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Exercise type in left atrial remodeling and incident atrial fibrillation

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BOSTON UNIVERSITY
SCHOOL OF MEDICINE

Thesis

**EXERCISE TYPE IN LEFT ATRIAL REMODELING AND INCIDENT ATRIAL
FIBRILLATION**

by

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BRENT ADAM HEIMLICH

ABSTRACT

Background

The adaptive plasticity of the heart enables it to maintain sufficient cardiac output under a wide array of physiological and pathological states. When metabolic demands are imposed on a chronic basis, such as during a long-term exercise regimen, the heart adapts to meet those demands. When these adaptations are due to exercise, physiological and, therefore, reversible remodeling occurs, as opposed to the irreversible process of pathological remodeling secondary to cardiac injury. While sharing similarities, endurance and resistance exercise engage the heart, and more specifically, the left atrium in vastly different manners, leading to dissimilar patterns of remodeling and disparate outcomes in the subsequent incidence of atrial fibrillation.

Literature Review

Existing research has largely centered around defining the limits of physiological remodeling to accurately differentiate it from pathological remodeling. Not only is there a great deal of overlap between the two, but these phenomena can often coexist, making it difficult to distinguish which process is at play. It is largely agreed upon in the scientific community that chronic high intensity endurance exercise results in reversible left atrial

enlargement and the most credible evidence shows it is indeed associated with an increased incidence of atrial fibrillation. Reliable data for resistance athletes, however, is less convincing.

Proposed Project

This will be a prospective cohort study of 3,600 student athletes engaged in either endurance or resistance training (with a non-athlete control group) to be followed over 120 days to assess for differences in their patterns of left atrial remodeling. A second phase will consist of a 10-year follow-up to compare the incidence of atrial fibrillation in each cohort. We hypothesize that both the remodeling patterns and the subsequent incidence of atrial fibrillation will be different between the three groups.

Conclusion

In performing this study, we will compile one of the largest study populations to date in order to accurately detect clinically significant changes in cardiac structure and function which, while largely adaptive and beneficial, can also lead to life threatening arrhythmias later in life. Exercise type unquestionably plays a key role in the reason why and the rate at which these physiological processes occur. A deeper understanding is imperative to fully determine the consequences of high intensity training.

Significance

These findings will allow athletes to better understand the effects training has on cardiovascular health. As atrial fibrillation is the most common arrhythmia in athletes, the clinical ramifications of this study are immense.

TABLE OF CONTENTS

ACKNOWLEDGMENTS	iv
ABSTRACT.....	v
TABLE OF CONTENTS.....	viii
LIST OF TABLES	x
LIST OF FIGURES	xi
LIST OF ABBREVIATIONS.....	xii
INTRODUCTION	1
Background.....	1
Statement of the Problem.....	2
Hypothesis.....	3
Objectives and Specific Aims.....	3
REVIEW OF THE LITERATURE	5
Overview.....	5
Existing Research.....	13
METHODS	31
Study Design.....	31
Study Population and Sampling.....	31
Exposure Groups.....	33
Study Variables and Measures.....	34

Recruitment.....	35
Data Collection	36
Data Analysis	39
Timeline and Resources	39
Institutional Review Board	42
CONCLUSION.....	44
Discussion.....	44
Summary.....	46
Clinical and/or Public Health Significance.....	47
APPENDIX I	49
LIST OF JOURNAL ABBREVIATIONS.....	50
REFERENCES	51
CURRICULUM VITAE.....	55

LIST OF TABLES

Table 1. Study Variables and Measures.....	35
Table 2. Timeline and Resources.....	41

LIST OF FIGURES

Variations in Physiological Growth.....	7
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LIST OF ABBREVIATIONS

EA	Endurance athletes
NA	Non-athletes
RA	Resistance athletes

INTRODUCTION

Background

When the human heart is exposed to repeated bouts of stress for an extended period of time, alterations in its physical structure begin to appear, referred to as cardiac remodeling. These changes arise from either pathological or physiological processes and may influence the size, shape, or function of the heart. While these changes are often the result of cardiac injury, they can also be considered functional changes that allow the heart to adapt to maintain the ability to steadily distribute oxygen rich blood throughout the body. This, in turn, helps to maintain sufficient cardiac output to ensure sustained organ and tissue perfusion. This holds true regardless of the etiology of remodeling, whether left ventricular hypertrophy resulting from a long-standing pressure overload in pathological conditions like chronic hypertension or a generalized benign cardiomegaly resulting from years of intense exercise training.

In the context of physiological-induced changes, left atrial enlargement is a hallmark of the cardiac remodeling process, which occurs in response to chronic pressure and volume overload.¹ By analyzing this specific heart chamber, we can gain insight into what type of effects various stressors have on the defining features of the left atrium, such as wall thickness or volume index. These characteristics adapt to the hemodynamic flow through the heart and, as a result, elucidate how and why certain types of training, namely endurance and resistance, elicit the types of cardiac responses that they do.

