2024

Altitude and the development of atrial fibrillation in high endurance athletes

BOSTON UNIVERSITY

ARAM V. CHOBANIAN & EDWARD AVEDISIAN SCHOOL OF MEDICINE

Thesis

ALTITUDE AND THE DEVELOPMENT OF ATRIAL FIBRILLATION IN HIGH ENDURANCE ATHLETES

by

STEPHANIE WILSON

B.A., University of Colorado at Boulder, 2018

Submitted in partial fulfillment of the

requirements for the degree of

Master of Science

2024

Approved by

First Reader
Aaron W. Young, Ph.D
Assistant Director, Oral Health Sciences Masters Program
Assistant Professor Department of Pharmacology, Physiology, & Biophysics

Second Reader
John Weinstein, Ph.D, M.S.
Director of Research, Physician Assistant Program
Assistant Professor of Medicine

ALTITUDE AND THE DEVELOPMENT OF ATRIAL FIBRILLATION IN HIGH ENDURANCE ATHLETES

STEPHANIE WILSON

ABSTRACT

Introduction:

Atrial fibrillation (AF) stands as the predominant cardiac arrhythmia in the United States, carrying substantial morbidity and mortality implications. While exercise typically offers cardiovascular benefits, rigorous endurance activities, especially at high altitudes, might paradoxically heighten AF risk due to increased cardiovascular strain and remodeling. This study aims to investigate whether a significant association exists between high-altitude endurance training (>1500m) and AF incidence compared to training at sea level in high performance athletes.

Review of the Literature:

Atrial fibrillation (AF) is a prevalent arrhythmia characterized by atrial fibrosis, inflammation, and physiological stressors like exercise and altitude exposure. Recent studies emphasize atrial fibrosis as pivotal in AF development, marked by altered conduction velocities and re-entry circuit facilitation. Inflammatory markers such as CRP and fibrinogen correlate with AF onset and recurrence. While moderate exercise mitigates cardiovascular risk factors and inflammation, high-volume endurance exercise can increase AF risk, particularly in middle-aged male athletes. Altitude exposure poses

additional challenges, potentially exacerbating AF risk via pulmonary hypertension, right heart strain, and hypoxia-induced inflammatory responses. Chronic hypoxia adaptations, including heightened sympathetic tone and pro-fibrotic pathways, may further predispose individuals to AF, especially when coupled with intense endurance training.

Methods:

This study adopts a paired case-control design to examine the association between AF in high-performance athletes and altitude training. Participants from Massachusetts and Colorado sports centers will be grouped by altitude exposure (>1500m vs. sea level). Using Strava data, exercise metrics (speed, duration, elevation) will be analyzed to calculate average weekly metabolic equivalents (MET-h). Statistical analyses will assess AF prevalence relative to altitude exposure, employing descriptive methods to visualize dose-response trends.

Conclusion:

Despite its rising popularity among elite athletes, high-altitude training lacks comprehensive evidence of benefits and potential cardiovascular risks, notably AF. As global participation in endurance sports increases, understanding AF prevalence in athletes training at high altitudes is crucial for shaping long-term cardiovascular health guidelines.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AF……………………………………………….………………………Atrial Fibrillation

CHAD2S2-VASc………Congestive Heart Failure, Hypertension, Age, Diabetes, Stroke

CO……………………………………………………………………….…Cardiac Output

CVA……………………………………………...………..Cerebrovascular Accident

ECM……………………………………………...……….……..Extracellular Matrix

EF…………………………………………………………...……Ejection Fraction

HIF-1……………………….…………………………………Hypoxia Inducible Factor-1

HR……………………………………………………………………………Heart Rate

LV………………………………………………………………..……….Left Ventricle

MET-h………………………………………………Metabolic Equivalents per Hour

NE…………………………………………………………………….....Norepinephrine

NSR…………………………………………………………Normal Sinus Rhythm

PAP……………………………………………………….Pulmonary Artery Pressure

PSNS……………………………………………..…..Parasympathetic Nervous System

RA……………………………………………………………………Right Atrium

ROS……………………………………………………..Reactive Oxygen Species

RV…………………………………………………………………….Right Ventricle

SNS……………………………………………………Sympathetic Nervous System

SV……………………………………………………………….…….Stroke Volume

TIA……………………………………………...…………Transient Ischemic Attack

INTRODUCTION

Background

Atrial fibrillation (AF) is the most common arrythmia in the general population, affecting 1-2% of people worldwide [1]. It carries a massive global disease burden and has a wide array of physiologic consequences including stroke, cardiac arrest, heart failure, and more. The pathogenesis of AF is believed to be due to atrial fibrosis and disruption of normal atrial conduction pathways resulting in aberrant electrical excitation, along with imbalanced autonomic sympathovagal control of heart rate. The major risk factors for AF development are age and cardiovascular risk factors including hypertension, obesity, diabetes, smoking, peripheral vascular disease, pulmonary disorders, endocrine disorders, and congenital diseases [1–3]. Exercise is widely known to be cardioprotective, including reduction in the rate of AF development, to a certain degree[4]. However, several recent studies have found that high endurance exercise over long periods of time promotes increased cardiac stress, inflammation, and cardiac remodeling that can increase the prevalence of atrial fibrillation in high performance athletes[4]. For decades, the training model for many high endurance athletes has been to train at high elevation to maximize oxygen utilization during exercise[5]. While high altitude training has yet been explored as a risk factor for the development of AF, because it greatly augments cardiovascular stress, it could also play a role in AF development in endurance athletes.

Statement of the Problem

The development of AF is a complex process, requiring multiple components for arrhythmogenesis. Coumel et. al describes the triad of arrhythmogenic ingredients necessary to develop AF as the substrate, modulator, and trigger[6]. Long term endurance exercise has been shown to provide all three components, and recent studies have found AF incidence in endurance athletes to be 5 times higher than the general population, especially among middle-aged men[7]. Chronic exposure to altitude has also been shown to provide all three components[8], although AF rates in individuals living at high altitude has not been specifically studied. Recent years have seen a massive increase in endurance sport popularity and there has been a post-COVID explosion of migration to the 'mountain states' within the US[9]. The rate of high-altitude endurance training is higher than ever; however, the long-term cardiovascular implication of this training is unknown. Because both high altitude and endurance training cause specific cardiovascular and neuroregulatory remodeling which satisfy Coumel's requirements for arrhythmogenesis, the potential for AF development could be significantly enhanced when both exposures are combined. This, too, has never been studied. Given the significant morbidity and mortality of AF, the possibility of amplified AF development secondary to high-elevation endurance exercise necessitates further exploration.

Hypothesis

High intensity endurance exercise (>42 MET-h/wk) performed primarily at elevation greater than 1500m will result in increased incidence of atrial fibrillation compared to those primarily training at sea level.

Objectives and Specific Aims

The main objective of this study is to determine if a link exists between high altitude endurance sports and the development of atrial fibrillation. This will be the first study of its kind and while it will not definitively delineate the relationship between high altitude training and atrial fibrillation in endurance athletes, its goal is to explore if an association exists for future studies. Specifically, this study aims:

- To determine if there is a difference between the incidence of atrial fibrillation in high endurance athletes who train at altitude versus those who train at sea level.
- To explore whether there is a dose-dependent relationship between the average elevation at which endurance exercise is performed and the incidence of AF.

REVIEW OF LITERATURE

Overview of Research Topic

The Normal Cardiac Cycle

The normal flow of blood through the heart and the body is based on a highly regulated, efficient system involving synchronized electrical excitation of cardiac myocytes and coordinated contraction of the atria and ventricles. The initiation of cardiac squeeze is based in the autonomously contractile cells of the heart which beat in specific patterns based on the flow of electrical signals from atrial foci. This system causes the heart to contract and relax in a precise rhythm, regardless of how fast or slow the heart is beating. Arrythmias are any cardiac issue in which the normal cardiac rhythm is disrupted or irregular [2] and can result in a wide variety of physiologic consequences.

In the normal cardiac cycle, the sinoatrial node of the right atrium acts as the pacemaker, originating the depolarization of cardiac myocytes which propagate through the tissue along electrical conduction pathways and synchronize atrial contraction[10]. The electrical conduction cycle undergoes a forced pause when it reaches the atrioventricular node due to changes in ionic conduction through the specialized myocytes of this node. This allows time for ventricular diastolic filling before electrical propagation continues down the Bundle of His and Purkinje fibers, causing synchronized ventricular contraction[10]. The whole cycle then restarts with the AV node ready to initiate the next inciting action potential.

Since the atria carry important electrical foci which coordinate the automaticity of the cardiac pacemaker cells, disruption of normal atrial function therefore not only affects ventricular filling, but also allows disorganized cardiac squeeze and incompetent delivery of oxygenated blood to the body. While the atria carry only a fraction of the strength of the ventricles, the extra atrial blood ejected, called atrial kick, is responsible for up to 30% of ventricular filling. [11] Disruption of this highly coordinated process, therefore, has the potential for massive effects on overall cardiac output. The loss of atrial kick, furthermore, reduces blood flow from atria to ventricles, resulting in the excess blood pooling and stagnating within the atria, where it is more susceptible to clot formation[11].

Epidemiology of Atrial Fibrillation

Atrial fibrillation (AF) is the most common type of cardiac arrythmia in the US and the leading cause of cardiac stroke. [12] The worldwide prevalence of AF is ~1% but it is found in ~9% of individuals over the age of 75 with the lifetime risk of developing AF increasing to 22% after 80 years of age.[12] Atrial fibrillation occurs when the atria conduct an irregularly irregular rhythm with resulting ventricular rates between 80-180 bpm due to disruption of typical electrical pathways or overactivation of electrical foci within the atrial conduction system [12]. The pattern is considered “irregularly irregular” because it follows no distinguishable pattern of contraction. ECG will show a disorganized ventricular pattern with no distinguishable p waves [12]. These findings indicate disorganized electrical conduction through the atria, which then suggests disorganized contraction of the atria[12]. Additionally, because the electrical signal is not travelling through the normal conductive pathway, the likelihood of effective transmission of the electrical signal through the AV node, to the ventricles, is compromised. As such, the ventricles begin to contract in a pattern and rate that is increasingly independent from atrial contraction. Patients may be symptomatic from the irregular rhythm, most often presenting with extreme fatigue, palpitations, and shortness of breath, or may be entirely asymptomatic[13]. Diagnosis is made with cardiac rhythm monitoring including ECG for current arrythmias, loop recorders, event monitors, and stress ECGs[14].

AF can last for any given amount of time and is considered paroxysmal if it spontaneously reverts to normal sinus rhythm spontaneously within 7 days [2,12]. Persistent AF requires intervention, whether electrical or pharmacologic for reversion to normal sinus rhythm,[12,13] while permanent AF is resistant to any intervention with abandonment of cardioversion attempts[12]. In permanent AF, the arrythmia is accepted as the underlying baseline rhythm and rate controlled with medication to minimize symptoms and tachycardia-induced cardiomyopathies[12,13].

The prevalence of AF is increasing globally and has grown 3-fold in the last 50 years according to the Framingham Heart Study[1]. The Global Burden of Disease project estimates the lifetime risk of AF as about 1 in 4 white men and women older than 40 years old in 2004; a decade later, the lifetime risk estimates reached about 1 in 3 white individuals and 1 in 5 for black individuals[1]. In the US alone, at least 3-6 million people have AF and the numbers are projected to reach ~6-16 million by 2050 [1].

