

Atrial Electromechanical Function in Middle-aged Endurance Athletes with and without Atrial Fibrillation

by

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Abstract

Highly endurance trained athletes have an elevated risk for developing paroxysmal Atrial Fibrillation (PAF). The cardiac response to exercise is unknown in this population. Fourteen endurance-trained (H-EA) males (56.6 ± 5.1 years) were compared to eight endurance-trained males with PAF (EA-AF) (52.5 ± 6.8 years) during cycle-ergometry at light (100 bpm) and moderate (130 bpm) exercise. Resting atrial volumes did not differ between H-EAs and EA-AFs. Left ventricular EDV, LA reservoir and LA booster volumes were significantly lower in EA-AFs during light and moderate exercise, and there was a trend for greater passive emptying during light exercise. There were no differences in phasic strain, diastolic function, or atrial electro-mechanical delay. The findings of the present study suggest that resting measures of volume and function are inadequate to identify markers of PAF in athletes. Evidence of reduced atrial phasic volumes during elevated demands may be indicative of atrial stiffening in PAF athletes.

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List of Abbreviations

AEMD	Atrial Electromechanical Delay
AF	Atrial Fibrillation
AV	Atrioventricular
AVPD	Atrioventricular Plane Displacement
BSA	Body Surface Area
CITP	Carboxyterminal telopeptide of collagen type I
CO	Cardiac output
ECG	Electrocardiogram
ECHO	Echocardiography
EDV	End-diastolic volume
EF	Ejection fraction
ESV	End-systolic volume
HR	Heart Rate
IGF-1	Insulin-like growth factor-1
LGE	Late gadolinium enhancement
LA	Left Atria
LA_{MAX}	Left atrial maximal volume
LA_{MIN}	Left atrial minimal volume
LA_{NEG}	Left atrial negative strain
LA_{POS}	Left atria positive strain
LA_{P<small>R</small>E-A}	Left atrial pre-contractile volume
LV	Left ventricle
MRI	Magnetic resonance imaging
PAF	Paroxysmal atrial fibrillation
PICP	Propeptide of collagen type-I
RA	Right atria
RA_{MAX}	Right atrial maximal volume
RA_{MIN}	Right atrial minimal volume
RA_{P<small>R</small>E-A}	Right atrial pre-contractile volume
RV	Right ventricle
SAPWD	Signal Averaged P Wave Duration
STE	Speckle tracking echocardiography
SV	Stroke volume
TDI	Tissue Doppler Imaging
T_{TOTAL}	Time to total strain
TIMP-1	Tissue inhibitor of matrix metalloproteinase-I
T_{NEG}	Time to negative strain
T_{POS}	Time to positive strain

List of Equations

LV Stroke Volume	(LV EDV – LV ESV)
LA Reservoir Volume	(LA _{MAX} – LA _{MIN})
LA Conduit Volume	(LV SV – LA Reservoir)
LA Passive Emptying Volume	(LA _{MAX} – LA _{PRE-A})
LA Active Emptying Volume	(LA _{PRE-A} – LA _{MIN})
Reservoir Emptying Fraction	(LA _{MAX} – LA _{MIN})/LA _{MAX}
Passive Emptying Fraction	(LA _{MAX} – LA _{MIN})/LA _{MAX}
Active Emptying Fraction	(LA _{PRE-A} – LA _{MIN})/LA _{PRE-A}
Inter AEMD	(Lateral PA – Tricuspid PA)
Intra-right AEMD	(Septal PA – Tricuspid PA)
Intra-left AEMD	(Lateral PA – Septal PA)

Chapter I: Introduction and Rationale

1.1 Introduction

Regular moderate physical activity performed in accordance with current physical activity recommendations (150 minutes of moderate-vigorous exercise)(1) is strongly associated with beneficial health effects, an improved quality of life, and substantial reductions in cardiovascular disease risk (2-7). A well-established inverse relationship exists between a higher exercise capacity and the risk for mortality (8) in the general population, and extended longevity in elite athletes compared to sedentary counterparts (9). Importantly, profound reductions in the risk for cardiovascular disease can be elicited even with small dosages of physical activity (10). More recently, higher levels of physical activity well-beyond the recommended guidelines, particularly participation in marathons and triathlons, have become increasingly popular, especially in the middle-aged cohort (11). In North America alone, there were close to 600,000 finishers of the full marathon (12), and just under 2 million finishers of the half-marathon in 2017 (11).

Several beneficial physiological adaptations are elicited secondary to endurance training, including a reduction in blood pressure and improved cardio-respiratory fitness (13). In particular, long-standing endurance training induces structural and functional remodeling of the heart, resulting in a phenotype collectively identified as the ‘Athlete’s Heart’ (14, 15). The most prominent changes in response to extensive training include enlargement of the left and right atria (16), enlargement and thickening of the ventricles (17), and a reduction in resting heart rate (bradycardia <60 bpm). Together, these adaptations assist to enhance stroke volume and thereby augment cardiac output required to maintain oxygen supply to working muscles (18). While these adaptations enable the cardiovascular system to meet the demands of intensive activity, some of the morphological changes of the Athlete’s Heart share certain characteristics observed in disease states, such as hypertrophic cardiomyopathy (15).

While moderate exercise exposure contributes to the prevention and management of numerous diseases, there is evidence of an increased risk for cardiac arrhythmias in athletes, particularly Atrial Fibrillation (AF) (19-21). Emerging data suggests that the relationship between exercise dose and cardiac outcomes may resemble a “U-shape” (3, 22, 23), where higher dosages of

exercise confer health benefits, but ‘excessive endurance training is actually associated with a higher risk for adverse outcomes (22-28), including elevated risk for AF (29). In fact, middle-aged endurance athletes demonstrate a 5-fold increased risk for AF compared to healthy sedentary adults (28, 30-33).

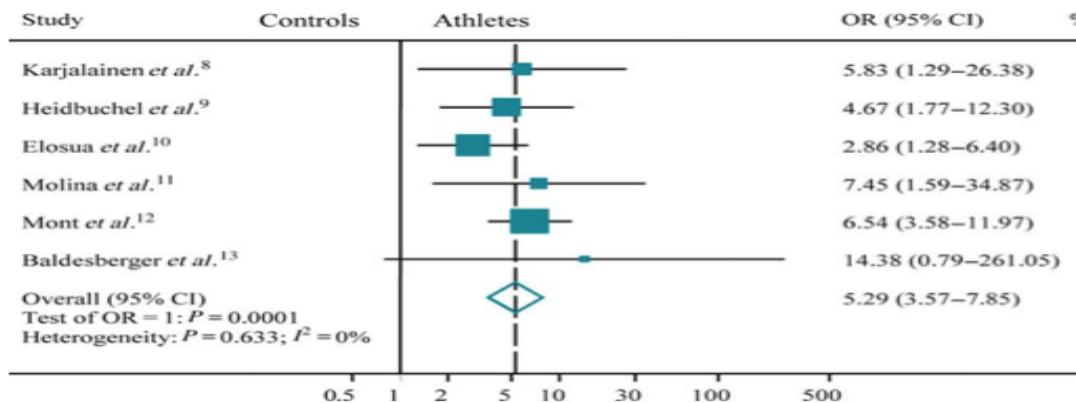


Figure 1: The increased odds ratio associated with athletes and risk for AF. From Abdulla and Nielsen, 2009 pg. 1158 (34).

Despite the growing concern of elevated AF risk in athletes, the mechanisms responsible for ‘exercise induced’ AF remain unclear. In the general sedentary population, one of the most well established risk factors for AF is left atrial (LA) enlargement (35, 36), typically secondary to hypertension. In the athlete, left atrial remodeling (enlargement) is a common physiologic adaptation to endurance training (15). However, the relationship between atrial size and AF risk has not been established directly in athletes, and while AF remains relatively uncommon in most athletes, similar frequencies of arrhythmias are reported in athletes with LA enlargement or those with normal LA dimensions (37). Recent retrospective data report larger LA volumes in older athletes with AF (38), but a causal link has yet to be elucidated in humans.

In healthy athletes, athletic training is also characterized by preserved and even superior cardiac function at both rest and exercise. In some states of cardiovascular disease, cardiac dysfunction may occur at rest and worsen further with exercise (39). One recent retrospective study of veteran athletes with paroxysmal AF (PAF) has established impaired atrial function with preserved ventricular function at rest and in sinus rhythm (38). While episodes of AF during exercise lowers endurance capacity in the general population (40), it is unknown if athletes with a history of PAF have altered atrial and ventricular function during exercise while in sinus rhythm.

Consequently, it is unknown if atrial remodeling secondary to exercise-induced AF alters cardiac performance at rest, or if acute exercise may unmask subtle alterations in function.

In the general population, in addition to LA dimensions, electrical conduction durations have also been used to predict the onset of AF. Specifically, a prolonged P wave duration is predictive of AF (41), yet both atrial volumes and P wave morphology/durations may have limited utility in predicting AF in an athletic individual (37, 38, 42) independent of atrial size. Accordingly, identifying an alternative prognostic measure may help to identify AF risk in athletes. Atrial electromechanical delay (AEMD), which serves as a measure of intra-atrial conduction, reflects both structural and electrical remodeling. In clinical cohorts, AEMD correlates to the presence of intra-atrial fibrosis (43) and has served as a robust and sensitive predictor of AF prior to onset. Ventricular electromechanical delay has also been shown to acutely prolong after intensive, sustained exercise (44). However, AEMD has not been reported in middle-aged athletes with or without AF, along with detailed cardiac dimension and functional phenotyping.

1.2 Rationale

Given the increasing participation rates in endurance sport, the implications of training and the athletic heart are increasingly relevant. While there is extensive data describing cardiac structure, function, and electrical conduction in sedentary patients with AF in the presence of cardiovascular morbidity, there are limited phenotypic data in endurance athletes with paroxysmal AF (PAF). To date, one retrospective study has characterized atrial volumes and function in older athletes at rest (38), but atrial function in response to exercise has yet to be examined in athletes with PAF. A comparison of atrial structure and function in athletes with and without PAF during exercise may provide further insight into the cardiac effects of PAF in this population, and provide reference data on athletes with PAF who continue to train. As the population ages, there is potential for a greater incidence of exercise-induced AF. Therefore, identifying cardiac structural, functional, and electrical endpoints that can provide prognostic indicators for athletes who have not yet developed PAF will be of clinical value.

1.3 Objectives

The primary objectives of the present study is to:

- 1) Characterize the cardiac phenotype of endurance athletes with PAF to age-matched endurance athletes without PAF, with an emphasis on the left heart. This will identify structural characteristics that may be influenced by the presence of PAF despite similar exercise history between cohorts.
- 2) Characterize atrial phasic function at rest and the cardiac response to submaximal exercise in middle-aged endurance trained athletes with and without PAF. This will help to determine if PAF in the athlete is associated with altered function compared to non-PAF athletes. A comparison of function at both rest and exercise will also allow insight into whether PAF alters the cardiac response to exercise.
- 3) Compare atrial electromechanical delay in endurance-trained athletes with PAF to healthy endurance athletes without PAF, and determine if differences between groups are independent of atrial size.

1.4 Hypotheses

- 1) Left ventricular and left atrial volumes will not differ between athletes with PAF and those without.
- 2) Phasic function will be impaired in athletes with PAF at both rest and during submaximal exercise. Specifically, LA reservoir function will be most significantly reduced, with progression of impairment from rest to exercise.
- 3) Left-AEMD will be significantly prolonged in PAF athletes compared to healthy athletes independent of left atrial volume.

Chapter II: Review of Literature

2.1 Introduction

This review will begin with an introduction to the cardiovascular response to exercise. The phenotype of the ‘Athlete’s Heart’ and its associated structural and functional remodeling will be described, with an emphasis on the atria. The etiology of Atrial Fibrillation and the accompanying cardiac remodeling and functional remodeling will be reviewed. Finally, markers of predicting AF will be discussed, with a focus on atrial volumes, atrial strain, and AEMD, and the use of echocardiography for obtaining these measures.

2.2 The Cardiovascular Response to Dynamic Aerobic Exercise

The heart is a muscular organ, located in the chest underneath the sternum, and serves to circulate blood through a closed circulatory system. The heart consists of four chambers in which the two upper chambers, termed the atria, provide blood to the two ventricles below, which eject blood to the pulmonary and systemic circulations (45). During resting conditions, approximately 5 liters of blood is circulated throughout the body. At the onset of exercise, cardiac output (CO) increases proportionally with work load by an increase in heart rate (HR) and stroke volume (SV) (46) to meet the elevated demands of working muscles. During exercise, SV is modified by an increase in end-diastolic volume (EDV) and a decrease in end-systolic volume (ESV). In accordance with the Frank-Starling mechanism, greater venous return to the heart during exercise increases myocardial stretch, thereby causing a greater force of cardiac contraction and ejection of blood (47). In addition to increases in CO, oxygen extraction by working skeletal muscles is increased (48). Finally, in both the systemic and pulmonary circulation, blood pressure rises and a concomitant drop in total peripheral resistance occurs to enable tissue perfusion (49).

2.3 The Athlete’s Heart

In response to chronic athletic training, physiologic cardiac adaptations are elicited to enable a high work capacity. The earliest description of the ‘athletic heart’ was in 1899 in a cohort of Nordic skiers and university rowers, using auscultation and percussion techniques (50, 51), and

since then two-dimensional echocardiography has rapidly enabled the characterization of exercise-induced remodeling (52). The ‘Athlete’s Heart’ is a characteristic phenotype of structural, functional and electrical remodeling that emerges to improve cardiovascular efficiency, occurring with as little as 6 months of endurance training (18, 53). One of the most prominent changes is hypertrophic growth of the heart that occurs with preserved contractile function, which is distinct from the dysfunction that accompanies pathological remodeling in states of disease (54). The cardiac growth that occurs with athletic training can further be designated as concentric or eccentric (55), which is distinguished on the basis of ventricular chamber size and chamber thickening.

The type and extent of cardiac remodeling varies amongst athletes, and is dependent on the loading placed on the cardiovascular system. Dynamic endurance exercise, such as running and cycling, results in increased CO, a reduction in peripheral resistance, and a moderate increase in systemic blood pressure, thus subjecting the heart to a volume overload (15, 52). Accordingly, endurance training elicits an ‘eccentric’ phenotype characterized by cardiac chamber dilation. This is in contrast to strength-trained athletes who undergo ‘concentric’ cardiac hypertrophy, which is characterized by profound increases in ventricular thickness (56). Notably, most athletes will fall on a continuum of remodeling as adaptations occur as an interaction between training and genetic phenotype. While ‘eccentric’ and ‘concentric’ is used to broadly describe the adaptations to training, all four chambers of the heart undergo unique structural and functional adaptations that contribute to its efficiency (Figure 2).

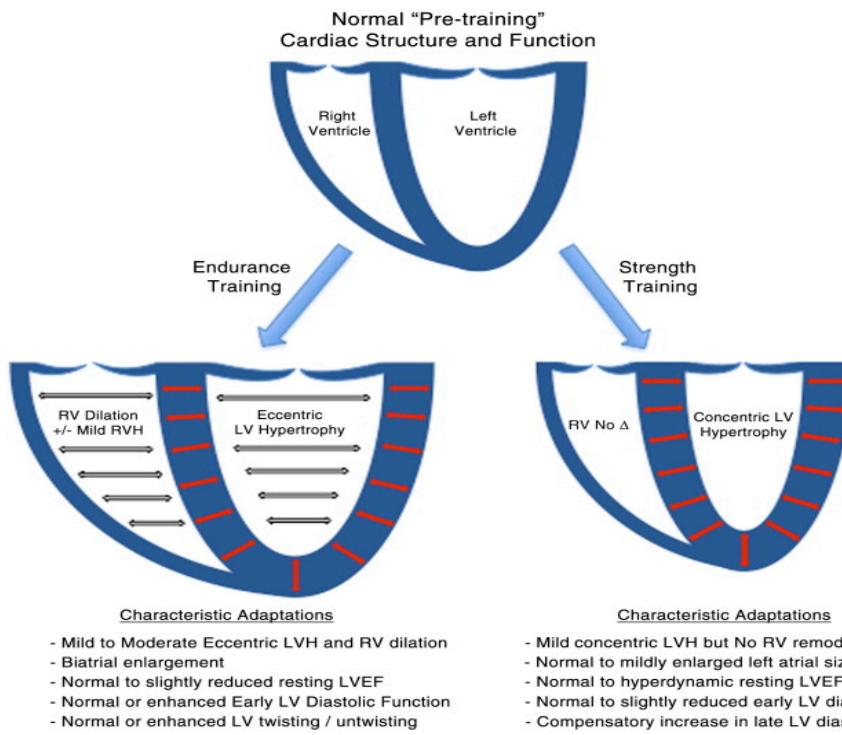


Figure 2: Summary of eccentric and concentric remodeling of the ‘Athlete’s Heart.’ From Weiner and Baggish, 2012 pg. 382 (52).

2.3.1 Ventricular Remodeling in the Athlete

2.3.1.2 Ventricular Structural Remodeling

In response to dynamic endurance exercise, athletes demonstrate an increase in left ventricular (LV) cavity dimension and mild LV wall thickening (57, 58). Markedly dilated LV chambers have been described in endurance athletes, in which LV end diastolic diameters may range from 38 mm up to 66 mm in women, and 43 to 70 mm in men (52). In some elite endurance athletes, LV EDVs may exceed ‘normal’ clinical upper dimensions, exceeding volumes of 300 mL (15, 59), and following several years of de-training, LV dilation may persist (60). The increase in LV EDV is accompanied by a proportional increase in LV wall thickness, though only few athletes display thickening that exceeds normal upper limits (14, 52, 61, 62). In a small percentage of endurance athletes, LV remodeling has been associated with the presence of fibrosis, though the significance of ventricular fibrosis has yet to be determined in this cohort (63-65).

It is noteworthy that female athletes demonstrate less profound cardiac remodeling of the LV, in both cavity dimensions and wall thickness, even after adjustment for size and body composition (61, 66). Moreover, there appears to be a degree of sport specificity for LV remodeling as athletes engaging in cycling, swimming and rowing demonstrate the largest ventricular dimensions (58). Age also correlates with increased LV dimensions, in which a 1-year age increase is associated with an increase of 0.2 mm in cavity dimension and 0.1 mm in wall thickness (58), though this correlation is likely a reflection of years of training.

Early characterization of the athlete's heart was primarily focused on the LV (58-60), however recent literature has begun to document right ventricular (RV) morphology. Endurance athletes display enlarged RV cavity dimensions and mild RV wall thickening (15, 18, 67-70). Magnetic resonance imaging (MRI) has confirmed significantly greater RV EDV and RV mass in endurance athletes compared to sedentary individuals (68). Furthermore, the relative increase in mass and volume of the RV is more prominent compared to that of the LV following intensive endurance training (18) which is attributed to the more profound increase in RV wall stress elicited during exercise (15). Right ventricular EDV may exceed upward values of 350 mL in some male athletes (15).

Notably, some of the ventricular remodeling associated with the Athlete's Heart has remarkable similarities to hypertrophic cardiomyopathy. However, there are distinct differences in the stimuli to trigger remodeling in a disease state versus in a healthy athlete. Physiological hypertrophy is driven by insulin-like growth factor 1 (IGF1) and its downstream cascade of phosphoinositide 3-kinase and Akt1 activation (71, 72). This is distinct from the pro-hypertrophic hormones, Angiotensin II and endothelin-1, that are up-regulated in heart failure patients (73). The differences between pathologic and physiologic remodeling can further be distinguished by comparing functional cardiac measures, which are maintained in the athlete.

2.3.1.3 Ventricular Functional Remodeling

Chronic endurance training is associated with preserved ventricular function, and even enhanced function, as demonstrated by echocardiograph imaging and a limited number of MRI studies (15). One of the most significant functional changes associated with endurance training is an increase in SV at both rest and maximal exercise (74) attributed to enhanced LV diastolic

function. Left ventricular compliance is improved at both rest and exercise to enable adequate filling at high heart rates (62). Accordingly, athletes demonstrate superior utilization of the Frank-Starling mechanism (56, 67, 70, 75), though some literature describes systolic function to be unchanged (70, 76), or even lower in athletes with severely dilated LVs (15, 77).

Data surrounding right ventricular function appears to be inconsistent. Some literature demonstrates augmented RV systolic and diastolic function in endurance athletes (17, 68, 70, 78), while others report no difference (79), or slightly reduced RV function compared to non-athletic controls (67). Relatedly, following an acute bout of intense exercise, athletes have displayed reductions in RV function (80). Interestingly, a small percent of athletes with low RV ejection fraction and long standing sport history have presented with delayed late gadolinium enhancement (LGE) in the RV interventricular septum (81).

2.3.2 Atrial Morphology

The atria are the uppermost chambers of the heart, situated above the ventricles, and are separated from one another by the interatrial septum. Both atria are comprised of a venous component, an appendage, and vestibule (82), and while they are composed of similar features, they have distinct morphological characteristics that assist in differentiation.

2.3.2.2 *The Left Atrium*

The left atrium (LA) is positioned most posteriorly of the cardiac chambers, receiving oxygenated blood from the pulmonary veins and directing blood to the LV. The left atrial chamber commences at the junction of the pulmonary veins and atria, and ends at the atrioventricular division by the mitral valve. Situated superiorly, the left atrial appendage extends from the body of the atrium and is considerably smaller than that of the right heart (82). Interestingly, in patients with AF, the left atrial appendage appears to be 3-fold larger and smoother than healthy counterparts, which may contribute to thrombus formation in this population (83).

The walls of the LA are relatively thin, with the greatest thickness primarily being in the posterior of the chamber (84). In comparison to the right atrium, the walls of the LA are relatively smooth (85). Sleeves of muscle from the walls of the left atrium extend to surround the pulmonary

vein walls – which strongly contribute to the ability of the pulmonary veins to initiate focal atrial arrhythmias (86).