Finally, the left atrium is also of particular interest owing to its involvement in the pathophysiology of atrial fibrillation, an arrhythmia which occurs more often in athletes

than in sedentary controls.² By identifying those cardiac adaptations specific to each type of training, we can begin to identify potential associations between training type and the subsequent incidence of atrial fibrillation. Positive findings, even on one small aspect of pathophysiology, will provide additional information on this clinical challenge that impacts many athletes.

Statement of the Problem

The etiologies of left atrial enlargement and subsequent atrial fibrillation are vast and include congenital and acquired risk factors, such as advanced age, hypertension, obesity, genetics, diabetes, heart failure, ischemic heart disease, hyperthyroidism, valvular disease, arteriovenous fistulas, chronic kidney disease, moderate to heavy alcohol use and smoking, amongst others.³ Since atrial fibrillation is the most common arrhythmia in athletes, it is imperative to accurately explore the subtleties of how left atrial enlargement develops in the first place. Since the degree of remodeling of the left atrium is predictive of atrial fibrillation, it is essential that we understand the process of that remodeling. By analyzing the types of stressors that the hearts of athletes are exposed to, we can differentiate between physiological remodeling and pathological remodeling. Within the scope of physiological remodeling, it is clear that activity can stress the heart in different ways, which largely depend on the specific demands required for its execution. It is, therefore, possible that certain activities could act as stressors on the heart chamber in vastly different manners.

While much of the existing literature centered around this topic explores various facets of the association between high intensity endurance training and left atrial enlargement, data is exceedingly sparse on qualifying the association between high intensity resistance training and left atrial enlargement. Secondary to this process, we must understand how the various stressors culminating in left atrial enlargement impact the subsequent development of atrial fibrillation. The clinical ramifications are fascinating and allow one to provide athletes a response tailored to their respective training background.

Hypothesis

The pattern of left atrial remodeling will differ between college non-athletes, high intensity endurance college athletes and high intensity resistance college athletes. Across a period of 10 years post remodeling, the incident risk of atrial fibrillation will differ between the 3 cohorts.

Objectives and Specific Aims

This study will thoroughly elucidate the primary mechanisms of remodeling of the left atrium in athletes, as well as determine how the mechanisms are impacted by the type of stress imposed upon the cardiovascular system. The primary objective is to determine the difference in the pattern of physiological cardiac remodeling in the left atrium, depending on the specific type of training regimen an athlete may adhere to. The secondary objective focuses on the clinical significance of this remodeling -- is one type of training

associated with a higher incidence of atrial fibrillation over the course of a 10-year follow-up. Specifically, this study aims to:

1. Determine the difference in size and volume of the left atrium between athletes of different training regimens and non-athlete controls.
2. Establish the difference in left atrial function between athletes of different training regimens and non-athlete controls.
3. Assess the variability in left atrial strain values between athletes of different training regimens and non-athlete controls.
4. Identify the association of exercise type with specific left atrial remodeling patterns predisposing athletes to atrial fibrillation.

REVIEW OF THE LITERATURE

Overview

There is a well-established consensus as to the many short- and long-term benefits of exercise on human health. From the prevention of chronic diseases like obesity and diabetes mellitus, to reducing the incidence of a multitude of malignancies from lung cancer to colon cancer, or even its therapeutic effects on clinical depression and chronic sleep disturbances, exercise has been proven a crucial component of good health practice.⁴ However, these benefits also come at a physiological cost.