Risk factors for the development of AF include advanced age, underlying cardiovascular and pulmonary disease, endocrine disorders, genetic factors, and increased alcohol consumption. Most cases are non-genetic and relate to underlying cardiovascular disease with aberrant excitation of an atrial electrical focus [1,12]. This often occurs around the pulmonary veins and creates self-propagating electrical circuits that allow dyssynchronous early re-entrant activation of the myocytes after a premature beat and ultimately causes atrial fibrillation in a continuous cycle[12]. The result is widely variable rates of atrial and ventricular tachycardia with disorganized contraction ultimately causing turbulent blood flow and reduced cardiac output. The turbulent blood flow within the atria and loss of atrial kick increases the likelihood of clot formation, most often in the left atrial appendage[7,12]. The clot can dislodge, travelling to the brain or other parts of the body making AF the number one cardiac cause of stroke worldwide[1,7]. Current guidelines recommend all patients diagnosed with AF be evaluated on the CHA2DS2-VASc scale which risk stratifies patient clot burden based on age, gender, prior CVA/TIA, and presence of concurrent cardiovascular disease including hypertension, peripheral vascular disease, diabetes, and heart failure[12]. Those who score a 2 or above are recommended to initiate antithrombotic therapy to prevent the risk of stroke[15]. Regardless of the stroke risk, the morbidity and mortality associated with AF can be great. A study of 1530 patients found that a history of AF, even new onset AF, was associated with higher rates of hospitalization, heart failure, cardio-resuscitation, and death[7].

Pathogenesis of Atrial Fibrillation

There are several hypotheses for the pathogenesis of AF primarily centered around fibrosis of the atria which result in abnormal myocytes that do not conduct the same as their surrounding cells[4,7,12]. In the late 1960s and 70s, Phillipe Coumel proposed what is now known as the Coumel triangle of arrhythmogenesis that there are three main factors necessary for the development of an arrythmia: arrhythmogenic substrate, a triggering factor, and modulating factors--most commonly the autonomic nervous system[6,16]. As for the development of arrhythmogenic substrate any condition resulting in inflammation, stress, damage, or ischemia to the myocardium can result in AF due to increased cardiac remodeling via collagen and fibrin deposition[1,12]. This causes derangements in the normal electrical flow through atrial foci because collagen and fibrin inhibit the typical rate of electrical conduction in cells[1,12]. Under normal conditions, fibroblasts maintain the structural integrity of cells and are in part responsible for scar formation and the healing process throughout the body. Cardiac myocytes are highly specialized and do not regenerate; instead they undergo reparative and reactive fibrosis with insertion of extracellular matrix (ECM) into the interstitial spaces to maintain functionality when damaged[4]. Over time, this fibrosis and deposition of ECM disrupts regular myofascial bundles and interferes with the spacing of gap junctions necessary for propagating depolarization waves[4]. The result is slowed conduction velocity of action potentials which can eventually cause complete longitudinal conduction blocks and aberrant excitation of surrounding cells that should not be involved in the electrophysiologic circuit[4]. This creates a pathway which allows self-propagating premature re-entrant depolarization of cells following an early atrial beat[17] .

Recently oxidative stress has also been examined as a potential arrhythmogenic source of AF, specifically the formation of reactive oxygen species (ROS) which can directly affect ion channels[4]. ROS can enhance the late Na+ current causing early afterdepolarization and delayed afterdepolarization, downregulate the total Na+ current promoting re-entry circuits, and upregulate the L-type Ca^{2+} channels to promote early afterdepolarization through altering this intracellular calcium balance[4]. In addition to electrochemical changes, hydroxyl free radicals also contribute to myofibril structural changes which can promote fibrosis and, thereby, foster AF[4].

Inflammation is similarly suspected to play a role in the development and continuance of AF through structural and electrochemical changes that promote arrhythmogenesis. Inflammatory stress triggers the release of angiotensin II which, under certain stress state conditions, further encourages the release of pro-inflammatory cytokines and recruits immune cells that initiate the fibrotic pathway for cardiac structural remodeling[4]. This pathway also secondarily activates ROS and therefore causes calcium and sodium storage and release abnormalities[4]. The presence of atrial fibrillation itself is a stress state, stimulating sustained release of inflammatory biochemicals and, therefore, promoting continuous AF[4]. It should be noted that the process of aging itself involves chronic subclinical inflammation, perhaps explaining in part the massive increase in AF incidence over the age of 65[1].

As for modulating factors for AF, the autonomic nervous system has long been implicated as a key player for AF[6,16]. While cardiac myocytes contain automaticity with the SA node to lead the cardiac cycle, cardiac innervation via the parasympathetic vagus nerve and sympathetic paravertebral ganglia are crucial for neuromodulation of heart rate. Heart rate control is essentially managed by these competing branches with one dominating the other depending on the activity and stress state of the individual. The vagus nerve typically has a restraining effect on HR, as evidenced by pharmacologic blockade of the vagus nerve which results in increased HRs above its intrinsic rate[18], and is predominant during periods of rest. Conversely, sympathetic adrenergic activity results in increased HRs and is predominant during periods of activity and stress states.

Because of the body's intrinsic neuroplasticity, cardiac neural remodeling occurs constantly and can be especially prevalent following cardiac injury[19]. Activation of adrenergic pathways promotes AF by enhancing automaticity, causing early afterdepolarizations and/or causing delayed afterdepolarizations secondary to alterations in intracellular calcium storage and release[19]. Activation of vagal pathways strongly abbreviates atrial refractoriness by enhancing inward potassium channels and has a more profound effect than adrenergic activation[19]. The result of derangements in either pathway is abnormal premature activation of myocytes which can lead to the development and propagation of AF. Autonomic AF development can be subcategorized into adrenergic AF and vagal AF[20]. Adrenergic AF typically occurs in a diurnal cycle and is triggered by hormones, stress, and physical activity[20]. Vagally mediated AF often occurs in younger males in the absence of structural heart disease and with chronic resting bradycardia, tends to be resistant to spontaneous termination, and is often triggered at rest[20]. Although adrenergic and vagal AF are often dichotomized, imbalances in both autonomic branches can coexist within the same patient and in fact for those with autonomic AF, 6% are categorized as vagal, 15% adrenergic, and 12% mixed[20].

As for AF triggers, anything that causes activation of the vagal or sympathetic branches in the presence of cardiac autonomic imbalance and arrhythmogenic substrate can lead to episodes, making it extremely difficult to predict or prevent[19–21]. The majority of anti-arrhythmic drugs on the market are specifically designed to suppress the intracellular changes caused by cardiac autonomic derangement[20].

Cardiovascular Response to Exercise

The American Heart Association designates a sedentary lifestyle as one of the 5 major risk factors for cardiovascular disease, along with hypertension, hyperlipidemia, obesity, and tobacco use[22]. Regular exercise significantly mitigates these determinants through a variety of physiologic responses with additional favorable effects on other risk factors including weight reduction, blood pressure reduction, and prevention of atherosclerotic plaque buildup[22,23]. Furthermore, regular aerobic exercise has been found to increase insulin sensitivity, improve muscular function and bone health, increase maximal oxygen consumption, and reduce anxiety, contributing to both reduction in mortality and improvement in quality of life for many patients[22,23].

In 1996 the Center for Disease Control and National Institute of Health released the Surgeon General's Report on Physical Activity which aimed to redefine preventive health promotion and concluded that every American should participate in 30 minutes or more of moderate intensity activity on most days of the week[22]. The Surgeon General's Report defined moderate activity as any activity with similar intensity to brisk walking at a rate of 3-4 miles per hour, including any forms of occupational of recreational activity for an intensity of 3 to 6 MET-h[22]. One MET-h is the amount of energy required at rest, equal to approximately 70 kcal per hour[22]. MET-h can also be defined by oxygen consumption, where one MET is an O_2 uptake of 3.5 mL/kg/min, the average consumption of an adult at rest and corresponds to an energy usage of 1 kcal/kg/hr[24]. For example, light intensity exercises such as stretching or yoga, is 2-3 MET-h, while moderate intensity exercise, such as bicycling at 9mph, is 5.9 METs-h, and high intensity exercise, such as running at 8mph, is 12.9 MET-h[25]. The number of MET-h for a particular exercise is dependent on the speed and intensity at which it is performed, and using this measure to define exercise productivity rather than duration can be helpful for many patients aiming to meet their exercise goals[25]. It is important to note that although METs can be measured from O_2 uptake, improvement in VO_2 max (a measure of cardiorespiratory endurance) as a result of physical fitness does not affect the metabolic equivalents of that task[26]. Despite the rather conservative exercise guidelines from the Surgeon General's Report, the recommendations for 10-20 weekly MET-h of physical activity for health promotion have not changed since 1996.

In addition to the vascular, weight, and anxiolytic adaptations promoted by regular moderate intensity exercise, the heart itself also undergoes physiologic remodeling to help it meet increased demands caused by physical activity[22]. During exercise, augmented oxygen utilization from the muscles results in hypoxia driven increases in heart rate and stroke volume (resulting in increased cardiac output) to match the demand[27]. While systemic vascular resistance slightly drops to help deliver oxygen to the muscles, the overall result is a moderate rise in blood pressure due to the increased CO[27]. Increased intermittent pressure and volume overloads on the heart during exercise result in concentric and eccentric ventricular enlargement, typically with preserved or increased contractile function[27]. This is opposed to pathologic hypertrophy which decreases contractility[22]. In fact, left ventricle (LV) systolic function has been shown to be normal in athletes both at rest and during exercise, while LV diastolic function is typically normal at rest but is enhanced during exercise representing improved ventricular filling at high HRs[27]. In regard to the right ventricle (RV), there have few studies of post-exercise systolic and diastolic function, however the rise in pulmonary artery pressure as compared to systemic pressure during exercise is greater, resulting in increased RV afterload due to the reduced ability of the pulmonary vascular to dilate[28]. The consequences of the resulting RV enlargement are not definitively known, however Sanz-de la Garza et. al suggests that this remodeling is suspicious for arrhythmogenic cardiomyopathy in highly trained athletes[29].

Regular exercise is also associated with sinus bradycardia as a result of increased vagal tone[18]. During exercise, HR increases from rest to 100bpm is characterized by vagal withdrawal, while subsequent increases over 100bpm results from increasing sympathetic control[30]. However, with continued training and improved oxygen utilization during activity, there is a reduction in sympathetic drive at higher levels of exercise and increased parasympathetic (vagal) activity during rest secondary to neuromodulation[31]. The resulting resting bradycardia in trained athletes has been a major subject of study since the 1970s, and increased vagal tone is often used as a measure of physical fitness today[18]. Several of these studies have indicated that middle-aged athletes exhibit the highest parasympathetic activation and lowest sympathetic activation during exercise and at rest, which has been extrapolated to argue that endurance exercise attenuates the effects of aging in this population[32]. However, more recent research regarding AF in middle-aged athletes argues that this imbalance in sympathetic nervous system (SNS) and parasympathetic nervous system (PSNS) control of HR acts as a modulator in Coumel's triad of arrhythmogenesis[20]. High vagal activity is critically important for higher tolerance of intense training regimens[18], however the risk of developing pathology associated with autonomic dysfunction is certainly a factor to consider when using exercise to mitigate cardiovascular disease.