2.3.2.3 The Right Atrium

The right atrium (RA) receives deoxygenated blood from the systemic circulation and directs blood flow through the tricuspid valve to the right ventricle. Due to the low-pressure venous system, the RA operates under notably less pressure than the LA (87). Structurally, the RA is considered to have a more complex configuration in comparison to the LA (84). The main anatomical feature of the RA is its large appendage, forming the entirety of the anterior wall (82). Clinically, an important feature of the RA is the crista terminalis, a muscle bundle that is comprised of non-uniform fiber arrangement, which can act as a substrate for atrial arrhythmias (88). An important feature of the RA is the cardiac pacemaker, the SA node, located between the crista terminalis and the superior vena cava. The AV node is also located in the RA and is known to contribute to atrioventricular re-entrant tachycardias (89).

2.3.3.2 Atrial Phasic Function

The atria have three distinct functional phases- namely the reservoir phase, the conduit phase, and the booster phase- that contribute to the modulation of ventricular filling. The atrium serves as a ‘reservoir’ to store venous return prior to contraction, as a ‘conduit’ to passively transfer pulmonary flow during ventricular diastasis, and as a ‘booster’ to actively empty its contents to the ventricle and establish final EDV (Figure 3).

The first phase of atrial function, the reservoir phase, commences upon closing of the atrioventricular valves (AV), and corresponds to the filling of the atrium by pulmonary inflow (90). The reservoir phase is composed of an early and a late phase. The early phase corresponds to a reduction in atrial pressure as a result of atrial relaxation from the preceding contraction and atrial compliance, thereby allowing venous inflow into the chamber (91, 92). Relatedly, high atrial compliance also contributes to steady ventricular filling by passive emptying in the succeeding phase (92). The late reservoir phase utilizes the descent of the cardiac base and lowering of the atrioventricular plane during ventricular systole to allow further filling (90). Reservoir function is tightly coupled to ventricular function as the average rate of atrial area change is dependent on ventricular longitudinal shortening (90) which creates a suction effect, drawing blood into the atria

(91). Furthermore, atrioventricular plane displacement (AVPD) increases with workload, which supports the increase in reservoir function observed during exercise (93). The contribution of the ventricle to atrial filling differs between atria, as the RV undergoes greater AVPD compared to that of the LV, thereby producing a larger RA reservoir function compared to the LA (94).

The second phase, termed the conduit phase, follows atrial filling and begins at the opening of the AV valves. The term ‘passive emptying’ is often used interchangeably with ‘conduit phase,’ though it is noteworthy that two distinct components contribute to this stage. During this phase, ventricular pressure drops and the AV valves open (95), allowing the passive emptying of blood that was stored in the atria (reservoir) into the ventricles (96). Second, upon the decline of ventricular pressure (despite increasing volume), the ventricle produces a suction effect that causes rapid blood flow from the pulmonary veins directly into the ventricle, functioning as a conduit. Notably, the blood stored in the atria and the blood in the pulmonary veins cross to the ventricle simultaneously, as opposed to serially (97). Thus, ‘passive emptying’ is considered a property intrinsic to atrial function, whereas conduit flow is instead representative of ventricular function given the dependence on the suction effect and ventricular relaxation (97). Relatedly, an impairment in ventricular diastolic function may reduce conduit function (96). As the pressure gradient across the AV drops, flow correspondingly slows, and allows transition to the next functional phase.

The third function is termed the contractile or booster pump phase, in which the onset of the depolarization wave from the SA node stimulates atrial contraction and the ejection of blood into the ventricle (98). Atrial booster function is highly dependent on atrial properties (97). The contractile ability of the atria are dependent on atrial preload (and therefore reservoir volumes), as atrial stretch will augment contractility in accordance with the Frank-Starling mechanism (99). Moreover, atrial booster function is also influenced by ventricular afterload (100), as impaired ventricular diastolic function and ventricular stiffness will decrease the transfer of blood during atrial contraction (101). Under normal conditions, booster pump function contributes 15 to 20 percent of ventricular filling (102); this is augmented in states of decreased passive emptying, such as during elevated heart rates with exercise (93).

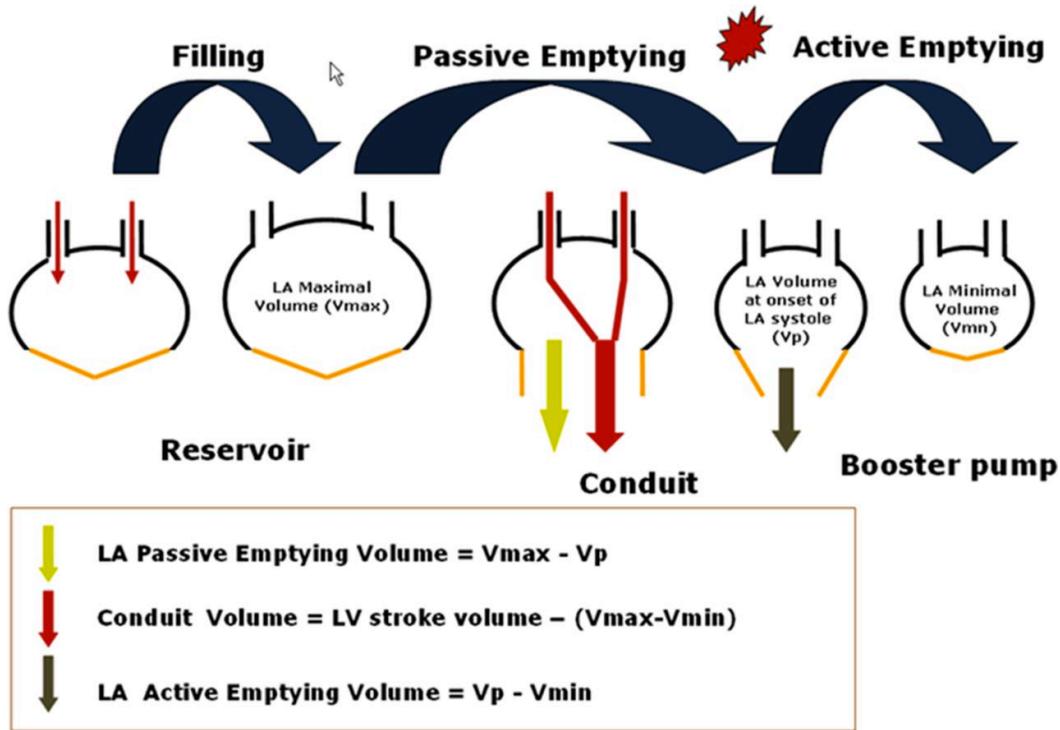


Figure 3: Atrial Phasic function and their respective formulas. From Rossi et al. 2014, pg 1043 (103).

2.3.3 Atrial Remodeling in the Athlete

2.3.3.1 Atrial Structural Remodeling

Atrial structure has been relatively understudied compared to the ventricles, however atrial remodeling is typically proportional to the enlargement of the ventricles with endurance training (15). In a variety of endurance-trained cohorts, athletes present with significantly larger LA dimensions, even when normalized for body size (37, 69, 78, 104, 105). Moreover, some left atrial dimensions in young and older athletes exceed the normal reference limits (40 mm), with some reporting dimensions above 45 mm (37, 104), and can overlap with those seen in cardiac disease (37). Cumulative lifetime hours of exercise training serves as an important determinant of left atrial size, in which a greater number of hours is associated with greater LA dimensions (106).

The clinical upper volumetric limits for atrial remodeling define mild LA dilatation as $>34 \text{ mL/m}^2$, $>42 \text{ mL/m}^2$ as moderate, and severe as $> 48 \text{ mL/m}^2$ using echo biplane methods (107). Mild, moderate and severe LA enlargement in a cohort of young elite rowers was identified in 27%, 11% and 4.4%, respectively (108). A recent meta-analysis suggests a 30% increase in indexed LA

volume in elite athletes compared to the general population (109). Thus, LA enlargement as a consequence of intensive training is common, and can be observed following a relatively short period (110). In addition to increased LA maximal volume, endurance athletes have higher pre-contractile and minimal LA volumes compared to age-matched sedentary individuals (111).

The remodeling of the RA in response to endurance training has not been well-characterized. Similarly to the LA, RA enlargement occurs in athletes (112). The RA is particularly susceptible to volume overload compared to the LA due to its thin wall. An interesting and more recent observation emerging in the literature is the difference in RA enlargement relative to the LA. In healthy athletes, the RA displays larger maximal volumes than the LA (65.1 ± 20.7 mL; 55.9 ± 17.5 mL, respectively), with a similar trend for pre-contractile and minimal volumes (113). Thus, there is a larger RA: LA remodeling ratio, however the clinical relevance of this observation is yet to be established (114).

Atrial remodeling has been primarily studied in male endurance athletes. However, there appears to be sex differences in response to training. Male athletes demonstrate significantly larger absolute LA and RA volumes compared to training-matched and age-matched females - though when indexed to body surface area (BSA), this difference only persists in the RA (115). The differences in atrial remodeling may be explained by gender differences in blood pressure, which is more pronounced in male athletes (115). Interestingly, female athletes demonstrate a lower prevalence of exercise-induced AF (116). While LA enlargement is a hypothesized cause for AF in athletes, the similar relative size of the LA between males and females suggests this alone may not be sufficient for developing AF. The gender differences contributing to the sex-specific risk of vigorous exercise remain to be elucidated.

2.3.3.2 Atrial Functional Remodeling

It is well established that during exercise, ventricular function is significantly enhanced with training. However, significantly less literature is available regarding atrial function in athletes. At rest, healthy endurance athletes display preserved phasic volumes despite atrial enlargement (114, 117-119). Athletes have presented with superior conduit, passive and active emptying volumes compared to non-athletic counterparts (120, 121), and larger reservoir functional volumes that aid increased pulmonary venous return. These improvements in volumetric flow are likely the

consequence of increased atrial compliance at end systole (114). However, it is acknowledged that greater phasic volumes may not always be indicative of greater function.

Accordingly, tissue deformation analysis (strain) has provided superior insight into functional adaptations. In a cohort of young endurance trained and strength-trained athletes, no differences were identified in resting atrial strain at any phase of the cardiac cycle (114), though resting booster strain may be reduced in athletes at rest compared to controls (122). In contrast, in comparison to sedentary individuals, athletes demonstrate superior LA conduit strain and rapid passive emptying, which may be attributed to superior LV performance and elastic properties of the LA (123). However, there appears to be little consensus across the literature as some data report reductions in peak LA and RA strain in elite athletes (78). Following a 16-week intensive training period, athletes had reduced peak atrial longitudinal strain and peak atrial contractile strain, though this was regarded as an adaptive phenomenon attributed to economized heart function at rest (16).

Few studies have explored atrial function during elevated demands. During exercise in middle aged athletes, LA reservoir function, conduit function and booster function are augmented (124). Specifically, during light exercise (100 bpm), LA reservoir volume increases significantly in conjunction with AVPD. Upon moderate exercise loads (HR of 130 bpm) LA filling is observed to plateau concurrently with AVPD, and LA maximal volume decreases (113), suggesting the contribution of LV shortening only supports atrial filling at light intensities (124). This is likely a protective response to prevent the LA from excessive dilation at higher intensities. Passive emptying volume is also increased during light exercise, with no change in active emptying. At moderate workloads (heart rate of 130), the passive component is reduced and active emptying is initiated earlier, utilizing the Frank Starling mechanism to optimize LV filling at higher heart rates (124). Accordingly, at peak exercise rates, reductions in passive emptying time is counteracted with a rise in active emptying (A-wave) (113).

The literature describing atrial strain during exercise in athletes is sparse. In a cohort of athletes and sedentary age-matched controls, peak positive and peak negative atrial strain were similar at resting conditions despite larger atrial volumes. Atrial strain increased during exercise, though athletes had lower deformation parameters in both the RA and LA compared to controls (113). Notably, this lower increment in strain was associated with a lower active emptying volume, and may have related to having significant atrial dilation. While a larger atrial volume and less

deformation potentially provides greater functional reserve, this may contribute to increased atrial wall tension in athletes with extensive chamber dilation (113, 122). Importantly, elevated wall stress can trigger atrial fibrosis (125) and increase the potential for arrhythmia development.

2.4 Atrial Fibrillation

Atrial fibrillation is an atrial tachyarrhythmia that is characterized by uncoordinated atrial activation and subsequent deterioration of atrial mechanical function (126). It is the most common type of cardiac arrhythmia (127, 128), in which 2.2 million individuals in North America are currently living with a diagnosis (129). The morbidity and reduced functional status associated with AF presents significant burden on the healthcare system, given the concomitant 5 fold increased risk of stroke (130). The prevalence of AF is higher in men (1.5 fold greater risk than females) (131), and doubles with each decade of age (132-134). A sedentary lifestyle and its accompanying comorbidities are associated with AF. Specifically, hypertension, heart disease (128), diabetes, obesity, sleep apnea, and tall stature (135) have been correlated with AF risk (131, 136), along with lifestyle practices including excessive alcohol consumption, smoking and poor cardiorespiratory fitness (132).

On an electrocardiogram, AF is described by an absence of consistent P waves in which there are rapid fibrillatory waves that are irregular in shape, size and timing (126). Atrial fibrillation can be classified according to the basis of episode termination. Specifically, paroxysmal AF is characterized by brief episodes (lasting 24 to 48 hours) that stop spontaneously; persistent AF typically lasts more than one week in duration and requires cardioversion to restore sinus rhythm; permanent AF cannot be converted to sinus rhythm (137). Paroxysmal AF may progress to longer, non self-terminating bouts, and AF that may be initially responsive to pharmacology or cardioversion can become resistant (137). Notably, paroxysmal AF may be difficult to diagnose given the asymptomatic nature and brevity of episodes; 24-hour Holter monitors may assist in these cases (126).

2.4.1 Atrial Structure and Function in Atrial Fibrillation

Atrial fibrillation is associated with remodeling that primarily alters atrial structure and function (138). In the sedentary population, LA size is a strong risk factor for AF (139, 140). Patient populations with AF have notably larger left atrial sizes compared to healthy controls (141, 142). For every 5 mm increase in LA diameter, the risk of AF development increases by 39% as demonstrated in the Framingham Heart study (36). Additionally, the recurrence of AF further increases LA size, however in the case of paroxysmal AF less notable increases in LA size occurs with time, suggesting a different underlying mechanism may exist (143). The temporal relationship between LA size and AF also remains unknown (143). However, LA size increases across paroxysmal, persistent and permanent AF, respectively, suggesting remodeling is intensified by the condition (144). In addition to alterations in atrial chamber size, AF is associated with a pattern of histological changes, namely the development of fibrosis in the atria (145).

In patient populations, atrial function declines across the spectrum of AF. Measures of LA function have been suggested to be more sensitive predictors of new onset AF (146), recurrent AF following ablation (147), and risk of stroke in the presence of AF (144). Accordingly, impairments in atrial function have been documented in patients despite having normal size (144). In patient populations, comorbidities such as hypertension and diabetes will alter LA function, thus rendering it difficult to isolate changes specific to AF. Therefore, ‘lone’ AF presents a unique opportunity to identify AF-specific functional remodeling. Patients with paroxysmal lone AF have impaired atrial phasic function as measured by echocardiography and MRI (148, 149). Despite comparable LA volumes between controls and patients, all 3 phases of atrial function are reduced in the presence of AF, suggesting LA enlargement is not the sole contributor to atrial dysfunction (148). Moreover, left atrial function progressively declines across the spectrum of AF (paroxysmal, persistent and permanent, respectively) (144, 148). As assessed by echocardiographic strain, LA reservoir function has been identified as a robust and accurate predictor for onset of AF independent of clinical risk factors, and is superior to LA volume for prediction purposes (150-152). In response to chronic volume or pressure overload, the atrium undergoes myocardial stretch, which can stimulate chamber dilation and fibrosis. Such alterations in atrial architecture can interfere with electrical conduction and promote a substrate suitable for triggering AF (150). Given that LA reservoir function is tightly related to atrial compliance, atrial relaxation (153), and ventricular longitudinal

shortening, functional assessment provides more thorough insight into the extent of atrial remodeling compared to LA maximal volume alone.

Significantly less literature exists regarding RA structural and functional remodeling with AF exists. In patients with chronic AF, RA enlargement has been identified (154). Similarly to the LA, parameters of function, namely RA longitudinal strain, serve as stronger predictors of AF compared to volume (155).

2.4.2 Electrical Function in Atrial Fibrillation

Intra-atrial and inter-atrial conduction disturbances and heterogeneous propagation of impulses have been identified as a feature of atria prone to fibrillate (156). Signal-averaged P wave duration (SAPWD) serves as a non-invasive method of detecting intra-atrial conduction delays and as a surrogate for atrial fibrosis. SAPWD has been used for the prediction of AF in patients with coronary artery disease, hyperthyroidism, and hypertrophic cardiomyopathy (140, 157-159). The probability of developing AF in patients with a P wave duration > 140 ms is suggested to be 3 fold the risk of those patients with a duration $<$ than 140 ms (140).

A novel method of measuring atrial electrical function, termed atrial electromechanical delay (AEMD), has proven to be a sensitive predictor of AF in a variety of populations (160-162). As measured by tissue Doppler imaging, AEMD is defined as the temporal delay between the onset of electrical activity and the realization of force in the atria (163). AEMD has been correlated with both LA size and SAPWD, reflecting both structural and electrical remodeling of the atria (164). Pathological remodeling in atrial tissue, such as atrial fibrosis and scattered fibrotic foci, are suggested to be significant determinants of AEMD duration as they lead to non-homogeneous electrical impulses (43).

Intra and inter-atrial mechanical delay has been demonstrated to be significantly higher in patients with idiopathic AF compared to healthy controls, despite comparable atrial sizes (165). Moreover, AEMD duration predicted recurrence of AF at 1 month following cardioversion in patients with persistent AF (43). Specifically, intra-left AEMD is a significant marker for the development of AF, and correlates to P-wave dispersion, left atrial diameter and left atrial area (160). An intra-left AEMD cut-off value of 25 ms was suggested for predicting development of AF (160). It is suggested that AEMD may increase in the early stages of AF, even without the presence

of atrial dilation, rendering AEMD as a sensitive predictor of AF development compared to atrial size or volume (142), and patients prone for AF development may be identified prior to an arrhythmic event.

2.5 Atrial Fibrillation in the Athlete

A ‘U’ shaped relationship was first described between general mortality risk and dosages of exercise exposure. Maximal longevity was associated with moderate doses of running (3 times weekly, 6 to 12 miles per week, and a modest pace), whereas strenuous joggers had mortality rates that did not differ from sedentary non-joggers (23). One of the earliest studies to establish a relationship between endurance exercise and AF was in veteran orienteers, in which top ranked male athletes displayed a 5 fold greater risk for AF compared to controls (19). Similar findings were demonstrated in former professional cyclists who had accumulated 25 000 km/year. AF was significantly more common compared to age-matched golfers who had never engaged in endurance training, and presence of AF correlated with number of cycling years (166). In cross-country skiers, faster finishing times and a greater number of races completed was associated with a higher incidence of AF (167). Consequently, a 3-fold increased risk for AF with the practice of > 1500 lifetime hours of sport has been identified (168). Moreover, a dose-response relationship between lifetime training hours (low: <1500 hours, intermediate: 1500 to 4500 hours, high: > 4500 hours) has been characterized, in which SAPWD and corresponding risk for AF increases, respectively (119). Following systematic review, an odds ratio of 5.2 was described for athletes compared to sedentary controls (34).

The prevalence of AF in athletes appears to be variable, ranging from 0.2% to 13% (166, 169-172), though the lower prevalence of AF identified in some studies may be attributed to the lack of heterogeneity in the cohort examined and investigation of younger cohorts (37). Exploring an older cohort of athletes engaging in purely endurance sports would likely provide a higher prevalence rate, as onset is typically coupled with years of training.

The clinical presentation of exercise-induced AF is typically in a middle-aged male who has been engaged in long-standing endurance sport for several years (30, 173). The presentation of AF is usually paroxysmal and episodes are experienced at a period of high vagal tone, often at night or following a meal, or can be triggered during stress (30). Athletes usually present with a higher

prevalence of vagal AF as opposed to sympathetically driven AF. However, in sympathetically driven AF the onset of first symptomatic episode has been observed to occur at a younger age (174). AF in the athlete occurs in the absence of other risk factors such as structural heart disease, hypertension, diabetes, or smoking (173). They will often present with preserved ejection fraction (~55%) and normal ventricular diastolic function (173).

Notably, male athletes are at significantly higher risk for AF (10-fold) compared to female athletes (20), presumably due to more pronounced cardiac remodeling. Despite comparable training volumes, male athletes have larger atrial volumes, a longer SAPWD, higher blood pressure, and greater levels of sympathetic and parasympathetic tone (175, 176), though this has not been definitively established due to a lack of study in female athletes. However, this difference could be attributed to the number of years of vigorous exercise accumulated by males and females. Males report younger ages of vigorous exercise initiation, and a longer duration of vigorous exercise exposure (115), though female participation in endurance sporting events has increased dramatically in the last few decades (11). As the number of females engaging in high intense endurance exercise increases, there may be greater insight into whether gender differences in the response to vigorous exercise persist. Interestingly, while LA volumes are proposed to contribute to exercise-induced AF, when normalized for body surface area, females and males no longer differ (115), suggesting enlarged LA volumes alone may not be sufficient to cause AF.

2.5.1 Pathophysiology of Exercise-induced AF

The etiology of exercise-induced AF remains speculative and remains studied largely through animal models. The mechanisms are likely multifactorial, in which atrial ectopic beats, increased vagal tone, atrial enlargement, inflammation, fibrosis and genetics have all been proposed as potential mechanisms for exercise-induced AF (177).

