteria for Athletes with AF: The same criteria of athletic training as the athletes without AF (H-ET) will be used. This cohort will be recruited on the basis of having being diagnosed with paroxysmal AF in the last four (4) years. Specific criteria for paroxysmal AF diagnosis are: an absence of consistent P waves, irregular fibrillatory waves, variation in RR intervals, and atrial tachycardia (350-600 bpm) lasting for longer than 30 seconds and terminating in 48 hours time. Diagnosis will be verified using clinical charts that include either ambulatory 12-lead ECG readings or Holter monitor detection of AF. Subjects will be included regardless of medical treatment for AF which may include rate and/or rhythm control, either chronically or acutely (‘pill-in-a-pocket’ upon onset of episodes). All participants must be in sinus rhythm during all assessments.

Global Exclusion Criteria: 1) >1 hour of resistance training per week (risk of concentric remodeling), 2) BMI < 20 kgm⁻² or > 25 kgm⁻², 3) treatment or prior diagnosis of coronary artery disease or cardiomyopathy, valvular disease, hypertension, heart failure, diabetes, history of thyroid disorder, diagnosis of sleep apnea, current/recent viral or chronic illness, chronic inflammatory disease, 4) recreational drug use or excessive alcohol consumption (using accepted standards) 5) previous or current smoking, 6) contraindication to MRI.

Exclusion Criteria specific for AF group: 1) presence of atrial flutter, 2) previous ablation, 3) cessation of exercise > 6 months post diagnosis of AF, 4) inability to provide verification of AF diagnosis.

2.2 Sample Size

The primary outcome measure for the first hypothesis is atrial reservoir function, as measured by myocardial strain imaging by echocardiography. There are no data describing atrial phasic function in athletes with AF. Accordingly sample size was determined using the average difference in reservoir strain in a cohort of middle aged (51.78 ± 6.83 years) patients with lone AF, compared to healthy middle aged (48.97 ± 7.65 years) controls with no presence of AF or other cardiovascular related disease. Left atrial reservoir strain was reported as: (29.01 ± 5.63 %) in patients with AF compared to (35.5 ± 4.77 %) in healthy adults. Accordingly, the mean difference between groups was 6.49 ± 5.2 . Thus, based on an alpha of 0.05 and power of 0.8, 11 participants are necessary in each group.

The primary outcome measure for the second hypothesis is AEMD. No previous literature has examined AEMD in endurance athletes, nor is there established reference values for healthy adults. Previous literature has demonstrated patients with paroxysmal AF to have significantly greater delays in inter-atrial EMD, as well as both left and right AEMD. However, it has been suggested that specifically intra-left AEMD is a significant marker for the development of AF, and was correlated to P-wave dispersion, left atrial diameter and left atrial area ⁽⁴⁵⁾. Accordingly, sample size was determined using the difference in left AEMD in a cohort of otherwise healthy middle-aged patients (48.3 ± 11.1 years) with lone AF compared to healthy middle-aged (45.2 ± 4.8 years) controls with no presence of lone AF. Left-atrial EMD was reported as: 21.8 ± 9.1 ms in AF patients and 14.1 ± 4.9 ms in controls (difference of 7.7 ± 7 ms). Thus, based on an alpha of 0.05 and power of 0.8, 15 participants are necessary in each group (n=30).

Accordingly, the more conservative calculation of 15 per group will be used. However, in our experience, poor imaging quality lead to unanalyzable data may occur in 10-15% of the sample, therefore we will recruit 17 per group to ensure adequate statistical power.

2.3 Recruitment

Healthy endurance athletes will be recruited from our email list serve of previous ‘Cardiac Consequences of Endurance Exercise’ participants. Interested participants will contact either the principal investigator or co-investigators through email or phone.

Subjects with AF will be recruited by advertisement to local athletic clubs, emails to the GTA cardiology community for referrals and word of mouth. We have considerable experience in the recruitment of healthy endurance and recreationally trained subjects from both cycling and running clubs within the GTA. In addition we will seek referrals from cardiology and electrophysiology practices within the GTA using existing collaborative ties at teaching hospitals and by personal communication. We also have access to contact information of several athletes with AF who were excluded from our previous study who expressed interest in participating in a research study should one arise. These individuals will be provided with an email recruitment advertisement in which they will be prompted to contact the investigators by telephone or email in interested.

Initial screening for major inclusion/exclusions will be performed by the student investigator by telephone. If there is interest in participating following a telephone discussion, an information package including the informed consent will be sent electronically if possible, and subjects will be requested to meet in the Heart Health

laboratory located within the Goldring Center for High Performance Sport at the University of Toronto to submit their informed consent, receive further information should there be additional questions and undergo the initial assessment.

2.4 Methods

General Procedures

All participants will be assessed at the same time of day. Participants will be asked to abstain from exercise on the day before and the day of each study visit.