Cardiovascular Response to Altitude

Altitude exposure has also been linked to cardiovascular remodeling secondary to hypobaric hypoxia which increases with elevation, and detectable physiologic changes begin at 1500m[8]. Altitude ranges are commonly defined as high altitude 1500-3500m, very high altitude 3500-5500m, and extreme altitude >5500m[33]. Globally, roughly 500 million people reside at altitudes >1500m, 81.6 million at >2500m, and 14.4 million at >3500m[34] and these areas represent popular travel destinations with 100 million visitors per year[33]. The stresses of high altitude on the body are extreme and result in major physiologic changes to adapt to chronic hypoxia. Although the composition of air remains constant at 21% oxygen with increasing elevation, decreases in barometric pressure cause reduction in the partial pressure of oxygen in the inspired air, and thus the blood resulting in hypoxemia[8]. To compensate in the short term, hyperventilation occurs causing respiratory alkalosis, kidney function increases excretion of HCO3-, and diuresis results in decreased circulating plasma volume thereby concentrating hemoglobin and, thus, O_2 in the blood[35]. The cardiovascular response to this acute hypoxia and respiratory alkalosis is an increase in heart rate (HR) and cardiac output (CO) with a slight resulting increase in blood pressure[36]. After time, reduced oxygen delivery to kidney cells results in the release of erythropoietin causing increased hemoglobin in the blood and thereby allowing higher O_2 carrying capacity[35]. This acclimatization, which occurs over days to weeks of altitude exposure, allows cardiac output to return to normal by reducing stroke volume (SV)[36]. Despite normalization of CO, cardiac work remains increased as evidenced by persistently increased HR[8]. The physiologic consequence of this increased work is negligible for the majority of individuals, however the American College of Cardiology cautions elevation exposure for those with preexisting cardiovascular disease due to exacerbation of heart failure, ischemic heart disease, systemic arterial hypertension, pulmonary hypertension, and arrythmias[37].

Synthesis of Existing Research

With the growing worldwide health burden of AF growing, there have been several studies attempting to fully elucidate the cause of this common arrythmia. Epicardial mapping of 24 patients with chronic AF by the Cardiovascular Research Institute showed atrial fibrotic block lines running parallel to atrial conduction pathways[4]. Further investigation by Sebastein P. J Krul et. al examined 35 atrial appendages removed during AF surgery, which had thick fibrotic strands and showed that longitudinal conduction velocity within these atrial appendages was slowed in direct relation to the level of fibrosis, while transverse conduction velocity was unaffected ($p=0.012$)[17]. The result was a pattern of zig-zag activation with re-entry circuits enabling the perpetuation of AF and substantiating the role of fibrosis as an arrhythmogenic substrate[17]. Delving even further, Hansen et. al mapped sub-endocardial and sub-epicardial activation patterns and compared these to MRIs to create structural-functional ex-vivo atrial models which confirmed that fibrotic longitudinal conduction delays were a main driver of aberrant re-entrant atrial activation and, therefore, a major component of AF development ($p>0.001$)[38]. Overall, these studies helped to establish atrial fibrosis as integral in the development of AF.

The role of inflammation in arrhythmogenesis is also a recent topic of investigation with several studies over recent years demonstrating its impact on the development of AF. A large study of 24,734 women examined the role of inflammation and AF through biochemical markers of inflammation including CRP, fibrinogen, and ICAMs and found that inflammatory biomarkers were strongly associated with development of AF in patients ($p=0.0006$)[39]. Furthermore, a follow-up study in Greece found that increased levels of CRP were significantly associated with recurrent AF ($p<0.001$), and that restoration of normal sinus rhythm (NSR) or permanent restoration of NSR, such as by ablation, was associated with lower CRP levels ($p<0.001$)[40]. While AF pathogenesis is complex and not fully understood, it is a multi-factorial process with many risk factors increasing its likelihood.

Exercise and Atrial Fibrillation

The pathophysiologic basis of AF suggests that reduction in overall cardiovascular risk factors such as diabetes, hypertension, obesity, atherosclerosis, and tobacco use would reduce the chronic inflammatory steady state that these conditions promote and reduce the presence of ROS and cardiac fibrosis. This has, indeed, found to be true; the reduction in overall cardiovascular risk factors through diet, exercise, and weight maintenance significantly decreased the incidence of non-genetic AF cases[1]. Moderate physical activity which features cardiovascular exercise has been found to be cardioprotective in reducing systemic inflammation independent of weight loss in obese/overweight individuals[1]. Conversely, several recent studies have found that high volume endurance exercise actually increases the incidence of AF in athletes[1], with a meta-analysis of AF in endurance athletes demonstrating that the AF risk approaches 5 times higher in this group as compared to the general population[7]. It is notable that this increased risk has been observed only in those high cardiovascular endurance athletes such as runners, cyclists, and skiers and has not been similarly identified in other sports such as boxing, wrestling, and weight-lifting[41]. These high intensity endurance sports like marathons, ultramarathons, triathlons, distance bike races, cross-country ski races, and ironman races can lead athletes to regularly train 200-300 MET-h per week which is 10 times the standard exercise recommendation for enhanced cardiovascular health[42]. Endurance exercise at this extreme level can cause acute volume overload of the heart which results in transient decreased ejection fraction and acute stress state reactions including release of cardiac biomarkers[42]. While this quickly returns to normal following discontinuation of exercise, when performed repeatedly over a long period of time, it can result in atrial fibrosis in some athletes providing the substrate for AF propagation[42].

Chronic cardiac stress caused by vigorous exercise over long periods of time has recently been found to contribute to AF pathogenesis[1]. One meta-analysis out of Denmark in 2008 examining 655 athletes and 895 controls showed the overall risk of AF was significantly higher in athletes with an odds ratio of 5.29[43]. A review from the Journal of Atrial Fibrillation in 2010 suggested that the incidence of AF in male athletes is 1.8-8.8 times higher than the AF risk in sedentary men[44]. A 2013 meta-analysis in the European Journal of Preventive Cardiology identified the AF risk was increased 5-fold in middle-aged endurance athletes with a pronounced male predominance[45]. Regardless of the inconsistencies concerning the exact value of increased AF risk in male athletes, there is clearly a significant association between high endurance exercise and arrhythmogenesis. It should be noted that across all these studies, higher prevalence was isolated to only male athletes. This could truly be related to increased risk in men alone rather than sampling bias, however the effect of high endurance exercise and the development of AF in women is not well defined in the literature.

A longitudinal study in Norway of long-term endurance cross-country skiers of 149 athletes from three age groups from 1976 and 1981 with follow up in 2004-2008 found a much higher prevalence of AF (12.8%) as compared to the general population (1-2%)[46] with the major associated risk factors for lone AF being bradycardia ($r=0.29$, $p=0.012$) and left atrial enlargement ($p<0.001$)[46]. While left atrial enlargement has traditionally been studied more closely in athletes, chronic physical exercise typically causes bi-atrial enlargement[27]. This can be evidenced by an MRI study of male endurance athletes and matched untrained controls which showed increased RV mass in endurance athletes by 37% which was equal to LV enlargement[27]. Patil et. al found that RV function is more profoundly affected by chronic excessive exercise than the LV, especially when proper recovery time between training sessions is denied[47]. Wilhelm et. al suggested that the thinner walls of the right atrium and ventricle are more prone to exercise-induced remodeling from repetitive stress and volume overload during training resulting in increased AF prevalence[45]. This is because the most common sites of AF genesis are the RA followed by the RV ($p<0.001$)[48]. In fact, a study of 46 athletes with major arrhythmic events was followed over 5 years and found that 89% of the arrhythmia cases arose from the right heart and were associated with increased RV size and decreased RV systolic function as compared with athletes without arrythmias and nonathletes ($p<0.05$)[49]. Endurance sports disciplines, increased duration of training, and male gender have been identified as predictors of increased RV remodeling[29] and, by far, the most common cause of RA enlargement is RV enlargement[50]. MRI radiofrequency tagging of dogs showed that early with RV pressure overload, RA function is significantly altered with reduction in compliance consistent with myocardial fibrosis ($p=0.04$) and that this occurs even before chamber enlargement[51]. While not all cases of RV enlargement lead to RA pathogenesis, fibrotic remodeling of the RA and disruption of typical electrical circuits is a popular hypothesis for the arrhythmogenic development of AF in athletes. Why some elite athletes develop AF and others do not despite similar training programs is unknown and the degree of RV dilation has been inconsistent in predicting future arrhythmia[29].

Another possible arrhythmogenic contribution to the development of AF in athletes is related to inflammatory stress states. While low to moderate intensity exercise has been shown to decrease inflammation by reducing adipose tissue, promoting anti-inflammatory cytokines production in contracting muscle, and inhibiting toll-like receptors (TLRs) on monocytes and macrophages, there appears to be a dose-response relationship depending on the duration and intensity of the exercise[52]. A 2023 meta-analysis of 38 randomized control trials found that reduction in CRP level by long term endurance exercise decreased with increasing exercise intensity ($p=0.005$)[52]. Similarly, blood tests from 11 male athletes following an ultra-endurance MutliSport Brazil race showed marked systemic inflammatory markers and significant oxidative stress (0=0.005)[53]. A study of post-exercise inflammatory markers after reaching 75% versus 100% VO_2 max in 2021 demonstrated suppression of the anti-inflammatory markers at maximal activity levels but not at submaximal levels ($p<0.05$)[54]. While pro-inflammatory processes occurring directly after exercise may be an adaptive response for reparation of physical strain done during training, a 2020 systematic review found that persistent high intensity exercise, especially performed without adequate recovery periods, was associated with immune dysregulation, higher inflammatory markers, and susceptibility to illness as compared to moderate intensity exercise[55]. The role of inflammation in the development and perpetuation of AF has been well-defined and likely plays a major role in the development of AF in long-term endurance athletes.

The precise amount of physical activity which is no longer cardioprotective, and instead becomes a risk factor for AF, has been widely debated over recent years with no single consensus reached. A 2018 non-linear meta-regression analysis analyzing the dose-response curve between exercise and AF showed that there is a J-shaped relationship between exercise frequency and AF risk exercise [56]. Exercise at 5-20 MET-h/week was correlated with reduction of AF development whereas volumes exceeding 20 MET-h/week showed no relation with risk ($p<0.001$)[56]. Conversely, a Spanish cross-sectional study examining the dose-response curve of high intensity exercise and AF did not find a J-shaped association but instead a U-shaped association with the accumulated lifetime endurance sport activity of 2000 hours or more resulting in increased prevalence of AF compared to sedentary individuals (OR 3.88 [1.55-9.73])[57]. Elosua et al. quantified that 1500 cumulative lifetime hours of endurance sports activities increased the prevalence of AF in the absence of structural heart diseases(OR 2.87 [1.20-6.91])[58], while Wilhelm et. al noted that there was increased AF risk after 4500 cumulative lifetime hours ($p<0.05$)[45]. Ultimately, while there is a consensus regarding the relationship between high endurance exercise and the development of AF, the exact therapeutic index for exercise and AF is not well defined.