2.5.1.1 Atrial Ectopy

In the general population, paroxysmal AF is commonly triggered by focal ectopic discharges in the pulmonary veins around the LA junction (178). However, conflicting results surrounding atrial ectopic beats and AF have been presented in athletes. Atrial ectopy has been suggested to increase as a consequence of sympathetic activity during exercise (179). However this

was not confirmed in former professional cyclists as there was no increase in the frequency of ectopic beats in the presence of AF (166).

2.5.1.2 Autonomic Tone

Variations in sympathetic and parasympathetic activation have been associated with AF in both patient and athletic cohorts (177), with sympathetically driven episodes being more prevalent in diseased atria, and vagally mediated episodes being more common in cases of lone AF (174). Models of partial vagal denervation via cardiac ablation have demonstrated efficacy for preventing arrhythmic episodes (180), thus emphasizing the role of autonomic dysfunction in AF. Endurance training is associated with a profound decrease in resting heart rate, termed bradycardia ($HR < 60$ bpm), which can be attributed to increased vagal tone (175, 181, 182) and intrinsic adaptations of the sino-atrial node (183). Notably, a slow heart beat correlates to long-term risk of atrial arrhythmia in athletes (184). Increased vagal tone promotes shortening of the atrial refractory period (185) by a decrease of the inward current through L-type calcium channels (186). As a result, a shortened excitation wavelength facilitates re-entry, and increases the chance for spontaneous electrical events (187, 188). However, AF can also be triggered by adrenergic stimulation, such as during intense exercise. High levels of sympathetic activity can induce micro re-entry by a shortened atrial action potential. Although, vagal stimulation increases the heterogeneity of atrial effective refractory periods and the variability of activation frequency, which has not been identified with sympathetic stimulation (189). Thus, heightened parasympathetic activity may result in a greater arrhythmic susceptibility.

2.5.1.3 Atrial Enlargement

Atrial dilation is a significant predictor for AF risk in the general population (139, 140). Atrial dilation is suggested to slow conduction velocity of the depolarization wave, causing increased spatial heterogeneities in conduction (160). Enlargement of the LA is a hallmark of the Athlete's Heart (14, 175, 179), though whether there is a causal relationship between enlargement and AF in athletes remains inconclusive. LA volumes were greater in athletes with PAF compared to those without (31, 38), an equal prevalence of AF in athletes with (0.9%) and without (0.8%) LA dilation has also been shown (37). Importantly, in an animal training model, atrial dilation alone

was not sufficient for promoting AF vulnerability, as AF resolved with detraining despite atrial dilation persistence (190).

2.5.1.4 Inflammation and Fibrosis

In order to persist, AF requires a substrate that allows fibrillation and altered conduction. Excessive endurance training has been associated with inflammation, which can encourage the development of fibrosis and interruption of cardiac muscle fiber bundle continuity, resulting in conduction disturbances (191, 192). Markers of collagen synthesis, including plasma carboxyterminal propeptide of collagen type I (PICP), carboxyterminal telopeptide of collagen type I (CITP), and tissue inhibitor of matrix metalloproteinase type I (TIMP-1), appear to be elevated in middle-aged elite endurance athletes compared to sedentary controls (193). Furthermore, increased quantities of IL-6 and TNF- α have been identified post-intensive exercise (80, 194). Although inflammatory molecules return to baseline in 24 hours, repeated acute bouts of exercise may subject athletes to fibrotic remodeling. Animal models have displayed ventricular fibrosis following 16 weeks of intensive endurance training (190, 195), and cardiac MRI has identified ventricular fibrosis in veteran endurance cohorts, which was not present in age matched controls or younger elite athletes (196).

While sedentary patients with lone AF often have varying degrees of inflammation and fibrosis in atrial tissue, atrial fibrosis has yet to be confirmed in athletes with AF (145). Animal models of AF have increased mRNA protein expression of collagen-producing markers in the atria (TGF-B1) with endurance training, representing evidence of adverse cardiac remodeling with intensive exercise (195). More recently, TNF- α and p38 activation have been identified as direct mediators of exercise-induced AF in animal models as their inhibition prevented atrial fibrotic remodeling and AF vulnerability (197). Once AF is initiated, fibrosis appears to progress as greater LGE has been identified in patients with persistent AF compared to paroxysmal patients (198). The presence of LGE correlates with risk of AF recurrence (199), and is negatively associated with atrial phasic function, supporting that fibrosis contributes to the progression of atrial dysfunction (149).

2.5.1.5 Genetics

Despite the cardiac remodeling that occurs with endurance training, not all endurance athletes will develop AF, suggesting a role for genetics. One hypothesis postulates that a genetic predisposition to atrial arrhythmias and having prolonged high intensity exercise exposure can cause AF to occur at an earlier age compared to the presence of genetic variants or exercise engagement alone (200). Alternatively, it is also possible that genetic variants and exercise exposure may have synergistic effects. Exercise can modify sinus node genes (HCN4 gene and the I_f current) (201), and mutations have been associated with AF (202). Similarly, a variant in the KCNQ1 gene that contributes to the cardiac repolarization phase has been identified in AF (203), though its effects were only evoked under conditions of stretch. Thus, under conditions of dilation or myocardial stretch, as in the case of exercise, there may be genetic triggers for AF. Interestingly, having a genetically determined predisposition for AF could promote recurrence of arrhythmias in athletes even following cardiac ablation procedures (200).

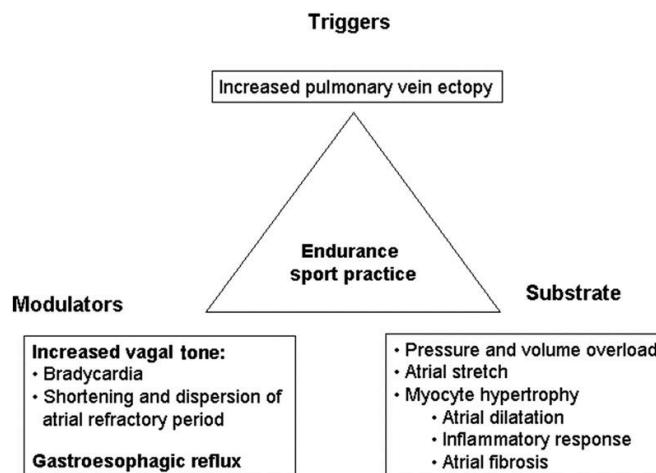


Figure 4: The proposed causative mechanisms of exercise-induced AF. From Mont et al. 2009, pg 14 (30).

2.6 Structure and Function in Athletes with Atrial Fibrillation

2.6.1 Cardiac Structure and Function

The literature examining atrial function in athletes with PAF is limited. One retrospective study compared male veteran endurance athletes with PAF (59.9 ± 7.4 years) to healthy age-matched veteran athletes (61.8 ± 6.4) who were engaging in an average of 6 hours of training per week. Left

ventricular diameters and volumes did not differ between groups, nor was there a difference in functional parameters (ejection fraction, global longitudinal strain, or Doppler indices of diastolic function) in sinus rhythm. In contrast, left and right atrial minimal and maximal volumes were larger in athletes with PAF, and all three phases of resting function, as assessed by strain, were significantly impaired (38). Interestingly, upon assessing cardiac function using volumetric parameters (phasic ejection fractions), only the reservoir and booster phase was impaired in the athletes with PAF, while passive emptying fraction did not differ between groups (38). Accordingly, atrial function as assessed by strain was superior to the volumetric method for detecting athletes with PAF, with LA and RA reservoir strain being most sensitive.

While atrial volumes were larger in athletes with AF, there was a significant amount of overlap with controls- however when function was compared, there was substantially less similarity, emphasizing the sensitivity of strain for differentiating physiology and pathology. Left atrial reservoir strain < 30% is considered to be a significant alteration of reservoir function in the general population (204). Athletes with PAF were below this cut off (LA reservoir strain: 29.3%), while no control athletes had lowered reservoir function (38).

2.6.2 Electromechanical Function

The characterization of electrical function in athletes has been limited primarily to healthy cohorts. Following a 30-km cross country run, ventricular repolarization abnormalities associated with risk of ventricular arrhythmias were identified in older athletes, suggesting a transient state of electrical instability may occur with endurance exercise (205). Following marathon running, P-wave duration increased in athletes and was associated with myocardial edema and pro-inflammatory markers (194). Lifetime hours of training are also associated with conduction delays, in which SAPWD increased with more training hours (<1500, 1500 to 4500, > 4500 hours, respectively), and the number of premature atrial contractions rises incrementally across these groups (119).

In veteran endurance athletes with PAF, P-wave characteristics (duration, amplitude and PR duration) appear to be comparable to healthy athletes (38) despite larger atrial volumes. Thus, the utility of P-wave morphology to identify those at risk for AF may in fact be limited, and more sensitive measures are required. Consequently, AEMD has served as a viable method of predicting

onset of AF in the general population, however it has been understudied in the athletic population. One study demonstrated prolonged ventricular electrical mechanical delay following ultra-endurance exercise in healthy athletes (44), though despite the potential utility of AEMD to be a refined indicator of disease progression, there is no existing literature investigating AEMD in endurance athletes with AF.

2.7 Assessment of Atrial Function: Echocardiography

2.7.1 *Atrial Dimensions and Volumes*

Cardiac size and function is commonly assessed using echocardiography due to its availability, portability and non-invasive nature. Although the most commonly used measure of atrial dimension is the LA anteroposterior measure in the parasternal-long axis view, the accuracy of this technique for assessing atrial size is limited (107). Assessment of LA size using diameters is based on the assumption of uniformity in left atrial enlargement- however the relationship between LA dimension and LA volume is nonlinear and this disparity is more pronounced with larger chambers (139, 206). Accordingly, the utility of LA size for the prediction of AF risk has been shown to be inferior to LA volume assessment in cohorts with enlarged atria (139).

Left atrial volume has been shown to be a powerful predictor of a variety of cardiac diseases as it accounts for alterations in chamber size that occur with dilation (107). LA volume should be measured using the bi-plane disk summation algorithm (modified Simpson's rule), in which LA endocardial borders are measured in both four and two chamber views (107). Although 2D echocardiography has been shown to underestimate volumes (107), it has been well correlated with LA volumes measured by 3D echocardiography (207) and cMRI (208). Right atrial volumes should be assessed in a similar manner to the LA. There are no orthogonal RA views that can be used for biplane calculation, thus a single view disk summation technique is proposed for volume assessment (107). Of note, RA volumes are underestimated with 2D echocardiography compared to 3D echocardiography (209), and can appear to be smaller than LA volumes (210).

2.7.2 *Atrial Phasic Volumes*

Left atrial phasic volumes are to be measured at different time points of the cardiac cycle, and should be normalized to body surface area (107). Atrial maximal volume (LA_{MAX}) is measured

at the end of ventricular systole, prior to the opening of the mitral valve. Atrial pre-contraction volume (LA_{PRE-A}) is measured prior to atrial contraction, at the onset of the P-wave. Lastly, atrial minimal volume (LA_{MIN}) is measured at the closure of the mitral valve (121), corresponding to the point at which the atria is at its smallest volume. Accordingly, LA phasic volumes can be determined as follows: LA reservoir volume as the difference between LA_{MAX} and LA_{MIN} ; LA conduit volume as the difference between LV stroke volume and LA reservoir volume, LA passive emptying volume as the difference between LA_{MAX} and LA_{PRE-A} ; and LA booster pump volume is determined as the difference between LA_{PRE-A} and LA_{MIN} (121). Using the above atrial volumes, LA emptying fractions (EF) can be calculated. Left atrial reservoir EF is determined as: $(LA_{MAX} \text{ vol} - LA_{MIN} \text{ vol})/LA_{MAX} \text{ vol}$. Left atrial passive EF is determined as: $(LA_{MAX} \text{ vol} - LA_{PRE-A} \text{ vol})/LA_{MAX} \text{ vol}$. Left atrial booster EF is determined as: $(LA_{PRE-A} \text{ vol} - LA_{MIN} \text{ vol})/LA_{PRE-A} \text{ vol}$ (100, 144).

2.7.3 Atrial Phasic Function: Speckle-Tracking

Recently speckle-tracking echocardiography (STE) has become a validated and alternative tool for strain imaging and the measurement of cardiac function. Strain, described as the fractional change in the length of a myocardial segment relative to baseline, allows insight into regional and global myocardial deformation (211). The tracking algorithm in STE allows the identification of myocardial patterns or “speckles” on conventional echocardiographic images and tracks these speckles frame-by-frame (212). Speckle-tracking enables multidirectional tracking, and thus serves as a superior method to tissue Doppler Imaging (TDI) due to its ability to calculate myocardial velocities, displacement, and strain in any direction (211). Moreover, STE is a rapid and easy-to perform technique as it is semi-automated and angle-independent (213), and has high reproducibility (214).

Left atrial phasic function can be assessed using STE, in which the onset of the P-wave is used as a reference point, in contrast to the use of R-wave onset used for LV assessment (215). Use of the P-wave allows recognition of atrial phasic function: peak positive global LA strain corresponds to LA conduit function, peak negative global LA strain corresponds to LA booster function, and the sum of these values (total global LA strain) corresponds to LA reservoir function (215, 216). Similar analyses can be done for the RA, with good feasibility (217) and reproducibility (218).

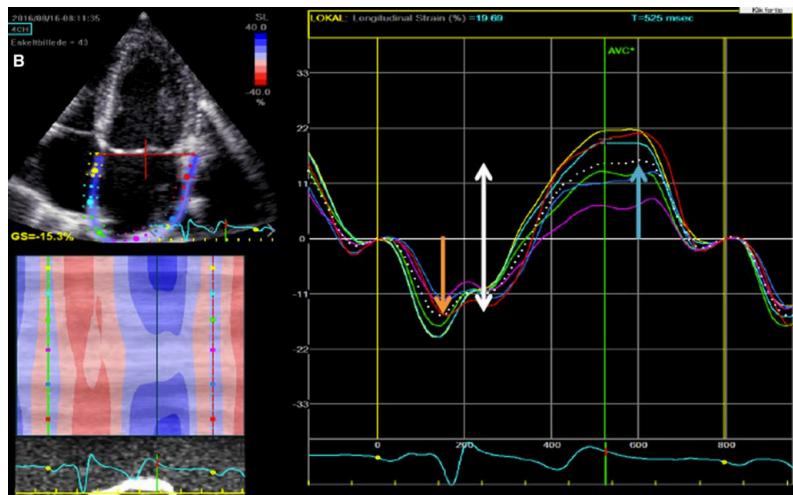


Figure 5: Resting atrial phasic strain profile in 4-chamber view gated to the onset of the P wave; Reservoir strain indicated by the white arrow, conduit strain is indicated by the blue arrow, and contractile strain by the orange arrow. From Olsen et al. 2016, pg 6 (219).

2.7.4 Determination of Atrial Electromechanical Delay

AEMD (ms) is assessed using tissue Doppler echocardiography, according to methodology described by Ozer et al. (162). Tissue Doppler echocardiography is performed using transducer frequencies of 3-4 MHz. Spectral pulsed Doppler signal filters should be adjusted to a Nyquist limit of 15-20 cm/s, and a sweep speed set to 50- 100 mm/s to optimize spectral delay of myocardial velocities. In apical 4-chamber view, the pulsed Doppler sample volume is placed at the lateral and septal sides of the mitral annulus, as well as the right-ventricular tricuspid annulus. The time intervals from the onset of the P wave (on ECG) to the beginning of the Am wave (on echo) are 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 (SA) node. The difference between any two reference points reflects the mechanical delay between these two points. Inter-AEMD is defined as the difference between the lateral PA and tricuspid PA, intra-right AEMD is defined as the difference between the septal PA and tricuspid PA, and intra-left AEMD is defined as the difference between the lateral PA and the septal PA (162).

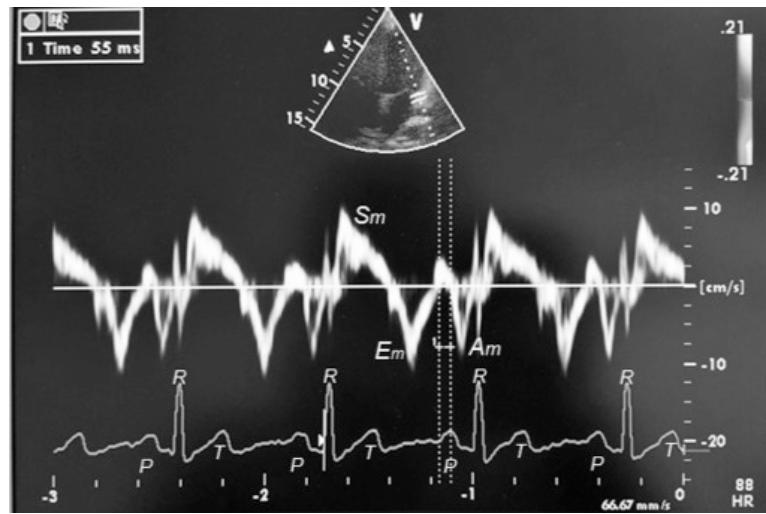


Figure 6: Atrial electromechanical delay measured from the onset of the P-wave on the ECG, to the onset of the late (A) diastolic doppler wave (atrial contraction). From Bulut et al. 2017, pg 124 (220).

Chapter III: Manuscript for Journal Submission

Abstract

Regular endurance exercise in accordance with physical activity guidelines lowers cardiovascular disease. Emerging evidence suggests that ‘excessive’ endurance training may increase risk of certain adverse cardiac outcomes including atrial fibrillation (AF) in middle-aged endurance athletes. However, there are limited data describing resting cardiac function in athletes with AF, and there is no existing data on cardiac function during exercise in this cohort. Traditional methods of predicting PAF, such as left atrial (LA) volume and P-wave duration, appear to have limited utility in athletes, suggesting novel markers for AF risk would have clinical value. The purpose of the present study was to characterize the atrial functional response to exercise in athletes with PAF. A second objective was to identify functional measures, namely atrial electromechanical delay (AEMD), that may be used as a predictor of PAF in athletes. Fourteen endurance-trained (H-EA) males (56.6 ± 5.1 years) and eight endurance-trained males with paroxysmal AF (EA-AF) (52.5 ± 6.8 years) underwent two-dimensional echocardiography at rest and during cycle-ergometry at light (100 bpm) and moderate (130 bpm) intensities. LA volumes did not significantly differ between H-EAs and EA-AFs (LA_{MAX} : 48.6 ± 12.6 mL vs. 45.3 ± 6.7 mL; LA_{PRE-A} : 27.6 ± 7.0 mL vs. 28.0 ± 8.5 mL; LA_{MIN} : 14.9 ± 5.1 mL vs. 15.7 ± 4.9 mL). At the onset of exercise, LV EDV, LA reservoir volume and LA booster volumes were significantly lower in EA-AFs, with a trend towards greater passive EF in EA-AFs at a HR of 100 bpm ($p=0.07$). There were no differences in AEMD (inter: 32.4 ± 16.3 ms vs. 32.8 ± 8.0 ms; right: 13.8 ± 7.5 ms vs. 9.9 ± 4.2 ms; left: 19.4 ± 10.2 ms vs. 20.9 ± 4.5 ms). The findings of the present study suggest that resting measures of volume and function are inadequate to identify PAF in athletes. During submaximal exercise, reductions in LA phasic volumes are unmasked in athletes with PAF, which may be indicative of atrial stiffening.

Introduction

Regular endurance exercise in accordance with most physical activity guidelines lowers cardiovascular disease risk (2-5, 7, 221). An inverse dose-response relationship between physical activity and risk reduction has been widely reported (3, 22, 23), but recent data suggests this relationship may be “U-shaped,” as ‘excessive’ exercise performed well-beyond these guidelines may increase the risk of certain adverse cardiovascular outcomes, including atrial fibrillation (AF) which may be 3-5 times more prevalent in long-standing endurance athletes compared to age-matched healthy sedentary adults (28, 30-33). Despite increasing concern about AF-risk in these individuals, there are only limited data examining the cardiac phenotype of athletes with ‘exercise-induced’ AF.

While numerous substrates have been proposed in exercise-induced AF, it remains idiopathic. Atrial enlargement is a predictor for AF risk in sedentary populations (36, 222), and while left atrial maximal and minimal volumes are enlarged in endurance athletes, there is a similar prevalence of AF in athletes with and without atrial enlargement (37, 42, 190), suggesting limited prognostic value of atrial volume in identifying AF risk in this cohort. Echocardiographic quantification of atrial phasic function has emerged as a reliable methodology to identify cardiac dysfunction (144, 148, 150), but little is known about atrial function during exercise in athletes with PAF, whether dysfunction exists, and if both atrial size and function is coupled to functional capacity in patients with PAF. In addition, despite the well-described direct correlation between prolonged P-wave duration and AF prevalence in the sedentary populations (223), athletes with PAF demonstrate normal P-wave morphology and duration (38), suggesting P-wave characteristics are inadequate for identifying athletes at risk for AF. Atrial electromechanical delay (AEMD) has been shown to increase in the early stages of AF independently of atrial size (160-162, 224), rendering AEMD as a more sensitive predictor of AF development compared to atrial volume (142). Accordingly, prolonged AEMD may be a more sensitive method of identifying athletes prone for AF development.

Accordingly, the objective of the present study was to characterize atrial phasic function during submaximal exercise in endurance-trained athletes with PAF in sinus rhythm. We expected atrial volumes to be comparable between groups, though atrial function at rest and exercise would

be impaired in the athletes with PAF. Our second objective was to test the hypothesis that AEMD is prolonged in endurance athletes with PAF, irrespective of maximal atrial volume.