Visit One: Participant Screening/Consent/ Graded Exercise Testing /

Echocardiography

The first visit will take place at the Heart Health Laboratory. Prior to attending the first visit, participants will have received consent forms and a 2-week Exercise Diary through email. Participants will complete consent form and have the opportunity to ask questions as needed upon their first visit, as well as return the 2-week Exercise Diary. Participants will be then familiarized with the procedures of the study. Participants will undergo basic anthropometric assessment to determine body mass (weight and height) and resting blood pressure. Following this, participants will be fitted with a 12-lead ECG and proceed to complete resting and submaximal exercise echocardiography, performed by a trained sonographer. Emphasis will be on left atrial volume, phasic function and AEMD. Exercise will be on a semi-recumbent cycle ergometer designed for stress echocardiography (Ergoline 1200EL). Imaging will be performed at rest, followed by a two-minute warm up. Participants will then cycle at 100 bpm for 5 minutes and at 130 bpm for 5 minutes; imaging will be initiated 2 minutes into each stage. During a 30-min rest period, participants will complete a Lifetime Physical Activity Questionnaire

Participants will then proceed to have a maximal cardiopulmonary exercise treadmill test with a HR monitor (Polar V800).

Visit Two: Resting Signal Averaged ECG/ Cardiac Magnetic Resonance Imaging/Holter Monitor

The second visit will only be required for athletes with atrial fibrillation (AF-ET), as the healthy endurance athletes will have completed this visit during their participation in a previous REB-approved study. Visit 2 will be completed at St. Michael's Hospital. Prior to attending this visit, participants will undergo venipuncture by trained phlebotomist for assessment of serum creatinine and calculation of GFR to confirm normal kidney function, required for LGE administration (see below). On the day of, participants will first have a standard signal averaged ECG performed. Following this, subjects will undergo resting cardiac imaging using (cMRI) (Siemens MAGNETOM Skyra 3.0T with TIM and DOT technology) by a trained technician. Proceeding cMRI, participants will be fitted for a 48 hour Holter monitor that will assess cardiac rhythm over 2 days (at home), in which participants will refrain from exercise for the first day, and will complete a typical bout of exercise on the second day.

2.7 Detailed Procedures

2.7.1 Graded Exercise Testing

A graded exercise test will be completed at the Heart Health Laboratory. Maximal oxygen consumption (VO₂MAX) will be determined by indirect calorimetry obtained during graded exercise testing on a motorized treadmill (Full Vision TMX4125) using a calibrated metabolic cart (VMax Encore, CareFusion). Expired gases will be collected and averaged over 10 second intervals. Maximal effort will be confirmed by a plateau of

oxygen uptake despite increasing workrates and secondary criteria will include achievement of age- predicted maximum heart rate $(208 - (0.7 \times \text{AGE})) \times [60]$ and a respiratory exchange ratio > 1.15 . Standard measures of expired gases will be performed. Continuous measures of HR during exercise using a electronic heart rate monitor (Polar Inc.) will be integrated to data recording of the metabolic cart. A 3-lead ECG will be established and recorded every minute. A physician will be on site during exercise testing with an AED located within 5 meters.

2.7.2 Resting and Submaximal Echocardiography

Participants will undergo transthoracic echocardiography (GE E9 Imaging System) at the Heart Health Laboratory, provided the individual is in sinus rhythm. Imaging will be performed by a trained sonographer, and images will be obtained according to the criteria of the American society of echocardiography guidelines. Subjects will be initially placed in a supine position on a purpose-built imaging/cycle ergometer (Ergoline 1200E), for assessment of resting cardiac structure and function. During exercise, subjects will be repositioned to a 45 degree semi-upright position with minor left caudal tilt to optimize imaging. Cycle ergometry will be performed concurrent with echocardiography.

For all acquisitions, two-dimensional apical (two and four chamber view) and parasternal (long and short axis) imaging will be performed for dimensional and functional parameters of the atria and of the ventricles at a frame rate of 60-80 (fps). Volume and size measurements will be normalized to body surface area. Echocardiograph imaging will primarily be used for functional measures at rest and exercise; structural assessment of chambers will be determined using cMRI. Emphasis

will be on left atrial reservoir function, as this parameter has provided robust insight into AF-associated impairment even in the presence of normal LA size. Left atrial volumes will be measured at different time points of the cardiac cycle. Atrial maximal volume (LA max) will be measured at the end of ventricular systole, prior to the opening of the mitral valve; atrial pre-A volume (LA PRE-A) will be measured prior to onset of atrial contraction (beginning of P wave); atrial minimal volume (LA min) will be measured at the closure of the mitral valve. Accordingly, LA phasic volumes and emptying fractions will be calculated. Left and right ventricular volumes and ejection fraction will be calculated by the modified bi-plane Simpson's method. Images for LA strain will be obtained using Speckle Tracking echo. Strain measures will include global longitudinal strain, peak atrial longitudinal strain, and atrial phasic strain (reservoir: during ventricular systole, conduit: during early ventricular diastole and booster: during late ventricular diastole). Left ventricular strain during ventricular systole, early diastole and late diastole will also be measured. Pulsed-wave Doppler interrogation of transmitral flow will be obtained at the septal and lateral mitral annulus to determine flow velocities during early (E) and late (A) diastole, as well as the E/A ratio. Tissue Doppler imaging will also be performed at the septal and lateral mitral annulus to determine myocardial systolic (Sm), early diastolic (Em) and late diastolic (Am) velocities. Care will be taken to minimize gain and all analyses of DTI and Doppler flow patterns will be conducted according to current ASE guidelines⁸⁴⁻⁸⁶. The collection of these images will allow us to calculate intracardiac volumes and indices of diastolic and systolic function.