Applying Coumel's triad of arrhythmogenesis to high endurance athletes, imbalance of the ANS with vagal predominance is a prominent factor. Increased vagal tone has been causally linked to vagally mediated AF at rest and with low-intensity physical work[20] due to bradycardia and increased HR variability[59]. The consequence of increased vagal tone in the cardiac electrophysiologic circuit has been demonstrated via ECG with increased RV and LV voltage, ST elevation and depression, peaked T waves, and T wave inversion in 10-40% of athletes[60]. Although these changes were historically considered a normal variant due to exercise, they are now believed to contribute to the development of AF in high endurance athletes[59]. Because of increased baseline vagal tone, vagally induced AF is more common in athletes at roughly 33% of autonomic AF cases[59]. However, adrenergically mediated AF is still quite prevalent (23%) due to increased sympathetic stress and catecholaminergic surges during strenuous endurance exercise[59]. In fact, recent speculation suggests that AF modulation in overtrained athletes is due to increased basal vagal tone coupled with frequent bursts of high intensity exercise inducing adrenergic over-stimulation[59]. Rebecci et. al suggests that fluctuations in autonomic tone, especially rapid oscillations, play a key role in initiating and perpetuating AF[20].

Athletes tend to be more symptomatic for AF, likely secondary to increased awareness of biophysical changes and reduction in performance[61]. The treatment of AF in athletes also proves challenging and individuals often must significantly cut back their training regimens due to exercise intolerance, fatigue, and training-induced AF exacerbations. For those who wish to continue training, typical rate-controlling medications blunt the HR response to activity resulting in submaximal exercise response[61]. Anticoagulation therapy for those athletes with a CHA2DS2-VASc of 2 or greater often necessitates an avoidance of outdoor activities that could lead to falls. De-training for a washout period of 2 months has been suggested and has indeed shown a reduction in AF susceptibility in rat models, however these studies failed to show resolution of atrial dilation and fibrosis[62]. Ultimately, the insult AF diagnosis causes in these highly motivated individuals should be considered as a key morbidity which will significantly alter the remainder of their lives.

Altitude and Atrial Fibrillation

The role that altitude plays in the development of AF is not well elucidated. While increasing elevation is known to be a risk factor for exacerbation of pre-existing arrhythmias[33], the comparative rates of AF in high altitude areas and low altitude areas is not reported and, thereby, may not appear to be noteworthy. However, altitude exposure promotes a variety of physiologic and biochemical changes adaptations which have the potential to be pro-arrhythmic and AF within this population should be further investigated.

Cardiac adaptations to altitude occur immediately upon exposure to increased elevation with detectable physiologic changes beginning at 1500m[8]. Recent studies have also highlighted the role of structural cardiovascular changes in response to altitude exposure, although the elevation at which this occurs is also not well elucidated. The pathogenesis of these structural changes is rooted in increased pulmonary artery pressures causing pulmonary hypertension and right heart strain[63]. While pure altitude-induced pulmonary hypertension is rare, estimated to occur in roughly 1% of exposed individuals[63], it has traditionally been studied in the setting of heart failure which could underreport its prevalence. Some studies of Andean populations estimate its prevalence as high as 18-55% with a male predominance[64] with the potential secondary risk being RV and RA enlargement. An echocardiographic study of 78 healthy Andean dwellers living permanently at 3800m and 5100m found that increased altitude resulted in increased right heart dilation with impairment of RV systolic function in conjunction with higher mean pulmonary arterial pressures at both rest and exercise ($p<0.01$)[65]. Similarly, an echocardiographic study of recently adapted Han migrants (3-12 months) and long term Han migrants (5-10 years) to Tibet showed enlarged RVs with increased RV longitudinal strain ($p<0.05$) but preserved LVEF compared to lowlanders within the recent migrant group which improved but did not recover in the long-term migrant group ($p<0.05$)[66]. These models demonstrate RV adaptation to increased hypoxic stress due to altitude which can provide arrhythmogenic foundation. Interestingly, native Tibetans had minimally altered cardiac changes as compared to lowlanders ($p<0.05$), suggesting potential evolutionary adaptations within certain groups and perhaps also explaining the lack of profound AF rates within these populations[66]. A longitudinal study of pulmonary artery pressures in different high-altitude environments from 2007 offered a similar perspective and found that, in general, there were reciprocal increases in pulmonary artery pressure and altitude ($p<0.01$) but with two notable exceptions[67]. In Lhasa, Tibet where there are natives with some of the oldest ancestry in the world, there were unexpectedly normal PA pressures (15 ± 1), while there were unexpectedly high PA pressures in Leadville, Colorado (24 ± 7) which is of primarily European ancestry whose lineage is relatively new to altitude[67].

It is known that pulmonary artery pressures increase with age due to vascular endothelial stiffening[68] and the role of altitude on this process has been unclear. A study of hypoxia induced pulmonary hypertension and RV hypertrophy in rat models sought to differentiate the differences between hypobaric hypoxic changes and the natural aging process[69]. Young, intermediate age, and older rats were exposed to hypobaric hypoxia for a period of 20 days and hypertrophy and pericellular myocyte fibrosis in response to chronic hypobaric hypoxia was augmented by the aging process in intermediate aged rats ($p<0.001$), but not in advanced age rats ($p<0.005$)[69]. Chouabe et. al suggested this could be due to terminally differentiated myocytes and physiologic loss of musculature in the advanced age group and that the natural aging process decreases the degree of heart remodeling induced by chronic hypoxia[69]. This may explain why AF rates do not appear to be higher in older individuals living at high altitude as compared to sea level. The study also demonstrated that RV hypertrophy induced by chronic hypoxia resulted in significant decreases in autonomic sympathetic activity, specifically within the RV regardless of age ($p<0.001$)[69]. The rate of AF in middle-aged adults living at altitude has not been investigated, but these studies suggest that the AF rate within this group could be greater than those at sea level due to increased cardiac remodeling.

In addition to promoting RV enlargement, chronic hypoxia has been shown to directly increase the pro-fibrotic pathway providing substrate for AF pathogenesis. Studies of obstructive sleep apnea in rat models found that chronic hypoxia induced changes in calcium utilization ($p<0.01$) and altered expression of gap junctions in cardiomyocytes ($p<0.05$), promoted electrical remodeling ($p<0.05$), and provoked angiotensin II production ($p<0.01$)[70,71]. All of these factors provide a foundation for AF development and propagation. As previously noted, angiotensin II has been implicated in the pro-inflammatory pathway that initiates fibrotic remodeling of cardiac structures[4]. In human models, a study assessing the pulmonary artery pressure (PAP) response to altitude transported 154 participants to 3700m from sea level and found that angiotensin II levels rose significantly from 0.6 to 0.79 ($p<0.001$)[72]. Bian et. al concluded that hypoxia may signal the activation of the renin-angiotensin-aldosterone system[72], thereby creating the potential for atrial fibrosis. Hypoxic exposure also upregulates the transcription of HIF-1, which is involved in inflammation, oxygen supply, cell proliferation, homeostasis, and apoptosis[73]. HIF-1 expression is elevated in patients with AF and is believed to play a key role in hypoxia induced cardiac structural remodeling and atrial fibrosis[73]. A 2015 study of rats exposed to various altitudes (500m, 3842m, and

4767m) demonstrated a direct positive correlation between increasing elevation and the expression of HIF-1 ($p<0.05$)[74]. Chronic high altitude exposure has also been shown to increase oxidative stress as indicated by increases in MDA, SOD, and GPx[75]. Oxidative stress is considered a potential arrhythmogenic source of AF due to alterations in ionic currents resulting in early afterdepolarization as well as myofibril structural changes which can promote fibrosis[4].

Acute exposure to hypobaric hypoxia causes increased sympathetic tone which remains elevated even after acclimatization[76]. Mazzeo et. al studied the adrenergic response to altitude via arterial norepinephrine (the main neurotransmitter of the sympathetic nervous system) and found that it had increased 52% above the values at sea level after 21 days at 4300m ($p<0.05$)[77]. There are some suggestions that prolonged altitude exposure results in downregulation of beta-adrenergic receptors, which could account for the extreme increase in circulating norepinephrine (NE) seen at elevation[77]. This assertion is backed up by neurographic recordings of muscle nerve activity which found a 400% increase in resting sympathetic discharge compared to sea level ($p<0.05$) with only mild increases in resting baseline HR[78]. Conversely, Boushel et. al transported subjects to 5260m for 9 weeks and noted enhanced parasympathetic activity, which could also explain the lack of extreme baseline tachycardia after adaptation to chronic altitude exposure by counterbalancing enhanced sympathetic activity[79]. The study showed that vagal blockade resulted in an 80bpm increase in HR at rest in subjects at 5260m ($p<0.05$) while vagal blockade of subjects at sea level resulted in a HR increase of only 10bpm ($p<0.05$)[79]. This is in contrast to prior studies at the same elevation in which atropine blockage of sympathetic tone resulted in a HR increase of only 10bpm[79]. The study, however, also highlighted enhanced basal sympathetic drive despite increased vagal activity. It demonstrated an increased resting HR of 15bpm at altitude as compared to sea level even after prolonged acclimatization, suggesting that sympathetic adrenergic control of HR is not attenuated[79]. The likely result of this neuromodulation is 'a new normal' of symathovagal balance. However, as previously discussed, any alterations in this balance introduces possible dysregulation and thereby the promotion of AF[20].

Altitude, Exercise, and Atrial Fibrillation

Like the lack of research regarding AF development in high-elevation individuals, the role that altitude plays in exercise-induced AF has not been explored. Because of the increased cardiovascular strain caused by altitude and cardiac remodeling caused by endurance training, it is likely that high-altitude endurance exercise augments the development of AF. As discussed, the rate of AF among middle-aged high endurance athletes is 5 times the rate of AF in the general population[7]. The pathogenesis of this is believed to be due to increased ventricular remodeling and fibrosis secondary to continuous cardiac loading[1,27,29,45,47–49], as well as disruption of autonomic HR control with increased vagal predominance[16,61]. Altitude, too, results in ventricular remodeling secondary to increased pulmonary pressures in response to hypoxia[63–67,69] and activation of pro-fibrotic pathways[70–75] that may be implicated in the development of AF. While the rate of AF in the general population of individuals residing at high-altitude may not be higher than those residing at sea level, high endurance athletes training at altitude provide the foundation for a 'double hit' promoting ventricular remodeling and AF development.

Exercise at altitude aggravates the physiologic stressors of hypobaric hypoxia, creating increased oxygen demand, augmenting sympathetic drive, and increasing the HR which is already elevated baseline due to elevation[80]. It also causes in an abrupt rise in pulmonary artery pressure (which is already high due to elevation[63]) secondary to mismatch in stroke volume and inadequate oxygen perfusion, resulting in enhanced right ventricular wall stress[81]. This decreases maximal cardiac output, which is interestingly even greater in fully acclimatized individuals[36]. As exercise workload increases, the rising HR eventually meets its maximal threshold which is lower than that at sea level, despite baseline elevation[80]. The reason for this HR and CO blunting at sub-maximal exercise levels is suspected to be protective to prevent hypoxic myocardial damage[80]. The immediate result is reduced exercise capacity at lower intensities of work with performance deficits beginning at 1600m for events 2-5 minutes but occurring at elevations as low as 700m for events lasting >20 minutes[8]. The long-term results of these repetitive bouts of extreme stress, represented by chronic endurance exercise performed at high altitudes, has not been studied. However, based on the increased cardiac workload, augmented pulmonary hypertension, and chronic hypoxic insult, enhanced ventricular remodeling and intermittent cardiac demand ischemia are potential consequences. Myocardial injury and fibrotic remodeling, again, establish the arrhythmogenic substrate for AF.