Methods

Experimental Design

Participants initially completed a preliminary screening form to characterize medical history, a 2-Week Exercise Diary providing a summary of current training regimes, a modified Lifetime Physical Activity Questionnaire to characterize long-term training history, and AF participants completed additional screening to document their AF history and burden (number of years since diagnosis, episodes, symptoms, and triggers). Following this, subjects completed resting measures of blood pressure, height and weight. Participants then completed resting and submaximal echocardiography (ECHO). Finally, after a period of recovery, participants were fitted with a 12-lead electrocardiogram (ECG), and completed a graded maximal exercise test on either a treadmill or cycle ergometer. All participants provided informed written consent prior to the study, which was approved by both hospital and university research ethics boards and conformed to the Helsinki Declaration on the use of human subjects.

Subjects

Endurance trained male endurance athletes between the ages of 45 and 65 years old were recruited with a history of vigorous year-round training. Inclusion criteria required participation in endurance sport and year round training for a minimum of 10 years (i.e runners, cyclists, or triathletes), with a history of competition (triathlon, marathons, Ironman, long distance cycling). Exclusion criteria included any cardiovascular disease except in athletes with PAF, sleep apnea, thyroid disorder, diabetes, and not currently smokers. Participants with PAF were recruited from local cycling, running, or swimming clubs, or by cardiologist referral providing they met inclusion/exclusion criteria. Athletes with PAF were eligible for study regardless of medications or a history of cardioversion. Participants were excluded if they had undergone a cardiac ablation or if they were unable to maintain sinus rhythm during assessments.

Exercise Protocol

Subjects began lying supine on a cycle ergometer (Ergoline 1200E) and were fitted to the bed in a position that would not constrict the ability to exercise. Subjects were then brought into a tilt at approximately 30 degrees. Following a 5-minute period of rest and imaging in this position, participants then began exercise. The first stage consisted of light exercise, in which the work rate was manipulated for each participant to elicit a steady target heart rate (HR) of 100 beats per minute (bpm) for 5 to 7 minutes. The second stage consisted of moderate intensity exercise, in which the work rate was manipulated for each participant to elicit a steady target heart rate (HR) of 130 beats per minute (bpm) for 5 to 7 minutes. During rest and each stage of exercise, HR, blood pressure (BP), work rate, and rating of perceived exertion were recorded approximately 2 minutes into steady state. Similarly, after 1 to 2 minutes at the start of each stage, ECHO images were acquired prior to initiating the next stage. Exercise was discontinued if participants were no longer in sinus rhythm, or if SBP decreased > 10 mmHg from baseline, or was < than 90 mmHg.

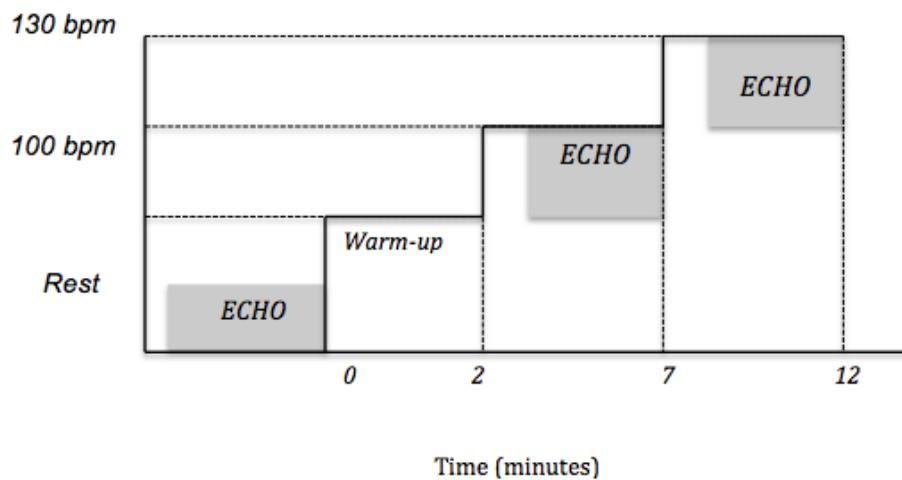


Figure 7: Exercise protocol during cardiac echocardiography.

Echocardiography

Echo images were acquired at rest and during exercise by a trained sonographer, using a commercially available system (GE E9 Imaging System). Two-dimensional apical (two and four chamber view) and parasternal (long and short axis) images were performed for dimensional and functional parameters of the atria and of the ventricles at a frame rate of 60-80 frames per second (fps) to optimize image quality for subsequent analysis. Images were normalized to body surface area (107). Pulsed-wave Doppler interrogation of transmitral flow was obtained at the septal and lateral mitral annulus to determine flow velocities during early (E) and late (A) diastole, and E/A

ratio. Tissue Doppler imaging was also performed at the septal and lateral mitral annulus to determine myocardial systolic (Sm), early diastolic (Em), and late diastolic (Am) velocities.

Echo images were analyzed offline by a single observer, and were averaged over three cardiac cycles. Intraobserver variability of atrial volumes, atrial strain and AEMD were evaluated using intraclass correlation coefficients for ten randomly selected subjects across both groups. LA and RA volumes had an ICC of 0.98 and 0.95, and atrial phasic strain and left-AEMD had an ICC of 0.87 and 0.84, respectively.

Left ventricular and end-diastolic volume (EDV) and end-systolic volume (ESV) of the ventricles and atria were measured in apical four-chamber (A4C) views using the modified bi-plane Simpson's method (107). Atrial volumes were measured at different time points of the cardiac cycle. Atrial maximal volume (LA_{MAX} and RA_{MAX}) was measured at the end of ventricular systole, prior to the opening of the atrioventricular valve (AV); atrial pre-A volume (LA_{PRE-A} and RA_{PRE-A}) was measured prior to onset of atrial contraction; and atrial minimal volume (LA_{MIN} and RA_{MIN}) was measured at the closure of the AV valve. Accordingly, phasic volumes were determined as: reservoir volume (Maximal volume – minimal volume), conduit volume as (LV stroke volume – Reservoir volume), passive emptying volume (Maximal volume – Pre A volume), and booster volume as (Pre A volume – Minimal volume). Similarly, emptying fractions (EF) were calculated as follows: Reservoir EF [(Maximal volume – Minimal volume)/Max volume] x 100, Passive EF as [(Maximal volume – Pre A volume)/Maximal volume] x 100, and Booster EF as [(Pre A volume – Minimal volume)/Minimal volume]/Pre A volume] x 100.

Atrial Strain

Myocardial strain and strain rate were analyzed offline using Speckle-Tracking (STE), in which ventricular and atrial endocardial borders were traced using a point-and-click method on images acquired in 4-chamber view. LA and RA strain were calculated using the onset of the P-wave as the reference point (204). Atrial resting strain was divided into phases in which peak negative strain was identified as atrial contractile strain (LA_{BOOST} and RA_{BOOST}), atrial peak positive strain was identified as atrial conduit strain (LA_{CON} and RA_{CON}), and the sum of the absolute negative peak and positive peak was identified as atrial reservoir strain (LA_{RES} and RA_{RES}). Strain rate (%/s) for each phase was also recorded. During exercise (100 and 130 bpm), left atrial peak

negative strain (LA_{NEG}) and peak positive strain (LA_{POS}) were recorded, in addition to time to peak negative (T_{NEG}), time to peak positive (T_{POS}) and time to total strain (T_{TOTAL}). Accordingly, peak negative strain corresponded to atrial booster strain, peak positive strain corresponded to atrial conduit strain, and the absolute total strain was defined as reservoir strain. Border tracking was previewed prior to processing to allow for visual confirmation of adequate endocardium tracking. During exercise, RA strain was unobtainable due to image dropout.

Electrical Function

Atrial electromechanical delay was measured at rest according to the methodology described by Ozer et al. (162). Pulsed Doppler 4-chamber images with the sample volume placed at the lateral and septal sides of the mitral annulus, and the right-ventricular (RV) tricuspid annulus, were used. The time interval from the onset of the P wave (on ECG) to the beginning of the Am wave (on echo) was measured from the lateral mitral annulus (lateral PA), septal mitral annulus (septal PA), and the RV tricuspid annulus (tricuspid PA). Inter-AEMD was defined as the difference between the lateral PA and tricuspid PA (lateral PA- tricuspid PA), intra-right AEMD was defined as the difference between the septal PA and tricuspid PA (septal PA-tricuspid PA), and intra-left AEMD was defined as the difference between the lateral PA and the septal PA (lateral PA-septal PA). An additional measure was used to assess total atrial conduction time using tissue Doppler imaging (PA-TDI interval). The time interval between the onset of the P-wave on the ECG to the peak of the Am wave (on echo) was measured at the lateral atrial wall at both rest and during exercise (225). Three measures were taken and the mean value was used.

Maximal Exercise Testing

All participants completed a graded maximal exercise test to determine maximal oxygen consumption (VO_2 max), using a calibrated metabolic cart (Vmax Encore, CareFusion). Participants were given the choice to complete the test on either a motorized treadmill (Full Vision TMX4125) or cycle ergometer (Lode, Groningen, Nederlands). A plateau of oxygen uptake despite an increase in workload confirmed maximal effort. A 12-lead ECG was worn during the test to monitor HR.

Statistics

Statistical analyses were performed using SPSS Statistics software version 24 (IBM Inc). Data was assessed for normality using a Shapiro-Wilk test. Demographic variables were assessed using a series of independent t-tests and a Mann Whitney U test. Non-normal data is presented as median, interquartile range. A two-factor repeated measures analysis of variance (ANOVA) was used to analyze continuous variables, with the main effects of time (rest, light exercise, and moderate exercise) and group (EA and EA-AF), followed by Bonferroni-corrected *post-hoc* tests. Non-parametric data was also analyzed using a two-way repeated measures analysis given that there is no equivalent non-parametric test that incorporates within and between group interactions. The ANOVA test was deemed appropriate in this case given its lack of sensitivity to moderate deviations from normality; the false positive rate of an ANOVA is not affected by violations of normality (226). A p-value of <0.05 was considered statistically significant for all analyses. All data are presented as mean \pm standard deviation (SD).

Results

Participant Demographics

A total of 25 subjects completed the study (H-EA n= 15; EA-AF n= 10). Three participants were excluded due to poor data acquisition. Subject characteristics are reported in Table 1. Participants from each group reported a similar frequency of exercise per week (EA: 5.5 ± 1.4 days, EA-AF: 5.3 ± 1.5 days, $p = 0.69$) and duration per training session (EA: 83.5 ± 37 minutes, EA-AF: 94.3 ± 53 minutes, $p= 0.62$). Endurance athletes without PAF reported insignificantly more intense training sessions, as calculated by a 2-week average of ‘training impulse’ (TRIMPs) (RPE x duration) ($p=0.18$). Participants’ 10 year vigorous hours of endurance exercise was calculated based on extrapolation of hours per week and on the basis of a 10-year minimum participation criteria. Despite engaging in a comparable frequency of exercise per week, VO_2 max was lower in the EA-AF participants (EA: 52 ± 5 mL/kg/min; EA-AF: 46.7 ± 4.9 mL/kg/min, $p = 0.03$); this was aligned with the AF athletes expressing a decrease in the intensity of their training since diagnosis. Demographic data of the PAF athletes is presented in Table 2; three athletes with PAF were on medications, and 3 had undergone cardioversion.

Cardiac Response to Exercise

All participants completed the three stages of image acquisition. Heart rate did not differ between groups at any stage of exercise (H-EA light: 98 ± 5 bpm, EA-AF light: 100 ± 4 bpm; H-EA moderate: 126 ± 6 bpm, EA-AF: 126 ± 8 bpm). There were no significant differences in systolic blood pressure responses (rest: 127 ± 12 mmHg vs. 132 ± 22 mmHg; light: 173 ± 27 mmHg vs. 175 ± 23 mmHg; moderate: 203 ± 28 mmHg vs. 206 ± 17 mmHg) or diastolic blood pressure (rest: 77 ± 11 mmHg vs. 76 ± 10 mmHg; light: 81 ± 9 mmHg vs. 79 ± 11 mmHg; moderate: 83 ± 20 mmHg vs. 84 ± 12 mmHg) during cardiac imaging. Work rate was comparable between groups throughout testing at both light (106 Watts vs. 112 Watts) and moderate intensities (170 Watts vs. 173 Watts).

Table 1. Participant Demographics

Variable	EA (n= 14)	EA-AF (n=8)
Age (years)	56.5 ± 5.1	52.5 ± 6.8
Height (cm)	179.5 ± 4.7	178.6 ± 5.9
Weight (kg)	74.5 ± 8.3	* 82.4 ± 6.1
BMI (kg/m^2)	23.1 ± 1.8	* 25.8 ± 1.5
HR (bpm)	53 ± 9	50 ± 9
SBP (mmHg)	120 ± 14	128 ± 5
DBP (mmHg)	81 ± 8	83 ± 3
VO_2 max (L/min)	3.9 ± 0.5	3.7 ± 0.4
VO_2 max ($\text{mL}/\text{kg}/\text{min}$)	52.1 ± 5	* 46.7 ± 4.8
2-Week Average TRIMPs	4024.7 ± 2231.8	2742.4 ± 1912
Hours per week	7.4 ± 4.7	8.7 ± 5.7
10 year vigorous hours	3380, 2600-4858	4095, 2605-6792
Alcoholic Drinks/week	6.1 ± 5.8	5.8 ± 6.7
Past Smoking History	5	1

Variables are presented as mean \pm SD. Non parametric data is presented as median, interquartile range. BMI; body mass index, HR; heart rate, SBP; systolic blood pressure, DBP; diastolic blood pressure, VO_2 max; maximal rate of oxygen consumption, CVD; cardiovascular disease. * denotes statistically significant difference between EA and EA-AF, P <0.05.

Table 2. Characteristics of EA-AF participants

Variable	EA-AF (n= 8)
Type of AF	Paroxysmal; episodes lasting up to 7 days
Years since AF diagnosis	2.2 ± 1.2
Age at diagnosis	50.5 ± 6.6
Number on Medications	4
Past cardioversion	3
Number of Years since cardioversion	1.3 ± 0.5
Exercise as a trigger for AF	62%, During exercise; intense session; start of season
Vagal triggers for AF	50%, Rest; following meal; lying down
Length of AF Episodes	Few seconds up to 5 minutes
Medications	(n=4) Ace inhibitors (Ramipril), Rate control (Bisoprolol, Diltiazem), Anti-coagulant (Lixiana)

Left and Right Ventricular Size and Function

LV and RV parameters are displayed in Table 3 and Table 4. There were no differences between groups in resting LV or RV size and function. LV EDV increased in both groups during light exercise, though EDV was significantly greater in H-EAs during light and moderate exercise. LV ESV significantly decreased at moderate exercise, and there was no difference between groups at any stage. LV and RV GLS was not different between groups at any stage.

Atrial Volumes and Function

Rest

Atrial parameters are presented in Table 5 and 6. Resting left atrial structure did not differ between H-EAs and H-AFs. Left LA_{MAX}, LA_{MIN}, and LA_{PRE-A} volumes were comparable between groups even when normalized for BSA. Absolute and relative RA_{MAX}, RA_{MIN}, and RA_{PRE-A} volumes did not significantly differ between H-EAs and EA-AFs. There were no significant differences in LA phasic functional volumes between groups. There were no differences in resting LA phasic EF,

however RA EF was significantly greater in the EA-AFs during reservoir and passive phases, and was trending for the booster phase ($p=0.1$).

Exercise

Upon onset of light and moderate exercise, LA_{MAX} significantly increased in H-EAs, while LA_{MAX} modestly increased in EA-AFs. There was a significant difference at light exercise between groups when normalized to BSA, though this was not significant at the moderate intensity. LA_{MIN} volume was not significantly different at any time point between H-EAs and EA-AFs. LA_{PRE-A} volume was significantly greater in H-EAs at light exercise and moderate exercise. RA_{MAX} did not increase in either group with the onset of exercise. RA_{MIN} significantly decreased with the onset of light and moderate exercise in H-EAs, but did not change in EA-AFs. RA volumes did not differ between H-EAs and EA-AFs at any time point.

LA reservoir volume significantly differed at the onset of light and moderate exercise, in which H-EAs had greater volumes. Conduit volume and LA passive emptying volume did not differ between groups at light exercise, though conduit volume was reduced at moderate exercise when normalized for BSA in PAF athletes. Booster volume significantly increased upon onset of light exercise in H-EAs and was significantly higher compared to EA-AFs throughout both stages of exercise. In the RA, reservoir volume did not change with onset of exercise in either group, though RA booster volume significantly increased in H-EAs at light exercise and was significantly greater than EA-AFs.

LA reservoir EF remained stable throughout all stages for both groups, and there was no difference between groups at any exercise stage. EA-AFs were trending towards a significantly higher LA passive EF compared to H-EAs during light exercise ($p=0.07$), and this relationship was significant for RA passive EF. LA booster EF increased in both groups upon onset of exercise, with no significant differences between groups. RA booster EF largely increased in H-EAs at onset of light exercise, while EA-AFs remained stable until increasing at moderate exercise. However, there were no significant differences.

Atrial Myocardial Deformation

Data is presented in table 5 and 6. Speckle tracking of the LA was feasible in 21/22 of participants at rest, 20/22 at light exercise and 11/22 during moderate exercise. RA speckle tracking was only performed at rest, as there was insufficient tracking ability at the onset of exercise. Resting LA and RA phasic strain did not significantly differ between groups at any phase. There were also no differences in strain rate at rest. At both stages of exercise, LA reservoir, conduit and booster strain was similar between groups. No differences in strain rate were present during exercise.

Electrical Parameters

Atrial electromechanical delay was assessed at rest, but was not acquired during exercise due to poor ability to image distinct Doppler waves. There were no significant differences in any of the parameters between groups. PA-TDI also did not differ during rest or exercise between groups.

Table 3: Left Ventricular resting and exercise parameters

Variable	Rest		Light (100 bpm)		Moderate (130 bpm)	
	H-EA	EA-AF	H-EA	EA-AF	H-EA	EA-AF
IVSd (cm)	1.1 ± 0.1	1.1 ± 0.2	1.1 ± 0.1	1.3 ± 0.4	1.2 ± 0.2	1.3 ± 0.2†
LVIDd (cm)	4.7 ± 0.4	5.0 ± 0.3	4.7 ± 0.4	4.7 ± 0.4	4.8 ± 0.5	4.7 ± 0.4
LVPWT (cm)	1.1 ± 0.1	1.0 ± 0.2	1.2 ± 0.2	1.1 ± 0.1	1.1 ± 0.1	1.1 ± 0.2
LVOT (cm)	2.1 ± 0.2	2.1 ± 0.2	2.0 ± 0.2	2.0 ± 0.2	2.0 ± 0.2	2.0 ± 0.2
LVM (g/m ²)	103.8 ± 12.4	100.0 ± 11	103.1 ± 13.1	104.7 ± 19.1	109.4 ± 14.4	110.1 ± 22.2
LVEDV (mL)	138.9 ± 14.1	133.1 ± 15.7	151.8 ± 17.4†	143.5 ± 17.5	151.0 ± 17.4†	140.9 ± 13.5
LVEDV (mL/m ²)	71.9 ± 7.5	66.1 ± 8.8	78.4 ± 6.6†	*71.2 ± 8.8	78.1 ± 5.8†	*69.9 ± 7.0
LVESV (mL)	58.7 ± 9.3	53.9 ± 8.2	49.1 ± 8.2	50.4 ± 11.4	41.2 ± 6.6†*	38.2 ± 11.3†*
LVESV (mL/m ²)	30.4 ± 4.7	26.7 ± 3.6	25.4 ± 4.5	25.1 ± 6.0	21.4 ± 3.7†*	18.9 ± 5.2†*
LVSV (mL)	80.7 ± 12.9	79.2 ± 15.5	104.7 ± 16.6†	93.1 ± 9.9†	112.5 ± 16.9†	102.6 ± 12.2†
LV EF (%)	57.6 ± 5.7	59.3 ± 6.4	67.4 ± 6.0†	65.2 ± 4.8	72.5 ± 5.2†*	73.0 ± 6.9†*
LVGLS (%)	-17.5 ± 2.9	-17.7 ± 1.6	-25.1 ± 3.7†	-22.0 ± 3.6†	-26.0 ± 2.8†	-23.9 ± 3.3†

IVS; interventricular septum, LVID; left ventricular end-diastolic diameter, LVPWT; left ventricular posterior wall thickness, LVOT; left ventricular outflow tract, LVM; left ventricular mass, LV EDV; end diastolic volume, LV ESV; end systolic volume, LV EF; ejection fraction, LV GLS; left ventricular global longitudinal strain. * denotes a statistically significant difference between H-EA and EA-AF, † denotes a statistically significant difference compared to rest, ♦ denotes a statistically significant difference compared to light exercise, p<0.05.

Table 4. Right ventricular resting and exercise parameters

Variable	Rest		Light (100 bpm)		Moderate (130 bpm)	
	H-EA	EA-AF	H-EA	EA-AF	H-EA	EA-AF
RVAd (cm ²)	20.7 ± 2.2	21.5 ± 6.7	22.3 ± 3.8	20.9 ± 5.6	20.7 ± 3.3*	20.9 ± 5.8
RVAs (cm ²)	11.4 ± 1.7	13.2 ± 7.1	10.7 ± 2.1	10.7 ± 4.1	10.2 ± 1.8	10.8 ± 4.2
FAC (%)	43.4 ± 7.1	41.0 ± 8.2	51.3 ± 4.2†	48.1 ± 6.4†	-	-
RV GLS (%)	-17.6 ± 3.7	-21.6 ± 0.5	-20.8 ± 3.0	-18.8 ± 0.5	-21.5 ± 3.2	-24.0 ± 3.3

RVAd; right ventricular diastolic area, RVAs; right ventricular systolic area, RV ET; ejection time, TCO; tricuspid valve closure and opening time, FAC; fractional area change, RV GLS; right ventricular global longitudinal strain. * denotes a statistically significant difference between H-EA and EA-AF, † denotes a statistically significant difference compared to rest, ♦ denotes a statistically significant difference compared to light exercise, p<0.05.