2.7.3 Atrial Electromechanical Delay

Tissue Doppler Echocardiography will be performed by transducer frequencies of 3-4MHz, adjusting the spectral pulsed Doppler signal filters until a Nyquist limit of 15-20cm/s and using the minimal optimal gain. The monitor sweep speed will be set to 50-100mm/s to optimize the spectral delay of myocardial velocities. In apical 4-chamber view, the pulsed Doppler sample volume will be placed at the lateral and septal sides of the mitral annulus and the right-ventricular (RV) tricuspid annulus to obtain tissue Doppler velocities. The time intervals from the onset of the P wave (ECG) to the beginning of the Am wave (on echo) will be measured from the lateral mitral annulus (lateral PA), septal mitral annulus (septal PA), and RV tricuspid annulus (tricuspid PA). The timing of mechanical activation of each sample point is dependent on the distances of each point to the sinoatrial node (SA). Accordingly, the RV tricuspid annulus is the earliest (closest) and the lateral mitral annulus is the latest (farthest) point to be activated by impulses from the SA node. The difference between any two reference points reflects the mechanical delay between these two points. Inter-AEMD will be defined as the difference between the lateral PA and tricuspid PA, intra-right AEMD will be defined as the difference between the septal PA and tricuspid PA, and intra-left AEMD will be defined as the difference between the lateral PA and septal PA.

2.6.3 Signal Averaged ECG

Signal averaged-ECG will be recorded at St. Michael's hospital. Acquisition and analysis will be performed in the same manner in which the athletes without AF would have received at a prior visit for another REB-approved study. Briefly, the subject will be in supine position, in a room free from electrical interference. Three bipolar orthogonal leads (x,y,z) will be used. Electrode placement will be according to the following: X

electrodes in the left and right mid-axillary line of the 4th intercostal space; Y electrodes in the left mid-clavicular line at the level of the abdomen; Z electrode placed in the mid-clavicular line in the 4th intercostal space. A P-wave template will be generated and averaged P-wave signals will be filtered using a spectral filter. Measurements will include filtered P-wave duration (ms) and root mean square voltage in the terminal 20 ms of the P-wave (mv).

2.7.4 Cardiac Magnetic Resonance Imaging

All athletes with AF will undergo resting cardiac magnetic resonance imaging (cMRI) at St. Michael's hospital, following methods used for previous REB-approved study). MRI will be performed supine in a 3.0T scanner (Siemens MAGNETOM Skyra 3.0T with TIM and DOT technology); images will be obtained on end-expiration breath holds. Vertical long-axis cine images will be prescribed from axial scout images by aligning the left ventricular (LV) apex with the center of the mitral valve. From these LV long-axis images, the horizontal long-axis plane will be obtained by aligning the midpoint of the left ventricular apex and mitral valve. These pilot 4-chamber and 2-chamber views provide the reference images on which a stack of contiguous short-axis slices will be prescribed, covering the left atrium and left ventricle. Depending on the LV long-axis length, 8-12 contiguous slices will cover the entire left ventricle. Providing normal creatine levels are verified (see above), delayed enhancement MRI will be acquired 10 minutes after contrast agent injection of gadolinium (0.1 mmol/kg body weight, Multihance, Bracco Diagnostic Inc, Princeton, NJ) (MRI contrast agent does not contain iodine and does not damage the kidneys. Subjects refusing gadolinium will still be studied. Imaging will be used for cardiac structure and volumetric assessments of the

atria and ventricles (max and min volume, EDV and ESV). All data analysis will be performed using CMR42 (Circle Imaging, Calgary, Canada). End-diastolic frames are defined as the image with the largest ventricular volume in each series, and end-systolic as the image with the smallest volume. Endocardial and epicardial borders on these frames will be manually traced. From this data, LV and RV ejection fraction, end diastolic/end systolic and stroke volume indices will be calculated. Manual tracing of endocardial borders of short-axis images at atrial end-diastole and atrial end-systole will allow for calculation of LA end-diastolic volume and end-systolic volume.

2.8 Data Analysis

All variables will be expressed as mean and standard deviation. Differences in outcome measures (AEMD, atrial phasic function, atrial dimensions) will be assessed using a series of independent t-tests between the athletes with AF and athletes without AF. A 2-way repeated measures analysis of variance (ANOVA) will be used to compare resting and exercise values between and within groups. Covariates will be included when appropriate, including age, years since AF diagnosis, and number of AF episodes. Atrial size and relation to ECG parameters may be studied for correlational analyses. Significance will be set at $p < 0.05$. Analysis will be performed using SPSS software.