As previously discussed, the stresses of long-term endurance exercise and altitude exposure both facilitate the initiation of pro-fibrotic pathways. It has been suggested that there is a dose-response relationship between exercise intensity/duration and regulation of inflammatory processes[52] with a steep acute rise in inflammatory markers and oxidative stress directly after intense exercise[53] and suppression of anti-inflammatory markers following maximal activity[54]. Altitude exposure, too, promotes oxidative stress[75] and stimulates angiotensin II production which facilitates cardiac fibrosis[4,70,71]. Hypobaric hypoxia also upregulates HIF-1 resulting in inflammatory cascades and initiation of pro-fibrotic pathways[74]. Because these processes are interrelated, it is likely that simultaneous exposure to both independent risk factors (altitude and endurance exercise) significantly enhance their inflammatory and fibrotic effects, promoting the development of AF.

Altitude exposure and endurance exercise are also both known to cause neuromodulatory changes in autonomic HR control. Endurance exercise results in increased vagal tone[18,31,32] and exposure to hypobaric hypoxia causes increased sympathetic drive[76,77,79]. Boushel et. al found that despite increased sympathetic drive at altitude, there is also significantly increased baseline vagal tone[79]. Exercise training at altitude could, thereby, increase baseline vagal tone even further, causing profound bradycardia and creating the potential for electrical conduction abnormalities, and, thus, AF [18,46,59]. Rebecci et. al suggests that fluctuations in autonomic tone, especially rapid oscillations, play a key role in initiating and perpetuating AF[20]. Exercise at altitude causes strong bursts of sympathetic activation due to the extreme cardiac demand and hypoxic stress[82], far more so than intense exercise or altitude exposure alone would cause. Enhanced vagal tone is already a risk factor for AF[20], and when coupled with these chronic-intermittent bursts of sympathetic activation, provides a compelling basis for greater AF genesis.

In contrast to the little research on cardiovascular remodeling secondary to high altitude exercise, the improvement in VO_2 max that comes from acclimatization is well defined[5]. This improvement in VO_2 max has been co-opted by endurance athletes across the globe with a massive increase in high altitude training centers worldwide and intermittent hypoxia training in an effort to improve endurance status[83]. In fact, the US Olympic Training Center resides at ~1840m in Colorado Springs, Colorado for this very reason. Despite the reputation of the 'live high train high' model, very few studies have actually shown benefit from training at high elevation and those that have lacked sufficient evidence for generalizability[83]. The only training model to produce measurable improvement in VO_2 max in endurance athletes actually recommends living at moderate altitude for improvement in oxygen utilization but training at low elevation to prevent blunting of CO[5]. More recent data has shown that even this may be untrue and that altitude exposure may play no role in improvement of physical endurance or exercise performance[83].

Ultimately, the physiologic consequences of endurance exercise training at altitude provides the foundation for enhancement of AF development. After exhaustive literature review, it appears this is an association that has never been studied. The long-term implications of AF diagnosis are not inconsequential and the diagnosis can be devastating for highly motivated athletes who can no longer participate in endurance exercise. The implications for future cardiovascular health should also be considered, as cardioprotective exercise recommendations should be amended if altitude augments negative cardiac remodeling in response to endurance training.

PROJECT METHODS

Project Design

This will be a paired case control study which recruits high performance athletes defined as 42 or more MET-h of endurance activity per week from sports performance centers in Massachusetts and Colorado to explore the link between AF in athletes and training at altitude. The altitude exposure group will be defined as those athletes who spend 75% or more of their time training at 1500m or above, while the non-altitude exposure group will be defined as those athletes who spend 75% or more of their time training at or around sea level, defined as less than 200m. A group of athletes will be recruited from The Mass General Brigham Cardiovascular Performance Center for the non-elevation exposure group and from the University of Colorado Division of Sports Cardiology for the altitude exposure group. Participants will be matched as closely as possible for exercise MET-h per week and demographics between the high altitude and low altitude groups. Participation will be voluntary and data regarding exercise METs and elevation exposure during exercise will be pulled from participants' pre-existing Strava data. The Strava data from the last year prior to AF diagnosis will be pulled from each participant. The data will then be compiled and analyzed for average speed, duration, and elevation of exercise for each participant. Speed and duration will be used to calculate average weekly MET-h over the year. Investigators will then analyze the prevalence of AF as compared to altitude exposure. Investigators will also perform descriptive analysis for visual comparison of the dose-response curves for average weekly MET-h of exercise and AF incidence for the two exposure groups, as well as the dose response curve for altitude exposure and the incidence of AF.

Project Population and Sampling

Participants will be sampled from sports medicine centers with sports cardiology departments in Boston from the Massachusetts General Cardiovascular Performance Program and from the University of Colorado Division of Sports Cardiology. Participants will be considered for this study if they achieve on average at least 42 MET-h per week of exercise. Endurance exercise is defined as aerobic isotonic activity and sport disciplines including cycling, rowing, distance running, distance swimming, biathalon/triathalon, and cross-country skiing will be included in this study in conjunction with their designation as high-endurance sports by the 2017 investigation of cardiac remodeling in elite athletes[84]. The cutoff of 42 weekly MET-h or greater was determined based on the definition of strenuous activity as an intensity of 6 METs or higher[85], and the research of Patil et. al recommending avoidance of greater than 7 hours weekly of strenuous cumulative endurance exercise due to potential detrimental cardiovascular remodeling[47]. Although the amount of exercise required to increase the risk of AF development is a topic for debate, Patil et. al provided one of the few exercise suggestions for the upper limit of strenuous activity, and, therefore, his research will be utilized for the parameters of this study. Participant eligibility will also be limited between to those between the ages of 40 and 60, since this group is most impacted by exercise-induced AF. Those younger than 40 will and older than 60 will be excluded due to the greater potential for other etiologies impacting AF development besides endurance exercise. Further exclusion criteria, including major risk factors for AF, are listed in Table 1.

Table 1. Exclusion criteria.

- Does not have at least 1 year of Strava data prior to diagnosis of AF
- Does not exercise at their designated altitude for at least 75% of their annual training
- AF diagnosed prior to the age of 40
- Cardiovascular risk factors including cardiovascular disease, hypertension, diabetes, obesity, and tobacco use
- Secondary AF risk factors including chronic obstructive pulmonary disease and liver, thyroid, infectious and inflammatory diseases
- Congenital heart disease, inherited heart disease including long QT syndrome
- Illicit drug use
- Alcohol abuse defined as >14 drinks per week for men, >7 drinks per week for women[86]
- Use of any heart rate modifying medications including beta-blockers and non-dihydropyridine calcium channel blockers

A minimum sample size of 197 was determined using a sample size calculator 2x2 contingency table for chi-square analysis where the possible exposure is altitude and the possible outcome is AF[87]. Using the guidelines established by Cohen et. al, 0.2 was used for the effect size corresponding to a 'small effect'[88] in conjunction with AF prevalence in patients age 40-60 which is roughly 1% in the general population and 5% in endurance athletes of this age group[89]. Statistical power was set at 0.8 with an alpha level of 0.05.

Traditional sample size calculation using proportions will not be possible for this study given it is the first of its kind and the proportion of AF affected athletes who exercise at elevation is unknown

Treatment, Intervention, or Exposure Group

This study will be stratified by exposure to altitude with AF as the outcome. Exposure to altitude will be determined via a survey sent to participants (Figure 1). Inclusion for the altitude exposure group will be defined as those athletes who train at least 75% of the time at 1500m or above. The 75% cutoff was determined to allow for\ participant flexibility throughout the sampled year of data and to account for potential travel outside their usual training altitude. The elevation designation was determined by the observation that intermediate altitude starting at 1500m is where detectable physiological changes begin[8]. Although choosing a higher altitude cutoff would theoretically produce more robust evidence for the association of elevation and AF, it would also significantly reduce the potential participant pool and as such 1500m was chosen. There will be no treatment or intervention in this study.

Project Variables and Measurement Tools

Altitude is the main variable in this study with participants sorted into the altitude exposure group or non-altitude exposure group. Average elevation of annual exercise will also be determined via Strava data for later analysis. Paired matching based on patient demographics and MET-h/wk between the two groups will be performed as well to try to limit confounding variables. MET-h of exercise will only be considered as a variable to plot the dose-response curves of exercise duration/intensity and AF incidence. AF is the only outcome considered in this study. AF incidence will be defined as any single AF episode, regardless of duration or required intervention, in the absence of any of the exclusionary criteria which could account for the episode or episodes.

The main measurement tool used in this study is Strava. Strava is an extremely popular internet app founded in 2009 which tracks physical activity and incorporates social network features[90]. It tracks a variety of activities and works without internet access for athletes to track the progression of their training and share it with their peers. It functions via multiple phone and smartwatch types, tracks routes, and details multiple exercise parameters including pace, duration, productivity, elevation gain/loss, heart rate, and split times. It is enormously popular, especially among endurance athletes, and has over 100 million subscribers[90]. Although this retrospective study operates under the assumption that participants will have and use this app regularly to document their exercise progression, because of its popularity among the athletic community, investigators do not anticipate significant difficulty recruiting participants with ample Strava data.

Figure 1. Sample survey for participant eligibility.

Name:___________________________ Date of Birth:_______________ Gender:_______

Current Address:_______________________________________ Hometown:______________

Race:_____________________ Ethnicity:___________________

1. How often do you participate in high intensity endurance (running >6mph, bicycling >12mph, cross-country skiing, etc.) exercise?
   a. <4 hr/wk b. 4-7 hr/wk c. 7-12 hr/wk d. >12 hr/wk
2. For how many years have you participated in high intensity endurance exercise?
   a. <1 yr b. 1-5 yrs c. 5-10 yrs d. >10 yrs
3. Which of the following elevations would best describe the altitude at which you participate in at least 75% of your high intensity exercise?
   a. Sea level b.1000-5000ft. c. 5000-7000ft d. >7000ft
4. Do you have and regularly use Strava to track your exercise training?
   a. Yes b. No
5. If yes, for how many years have you used Strava to track your exercise?
   a. <1 year b. 1-5 years c. 5-10 years d. >10 years
6. Have you been diagnosed with atrial fibrillation
   a. Yes b. No If yes, what year were you diagnosed?___________
7. If you have been diagnosed with atrial fibrillation, did you use Strava to track your exercise for at least 1 year prior to your diagnosis?
   a. Yes b. No
8. Do you use any of the following substances?
   a. Tobacco/nicotine
   b. b. Illicit drugs
   c. c. Alcohol exceeding 14 drinks per week for men or 7 drinks per week for women
9. Do you take any medications? If yes, please specify: ____________________________

____

____

____

10. Please review the following table and specify if you have been diagnosed with any of the listed conditions:

☐ Cardiovascular disease	☐ Hypertension	☐ Diabetes	☐ Obesity
☐ COPD	☐ Liver disease	☐ Thyroid disease	☐ Autoimmune disease
☐ Chronic inflammatory disease	☐ Congenital heart disease	☐ Inherited long QT syndrome	☐ Substance use disorder

Recruitment

Participation in the study will be voluntary, and subjects will be recruited based on interest expressed via short questionnaire during appointment check-in with the collaboration of the sports medicine facilities. After their online check in, potential participants will have the option to complete the brief questionnaire if they would like to participate in the study. It will ask only if patients would like to share their Strava data for participation in this study and contact information for further participation. A brief survey on Qualdratics will be sent via email to patients who wish to participate in the study to determine inclusion eligibility as shown above. During the recruitment phase, the data from Qualdratics will be analyzed and data regarding participant estimated average weekly activity and demographics will be used to initially sort participants into activity level groups as designated on the survey (<4h/wk, 4-7hr/wk, 7-12hr/wk, >12hr/wk). This will be used to help guide recruitment for exposure/non-exposure group matching, however 1:1 matching will not be performed until after data collection. True matching will be done based on objective Strava measurements rather than participants' subjective approximation of weekly exercise which likely over-estimates their average activity level. Similarly, the survey will be used to sort participants into high-altitude and low-altitude exposure groups for recruitment purposes, however Strava data will ultimately be used to confirm average altitude of exercise. The electronic records of eligible participants will be accessed to determine if they are AF+ or AF- and the date of AF diagnosis.