Table 5. Left atrial resting and exercise parameters

Variable	Rest		Light (100 bpm)		Moderate (130 bpm)	
	H-EA	EA-AF	H-EA	EA-AF	H-EA	EA-AF
LAD (cm)	3.0 ± 0.4	3.2 ± 0.6	3.3 ± 0.4 [†]	3.1 ± 0.7	3.3 ± 0.5 [†]	3.2 ± 0.8
LAAd (cm)	19.1 ± 2.6	18.7 ± 2.1	22.7 ± 2.4 [†]	20.2 ± 3.0	20.7 ± 1.6	19.3 ± 2.1
LA _{MAX} (mL)	48.6 ± 12.6	45.3 ± 6.7	64.1 ± 12.2 [†]	51.5 ± 16.1	55.3 ± 7.4	47.6 ± 12.0
LA _{MAX} (mL/m ²)	25.0 ± 5.8	22.2 ± 3.0	32.9 ± 5.8 [†]	* 25.3 ± 7.7	28.6 ± 3.9	23.3 ± 5.6
LA _{MIN} (mL)	14.9 ± 5.1	15.7 ± 4.9	19.4 ± 9.6	17.1 ± 11.8	15.8 ± 5.0	16.1 ± 8.8
LA _{MIN} (mL/m ²)	7.7 ± 2.5	7.8 ± 2.5	10.0 ± 4.9	8.4 ± 5.6	8.1 ± 2.5	7.9 ± 4.7
LA _{PRE-A} (mL)	27.6 ± 7.0	28.0 ± 8.5	51.5 ± 12.8 [†]	* 33.1 ± 16.4	55.2 ± 7.5 [†]	45.6 ± 14.7 [†]
LA _{PRE-A} (mL/m ²)	14.2 ± 3.2	13.8 ± 4.0	26.5 ± 6.1 [†]	* 16.3 ± 7.8	28.5 ± 3.9 [†]	* 22.3 ± 7.0 [†]
Reservoir (mL)	33.7 ± 10.0	29.4 ± 7.2	44.6 ± 6.4 [†]	* 34.4 ± 4.7	39.6 ± 7.7	31.4 ± 5.4
Reservoir (mL/m ²)	17.3 ± 4.6	14.4 ± 3.3	23.0 ± 2.6 [†]	* 16.9 ± 2.3	20.4 ± 4.0	* 15.4 ± 2.3
Passive EV (mL)	20.9 ± 6.3	17.2 ± 7.6	12.6 ± 11.0 [†]	18.4 ± 8.0	0.2 ± 0.3 ^{†*}	1.9 ± 4.2 ^{†*}
Passive EV (mL/m ²)	10.7 ± 3.0	8.5 ± 3.7	6.5 ± 5.7 [†]	9.1 ± 4.1	0.1 ± 0.2 ^{†*}	0.9 ± 2.2 ^{†*}
Conduit (mL)	49.6 ± 12.4	44.1 ± 4.2	64.4 ± 8.3 [†]	57.8 ± 10.8	78.8 ± 14.7 ^{†*}	67.2 ± 7.3 [†]
Conduit (mL/m ²)	25.4 ± 7	21.8 ± 2.8	32.7 ± 4.3 [†]	28.3 ± 4.1	39.8 ± 6.1 ^{†*}	* 33.1 ± 4.1 [†]
Booster (mL)	12.7 ± 5.2	12.1 ± 4.8	32.0 ± 12.8 [†]	* 16.1 ± 8.0	39.4 ± 7.7 [†]	* 29.5 ± 9.5 [†]
Booster (mL/m ²)	6.5 ± 2.5	5.9 ± 2.2	16.5 ± 6.3 [†]	* 7.9 ± 3.9	20.4 ± 4.0 [†]	* 14.4 ± 4.4 [†]
Reservoir EF (%)	69.0 ± 7.6	64.7 ± 10.5	70.8 ± 9.0	69.4 ± 10.1	71.4 ± 9.2	67.8 ± 13.3
Passive EF (%)	42.7 ± 5.2	38.1 ± 13.1	19.1 ± 15.6 [†]	36.8 ± 16.9	0.3 ± 0.6 ^{†*}	5.1 ± 11.6 ^{†*}
Booster EF (%)	45.8 ± 13.3	43.1 ± 9.1	61.9 ± 17.1 [†]	49.5 ± 17.2	71.3 ± 9.2 [†]	65.1 ± 16.1 [†]
PA TDI (ms)	159 ± 15	151 ± 15	148 ± 14	140 ± 16	143 ± 15 [†]	137 ± 17 [†]
Reservoir ε (%)	29.8 ± 4.3	28.4 ± 6.6	32.7 ± 8.4	36.4 ± 5.0 [†]	36.6 ± 9.0	34.7 ± 7.3
Conduit ε (%)	17.6 ± 3.9	17.2 ± 4.5	5.6 ± 4.5 [†]	11.2 ± 9.1	0.3 ± 0.4 ^{†*}	2.7 ± 5.5 ^{†*}
Booster ε (%)	-12.2 ± 2.9	-11.1 ± 2.4	-27.1 ± 10.2 [†]	-25.2 ± 11.3 [†]	-36.3 ± 9.0 ^{†*}	-32.0 ± 8.2 [†]
Reservoir SR (%/s)	1.3 ± 0.3	1.4 ± 0.3	2.1 ± 0.9 [†]	2.3 ± 0.5 [†]	3.2 ± 1.3 ^{†*}	3.0 ± 0.7 [†]
Conduit SR (%/s)	1.6 ± 0.4	1.6 ± 0.3	-	-	-	-
Booster SR (%/s)	1.4 ± 0.4	1.4 ± 0.2	2.5 ± 0.9 [†]	2.4 ± 0.8	4.6 ± 1.2 ^{†*}	3.4 ± 1.3 [†]
T _{TOTAL} (ms)	454.4 ± 96.9	412.4 ± 42.1	311.2 ± 18.3 [†]	292.9 ± 16.6 [†]	260.1 ± 19.6 ^{†*}	* 220.6 ± 23 ^{†*}
T _{NEG} (ms)	233.0 ± 17.1	232.3 ± 18.8	219.2 ± 20.0	213.7 ± 21.7	199.5 ± 22.1 ^{†*}	203.4 ± 13.8
T _{POS} (ms)	713.5 ± 48.1	* 644.7 ± 36.7	530.4 ± 26.3 [†]	506 ± 27.6 [†]	459.6 ± 24.7 ^{†*}	* 424 ± 20.6 ^{†*}
Inter AEMD (ms)	32.4 ± 16.3	32.8 ± 8.0	-	-	-	-
Right AEMD (ms)	13.8 ± 7.5	9.9 ± 4.2	-	-	-	-
Left AEMD (ms)	19.4 ± 10.2	20.9 ± 4.5	-	-	-	-

LAD; left atrial diameter, LAAd; left atrial diastolic area, LA Max; Left atrial maximal volume, LA Min; left atrial minimal volume, LA Pre-A; left atrial pre-contraction volume, Reservoir EF; reservoir emptying fraction, Passive EF; passive emptying fraction, Booster EF; booster emptying fraction, PA TDI; total atrial conduction time, Passive EV; passive emptying volume, ε; cardiac strain, SR; strain rate, T_{TOTAL}; Time to total strain, T_{NEG}; Time to minimal strain, T_{POS}; Time to maximal strain, Inter

AEMD; inter atrial electromechanical delay, Right AEMD; right atrial electromechanical delay, Left AEMD; left atrial electromechanical delay. * denotes a statistically significant difference between H-EA and EA-AF, † denotes a statistically significant difference compared to rest, ♦ denotes a statistically significant difference compared to light exercise, p< 0.05.

Table 6. Right atrial resting and exercise parameters

Variable	Rest		Light (100 bpm)		Moderate (130 bpm)	
	<i>H-EA</i>	<i>EA-AF</i>	<i>H-EA</i>	<i>EA-AF</i>	<i>H-EA</i>	<i>EA-AF</i>
RAAd (cm ²)	21.8 ± 3.4	21.0 ± 3.2	21.0 ± 3.4	20.9 ± 3.7	22.7 ± 3.1	24.9 ± 13.6
RAAs (cm ²)	14.9 ± 3.1	12.8 ± 3.2	12.9 ± 3.9†	12.0 ± 3.2	11.9 ± 3.5†	11.7 ± 3.3
RA _{MAX} (mL)	63.5 ± 11.8	60.4 ± 14.1	62.3 ± 14.7	62.9 ± 17.2	58.4 ± 12.7	54.3 ± 16.8
RA _{MAX} (mL/m ²)	33.0 ± 6.9	30.1 ± 7.8	32.1 ± 6.9	31.0 ± 9.1	30.2 ± 6.8	26.8 ± 8.6
RA _{MIN} (mL)	37.3 ± 5.3	29.4 ± 12.2	29.9 ± 11.1	29.4 ± 12.1	25.2 ± 4.9†	25.4 ± 8.8
RA _{MIN} (mL/m ²)	19.3 ± 2.9	14.7 ± 6.6	15.4 ± 6.1†	14.6 ± 6.1	13.1 ± 2.8†	12.6 ± 4.2
RA _{PRE-A} (mL)	48.8 ± 7.9	41.5 ± 14.3	53.6 ± 14.1	43.8 ± 13.5	58.2 ± 12.4†	54.8 ± 15.1†*
RA _{PRE-A} (mL/m ²)	25.3 ± 4.4	20.7 ± 7.7	27.6 ± 6.3	21.8 ± 6.5	30.1 ± 6.6†	27.3 ± 7.7†
Reservoir (mL)	25.6 ± 9.6	32.4 ± 9.9	31.3 ± 8.6	34.2 ± 5.1	32.9 ± 10.1	28.7 ± 8.9
Reservoir (mL/m ²)	13.4 ± 5.3	15.8 ± 4.4	16.1 ± 4.2	16.8 ± 3.6	17.0 ± 5.1	14.1 ± 4.8
Passive EV (mL)	14.7 ± 8.9	22.5 ± 5.7	8.7 ± 6.2	* 18.7 ± 9.7	0.2 ± 0.6†*	0.7 ± 1.7†*
Passive EV (mL/m ²)	7.6 ± 4.8	10.7 ± 2.5	4.5 ± 3.3	* 9.36 ± 5.1	0.1 ± 0.3†*	0.4 ± 0.9†*
Booster (mL)	10.9 ± 5.8	12.1 ± 5.3	22.6 ± 8.3†	14.4 ± 8.6	32.8 ± 9.8†*	29.4 ± 8.1†*
Booster (mL/m ²)	5.7 ± 3.1	5.99 ± 2.7	11.5 ± 3.9†	* 7.1 ± 4.15	16.9 ± 5.0†*	14.6 ± 4.4†*
Reservoir EF (%)	39.3 ± 9.8	*54.1 ± 14.0	50.8 ± 10.9†	56.2 ± 9.8	55.7 ± 7.9†	53.0 ± 6.1
Passive EF (%)	22.1 ± 9.6	*36.9 ± 11.9	13.7 ± 9.1	* 30.8 ± 14.3	0.3 ± 0.8†*	* 0†*
Booster EF (%)	21.7 ± 9.9	29.7 ± 9.6	42.6 ± 13.4†	32.5 ± 23.2	55.7 ± 7.8†	53.8 ± 5.7†*
Reservoir ε (%)	26.5 ± 8.1	30.8 ± 6.4	-	-	-	-
Conduit ε (%)	13.5 ± 5.7	17.9 ± 5.0	-	-	-	-
Booster ε (%)	-13.0 ± 3.9	-13.0 ± 4.4	-	-	-	-
Reservoir SR (%/s)	1.5 ± 0.45	1.7 ± 0.5	-	-	-	-
Conduit SR (%/s)	0.9 ± 0.3	1.1 ± 0.5	-	-	-	-
Booster SR (%/s)	1.6 ± 0.5	1.3 ± 0.5	-	-	-	-

RAAd; Right atrial end-diastolic area, RAAs; right atrial end-systolic area, RA Max; right atrial maximal volume, RA Min; right atrial minimal volume, RA Pre-A; right atrial pre-contractile volume, Reservoir volume; right atrial reservoir volume, Passive emptying volume; right atrial passive emptying volume, Booster volume; right atrial contractile volume, Reservoir EF; reservoir emptying fraction, Passive EF; passive emptying fraction, Booster EF; contractile emptying fraction, ε; cardiac strain, SR; strain rate. * denotes a statistically significant difference between H-EA and EA-AF, † denotes a statistically significant difference compared to rest, ♦ denotes a statistically significant difference compared to light exercise, p< 0.05.

Table 7: Doppler characteristics at rest and exercise

Variable	Rest		Light (100 bpm)		Moderate (130 bpm)	
	<i>H-EA</i>	<i>EA-AF</i>	<i>H-EA</i>	<i>EA-AF</i>	<i>H-EA</i>	<i>EA-AF</i>
Peak E (cm/s)	0.7 ± 0.1	*	0.8 ± 0.2	1.2 ± 0.2†	1.2 ± 0.2†	-
Peak A (cm/s)	0.6 ± 0.1		0.6 ± 0.1	0.9 ± 0.2†	0.8 ± 0.3†	-
E/A Ratio	1.2 ± 0.2		1.4 ± 0.2	1.4 ± 0.3	1.6 ± 0.3	-
Septal S' (cm/s)	8.5 ± 1.1		9.9 ± 1.4	13.0 ± 2.3†	13.6 ± 1.6†	16.6 ± 3.0†‡
Septal E' (cm/s)	10.2 ± 1.8		11.3 ± 1.6	15.3 ± 1.8†	16.0 ± 1.8†	20.0 ± 4.9†
Septal A' (cm/s)	10.3 ± 2.3		10.1 ± 2.0	16.4 ± 2.4† *	14.0 ± 2.4†	19.6 ± 7.2†
Septal IVCT (ms)	77.5 ± 24		60.6 ± 8.2	49.8 ± 11.5†	46.1 ± 3.5†	34.3 ± 6.6†‡
Septal IVRT (ms)	71.9 ± 15		61.0 ± 14.6	37.6 ± 9.0†	31.8 ± 10.8†	27.3 ± 5.9†‡
Septal E/e'	6.5 ± 1.4		7.2 ± 1.6	7.5 ± 1.6	7.5 ± 1.6	-
Lateral S' (cm/s)	11.1 ± 1.7		12.0 ± 2.2	15.8 ± 5.4†	15.9 ± 1.5	18.1 ± 2.3†
Lateral E' (cm/s)	14.2 ± 2.5		16.6 ± 3.4	19.2 ± 4.4†	19.7 ± 3.3	21.3 ± 5.0†‡
Lateral A' (cm/s)	9.2 ± 2.1		10.2 ± 1.3	13.6 ± 1.7†	13.6 ± 2.4†	16.2 ± 3.7†
Lateral IVCT (ms)	80.0 ± 21		71.1 ± 16.6	49.5 ± 8.2†	53.0 ± 12.0	34.8 ± 4.1†‡
Lateral IVRT (ms)	55.6 ± 11.7		62.5 ± 16.0	31.0 ± 10.2†	38.6 ± 8.9†	25.4 ± 4.6†
Lateral E/e'	4.7 ± 1.0		4.7 ± 0.3	6.3 ± 1.2	6.1 ± 0.6	-
Tricuspid S' (cm/s)	14.2 ± 1.8		14.5 ± 1.2	22.2 ± 2.9†	*19.0 ± 2.8†	25.9 ± 3.2†‡
Tricuspid A' (cm/s)	14.3 ± 4.7		14.3 ± 2.8	24.8 ± 4.6†	21.0 ± 6.1†	31.9 ± 4.7†‡
Tricuspid E' (cm/s)	12.6 ± 2.4		13.3 ± 2.1	18.3 ± 2.7†	17.0 ± 3.0†	22.7 ± 3.8†‡
						22.8 ± 4.3†‡

IVRT; isovolumetric relaxation time, IVCT; isovolumetric contraction time. * denotes a statistically significant difference between H-EA and EA-AF, † denotes a statistically significant difference compared to rest, ‡ denotes a statistically significant difference compared to light exercise, p< 0.05.

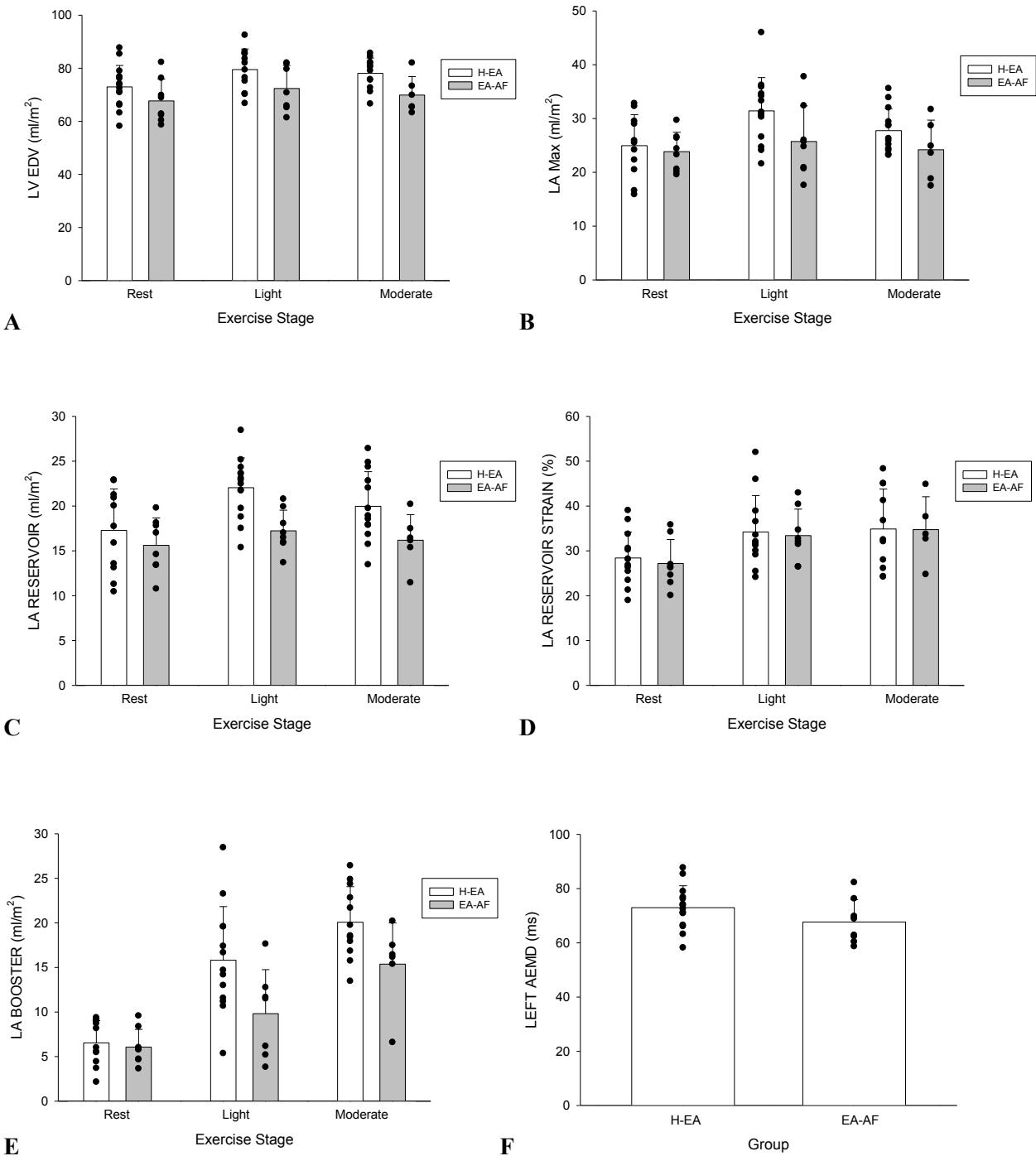


Figure 1. Mean and individual data spread for main endpoints. **A:** Left ventricular end-diastolic volume at rest, light and moderate exercise; **B:** Left atrial maximal volume at rest, light and moderate exercise; **C:** Left atrial reservoir volume at rest, light, and moderate exercise; **D:** Left atrial reservoir strain at rest, light, and moderate exercise; **E:** Left atrial booster volume at rest, light, and moderate exercise; **F:** Left-atrial electromechanical delay at rest.

Discussion

In the present study, cardiac structure and function were assessed using cardiac echocardiography during rest and exercise in middle-aged endurance athletes with and without PAF. To our knowledge, this was the first study to characterize the cardiac response to exercise in endurance athletes with PAF compared to an age-matched and exercise-matched population. The novel findings of the present study are: 1) no differences in resting LV and LA volumes were observed between middle-aged male H-EAs and middle aged male EA-AFs; 2) LV EDV and LA phasic volumes were lower in athletes with PAF at the onset of exercise, with a trend towards greater passive emptying compared to H-EAs and 3) atrial electromechanical function, as measured by AEMD, did not differ between athletes with and without PAF.

Resting Cardiac Structure

Our data confirms our hypothesis that resting LV dimensions and volumes were not significantly different between H-EAs and EA-AFs. The present data supports the findings of Hubert et al. (38) in which male veteran athletes with PAF had no differences in LV anatomy at rest compared to age-matched and sport history matched athletes without PAF. We also observed no differences in resting LA and RA maximal volumes or minimal volumes. This is in line with the findings of Pelliccia et al. (37), in which a similar prevalence of AF was present in athletes with and without atrial enlargement. All participants had LA volumes within the normal range (dilation considered $> 34 \text{ mL/m}^2$) (28) (H-EAs: mean 25.0 mL/m^2 EA-AFs: 22.2 mL/m^2). We suspect that there is significant overlap in volumes between groups due to their similar lifetime endurance training. The discrepancy between the present study and the findings of Hubert et al. may be explained by the extent of AF burden; our endurance athletes with AF all had relatively recent diagnoses (mean 2.2 ± 1.2 years), and those in Hubert et al.'s were unspecified. Since AF can promote further LA remodeling (227), LA dimensions are likely to increase as AF burden extends over many years, particularly when it progresses from paroxysmal to permanent AF (144). It is also unlikely that there was a reduction in atrial volumes in our EA-AF group secondary to detraining, since atrial enlargement persists even after detraining (190). These data suggest that assessment of resting atrial volumes may be an insensitive indicator of risk for PAF, which is congruent with animal models (190), suggesting that atrial enlargement alone is an unlikely cause of PAF in athletes.

Cardiac Parameters during Exercise

A novel aspect of the present study was the use of exercise to probe the cardiac response to elevated metabolic demands. At rest, we observed no differences in LV function or LA function (volumetric or strain). During exercise, LV EDV, LA maximal and LA pre-contractile volumes were lower in athletes with PAF, along with lower LA reservoir and booster volumes. LA enlargement with preserved LA reservoir function is a well-established characteristic of the Athlete's Heart (76), and while our H-EAs demonstrated greater LA phasic volumes during elevated demands, this was not the case for the athletes with PAF. Reservoir volumes are primarily determined by atrial compliance, atrioventricular plane displacement (AVPD) (228), and reduced atrial pressures to facilitate blood flow into the atria (93). Increased atrial stiffness has been observed in clinical populations of AF and heart failure (229, 230), and is associated with reductions in atrial reservoir volumes (76). An impairment of both the reservoir and booster volumes in our PAF athletes may reflect impaired atrial diastolic function and reduced compliance (231), which would compromise the Frank-Starling effect, thereby lowering exercise tolerance. While moderate workloads were well-tolerated, our EA-AFs reached a significantly lower VO₂ during maximal exercise. Although the PAF athletes were engaging in less intense training, it is possible that reductions in the central determinants of maximal oxygen consumption may have influenced this difference. The collective reduction of LA reservoir and booster volumes we observed likely contributed to the lower LV EDVs in PAF athletes at the onset of exercise. A larger LA reservoir and booster volume is advantageous for facilitating LV filling at high heart rates (216) and critical for augmenting cardiac output. Indeed, maximal oxygen consumption is positively associated with greater reservoir function (232).

We also observed a trend ($p=0.07$) for lower LA passive EF and significantly lower RA passive EF in our H-EA athletes, which is contrary to augmented passive atrial function and reduced booster function at low exercise intensities expected in healthy athletes (124). Accordingly, we observed greater passive function in PAF athletes during exercise. Patients with ventricular diastolic dysfunction demonstrate greater reliance on atrial conduit function for passive filling (233), and atrial passive emptying is shown to be greater in hypertensive individuals with PAF as a result of higher atrial pressures (234). It is possible that our PAF athletes' hearts were operating at higher atrial pressures and a greater pressure gradient, thereby increasing passive EF. This observation may reflect an adapted state to maintain SV in the absence of atrial booster function

during episodes of AF (235), or to compensate for impaired atrial compliance and reduced reservoir volumes. While LA enlargement is a marker of both the severity and chronicity of LA pressure elevations (236, 237), it is likely that we did not observe changes in LA enlargement in the EA-AFs due to the recency of their PAF.

Collectively, our findings suggest that in the initial stages of PAF, no traditional markers of cardiac dysfunction are present and cardiac function is preserved. Notwithstanding, differences in LV volumes and atrial phasic volumes can be revealed during submaximal exercise, which may be a manifestation of atrial stiffening. We observed no significant differences in other functional parameters (EF, LA ϵ or SR) during exercise, despite that reduced reservoir EF, booster EF (238) and reservoir strain (38) are significantly related to the development of AF and are considered to be superior measures for predicting AF (38). Follow-up is warranted to determine whether decreased phasic volumes may have functional implications in the future.

Atrial Electro-mechanical Function

Inhomogeneous propagation of electrical impulses is a well-established feature of atria disposed to fibrillate. A prolongation in AEMD has been useful for identifying and predicting onset of AF in those with presence of other cardiovascular disease (162, 220). Atrial electromechanical delay has not previously been studied beyond healthy sedentary populations or populations with comorbidities. In the present study, AEMD was assessed during rest at the lateral annulus, mitral annulus, and tricuspid annulus for determination of inter-AEMD, intra-left and intra-right AEMD. Contrary to our hypothesis, there were no differences in resting AEMD between athletes with and without PAF. Whether this finding would have persisted with the onset of exercise would have been valuable to assess, however due to poor distinct Doppler waves and P waves, AEMD was not acquired. In a previous study, ventricular electromechanical delay increased following intensive endurance exercise in a cohort of athletes, which was related to a decline in peak systolic tissue velocities (44). We also assessed total atrial conduction time during exercise using the PA-TDI interval, as this has been successful for predicting new onset AF and is associated with the degree of atrial fibrosis (225). In the present study, there were no significant differences between our H-EAs and EA-AFs in PA-TDI interval at rest, light, or moderate exercise.

It is possible that our failure to detect differences in AEMD and PA-TDI between our athletes with and without PAF is due to the relatively short-term AF burden for our EA-AF group. Indeed, the extent of atrial fibrosis is higher in patients with permanent AF compared to PAF (239). Moreover, AEMD and PA-TDI have been successful in the prediction and identification of AF in populations that typically have accompanying comorbidities. Thus, atrial fibrosis and the associated electro-mechanical delay in those populations may reflect remodeling not specific to PAF.

Limitations

This study is not without its limitations. Our sample size was small, limiting our ability to perform multivariate analyses. Secondly, at the onset of exercise, the ECG tracing produced fusion of the P wave and T wave, compromising the identification of the onset of the P wave in some cases, and potentially increasing the error in determining our absolute measures of atrial pre-contractile volume at elevated heart rates. However, we applied a consistent correction to all participants by extrapolating the resting P wave duration to the exercise ECG to determine each individual's relative onset of the P wave, ensuring consistency within and between groups. While two-dimensional echocardiography is well correlated with cMRI and 3-D echo, cardiac volumes can be significantly underestimated, which may have impacted our athletes' atrial volumes. LA strain analysis is also an emerging methodology, and our analysis was performed using techniques designed for the ventricles (240). Visual verification was used to ensure adequate wall tracking, yet imaging quality was compromised for the RA during exercise. Therefore, we were unable to determine if any differences in deformation of the RA may have occurred during exercise. Lastly, while our athletes with PAF remained highly active, almost all had reduced their training intensity compared to the H-EA group, which may have influenced our VO₂ max data.

Clinical Implications

The clinical implications of the present study are twofold. Firstly, traditional markers of AF risk used in sedentary populations may have limited utility in athletes. LA enlargement is one of the most significant risk factors for PAF, however our athletes with AF had LA anatomy that was comparable to athletes without AF burden. Moreover, AEMD did not identify PAF athletes from non-PAF athletes, suggesting this measure may be limited in athletic cohorts who are free of other

cardiovascular disease. Whether these measures would be useful in PAF athletes who are further down the remodeling process is yet to be confirmed.

Secondly, the results of our study suggest that cardiac function in response to submaximal exercise appears to be altered in PAF athletes. Left atrial phasic volumes were lower in PAF athletes, which translated to lower LV EDVs during light and moderate exercise. While measures of cardiac strain and diastolic function were not altered during exercise, reduced atrial phasic volumes may serve as markers of PAF in an athlete. Given that volumes had significant overlap between groups at rest, it is important to investigate differences that may be revealed under elevated demands. In athletes with reduced phasic volumes during exercise, follow up would be warranted to identify whether function is altered in the future.

Conclusions

In the present study, we investigated the cardiac response to light and moderate exercise in middle-aged endurance athletes with and without PAF. We observed no differences in left ventricular and left atrial resting volumes or function between groups. At the onset of exercise, LV EDV, LA reservoir, and LA booster volumes were reduced in athletes with PAF. Passive emptying trended towards being augmented in athletes with PAF, and may reflect increased atrial pressures and atrial stiffening. Despite differences in atrial phasic volumes, diastolic function and cardiac strain was preserved during exercise in PAF athletes. Furthermore, AEMD was not different between cohorts. The findings of this study suggest that resting atrial volumes and electrical-mechanical coupling in athletes with PAF are similar to healthy, age- and exercise-matched athletes, though the assessment of cardiac parameters during exercise may unmask subtle evidence of left atrial stiffening. Future investigation is necessary to determine whether atrial stiffening is a result of PAF in athletes, or if reductions in phasic volumes occur prior to disease onset.

Chapter IV: Extended Discussion & Conclusions

4.1 Technical Contributions

The following individuals contributed directly to this project:

1. **Dr. Jack Goodman:** contributed intellectually to the design of this project and editing of this document.
2. **Dr. Kim Connolly:** contributed intellectually to the design of this project.
3. **Dr. Paul Dorian:** contributed intellectually to the design of this project.
4. **Dr. Robert Bentley:** contributed to the intellectual design of this project and assisted with data collection during exercise testing and statistical analysis advice.
5. **Maggie Dohert:** was responsible for acquiring echocardiographic images.
6. **Meghan Glibbery:** contributed to data collection during exercise testing.

I contributed intellectually to the design of this study, was responsible for the recruitment of participants, data collection, and was solely responsible for the analysis of echocardiographic images from the study. I was the primary author of this document.

4.2 Subjects

Our athletes were recruited by several means including study poster advertisements to cycling, running and triathlon clubs in Ontario, and through collaborations with cardiologists in the GTA who identified suitable candidates that were interested in participating in the study. We recruited on the basis that athletes would have a history of long-standing vigorous endurance exercise (upwards of 10 years) and participation in competitive events. In this population, defining ‘vigorous’ exercise can be challenging, particularly when defining the intensity of exercise. The cut off for vigorous exercise as defined by the ACSM (≥ 6 METS) (241) has limited relevance for athletes who are routinely engaging in intensities upwards of 12 METS. Therefore, the use of overall volume (hours, days per week, RPE) served as a more meaningful method of characterizing participants’ exercise-training history. As a whole, our athletes were engaging in 5.3 ± 1.5 days, and 8.0 ± 4.7 hours of training per week, though it is noted that our PAF athletes were engaging in a lower intensity, as characterized by TRIMPs (considers duration and rating of perceived exertion).

During the recruitment process of the PAF population, we received approximately 30 responses, in which 6 had already received a cardiac ablation, and 14 were identified as eligible. Four of 14 were lost to follow-up, and the remaining 10 participated in the study. Interestingly,

while we were recruiting male athletes with PAF, we received several responses from female endurance athletes who were diagnosed with PAF and were interested in participating. It is possible that with a greater number of females partaking in endurance sport in the last few decades, the prevalence of exercise-induced PAF may actually be comparable to that of males.

When characterizing our athletes with PAF, participants were asked to describe their symptoms and triggers for episodes of AF. Responses ranged from having experienced a few episodes, to numerous episodes weekly. Approximately 50% of the athletes described the onset of their episodes to be related to exercise, which suggests PAF of sympathetic origin, and the remaining 50% described symptoms occurring at times of rest, which is likely of vagal origin. Almost all the athletes considered their AF to be restricting their ability to engage in usual training regimens, and were undoubtedly disappointed by this limitation. Our PAF athletes consisted of 3 runners, 5 cyclists, and 2 triathletes, which was similar to our distribution of H-EAs (7 runners, 5 cyclists and 2 triathletes). Of the 10 PAF athletes recruited, 5 reported prescribed medications that ranged from beta-blockers to blood thinners, though many reported discontinuing their use. Four of the 10 athletes had received cardioversions within the past two years, and 3 were anticipating a cardiac ablation procedure in the near future. During testing, all exercise was well-tolerated and no adverse events were experienced; one athlete was out of sinus rhythm, and this data was not used for analysis.

4.3 Data Analysis

Resting images were clear and analysis was feasible in all participants. Most of the images were left side focused, which may have resulted in underestimation of right-sided parameters. Images that were off axis were excluded from analysis. Prior to completing any analysis, intra-observer reliability was confirmed using intra-class correlation coefficients for main end points. Mean ICCs were all between 0.8 and 0.99. Results are presented in Appendix L.

Upon initiation of exercise, particularly at a HR of 130, image quality was reduced. Moreover, at the onset of exercise, ECG quality was severely reduced. At a heart rate of 100 bpm, several participants had fusion of the P wave and T wave making the atrial pre-contractile volume difficult to discern. This occurred in all participants at 130 bpm. Accordingly, we used individual average resting P wave durations as our reference point to estimate the onset of the P wave during

the exercise stages for analysis. We believe this was a suitable solution as P wave duration is relatively stable from rest to exercise (242), and this method was consistently used for all participants in both groups making relative comparisons possible.

Atrial strain acquisition was particularly difficult especially as our software was designed for LV assessment. RA strain at exercise was severely limited given that we had left focused images, causing a high degree of image dropout. At rest, our atrial strain profile followed the typical atrial phasic strain curve reported in previous literature (243). There are limited reports of atrial strain during exercise, and we have yet to find any reports visually describing the atrial strain profile during exercise. Our absolute strain profile at 130 beats had maximal strain (conduit) values of 0. We are unable to provide a reason for why this was the case, however despite the abnormality in this strain curve, relative comparisons between groups can be made. We defined our strain profile at exercise similarly to our method for rest; peak negative was defined as ‘booster strain,’ our positive peak as ‘conduit strain,’ and the absolute difference between these peaks as ‘total strain’ or ‘reservoir strain’ (Figure 8).

Atrial electromechanical delay also proved to be limited due to our ECG tracing. In several participants, the resting ECG did not have a clear P wave resulting from noise interference. Accordingly, this impacted our ability to determine the onset of the P wave for AEMD measurement. In order to resolve potential measurement errors and variability, an average P wave duration was determined for each participant, and then used to determine the onset of the P wave by measuring in the opposite direction from the end of the P wave (return to baseline). While this may have influenced the absolute numbers, the relative relationships between inter AEMD, left AEMD, and right AEMD would be comparable given the consistency of the method used for all participants.

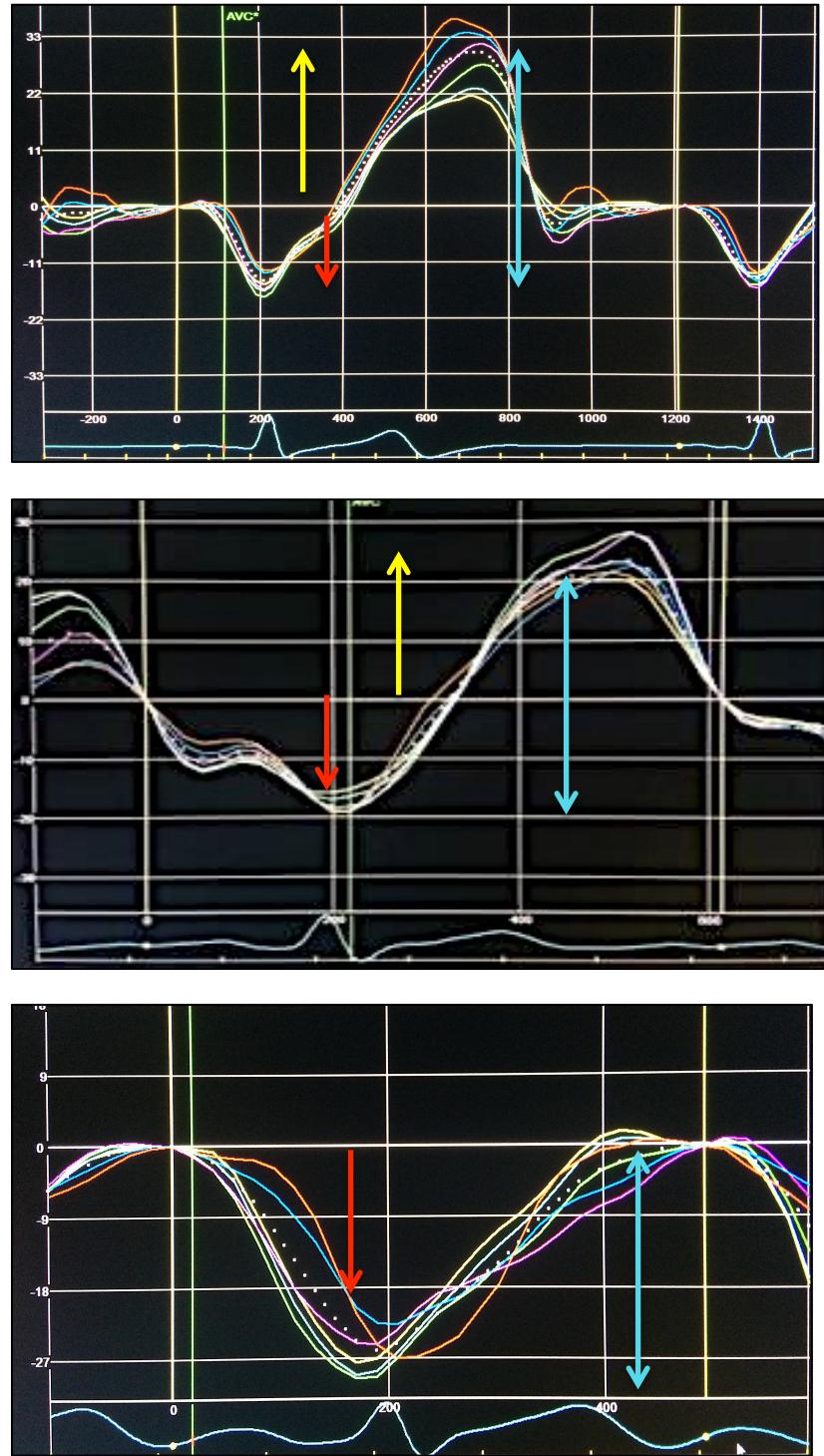


Figure 8. Atrial strain profile, at rest, light exercise (100 bpm), and moderate exercise (130 bpm), respectively. The negative peak (red arrow) was defined as booster strain, the positive peak (yellow arrow) was defined as conduit strain, and the absolute difference (blue arrow) was defined as reservoir strain.

4.4 Additional Results and Discussion

In accordance to our hypothesis, atrial volumes were similar between groups, and were unsuccessful for distinguishing PAF athletes from non-PAF athletes. Interestingly, one of our EA-AF participants had been diagnosed with PAF for considerably longer than the average number of years, and had a family history of AF. Resting cardiac volumes were significantly larger in this participant than all other PAF athletes (LA_{MAX} : 44 mL/m^2 , RA_{MAX} : 38 mL/m^2) and there was evidence of significant bi-atrial enlargement in both minimal and pre-contractile volumes. Whether this atrial enlargement was a cause or a consequence of AF cannot be determined with confidence, though our other athletes with PAF had normal atrial sizes, suggesting a longer burden of PAF contributed to atrial dilation. Ventricular parameters were within the average of our sample. Resting LA reservoir and booster volumes were larger in this participant compared to the PAF group (Reservoir: $14.4 \pm 3.3 \text{ mL/m}^2$ vs. 29 mL/m^2 , Booster: $5.9 \pm 2.2 \text{ mL/m}^2$ vs. 11 mL/m^2), though EFs and strain were within the average. In contrast, despite having a larger RA maximal volume, RA phasic volumes appeared to be within the range of our sample volumes, suggesting that the LA may be affected by to a greater extent.

For our second hypothesis, there were significant differences in cardiac function at rest and exercise between H-EAs and EA-AFs. While there were no significant differences in resting LA function, we did note that the PAF athletes had greater RA phasic EF at rest. We did not observe any differences in RV resting function that could be contributing to this difference. It is possible that the lower resting EF in H-EAs may reflect greater atrial economy (16), however no differences at elevated demands were noted. At the onset of exercise, LV EDV was reduced in the EA-AFs, along with lower LA reservoir and booster volumes, and a trend towards greater passive EF ($p=0.07$). The reductions in LA reservoir and booster volumes that we observed in the PAF athletes would suggest an increase in atrial stiffness that prevents the atria from effectively filling and contracting. We noted no differences in diastolic parameters of LV function, though measurement of pulmonary pressures in our cohorts would be warranted to determine whether atrial pressures were indeed elevated in the PAF athletes. There were also no differences in RA reservoir or booster volumes at moderate exercise loads, suggesting changes in atrial compliance may occur primarily in the LA. Although, passive emptying was greater in the RA of PAF athletes, which may imply increased atrial pressures precede any changes in atrial stiffness.

In the athlete who had a significantly longer burden of PAF, despite having larger LA maximal and minimal volumes, phasic volumes were similar to the average. Although, LA reservoir EF was lower compared to the mean of either group during light exercise (Reservoir EF H-EAs: $70.8 \pm 9.0\%$ and EA-AFs: $69.4 \pm 10.1\%$, versus 53%). We also observed a greater RA booster volume compared to the H-EAs and EA-AFs, accompanied by a reduced RA passive EF during light exercise in this participant. However, all other indices of function and strain values were similar to the group averages. Accordingly, this observation could suggest that irrespective of having larger volumes, function appears to be well preserved despite a long-standing burden of PAF.