Data Collection

Information from patient eligibility surveys will be collected and complied into a spreadsheet. Some questions on the survey including hometown and years of exercise training will not be used for eligibility but will be stored with patient demographic information for possible use in future analysis. Eligible patients will be stratified into either the altitude exposure group or the non-altitude exposure group based on their survey answers which will ultimately be confirmed with Strava data. Participants will be asked to come to the office for one appointment to share their Strava data with investigators. Strava data over a 1-year period will be taken for each participant; for those patients with diagnosed AF, it will be the year just prior to diagnosis. For patients without diagnosed AF, the most recent year of data will be collected. Data will be retrieved for each participant via Strava's Bulk Export option, de-identified and imported into Python. An algorithm in Python will be used to determine the average duration, speed, and elevation at which exercise was performed at over the representative year. Strava automatically sorts information on a sport dependent basis and this will need to be done individually for each sport for those participants who regularly participate in multiple endurance activities. Duration and speed will be used to calculate MET-h based on each activity's MET designation according to the Compendium of Physical Activities[91]. For participants with multiple endurance activity types, the average of their calculated METs across all activities will be used as the total. MET-h averages for participants between groups will be assessed and participants will be 1:1 paired based on their MET-h and demographic data using data matching software.

Analysis

The data will be analyzed first by comparing altitude exposure to the AF outcome variable. Both will be considered as dichotomous variables, with participants being either altitude exposure + or altitude exposure -, and either AF+ or AF-. This data will be analyzed using chi-square to determine the odds ratio of exposure (exercise at altitude) in those who are AF+ as compared to the non-exposure (exercise at sea level) in those who are AF+.

Next, dose-response curves will be used to plot the AF incidence by average yearly MET-h for each exposure group for visual comparison. While the data will be kept for potential future analysis, statistical comparison of the two dose-response curves is beyond the scope of this initial study and so only descriptive analysis will be used at this time. The dose response curve for all participants, regardless of exposure group, comparing the average elevation of training to the incidence of AF will also be plotted to visually investigate if AF incidence rises with increasing elevation.

Timeline and Resources

While data compilation and statistical analysis should not take more than a few months, participant recruitment might prove difficult given the exclusion parameters. Because of the increased AF rate encountered in cardiac specific sports performance centers, investigators anticipate at least one new participant per day. This study will be conducted this study over the course of 1.5 years with 1 year allotted to recruitment. Strava data collection will also occur continuously throughout year. The remaining months will be used to allow for final collection of data and statistical analysis. See Table 2 for a full projected timeline.

Table 2. Projected timeline

October 2024-December 2024	- IRB proposal submitted for approval

January 2025-January 2026	- Recruitment of participants - Data collection
January 2026-March 2026	- Completion of data collection - Data consolidation and analysis
March 2026-April 2026	- Preparation and submission of publication

Necessary resources include an office space for participant visits for data collection, access to patient electronic records for AF diagnosis information, and a computer capable of downloading and compiling Strava information into Python. Key personnel will include a primary investigator, two co-investigators to sort through patient surveys for participant eligibility, a statistician or data analyst to compile Strava data, and a clerical coordinator. This study will also require collaboration with the University of Colorado Division of Sports Cardiology and Mass General Brigham General Cardiovascular Performance Program to implement the participation questionnaire and grant access to the patient electronic medical records for AF incidence and date of diagnosis for study participants.

Institutional Review Board

This study will be submitted to the Boston University Medical Campus IRB as exempt status under 45 CFR part 46.104 subsection 2i: research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) and the information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects[92].

CONCLUSION

Discussion

There are a variety of confounding factors that impact this study. The first involves sampling bias within the athletic community. Highly trained athletes are often more in tune with biophysical changes in their performance and as such, may recognize the symptoms of AF more than the general population thereby increasing diagnosis rates. Furthermore, regional lifestyle differences among various athletic communities may result in differences in weekly and lifetime MET-between the elevation exposure groups. The limitations of this study predicate that lifetime MET-h are not considered, and long-term regular, vigorous exercise is a social commonplace in the mountainous regions more so than the general population at sea level[8]. While participants will be matched based on average weekly MET-h and demographic parameters, the total lifetime altitude exposure and exercise participation may play a role in potential AF development and cannot be controlled for. Other regional differences between groups which are not assessed in this study must also be considered, like socioeconomic status, medical literacy, education level, and occupation which may also play into the epidemiology and development of AF. Birthplace, ancestry, and duration of elevation exposure likely play roles in cardiac remodeling, however controlling for these factors goes beyond the scope of this initial study. Regardless, while the findings of this study will not conclusively delineate the relationship between high-altitude endurance exercise and AF, it will be the first study examining whether the AF incidence is indeed higher among this population, laying the groundwork for further investigation.

Summary

Studies have consistently shown that atrial fibrosis plays a crucial role in the pathogenesis of AF[38,41,45,47,48,59,73,93]. Fibrotic tissue disrupts atrial conduction, creating a substrate for re-entry circuits that perpetuate AF[12,17,38,93]. Inflammatory markers such as CRP have been associated with increased risk of AF development and recurrence[39,40,52]. Modulating inflammation through interventions like ablation or restoration of normal sinus rhythm (NSR) has shown promise in reducing AF incidence[40]. Moderate physical activity reduces cardiovascular risk factors and inflammation, thereby lowering the incidence of AF[1,22,52,55]. However, high-volume endurance exercise, particularly in sports like running and cycling, increases the risk of AF due to chronic cardiac stress and fibrosis[1,27,29,45,47–49]. Long-term endurance exercise can lead to significant cardiac adaptations such as atrial and ventricular enlargement, which are linked to increased AF risk[1,27,29,45,47–49]. Athletes, especially middle-aged male endurance athletes, have a higher prevalence of AF compared to the general population[7,20,27,29,44,45]. Altitude exposure poses unique physiological challenges such as hypoxia-induced pulmonary hypertension and increased sympathetic drive, which may contribute to AF development.[18,46,59,63,72,76,77,79,82]. The role of altitude in exacerbating AF risk, especially in combination with endurance exercise, warrants further investigation. Endurance exercise at high altitude intensifies physiological stressors like oxidative stress, inflammatory responses, and cardiac remodeling, all of which contribute to AF pathogenesis[4,71,74,75,84]. The combined effect of altitude and exercise may amplify these risks. Diagnosing and managing AF in athletes pose unique challenges, as traditional treatments like rate-control medications limit exercise capacity and strategies like de-training have shown mixed results in reducing AF susceptibility[61,62]. There is a need for longitudinal studies to establish precise thresholds of exercise intensity and altitude exposure that increase AF risk. Understanding these thresholds will guide recommendations for safe exercise practices in high-risk populations.

Clinical and/or Public Health Significance

High altitude training remains unparalleled in popularity amongst elite athletes, despite the lack of sufficient evidence for its benefit, and conversely, its probable detriment. Recent years have seen a substantial increase in endurance sport participation with the Strava Year in Sport Community Survey showing double the participation in marathon races in 2022 as compared to 2021 and a 22% global increase of cyclists with at least one 100-mile ride[94]. The Journal of Sports Medicine notes an exponential increase in Ultra endurance events, defined as sporting activities lasting >6 hours, within the last 25 years[95]. Furthermore, the US has experienced a massive migration of citizens to the 'mountain states' since 2019 with domestic net influx populations of 23.3 thousand to Colorado, 14.4 thousand to Wyoming, and 63.8 thousand to Montana[9]. The result is a notable increase in endurance sport participants practicing at altitude, and extreme races at high elevations have become the new frontier for many endurance competitors. In the US alone, participation in races such as the Leadville 100 (a 100 mile race at 3840m) and the Pike's Peak Marathon (a 26.3 mile race beginning at 2384m and climbing to 4302m) has grown substantially over recent years[96–98]. For many, these races are the ultimate test of fortitude and athleticism, however the long-term cardiovascular effects of these extreme challenges could be tremendous. Arrhythmogenesis seems a likely consequence. The lifestyle insult of an AF diagnosis is immense for any individual but the restrictions placed on highly motivated endurance athletes diagnosed with AF proves truly devastating. The prevalence of AF in high endurance athletes training at elevation needs to be identified to assess whether the risk of development is higher at increasing altitudes. Only then can the best exercise recommendations for long-term cardiovascular health be determined.

BIBLIOGRAPHY

1. Epidemiology of Atrial Fibrillation in the 21st Century | Circulation Research. Accessed September 11, 2023. https://www.ahajournals.org/doi/10.1161/CIRCRESAHA.120.316340

2. Arrhythmias - What Is an Arrhythmia? | National Heart, Lung, and Blood Institute, National Institutes of Health. Published March 24, 2022. Accessed March 22, 2024. https://www.nhlbi.nih.gov/health/arrhythmias

3. What is Atrial Fibrillation? www.heart.org. Accessed March 22, 2024. https://www.heart.org/en/health-topics/atrial-fibrillation/what-is-atrial-fibrillation-afib-or-af

4. Sagris M, Vardas EP, Theofilis P, Antonopoulos AS, Oikonomou E, Tousoulis D. Atrial Fibrillation: Pathogenesis, Predisposing Factors, and Genetics. *International Journal of Molecular Sciences*. 2022;23(1):6. doi:10.3390/ijms23010006

5. Levine BD, Stray-Gundersen J. "Living high-training low": effect of moderate-altitude acclimatization with low-altitude training on performance. *Journal of Applied Physiology (1985)*. 1997;83(1):102-112. doi:10.1152/jappl.1997.83.1.102

6. Coumel P. Paroxysmal Atrial Fibrillation: A Disorder of Autonomic Tone? *European Heart Journal*. 1994;15(suppl_A):9-16. doi:10.1093/eurheartj/15.suppl_A.9

7. Johnson DL, Day JD, Mahapatra S, Bunch TJ. Adverse Outcomes from Atrial Fibrillation;Mechanisms, Risks, and Insights Learned from Therapeutic Options. *Journal of Atrial Fibrillation*. 2012;4(5):477. doi:10.4022/jafib.477