Our final hypothesis regarding AEMD was rejected, and we accepted the null hypothesis. We found no differences in resting inter-AEMD or intra-left and right AEMD. It is possible that because our athletes with PAF were free of other traditional cardiovascular risk factors, their AF may instead relate to electrophysiological triggers in structurally normal atria, as opposed to triggers in diseased atria with stretch and fibrosis (244). Interestingly, in the athlete who had a longer burden of PAF, left-AEMD was longer compared to either H-EAs or EA-AFs (27 ms), suggesting a greater burden of the disease may relate to conduction abnormalities. However, LA maximal size was also larger in this participant. PA-TDI at all stages was also consistent with the averages of both groups, implying atrial conduction may not have actually been altered despite a significant number of years of AF burden. It is noteworthy that while this individual had both RA and LA enlargement, only left-AEMD was prolonged. To establish whether this is related to LA fibrosis would require further assessments.

4.5 Limitations

The assessment of cardiac function during submaximal exercise is a unique and novel addition to the literature surrounding AF in athletes, and is considered to be a strength of the present study. However, the inclusion of a sedentary healthy age-matched cohort may have improved the design of this study. The risk for AF is substantially higher in athletes compared to healthy sedentary individuals, and it is possible that our healthy athletes may have been below the threshold for detecting AF, thus skewing any possible comparisons with the PAF athletes. Although, it is noted that for the purposes of answering our specific research questions, the most appropriate control was a training-history matched healthy population.

Secondly, several of the PAF athletes had decreased the intensity of their training following diagnosis of AF. Therefore, this may have influenced our ability to draw any conclusions that any differences between groups was the result of PAF and not simply the effect of lower fitness levels (as exemplified by the lower VO₂ max). The effect of detraining in athletes is variable, though the literature suggests cardiac dimensions typically persist following several years (60). Long-term cessation of exercise may result in a reduction of up to 20% in VO₂ max and reductions in blood volume and cardiac output of approximately 7% (245). However, it is important to acknowledge that our athletes with PAF were performing an average of 8 hours per week of exercise, which is well beyond the recommended exercise guidelines of 150 minutes. Thus, we do not consider our PAF cohort to be detrained, and any reductions in performance and cardiac dimensions would likely be minimal. Moreover, our PAF athletes had a similar 10-year vigorous exercise history compared to our healthy athletes, which highlights the similar foundation of exercise training between groups that allows comparisons to be made.

Another significant limitation that must be acknowledged is the use of two-dimensional echocardiography. Although 2-D echo is well correlated with 3-D echo and cMRI, it significantly underestimates cardiac volumes (107) and may have influenced our athletes' atrial volumes which all fall within the 'normal' range. Several of our images were acquired with a left-side focus and significantly limited our ability to complete analysis of right atrial and ventricular parameters, particularly during exercise. In addition, most of the software available for completing cardiac analysis has been designed for the left ventricle and influenced our ability to complete speckle tracking analysis for the thin walled atria. Moreover, there exists considerable inter-vendor variability (211). While strain based techniques may be highly sensitive to cardiac dysfunction prior to changes in volumes (246), two-dimensional speckle tracking is limited by its inability to track tissue motion in three dimensions, which may have influenced some of our results if atrial contractility was affected in an area outside of our region of interest. Finally, whether speckle tracking has the ability to accurately assess atrial pressures remains uncertain, and the use of more robust techniques is therefore warranted.

4.6 Future Directions

The present study was one of the first to characterize cardiac anatomy and function in PAF athletes compared to an age-matched and training-matched population of healthy endurance

athletes at both rest and submaximal exercise. Although our sample size was small, our findings set the foundation for future work to investigate whether reduced atrial phasic volumes are the result of PAF or if they are symptoms that precede disease onset.

In order to develop a more robust understanding of the relationship between endurance sport, cardiac function, and AF, a longitudinal study would be warranted. Specifically, periodic assessment of our endurance athletes with PAF would provide insight into whether cardiac dysfunction follows with disease progression. Alternatively, a prospective study of a large cohort of young endurance athletes (in which a small percentage would likely develop AF) could allow identification of phenotypic predictors for arrhythmias. Assessment of cardiac parameters just prior to the development of first AF episodes would be most appropriate for determining any causal markers.

While echocardiographic assessment is relatively easy to administer, the use of cMRI would be beneficial for acquiring gold standard images and characterizing the cardiac phenotype of athletes with PAF. Techniques available for quantifying presence of atrial fibrosis or scar tissue would be necessary. Some of our findings both support and contradict the possibility of intra-atrial fibrosis, and having MRI data would significantly strengthen our understanding of exercise-induced AF. Similarly, the addition of heart rate variability measures would also strengthen the ability to make comparisons regarding underlying physiological differences between healthy athletes and athletes with AF, and should be incorporated in future studies.

Our study investigated cardiac function during submaximal exercise, however we observed lower VO₂ values during maximal exercise testing in our PAF athletes. While cardiac imaging is significantly more difficult at heart rates above 130 bpm, imaging at vigorous intensities (~150 bpm) could elucidate whether this finding is attributable to impairment in cardiac function. Moreover, endurance athletes are routinely subjected to higher exercise intensities, and the cardiac response to vigorous exercise may be more applicable for determining whether this is workload is tolerable in athletes with PAF.

An additional aspect that would be useful to include in future analysis would be the assessment of cardiac parameters following intense exercise. The literature exploring intense exercise and cardiac performance describes transient reductions in ventricular function (conduction and strain) following marathon competitions in athletes. Accordingly, investigation of the atrial

phasic response and AEMD post intense exercise in athletes with PAF would be an important addition for understanding the burden of atrial fibrillation in this population.

Lastly, several of our athletes were planning to undergo a cardiac ablation in the near future. Future investigation of cardiac parameters pre and post cardiac ablation would provide valuable insight into the changes in cardiac function that accompany this procedure and whether it is an efficacious option for athletes who seek to continue a high level of training.

4.7 Conclusions

In the present study, we investigated the cardiac response to light and moderate exercise in middle-aged endurance athletes with and without PAF. Contrary to our hypothesis, we observed no differences in resting ventricular or atrial size and function, suggesting that the assessment of cardiac parameters at rest is insufficient for identifying endurance athletes with PAF. At the onset of submaximal exercise LV EDV, LA reservoir, and LA booster volumes were reduced in athletes with PAF, and greater atrial passive emptying accompanied these changes, which may be reflective of altered atrial compliance. While traditional prognostic measures did not identify any differences between healthy endurance athletes and athletes with PAF, reductions in atrial phasic volumes during elevated demands may be a manifestation of disease. Future work should investigate the temporal relationship of these alterations to determine whether evidence of atrial stiffening occurs in advance of PAF.

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Appendix A: Consent to Participate in a Research Study



CONSENT TO PARTICIPATE IN A RESEARCH STUDY

TITLE	Atrial Electromechanical Function in Middle Aged Endurance Athletes With and Without Atrial Fibrillation
PRINCIPAL INVESTIGATOR	Dr. Paul Dorian, MD, St. Michael's Hospital Department Director, Division of Cardiology,
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STUDY FUNDING	Canadian Institute of Health Research (CIHR)

Conflicts of Interest

The principal investigator, co investigators, and research staff do not have any conflicts of interest, financial or otherwise, related to this study or its outcome.

Introduction

You are being asked to consider taking part in a research study. Please read this explanation about the study and its risks and benefits before you decide if you would like to take part. You should take as much time as you need to make your decision. You should ask the study doctor or study staff to explain anything that you do not understand and make sure that all of your questions have been answered before signing this consent form. Before you make your decision, feel free to talk about this study with anyone you wish. Participation in this study is voluntary.

Background Information

Regular physical activity, including vigorous exercise, lowers the risk for cardiovascular disease. Despite the widely accepted cardioprotective benefits of exercise, atrial fibrillation (AF) is approximately 5 times more common in long-standing endurance-trained athletes compared to active healthy individuals. With long standing endurance exercise training, significant changes in heart size and function occur. Highly trained endurance athletes generally have larger hearts and greater pump function at rest and during exercise. Both the upper (atria) and lower (ventricles) chambers of the heart enlarge and become more efficient. These adaptations have been termed the 'athletic heart syndrome'. While these changes are beneficial for endurance exercise performance, the atrial and ventricular remodeling that occurs with exercise is thought to increase the risk of developing heart rhythm problems, specifically AF. Despite recent interest in exercise-induced AF, there have been no studies examining the cardiac structure and function both at rest and during exercise in AF patients who continue to exercise intensively or at reduced levels since diagnosis, compared to endurance athletes who are free from AF. Our objectives are to research the cardiac structure and function of endurance athletes with and without AF at rest and during exercise.

Purpose

The purpose of this research study is to: 1) Characterize the exercise response of endurance athletes with AF. 2) Identify structural and functional differences at rest and during exercise in endurance athletes diagnosed with AF and age-matched healthy endurance athletes.

Procedures

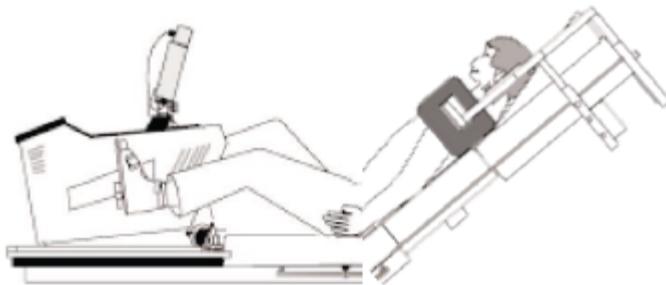
For our research study, we are recruiting a total of 34 participants, in which 17 participants will be endurance athletes with Atrial Fibrillation, and 17 participants will be endurance athletes without Atrial Fibrillation.

Your full participation in this study will require you to complete two sessions in total if you are an athlete with AF, lasting approximately 2 hours each. In addition you will be required to wear an ambulatory heart rhythm monitor for a 48 hour session after your visit (i.e at home). If you have not been diagnosed with AF, you will only be required to complete one visit, lasting 2 hours. Over the duration of the study you will complete basic measures of height and weight, followed by a submaximal exercise test with cardiac imaging, and maximal graded exercise test at the Heart Health Laboratory at the University of Toronto, Goldring Center (100 Devonshire Place, Toronto). Upon the completion of this session, you will complete a resting electrocardiogram (an assessment of the electrical rhythm of your heart), imaging of your heart at rest using Magnetic Resonance Imaging (MRI) (a type of test that uses radio waves and magnetic field to create an image), and a fitting for a 48 hour heart rhythm assessment at St. Michael's Hospital (30 Bond Street, Toronto). A more detailed account of what will happen over the course of the study is described below. **Note:** If you are an endurance athlete without a diagnosis of Atrial Fibrillation, you will only be required to complete visit one, as you have previously completed cardiac imaging as a part of your participation in the Athlete's Heart Study (visit 4).

Visit One: Prior to this visit, you will have received this consent form, as well as a 2-week Exercise Diary that can be completed at home and sent back (by email or hardcopy) to one of the study investigators. During this visit, you will meet with one of the study investigators in the lobby of the Goldring Center for High Performance at the University of Toronto. When you arrive, a researcher will show you the laboratory space and explain the research procedures during each visit. Your height, weight, heart rate, and seated blood pressure will be measured. These procedures are common for research of this nature. You will also complete a physical assessment screening questionnaire. You may refuse to answer any questions asked. The results of the tests/questions at the screening visit help the researchers to decide whether you can continue in this study.

You will next undergo a short but detailed resting ultrasound (pictures taken using sound waves) assessment of your heart, which will allow us to measure the resting function of your heart.

With you lying on your back in a semi-supine position (shown in figure below), you will then be fitted to a specialized bed-bicycle, which consists of a separate ergometer/bike and a computer display that contains preset and customizable exercise protocols, in which workload is increased in stages. To maintain cadence (rhythm) during exercise, the computer has a light indicator which indicates whether you are pedaling too fast or too slow to produce the desired workload.



During exercise, you will be monitored continuously by a 12 lead electrocardiogram (ECG). In this test, patches attached by wires to a machine will be put on your chest, so that the machine can record the pattern of your heart beats. In some cases we may need to trim or shave your body hair. We will also monitor your blood pressure and complete a heart ultrasound for measurement of heart volumes and function.

The test will be stopped if you notice fatigue, any chest pain, shortness of breath or undergo an episode of AF. The test will also be stopped if there is a fall in your blood pressure of more than 10 mm Hg from baseline or if your systolic blood pressure is less than 90 mm Hg.

The exercise protocol will consist of 4 stages, including a resting stage, a 2-minute warm-up stage, and two 5-minute stages of submaximal exercise at step-wise increasing

intensities based on achieving a heart rate of 100-130 beats per minute. In each of the resting and submaximal exercise stages, following 2-minutes to achieve steady state, data collection will begin. Echocardiographic assessment will be performed by a trained sonographer. The risk for healthy volunteers is minimal (0.05%) during an echocardiography test. Among a large series of subjects without known disease, there were approximately < 1 to 5 serious complications (including heart attack or other events requiring hospitalization) and 0.5 deaths for every 10,000 tests performed. As stated, during each of these stages we will obtain readings from the 12 lead ECG, as well as information from brief echocardiographic assessments. You will not feel any discomfort during these measurements.

Prior to starting your maximal exercise test, you will receive 30 minutes of seated rest. During this time, you will have the opportunity to complete the Lifetime Physical Activity Questionnaire. You will next be familiarized with a motorized treadmill used to determine your maximal oxygen consumption (VO₂max). Once accustomed to the treadmill, you will be equipped with a Polar heart rate monitor and a mouthpiece/headset attached to a metabolic cart. A maximal exercise test will then be performed using standard lab protocol, and the metabolic cart will measure breath-by-breath recordings of gas volumes and concentrations. The exercise protocol is designed to take no longer than 15 minutes.

Overall, this entire visit duration is expected to last 2 hours from start to finish. If at any stage of the study you feel unwell or would like us to stop, then please let us know and no further test will be performed.

Visit Two (for athletes with AFib only):

Prior to this visit, you will receive blood test requisition forms for you to have a blood test at any local laboratory or clinic of your choice. This blood test will tell us about your kidney function- we need to ensure you have normal kidney function prior to having special cardiac imaging (with contrast dye). Once you have received your blood test results, you will be able to proceed with visit 2. Blood test results will be kept in your participant file for record of clearance for cardiac imaging.

During this visit you will meet with one of the investigators in the lobby St. Michael's Hospital and will proceed together to the electrophysiology lab. You will receive a resting signal averaged electrocardiogram that will assess heart rhythm.

Following this, you will proceed to the cardiac imaging department where you will undergo resting cardiac imaging using Magnetic Resonance Imaging. An MRI is a non-invasive test that takes 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. Contrast dye is 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 allergic to iodine. Gadolinium is different from 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 contrast, or you do not wish to use this dye, it will not be given to you.

Following the completion of the MRI, you will be fitted with a special heart rhythm monitor (Holter monitor) to assess your heart rhythm continuously at home for a 48 hour time period (48 hour continuous ECG monitor). This can be returned within a 1 week period at a time that is convenient for you. During the 48 hour monitoring period you will be asked to refrain from exercise, however caffeine and alcohol consumption will not be restricted during this period. Once you have been fitted with a Holter monitor and you have had a chance to rest and ask any questions about the procedures, you are free to leave. You will be given ample time to review these procedures to make sure you understand what is involved before we commence the study procedure.

Overall, the second visit will take approximately 2 hours.

Calendar of Visits

Boxes marked with an X show what will happen at each visit:

Visit	Questionnaire	Exercise	Holter	ECG	Ultrasound or MRI	Time
Screening/Cardiac Assessment/ Maximal Exercise test (visit 1)	X	X		X	X	2 hours
Electrocardiogram/ Cardiac Imaging (visit 2)				X	X	2 hours
48-Hour Period After Visit Two			X			

Reminders

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

- You should not consume any food, caffeine or alcohol 12 hours before your study visits
- No prolonged exercise on day before study visits
- Tell study staff anything about your health that has changed

- Tell your study team if you change your mind about being in this study

Risks Related to Being in the Study

All of the study procedures are routinely performed at the University of Toronto and St. Michael's Hospital and are associated with minimal risk. The risk related to cardiopulmonary exercise testing is low. Among large series of subjects without known disease, serious complications (including myocardial infarction or other events requiring hospitalization) have been reported to occur in <1 to as many as 5 per 10,000 tests (0.05%). Furthermore, among a large series of subjects with cardiac arrhythmias, serious complications have been reported to occur in 2% of patients undergoing exercise testing, but the risk is likely much lower in lone AF. The risk related to submaximal exercise is also very low; it is also lower in those performing regular exercise. In the case of undiagnosed coronary artery disease, you may notice chest discomfort during exercise and there may be electrocardiographic abnormalities that we can detect on the monitor. In such circumstances, we will stop the exercise and let you recover. It is also possible that you may experience sore muscles after exercise or the following day but this is temporary.

There are no known risks associated with Holter monitoring or use of a 12 lead ECG, although your skin may be somewhat irritated from the electrodes and skin cleaning.

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, you may receive a prescription for lorazepam (Avitan, 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 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. Additionally, when used repeatedly, Gadolinium has been shown to accumulate in the brain, however the effect on the brain is not known at present.

Benefits to Being in the Study

You will not receive any direct benefit from being in this study. You may have an interest in knowing your fitness level (VO₂max), and this information will be made available to you. Information learned from this study may help to further our understanding of the resting and exercise cardiac function and structure of endurance athletes with and without AF.

Voluntary Participation

Your participation in this study is voluntary. You may decide not to be in this study, or to be in the study now and then change your mind later. You may leave the study at any time without affecting your current or future care. You may refuse to answer any question you do not want to answer, or not answer an interview question by saying “pass”.

Alternatives to Being in the Study

You do not have to join this research study if you do not wish. Because this study is not looking at ways to provide medical treatment to you, the alternative to taking part in this study is not to take part. Whether you choose to take part in this study or not, you will receive the same standard and level of care at St. Michael's Hospital.

Confidentiality

If you agree to join this study, the study doctor and his/her study team will look at your personal health information and collect only the information they need for the study. Personal health information is any information that could be used to identify you or identifying information with a link to some aspect of health information - this includes your:

- name,
- address,
- date of birth,
- new or existing medical records, that includes types, dates and results of medical tests or procedures.

Any personal identifying information that is recorded or stored for study purposes will be “de-identified” by replacing your personal identifying information with a “unique code/number”. The principal investigator is in control of the study unique code key, which is needed to connect the study data to you.

The information that is collected for the study will be kept in a locked and secure area

at both the University of Toronto, or St. Michael's Hospital for 7 years. Only the study team or the people or groups listed below will be allowed to look at your records. Your participation in this study also may be recorded in your medical record at this hospital.

The study team may also collect information from your medical record. The information that will be collected is described in the Study Visits and Procedures section. The study personnel will use this information to conduct the study.

By signing this form, you are authorizing access to your personal health information by the study personnel, the Research Ethics Boards (St. Michael's Hospital and the University of Toronto), government regulatory authorities or funding agency (CIHR). 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.

Participation and Withdrawal

Participation in any research study is voluntary. 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 decide to participate in this study you can change your mind without giving a reason, and you may withdraw from the study at any time without any effect on the care you and your family will receive at St. Michael's Hospital. If you choose to withdraw from this study at any time, please contact a member of the study team.

Your participation in the study may be stopped without your consent for the following reasons:

- if continuation in the study appears to be medically harmful to you;
- if it is discovered that you do not meet eligibility requirements
- if the study is cancelled

If you decide to leave the study, the information about you that was collected before you left the study will still be used. No new information will be collected without your permission.

In Case You Are Harmed in the Study

If you become ill, injured or harmed as a result of taking part in this study, you will receive care. The reasonable costs of such care will be covered for any injury, illness or harm that is directly a result of being in this study. In no way does signing this consent form waive your legal rights nor does it relieve the investigators, sponsors or involved institutions from their legal and professional responsibilities. You do not give up any of your legal rights by signing this consent form.

Expenses Associated with Participating in the Study

You will not have to pay for any of the procedures involved with this study.

You will be reimbursed \$50 for transportation and time upon completion of both study visits. If you wish to voluntarily withdraw from the study at any point and for any reason after completion of Visit 1, you will receive \$25 remuneration for your time. Should you experience an adverse response during Visit 1 (ex. injury) that prevents you from completing the visits, you will receive \$25 but no further compensation. If you must involuntarily withdraw during Visit 2, you will be entitled to full compensation (\$25 for both

visits). **Note:** If you are an endurance athlete without AF, you will only be required to complete 1 visit (i.e compensation will be \$25).

Study Results

The results of this study may be presented at a scientific conference or published in a scientific journal. If you are interested in obtaining the results of the study, you can contact the study doctor. We expect that the results of the study will be available in approximately 1-2 years. You will never be personally identified in any publication, report, or presentation that may come from this study.

Questions About the Study

If you have any questions, concerns or would like to speak to the study team for any reason, please call: Dr. Paul Dorian at -----.

If you have any questions about your rights as a research participant or have concerns about this study, call Dr. David Mazer, Chair of the St Michael's Hospital

Research Ethics Board (REB) or the Research Ethics office number at 416-586-4875. The REB is a group of people who oversee the ethical conduct of research studies. These people are not part of the study team. Everything that you discuss will be kept confidential.

Study Title: Atrial Electromechanical Function in Middle Aged Endurance Athletes With and Without Atrial Fibrillation

PI: Dr. Paul Dorian, MD, St. Michael's Hospital

Participant Statement of Consent

By signing this consent form, I acknowledge that:

- The research study has been explained to me, and my questions have been answered to my satisfaction.
- I have been informed of the alternatives to participation in this study.
- I know that I have the right not to participate and the right to withdraw without affecting the quality of medical care at St. Michael's Hospital for me and for other members of my family.
- The potential harms and benefits (if any) of participating in this research study have been explained to me.
- I have been told that I have not waived my legal rights nor released the investigator, sponsor, 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.
- I have been told that records relating to me and my care will be kept confidential and that no information will be disclosed without my permission unless required by law.
- I have been given sufficient time to read the above information.
- I will be given a copy of the signed and dated consent form.

Print Study Participant's Name

Signature

Date

(You will be given a signed copy of this consent form)

My signature means that I have explained the study to the participant named above. I have answered all questions.

Print Name of Person Obtaining Consent

Signature

Date

Appendix B: Preliminary Screening Form

Participant ID (if enrolled): _____

Date: _____

Preliminary Screening Form for Study Participation

This form will be completed prior to study participation.
A study investigator will ask the following questions and complete this form.

Please provide me with the following information about yourself:	
Address:	
Current Age (in years)	
Have you been performing Regular Exercise for more than 10 years (Y/N)	
How many years have you been consistently training for your sport?	
Exercise Frequency on Average (i.e times per week)	
Exercise Duration on Average (i.e minutes per session)	
Exercise Intensity on Average (i.e light, moderate, vigorous)	
Exercise mode (resistance, swimming, running etc.)?	

If resistance, state frequency (in times per week) and duration (in minutes).	
Participation in competitive events?	
<i>For runners, what is your personal best time in a half or full marathon?</i> <i>-For cyclists, what is your longest ride in the last 6 months, time of your longest race and distance time-trial?</i>	
Have you been diagnosed with and/or are you currently receiving treatment for any of the following:	If yes, please specify:
Arrythmia	
Atrial Fibrillation or Flutter	
Coronary Artery Disease or Cardiomyopathy	
Significant Valvular Disease	
Heart Disease	
Hypertension	
Syncope	
Palpitations	
Heart Failure	
Diabetes	
Asthma	

History of Thyroid Disorder	
Sleep Apnea or any Sleep-Disordered Breathing	
Current/Recent Viral or Chronic Illness	
Chronic Inflammatory Disease	
Use of Cardioactive Drugs including SSRI's	
Previous or Current Smoking	
Drug or Alcohol Consumption (recreational)	
Family History of: -Sudden Cardiac Death -Syncope -Heart Disease (< 65 years old)	

Current alcohol consumption <i>per week</i>	
Current prescription drugs (<i>List all</i>)	
Current non-prescription drugs (<i>Including supplements; List all</i>)	
Current smoking status (Yes or No)	
Current fish intake (<i>number of times per week</i>)	

Appendix C: Atrial Fibrillation Screening Form

Atrial Fibrillation Screening Form

Participant ID: _____

Date: _____

OHIP #: _____

When were you first diagnosed with Atrial Fibrillation?	Year: Age:
Since your FIRST diagnosis how many episodes of Atrial Fibrillation have you had?	
When was your most recent episode? How was it triggered?	
How long do your symptoms persist? Please describe your symptoms and <i>when they typically occur (day, night, after exercise..etc).</i>	
Has your doctor prescribed any medications? If so, please provide details.	

Have you ever had a cardioversion or a cardiac ablation? (if so, when?)	
How were you diagnosed with Atrial Fibrillation?	Self diagnosis Family Physician Cardiologist Other: _____
What are some 'triggers' for an episode of AF?	
If you get an episode of AF at rest: what do you do (i.e meds, wait it out) and how long does it last?	
If you get an episode of AF during exercise: what do you do, and how long does it last?	

Appendix D: 2-week Exercise Diary

Atrial electromechanical function in athletes with and without AF- Oct 2017
 PI: Dr. Jack Goodman

Exercise Training Diary

Participant ID: _____

Week 1

Date	Type of Exercise	Intensity (average HR if applicable)	Distance	Duration	RPE [see scale on last page]	Training Notes*

* training notes section can be used to describe the workout in greater detail. This may include HR, HR zone, and/or power output data (if available).

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 PI: Dr. Jack Goodman

** Heart Rate **Zone 1**: 50-60% HR max, **Zone 2**: 60-70% HR max, **Zone 3**: 70-80% HR max, **Zone 4**: 80-90%, **Zone 5**: 90-100%

What percentage of this weekly exercise duration is spent at low-to-moderate intensity (Heart Rate Zones 1 and 2)?

What percentage of this weekly exercise duration is spent at moderate-to-high intensity (Heart Rate Zones 3 and 4)?

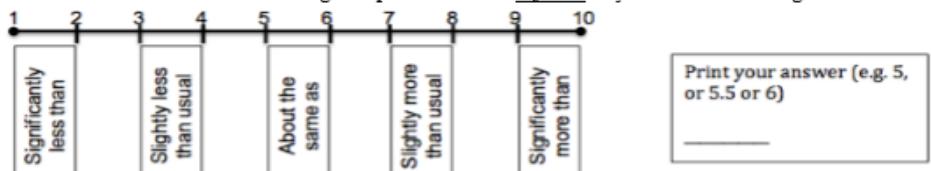
What percentage of this weekly exercise duration is spent at near maximal intensity (Heart Rate Zone 5)?

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 PI: Dr. Jack Goodman

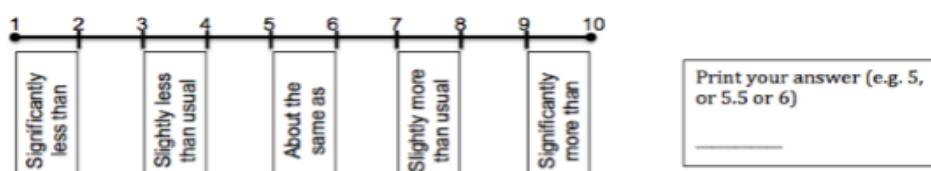
1) How do these 2 weeks of exercise training compare to the last 1 year of your overall training schedule?



2) How do these 2 weeks of exercise training compare to the last 5 years of your overall training schedule?



3) How do these 2 weeks of exercise training compare to the last 10 years of your overall training schedule?



Atrial electromechanical function in athletes with and without AF- Oct 2017
 PI: Dr. Jack Goodman

RPE Scale

How you might describe your exertion	Borg rating of your exertion	Examples
No Exertion	6	Reading a book, watching television
Very, very light	7	
	8	Tying shoes
Very light	9	
	10	Chores like folding clothes that seem to take little effort
Light	11	
	12	Walking through the grocery store or other activities that require some effort but not enough to speed up your breathing
Somewhat hard	13	Brisk walking or other activities that require moderate effort and speed your heart rate and breathing but don't make you out of breath
	14	
Hard	15	Bicycling, swimming, or other activities that take vigorous effort and get the heart pounding and make breathing very fast
	16	
Very hard	17	The highest level of activity you can sustain
	18	
Extremely hard	19	A finishing kick in a race or other burst of activity that you can't maintain for long
Maximal Exertion	20	

During your exercise bouts, we want you to recall how hard you felt the exercise work rate was. This feeling should reflect your total amount of fatigue, combining all sensations and feelings of physical stress, effort and fatigue. Do not concern yourself with any one factor, such as leg pain, shortness of breath or exercise intensity, but try to recall your total, overall feeling of exertion during your exercise session. Light activities fall between 6-10, moderate activities between 11-14 and vigorous activities between 15-20. We have provided some reference activities to help you in determining an accurate level of exertion. In describing your activity, you may select any value between 6-20. Try to be as accurate as possible.

Appendix E: Sport Specific History Questionnaire

Atrial electromechanical function in middle-aged endurance athletes with and without AFib- Version Feb7 2018

Questionnaire Instructions

We are interested in characterizing your sport and physical activity history. Please fill out this questionnaire using the following instructions.

Part 1: Sport-specific Training Questionnaire

- record all sport-specific training since the age of 19 until present
- sport-specific training refers to training that you did with a purpose or intent to improve performance in a given modality (for example, running to improve your 10 km, marathon time etc.)
- Please provide a rating of perceived exertion (RPE) for each training entry. When recording RPE, please try to base this on how intense the activity would have been *at the time* – we recognize perceived intensity may change over the years, but try your best to estimate what this would have been. We have provided an attached document to help you with understanding RPE.
- Please fill out the duration of intensity for a typical session (last 3 columns) using the categories provided in the questionnaire. This may be expressed as a percentage of your typical exercise duration, or in minutes.

Part 2: Recreational or Other Physical Activity History

- record all other physical activity or sport that you regularly have engaged in
* please only include those activities you perform at least 2 months of the year (and at-least once a week) from the age of 19 until present.
- this may include activities such as golfing, biking to work, tennis [as long as it is regularly performed]
- Please fill in RPE and intensity information just as you did above.

Part I: Sport Specific Training History Questionnaire

#	Description of Activity	Age Started	Age Ended	Freq. per week	# months per year	Sessional Duration	RPE	Avg Time in Cat. 2 *	Avg Time in Cat. 3*	Avg Time in Cat. 4*

* 2 = activities that require minimal effort

* 3 = activities that are not exhausting, that increase heart rate slightly and cause slight perspiration

* 4 = activities that increase heart rate and cause heavy sweating

Part II: Recreational/Other Physical Activity History

#	Description of Activity	Age Started	Age Ended	Freq. per week	# months per year	Sessional Duration	RPE	Avg Time in Cat. 2 *	Avg Time in Cat. 3*	Avg Time in Cat. 4*

* 2 = activities that require minimal effort

* 3 = activities that are not exhausting, that increase heart rate slightly and cause slight perspiration

* 4 = activities that increase heart rate and cause heavy sweating

Appendix F: Visit 1 Data Collection Form

Data Collection Form

Researcher: _____

Date: _____

Participant ID: _____

Consent form and full study explanation

Collect or complete 2-week Exercise Diary/ Preliminary Screening/AF form

Height: _____ cm **Weight:** _____ lbs _____ kg

Birthdate: _____ **Age:** _____

Notes (caffeine, exercise, alcohol):

Resting Blood Pressure:

	Reading 1	Reading 2	Reading 3	Reading 4
Systolic BP				
Diastolic BP				
HR				

- Familiarize participant with procedures and RPE scale
- Attach ECG and 2 sets of leads [**put on 4th electrode but not used yet**]
- Prepare echo couch- ensure flat to start (adjust seat, headpiece, arm and hip rest)
- Attach Blood pressure cuff once participant on bed (BPTru)
- Drop side-piece for technician to reach lateral chest wall
- Determine an appropriate work rate

Echo Data Collection Form

Stage	Time	HR	BP	Work Rate	RPE	Notes
1 (Rest)						
2						
3						

30 minutes of seated rest in back room (provide participant with LTPAQ)

Create participant file/Calibrate VO2 machine if needed

Follow VO2 max test procedures and use VO2 data collection form

Appendix G: Poster Advertisement



St. Michael's
Inspired Care.
Inspiring Science.

Recruiting Endurance Athletes!

Are you an endurance athlete who has been diagnosed with Atrial Fibrillation?

Regular exercise of a moderate intensity can improve heart function, reduce cardiovascular risk and extend lifespan. However, long-term intensive and prolonged exercise training can result in heart remodeling and increase the risk of heart problems like Atrial Fibrillation. This study aims to find out how the heart looks and functions in endurance athletes with a diagnosis of Atrial Fibrillation.

Who:

- **Males 45 to 65 years old**
- **Endurance trained for 10-20 years** (cyclists, runners, rowers, triathletes) and *still* training/competing
- Diagnosis of **paroxysmal Atrial Fibrillation**
- No history of other cardiovascular disease

Where:

- University of Toronto (Goldring Center) and St. Michael's Hospital (30 Bond Street)

What:

- Resting and exercise heart imaging via Echocardiography & MRI
- maximal cardiorespiratory exercise test (VO₂ max)
- cardiac rhythm assessment via Electrocardiogram
- **Able to attend 2 study visits (each 120 minutes);** compensation will be provided

Appendix H: Email Script and Social Media Posting

Re: "Call to Volunteer- Research Study"

Atrial electromechanical function in athletes with and without Atrial Fibrillation

Investigators at St. Michael's Hospital and the University of Toronto are conducting a research study to examine heart function in endurance athletes who have been diagnosed with **paroxysmal atrial fibrillation (AF)**, and are looking to recruit volunteers!

Participation in the study will involve cardiac imaging at rest and during exercise, in addition to a maximal exercise test to measure VO₂ max. To be eligible for the study you must:

- Have been Diagnosed with **Atrial Fibrillation** in the past 6 years
- Have NOT received an ablation
- Be **male** and between the ages of **45 and 65 years old**
- Have a long-standing (10 year +) **history of endurance training and competition** (minimum of ½ or full marathon performed multiple times over the past 10 years) and continue to exercise
- **Have NO other cardiovascular disease** or other chronic illness

If you believe you are eligible and interested in participating, please contact the study team for further details*.

*please note that email is not a secure means of communication

Appendix I: Technical Protocol

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

Description: A structural and functional observational study in healthy middle-aged endurance trained athletes and middle-aged endurance trained athletes with AF, conducted over the span of two laboratory visits.

Intervention: Parameters of cardiac structure and function will be assessed at rest and at submaximal exercise using ECG, echocardiography and cardiac MRI.

Purpose: To examine cardiac function at rest and in response to acute semi-upright cycling exercise in highly trained male endurance athletes with and without AF; and to observe the relationship between AF and atrial electromechanical timing.

Visit 1

Preparation:

- prepare Vmax (calibration and set up of headpiece)
- prepare/set up Ergoline 1200EL and blood pressure (Tango)

Equipment:

- Ergoline 1200EL semi-recumbent bike
- Tango BP monitor
- Electrodes
- Portable ultrasound
- VMax mouthpiece
- Nose clip
- Headpiece
- Alcohol swabs
- Sandpaper wipes
- Polar Heart rate V800 strap and watch
- RPE scale
- Ultrasound gel

Procedure- Back Room:

1. Subject arrives to Goldring lab following 4 hour fast, 12 hours no caffeine, 24 hours no alcohol/strenuous exercise
2. Subject is provided with explanation of the study and consent form package
3. Complete(d) 2-week Exercise Diary and preliminary screening form(s)
4. Height, Weight, Birth date
5. Resting Blood Pressure (4 measures using BPTru in back room)

Procedure 1- Main Testing Room:

1. Bring subject into main testing area
2. Attach electrodes (3 lead) for the echo, and another 3 leads for Tango:
→ shave area, wipe with alcohol swab, use sandpaper
3. Bring Tango BP to left side of cycle-ergometer
4. Prepare the echo couch to be mounted:
 - return it to horizontal position
 - retract the saddle as far as possible
 - adjust the hip and armpit support (should be level with armpit and hipbone)
 - adjust the pedal straps to participant's foot size
 - adjust the head rest until in contact with the shoulders when the head is placed on the head rest
→ ensure the hip and armpit support will not hinder movement during exercise, but that it is snug (to support body weight when on a tilt)
→ fold down the drop section (so sonographer can get to side of body)
5. Hook up the leads to the 6 electrodes (3 for each device) and tape down wires if needed to avoid interference
6. Familiarize the participant with RPE scale
7. Increase tilt of echo couch to 30 degrees
8. Determine what work rate should be appropriate to elicit HR of 100 and 130 bpm (in manual mode can adjust the work rate as needed) (discuss with participant)
9. Prep ultrasound head with transducer jelly
10. Initiate ultrasound imaging as per routine
11. Record heart rate and take resting blood pressure (2 minutes into stage)
12. Increase work rate wattage to elicit a steady state heart rate of 100 bpm, record this work rate and RPM once achieved
13. Initiate ultrasound imaging as per routine
14. Record HR, BP, WR and RPE once 1-2 minutes into steady state
15. Increase work rate wattage when all images at 100 bpm have been achieved, should elicit a steady state heart rate of 130 bpm
16. Record work rate and RPM once steady state achieved
17. Initiate ultrasound imaging as per routine
18. Record HR, BP, WR and RPE once 1-2 minutes into steady state
19. Upon completion of image acquisition, remove blood pressure cuff and leads (keep 6 leads on for VO2 max test/BP)
20. Return echo table to 0 degrees
21. Bring participant to back room for 30 minutes of seated rest and to complete their LTPAQ questionnaire

22. Wipe down equipment with dry or moist towel

Procedure 2- Main Testing room:

1. Turn computer on, and VMax machine on
2. Open VMax, Calibrate system:
 - Attach main VO2 piece to calibration syringe, follow steps as prompted on Vmax
 - calibrate using gas tanks **turn tanks on**, plug in VO2 wire to the VMax
 - turn tanks off**, plug VO2 wire back into main piece
3. Create new study file- input participant ID, date of test, date of birth, height, weight and sex
4. Roll Tango BP cart back beside metabolic cart
5. Prep participant for VO2 max
 - explain procedure of the VO2 max test
 - add additional electrode on right rib cage, hook up all leads (4)
 - fit headpiece
 - fit polar heart strap (V800) and watch on own wrist
 - fit mouthpiece and nose clip
6. Selection of pace (6 + mph)
7. Initiate test and follow protocol (i.e HR, BP, RPE)
8. Following completion of VO2 max test, remove all equipment
9. Provide participant with blood req form if has not already been completed and prompt them about booking visit 2 (if AF participant)
10. Save and store data to USB (patient results → tabular edit → save → OS Vision → drag file to USB)

Appendix J: Research Ethics Board Approval

Research Ethics Office
 Telephone:
 Facsimile:
 Email:

St. Michael's
 Inspired Care.
 Inspiring Science.

November 02, 2017

Dr. Paul Dorian,
 Department of Medicine, Division of Cardiology,
 St. Michael's Hospital

Dear Dr. Dorian,

Re: REB# 17-267 - Atrial electromechanical function in middle aged endurance athletes with and without atrial fibrillation

REB APPROVAL:	Original Approval Date	November 02, 2017
	Annual/Interval Review Date	November 02, 2018

Thank you for your application submitted on 29 August, 2017. At the St. Michael's Hospital (SMH) Research Ethics Board (REB) meeting held on September 19, 2017, the above referenced study was discussed and subsequently the views derived from this discussion have been documented and recorded. Please note that no member of the St. Michael's Hospital Research Ethics Board associated with this study was present or involved in its deliberation, review or approval.

The REB approves the study as it is found to comply with relevant research ethics guidelines, as well as the Ontario Personal Health Information Protection Act (PHIPA), 2004. The REB hereby issues approval for the above named study for a period of 12 months from the date of this letter. Continuation beyond that date will require further review of REB approval. In addition, the following are appropriate and hereby approved:

1. Protocol ver: 10/13/2017
2. Consent Form ver: 10/18/2017
3. Email + Telephone script ver: 9/23/2017
4. Poster A ver: 11/2/2017
5. Poster B ver: 11/2/2017
6. Exercise Training Diary ver: 9/1/2017

Furthermore, the following documents have been received and are acknowledged:

1. Master Linking Log - MLL ver: 9/28/2017
2. Questionnaire - Physical History ver: 8/1/2017
3. Data Collection Form - Screening checklist ver: 9/1/2017
4. AF Screening Form ver: 8/1/2017
5. Data Collection Form - VO2 DCF ver: 8/1/2017

During the course of this investigation, any significant deviations from the approved protocol and/or unanticipated developments or significant adverse events should immediately be brought to the attention of the REB. Please note that shared electronic health systems such as ConnectingOntario, PRO, RM&R, OLIS, HDI/RS, eCHN, DPV, and IAR do not permit access for research purposes.

All interventional trials where SMH is the Sponsor institution or where the lead Principal Investigator (PI) is at SMH are required to (1) register the study in a registry accepted by the International

Appendix K: Social Media Posting Research Board Approval

Research Ethics Office
 Telephone:
 Facsimile:
 Email:

April 26, 2018

Dr. Paul Dorian,
 Department of Medicine, Division of Cardiology,
 St. Michael's Hospital

Dear Dr. Dorian,

Re: REB# 17-267 - Atrial electromechanical function in middle aged endurance athletes with and without atrial fibrillation

REB APPROVAL:	Original Approval Date	November 02, 2017
	Annual/Interval Review Date	November 02, 2016

St. Michael's

Inspired Care.
 Inspiring Science.

Thank you for your communications dated March 14, 2018 regarding the above named study.

I have reviewed and hereby issue St. Michael's Hospital (SMH) Research Ethics Board (REB) approval for:

1. Scripts - Email/Facebook Post Script ver: 4/18/2018

Please note that no member of the St. Michael's Hospital Research Ethics Board associated with this submission was involved in its deliberation, review or approval.

During the course of this investigation, any significant deviations from the approved protocol and/or unanticipated developments or significant adverse events should immediately be brought to the attention of the REB. Furthermore, it should be acknowledged that shared electronic health systems such as ConnectingOntario, PRO, RM&R, CLIS, HCIRS, eCHN, DFY, and MBR do not permit access for research purposes.

For studies which are registered on a publicly available Clinical Trials registry (e.g. ClinicalTrials.gov), please ensure the record is updated to accurately reflect the status of the study.

The St. Michael's Hospital (SMH) Research Ethics Board (REB) operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans, the Ontario Personal Health Information Protection Act, 2004, and ICH Good Clinical Practice Consolidated Guideline E6, Health Canada Part C Division 5 of the Food and Drug Regulations, Part 4 of the Natural Health Product Regulations, and the Medical Devices regulations. Furthermore, all investigational drug trials at SMH are conducted by Qualified Investigators (as defined in the latter document).

Good luck with your investigations.

With best wishes

David J. Fisman
 Chair, Research Ethics Board
 DMJ-Fisman

Vice Chair, Research Ethics Board

Vice Chair, Research Ethics Board

Appendix L: Reliability Measures

Measure	ICC
LA Max Volume	0.98
LA Min Volume	0.99
LA Parasternal Dimension	0.92
LA Area	0.99
RA Max Volume	0.95
RA Min Volume	1.00
LA Reservoir strain	0.87
LA Conduit strain	0.87
LA Booster strain	0.86
Interatrial AEMD	0.84
Right AEMD	0.96
Left AEMD	0.84