8. Exercise and Elevation. American College of Cardiology. Accessed June 23, 2024. https://www.acc.org/Latest-in-Cardiology/Articles/2021/03/15/13/39/http%3a%2f%2fwww.acc.org%2fLatest-in-Cardiology%2fArticles%2f2021%2f03%2f15%2f13%2f39%2fExercise-and-Elevation

9. Domestic Migration to the Mountain States: Small Shifts with Big Implications – Placer.ai Blog. Accessed June 26, 2024. https://www.placer.ai/blog/domestic-migration-to-the-mountain-states-small-shifts-with-big-implications

10. Pollock JD, Makaryus AN. Physiology, Cardiac Cycle. In: *StatPearls*. StatPearls Publishing; 2024. Accessed March 26, 2024. http://www.ncbi.nlm.nih.gov/books/NBK459327/

11. Kurapati R, Heaton J, Lowery DR. Atrial Kick. In: *StatPearls*. StatPearls Publishing; 2024. Accessed March 22, 2024. http://www.ncbi.nlm.nih.gov/books/NBK482421/

12. Nesheiwat Z, Goyal A, Jagtap M. Atrial Fibrillation. In: *StatPearls*. StatPearls Publishing; 2023. Accessed September 11, 2023. http://www.ncbi.nlm.nih.gov/books/NBK526072/

13. Atrial Fibrillation - Types | National Heart, Lung, and Blood Institute, National Institutes of Health. Published November 30, 2022. Accessed March 27, 2024. https://www.nhlbi.nih.gov/health/atrial-fibrillation/types

14. Atrial fibrillation: Overview and management of new-onset atrial fibrillation - UpToDate. Accessed June 25, 2024. https://www.uptodate.com/contents/atrial-fibrillation-overview-and-management-of-new-onset-atrial-fibrillation?search=atrial%20fibrillation&source=search_result&selectedTitle=1%7E150&usage_type=default&display_rank=1

15. Marijon E. [Antithrombotic therapy in patients with atrial fibrillation]. *La Revue Du Praticien*. 2020;70(8):903-909.

16. Farré J, Wellens HJ. Philippe Coumel: a founding father of modern arrhythmology☆. *EP Europace*. 2004;6(5):464-465. doi:10.1016/j.eupc.2004.06.001

17. Atrial Fibrosis and Conduction Slowing in the Left Atrial Appendage of Patients Undergoing Thoracoscopic Surgical Pulmonary Vein Isolation for Atrial Fibrillation | Circulation: Arrhythmia and Electrophysiology. Accessed April 5, 2024. https://www.ahajournals.org/doi/full/10.1161/CIRCEP.114.001752

18. Gourine AV, Ackland GL. Cardiac Vagus and Exercise. *Physiology*. 2019;34(1):71-80. doi:10.1152/physiol.00041.2018

19. Chen PS, Chen LS, Fishbein MC, Lin SF, Nattel S. Role of the Autonomic Nervous System in Atrial Fibrillation: Pathophysiology and Therapy. *Circulation Research*. 2014;114(9):1500-1515. doi:10.1161/CIRCRESAHA.114.303772

20. Rebecchi M, De Ruvo E, Sgueglia M, et al. Atrial fibrillation and sympatho–vagal imbalance: from the choice of the antiarrhythmic treatment to patients with syncope and ganglionated plexi ablation. *European Heart Journal Supplemental*. 2023;25(Suppl C):C1-C6. doi:10.1093/eurheartjsupp/suad075

21. Atrial Fibrillation - Causes and Risk Factors | National Heart, Lung, and Blood Institute, National Institutes of Health. Published November 30, 2022. Accessed June 23, 2024. https://www.nhlbi.nih.gov/health/atrial-fibrillation/causes

22. Myers J. Exercise and Cardiovascular Health. *Circulation*. 2003;107(1):e2-e5. doi:10.1161/01.CIR.0000048890.59383.8D

23. Nystoriak MA, Bhatnagar A. Cardiovascular Effects and Benefits of Exercise. *Frontiers in Cardiovascular Medicine*. 2018;5:135. doi:10.3389/fcvm.2018.00135

24. Yang YJ. An Overview of Current Physical Activity Recommendations in Primary Care. *Korean Journal of Family Medicine*. 2019;40(3):135-142. doi:10.4082/kjfm.19.0038

25. Using METs to Track Physical Activity | Signos. Accessed June 21, 2024. https://www.signos.com/blog/using-mets-to-track-physical-activity

26. Amir M, Kabo P, Mappangara I, et al. Peak oxygen uptake and metabolic equivalents explained by six-minute walk test: A prospective observational study in predicting heart failure patient readmission. *Annals of Medicine and Surgery (London)*. 2022;77:103652. doi:10.1016/j.amsu.2022.103652

27. Fagard R. Athlete's heart. *Heart*. 2003;89(12):1455-1461.

28. Shave R, Howatson G, Dickson D, Young L. Exercise-Induced Cardiac Remodeling: Lessons from Humans, Horses, and Dogs. *Veterinary Sciences*. 2017;4(1):9. doi:10.3390/vetsci4010009

29. Sanz-de la Garza M, Carro A, Caselli S. How to interpret right ventricular remodeling in athletes. *Clinical Cardiology*. 2020;43(8):843-851. doi:10.1002/clc.23350

30. White DW, Raven PB. Autonomic neural control of heart rate during dynamic exercise: revisited. *Journal of Physiology*. 2014;592(Pt 12):2491-2500. doi:10.1113/jphysiol.2014.271858

31. Dixon EM, Kamath MV, McCartney N, Fallen EL. Neural regulation of heart rate variability in endurance athletes and sedentary controls. *Cardiovascular Research*. 1992;26(7):713-719. doi:10.1093/cvr/26.7.713

32. Gregoire J, Tuck S, Hughson RL, Yamamoto Y. Heart Rate Variability at Rest and Exercise: Influence of Age, Gender, and Physical Training. *Canadian Journal of Applied Physiology*. 1996;21(6):455-470. doi:10.1139/h96-040

33. Mallet RT, Burtscher J, Richalet JP, Millet GP, Burtscher M. Impact of High Altitude on Cardiovascular Health: Current Perspectives. *Vascular Health Risk Management*. 2021;17:317-335. doi:10.2147/VHRM.S294121

34. Tremblay JC, Ainslie PN. Global and country-level estimates of human population at high altitude. *Proceedings of the National Academy of Sciences*. 2021;118(18):e2102463118. doi:10.1073/pnas.2102463118

35. Wagner PD. Reduced maximal cardiac output at altitude — mechanisms and significance. *Respiration Physiology*. 2000;120(1):1-11. doi:10.1016/S0034-5687(99)00101-2

36. Naeije R. Physiological adaptation of the cardiovascular system to high altitude. *Progress in Cardiovascular Diseases*. 2010;52(6):456-466. doi:10.1016/j.pcad.2010.03.004

37. High Altitude Exposure Among People With Cardiovascular Conditions. American College of Cardiology. Accessed June 25, 2024. https://www.acc.org/latest-in-cardiology/ten-points-to-remember/2018/01/19/10/10/http%3a%2f%2fwww.acc.org%2flatest-in-cardiology%2ften-points-to-remember%2f2018%2f01%2f19%2f10%2f10%2fclinical-recommendations-for-high-altitude-exposure-of-individuals

38. Hansen BJ, Zhao J, Csepe TA, et al. Atrial fibrillation driven by micro-anatomic intramural re-entry revealed by simultaneous sub-epicardial and sub-endocardial optical mapping in explanted human hearts. *European Heart Journal*. 2015;36(35):2390-2401. doi:10.1093/eurheartj/ehv233

39. Multimarker approach to assess the influence of inflammation on the incidence of atrial fibrillation in women | European Heart Journal | Oxford Academic. Accessed April 5, 2024. https://academic.oup.com/eurheartj/article/31/14/1730/437829

40. Kallergis EM, Manios EG, Kanoupakis EM, et al. The role of the post-cardioversion time course of hs-CRP levels in clarifying the relationship between inflammation and persistence of atrial fibrillation. *Heart*. 2008;94(2):200-204. doi:10.1136/hrt.2006.108688

41. Turagam MK, Flaker GC, Velagapudi P, Vadali S, Alpert MA. Atrial Fibrillation In Athletes: Pathophysiology, Clinical Presentation, Evaluation and Management. *Journal of Atrial Fibrillation*. 2015;8(4):1309. doi:10.4022/jafib.1309

42. O'Keefe JH, Patil HR, Lavie CJ, Magalski A, Vogel RA, McCullough PA. Potential Adverse Cardiovascular Effects From Excessive Endurance Exercise. *Mayo Clinic Proceedings*. 2012;87(6):587-595. doi:10.1016/j.mayocp.2012.04.005

43. Abdulla J, Nielsen JR. Is the risk of atrial fibrillation higher in athletes than in the general population? A systematic review and meta-analysis. *Electrophysiology Europace*. 2009;11(9):1156-1159. doi:10.1093/europace/eup197

44. Li S, Zhang Z, Scherlag BJ, Po SS. Atrial Fibrillation in Athletes - The Story Behind The Running Hearts. *Journal of Atrial Fibrillation*. 2010;2(5):231. doi:10.4022/jafib.231

45. Wilhelm M. Atrial fibrillation in endurance athletes. *European Journal of Preventive Cardiology*. Published online January 30, 2013. doi:10.1177/2047487313476414

46. Grimsmo J, Grundvold I, Maehlum S, Arnesen H. High prevalence of atrial fibrillation in long-term endurance cross-country skiers: echocardiographic findings and possible predictors--a 28-30 years follow-up study. *European Journal of Cardiovascular Prevention and Rehabilitation*. 2010;17(1):100-105. doi:10.1097/HJR.0b013e32833226be

47. Patil HR, O'Keefe JH, Lavie CJ, Magalski A, Vogel RA, McCullough PA. Cardiovascular Damage Resulting from Chronic Excessive Endurance Exercise. *Missouri Medicine*. 2012;109(4):312-321.

48. Sánchez-Quintana D, López-Mínguez JR, Pizarro G, Murillo M, Cabrera JA. Triggers and Anatomical Substrates in the Genesis and Perpetuation of Atrial Fibrillation. *Current Cardiology Reviews*. 2012;8(4):310-326. doi:10.2174/157340312803760721

49. Themes UFO. Exercise-Induced Right Heart Disease in Athletes. Thoracic Key. Published June 14, 2017. Accessed June 25, 2024. https://thoracickey.com/exercise-induced-right-heart-disease-in-athletes/

50. Harrigan RA, Jones K. Conditions affecting the right side of the heart. *British Medical Journal*. 2002;324(7347):1201-1204.

51. Voeller RK, Aziz A, Maniar HS, et al. Differential modulation of right ventricular strain and right atrial mechanics in mild vs. severe pressure overload. *American Journal of Physiology-Heart and Circulatory Physiology*. 2011;301(6):H2362-H2371. doi:10.1152/ajpheart.00138.2011

52. Wang YH, Tan J, Zhou HH, Cao M, Zou Y. Long-term exercise training and inflammatory biomarkers in healthy subjects: a meta-analysis of randomized controlled trials. *Frontiers in Psychology*. 2023;14:1253329. doi:10.3389/fpsyg.2023.1253329

53. de Lucas RD, Caputo F, Mendes de Souza K, et al. Increased platelet oxidative metabolism, blood oxidative stress and neopterin levels after ultra-endurance exercise. *Journal of Sports Science*. 2014;32(1):22-30. doi:10.1080/02640414.2013.797098

54. Baygutalp F, Buzdağlı Y, Ozan M, Koz M, Kılıç Baygutalp N, Atasever G. Impacts of different intensities of exercise on inflammation and hypoxia markers in low altitude. *BioMed Central Sports Science, Medicine and Rehabilitation*. 2021;13(1):145. doi:10.1186/s13102-021-00375-0

55. Cerqueira É, Marinho DA, Neiva HP, Lourenço O. Inflammatory Effects of High and Moderate Intensity Exercise—A Systematic Review. *Frontiers in Physiology*. 2020;10. doi:10.3389/fphys.2019.01550

56. Ricci C, Gervasi F, Gaeta M, Smuts CM, Schutte AE, Leitzmann MF. Physical activity volume in relation to risk of atrial fibrillation. A non-linear meta-regression analysis. *European Journal of Preventive Cardiology*. 2018;25(8):857-866. doi:10.1177/2047487318768026

57. Calvo N, Ramos P, Montserrat S, et al. Emerging risk factors and the dose–response relationship between physical activity and lone atrial fibrillation: a prospective case–control study. *Europace*. 2016;18(1):57-63. doi:10.1093/europace/euv216

58. Elosua R, Arquer A, Mont L, et al. Sport practice and the risk of lone atrial fibrillation: a case-control study. *International Journal of Cardiology*. 2006;108(3):332-337. doi:10.1016/j.ijcard.2005.05.020

59. Sanchis-Gomar F, Perez-Quilis C, Lippi G, et al. Atrial fibrillation in highly trained endurance athletes — Description of a syndrome. *International Journal of Cardiology*. 2017;226:11-20. doi:10.1016/j.ijcard.2016.10.047

60. Mills JD, Moore GE, Thompson PD. THE ATHLETE'S HEART. *Clinics in Sports Medicine*. 1997;16(4):725-737. doi:10.1016/S0278-5919(05)70050-8

61. Atrial Fibrillation in Competitive Athletes. American College of Cardiology. Accessed June 25, 2024. https://www.acc.org/Latest-in-Cardiology/Articles/2019/08/16/08/20/http%3a%2f%2fwww.acc.org%2fLatest-in-Cardiology%2fArticles%2f2019%2f08%2f16%2f08%2f20%2fAtrial-Fibrillation-in-Competitive-Athletes

62. Stergiou D, Duncan E. Atrial Fibrillation (AF) in Endurance Athletes: a Complicated Affair. *Current Treatment Options in Cardiovascular Medicine*. 2018;20(12):98. doi:10.1007/s11936-018-0697-9

63. Naeije R. Cœur droit et altitude. *Revue des Maladies Respiratoires*. 2018;35(4):441-451. doi:10.1016/j.rmr.2017.01.013

64. Ulloa NA, Cook J. Altitude-Induced Pulmonary Hypertension. In: *StatPearls*. StatPearls Publishing; 2024. Accessed June 26, 2024. http://www.ncbi.nlm.nih.gov/books/NBK555925/

65. Doutreleau S, Ulliel-Roche M, Hancco I, et al. Cardiac remodelling in the highest city in the world: effects of altitude and chronic mountain sickness. *European Journal of Preventative Cardiology*. 2022;29(17):2154-2162. doi:10.1093/eurjpc/zwac166

66. Chen X, Liu B, Deng Y, et al. Cardiac Adaptation to Prolonged High Altitude Migration Assessed by Speckle Tracking Echocardiography. *Frontiers in Cardiovascular Medicine*. 2022;9. doi:10.3389/fcvm.2022.856749

67. Penaloza D, Arias-Stella J. The Heart and Pulmonary Circulation at High Altitudes. *Circulation*. 2007;115(9):1132-1146. doi:10.1161/CIRCULATIONAHA.106.624544

68. Lam CSP, Borlaug BA, Kane GC, Enders FT, Rodeheffer RJ, Redfield MM. Age-Associated Increases in Pulmonary Artery Systolic Pressure in the General Population. *Circulation*. 2009;119(20):2663-2670. doi:10.1161/CIRCULATIONAHA.108.838698

69. Chouabe C, Ricci E, Amsellem J, et al. Effects of aging on the cardiac remodeling induced by chronic high-altitude hypoxia in rat. *American Journal of Physiology-Heart and Circulatory Physiology*. 2004;287(3):H1246-H1253. doi:10.1152/ajpheart.00199.2004

70. Pei JM, Kravtsov GM, Wu S, Das R, Fung ML, Wong TM. Calcium homeostasis in rat cardiomyocytes during chronic hypoxia: a time course study. *American Journal of Physiology-Cell Physiology*. 2003;285(6):C1420-C1428. doi:10.1152/ajpcell.00534.2002

71. Gemel J, Su Z, Gileles-Hillel A, Khalyfa A, Gozal D, Beyer EC. Intermittent hypoxia causes NOX2-dependent remodeling of atrial connexins. *BioMed Central Cell Biology*. 2017;18(1):7. doi:10.1186/s12860-016-0117-5

72. Bian SZ, Zhang C, Rao RS, Ding XH, Huang L. Systemic Blood Predictors of Elevated Pulmonary Artery Pressure Assessed by Non-invasive Echocardiography After Acute Exposure to High Altitude: A Prospective Cohort Study. *Frontiers in Cardiovascular Medicine*. 2022;9. doi:10.3389/fcvm.2022.866093

73. Babapoor-Farrokhran S, Gill D, Alzubi J, Mainigi SK. Atrial fibrillation: the role of hypoxia-inducible factor-1-regulated cytokines. *Molecular and Cellular Biochemistry*. 2021;476(6):2283-2293. doi:10.1007/s11010-021-04082-9

74. Zhang F, Wu W, Deng Z, et al. High altitude increases the expression of hypoxia-inducible factor 1α and inducible nitric oxide synthase with intest-inal mucosal barrier failure in rats. *International Journal of Clinical and Experimental Pathology*. 2015;8(5):5189-5195.

75. Pena E, El Alam S, Siques P, Brito J. Oxidative Stress and Diseases Associated with High-Altitude Exposure. *Antioxidants (Basel)*. 2022;11(2):267. doi:10.3390/antiox11020267

76. Hainsworth R, Drinkhill MJ, Rivera-Chira M. The autonomic nervous system at high altitude. *Clinical Autonomic Research*. 2007;17(1):13-19. doi:10.1007/s10286-006-0395-7

77. Mazzeo RS, Bender PR, Brooks GA, et al. Arterial catecholamine responses during exercise with acute and chronic high-altitude exposure. *American Journal of Physiology*. 1991;261(4 Pt 1):E419-424. doi:10.1152/ajpendo.1991.261.4.E419

78. Hansen J, Sander M. Sympathetic neural overactivity in healthy humans after prolonged exposure to hypobaric hypoxia. *Journal of Physiology*. 2003;546(Pt 3):921-929. doi:10.1113/jphysiol.2002.031765

79. Boushel R, Calbet JA, Rådegran G, Sondergaard H, Wagner PD, Saltin B. Parasympathetic neural activity accounts for the lowering of exercise heart rate at high altitude. *Circulation*. 2001;104(15):1785-1791. doi:10.1161/hc4001.097040

80. Richalet J, Hermand E. Modeling the oxygen transport to the myocardium at maximal exercise at high altitude. *Physiological Reports*. 2022;10(8):e15262. doi:10.14814/phy2.15262

81. Kleinnibbelink G, van Dijk APJ, Fornasiero A, et al. Exercise-Induced Cardiac Fatigue after a 45-Minute Bout of High-Intensity Running Exercise Is Not Altered under Hypoxia. *Journal of the American Society of Echocardiography*. 2021;34(5):511-521. doi:10.1016/j.echo.2020.12.003

82. Cornwell WK, Baggish AL, Bhatta YKD, et al. Clinical Implications for Exercise at Altitude Among Individuals With Cardiovascular Disease. *Journal of the American Heart Association*. 2021;10(19):e023225. doi:10.1161/JAHA.121.023225

83. Lundby C, Millet GP, Calbet JA, Bärtsch P, Subudhi AW. Does 'altitude training' increase exercise performance in elite athletes? *British Journal of Sports Medicine*. 2012;46(11):792-795. doi:10.1136/bjsports-2012-091231

84. Adea JE, Leonor R, Lu CH, et al. Sport disciplines and cardiac remodeling in elite university athletes competing in 2017 Taipei Summer Universiade Observational Study Medicine ® OPEN 1. *Medicine*. 2020;99:e23144. doi:10.1097/MD.0000000000023144

85. Mendes M de A, da Silva I, Ramires V, et al. Metabolic equivalent of task (METs) thresholds as an indicator of physical activity intensity. *Public Library of Science One*. 2018;13(7):e0200701. doi:10.1371/journal.pone.0200701

86. Risky drinking and alcohol use disorder: Epidemiology, clinical features, adverse consequences, screening, and assessment - UpToDate. Accessed June 25, 2024. https://www.uptodate.com/contents/risky-drinking-and-alcohol-use-disorder-

epidemiology-clinical-features-adverse-consequences-screening-and-assessment?search=alcohol%20abuse&source=search_result&selectedTitle=2%7E150&usage_type=default&display_rank=2

87. Statistical Power and Sample Size Calculation Tools. Accessed June 25, 2024. https://cran.r-project.org/web/packages/pwrss/readme/README.html

88. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. L. Erlbaum Associates; 1988.

89. Karjalainen J, Kujala UM, Kaprio J, Sarna S, Viitasalo M. Lone atrial fibrillation in vigorously exercising middle aged men: case-control study. *British Medical Journal*. 1998;316(7147):1784-1785.

90. Strava | Running, Cycling & Hiking App - Train, Track & Share. Strava. Accessed June 25, 2024. https://www.strava.com/

91. Ainsworth B, Whitt-Glover M, IRWIN M, et al. Compendium of Physical Activities: an Update of Activity Codes and MET Intensities. *Medicine and Science in Sports and Exercise*. 2000;32:S498-504. doi:10.1097/00005768-200009001-00009

92. Protections (OHRP) O for HR. Exemptions (2018 Requirements). Published March 8, 2021. Accessed July 10, 2024. https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/common-rule-subpart-a-46104/index.html

93. Hinderer S, Schenke-Layland K. Cardiac fibrosis – A short review of causes and therapeutic strategies. *Advanced Drug Delivery Reviews*. 2019;146:77-82. doi:10.1016/j.addr.2019.05.011

94. Year in Sport 2022. Accessed June 26, 2024. https://www.strava.com/yis-community-2022

95. Scheer V. Participation Trends of Ultra Endurance Events. *Sports Medicine and Arthroscopy Review*. 2019;27(1):3. doi:10.1097/JSA.0000000000000198

96. Imogene Pass Run – A difficult race for well prepared athletes. Accessed June 25, 2024. http://live-raceresults.com/imogene/

97. Leadville Trail 100 Run - Leadville Race Series. Accessed June 25, 2024. https://www.leadvilleraceseries.com/run/leadvilletrail100run/

98. Results. Pikes Peak Marathon. Accessed June 25, 2024. https://www.pikespeakmarathon.org/results.html

CURRICULUM VITAE

[redacted]

[redacted]