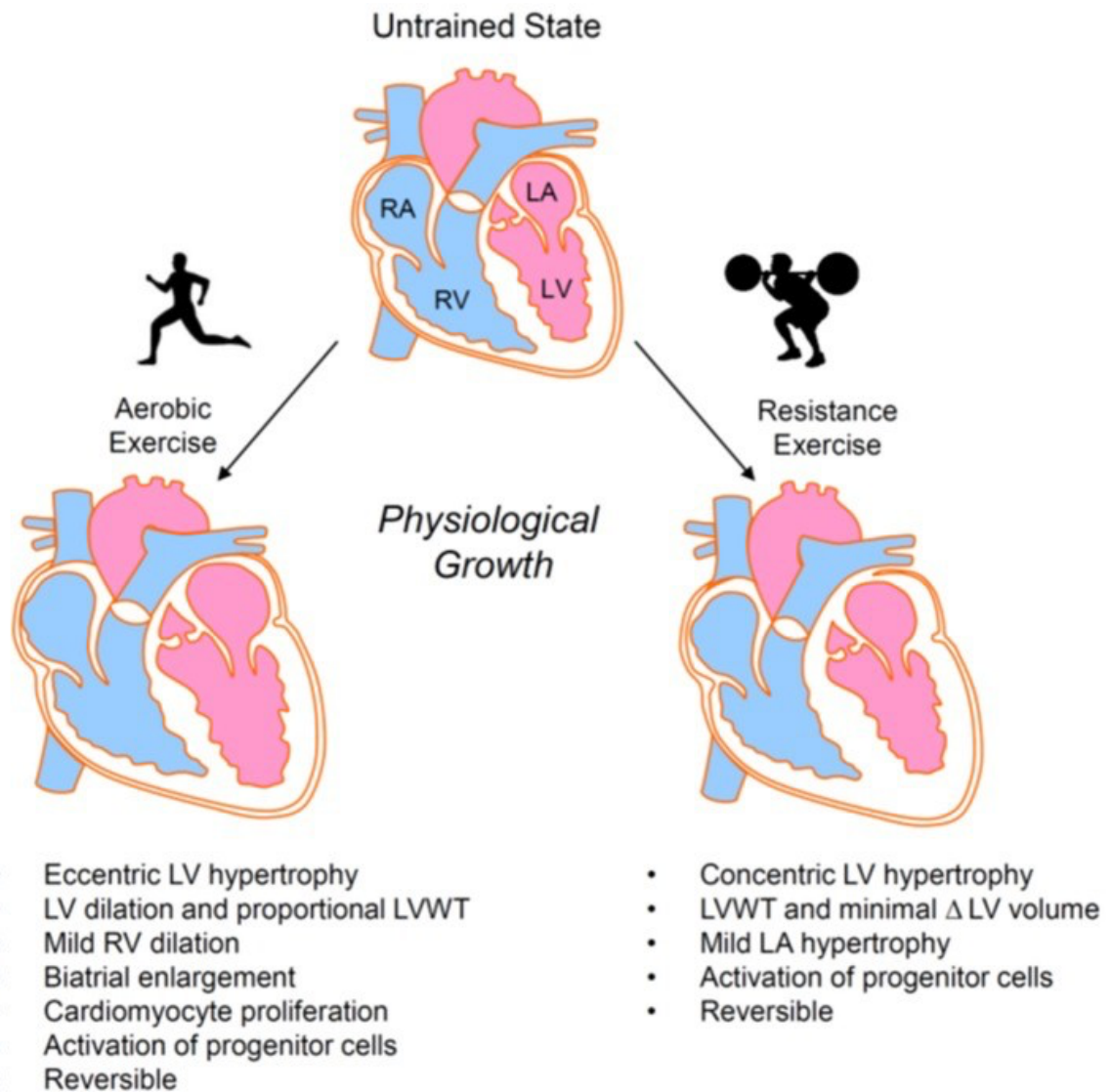
The cardiovascular system, which reaps a vast proportion of the physiological benefits of exercise, also undergoes a wide array of changes which may contribute to negative health outcomes including, but not limited to, heart arrhythmias like atrial fibrillation and atrial flutter. In fact, it is estimated that for every 10 years of regular endurance exercise (defined in one large study as 30 minutes or more of exercise, three or more times per week), the risk of atrial fibrillation increases by approximately 16%, while the risk of atrial flutter increases by 42%.⁵ Despite the obvious benefits of exercise, it is vital that we understand and clearly communicate the lesser known but significant risks.

Exercise Type

Exercise can be generally divided into two overarching categories: endurance (also referred to as dynamic or aerobic) and resistance (static, strength, anaerobic) exercise. As with any muscle in the human body, the healthy heart becomes stronger

when subjected to the demands of exercise. As a rule, endurance sports such as distance running or swimming increase the overall size of the heart, thereby enabling it to pump a greater quantity of blood with every beat (increased stroke volume), whereas shorter more intense workouts, such as weight lifting, thicken the heart walls thus enhancing contractility (the inherent strength of the heart's contraction during systole).⁶ On a metabolic level, conventional endurance exercise targets submaximal muscle contractions to increase aerobic power production.⁷ This type of training helps to generate new mitochondria and increases both capillary density and enzymes, which results in an enhanced ability of skeletal muscle to utilize oxygen.⁸ Conversely, resistance exercise targets short bursts of maximal or near maximal muscle contractions.⁷ This type of training promotes skeletal muscle hypertrophy and increases in strength through augmented myofibrillar volume without any reliance on oxygen for performance.⁹ Figure 1 provides a breakdown of how different forms of exercise induce different patterns of physiological remodeling on the human heart.

Variations in Physiological Growth



Aerobic and resistance exercise elicit significantly different forms of physiological cardiac remodeling adopted from Fulghum et al.

It is important to note that despite these general rules, all muscles, the heart included, are composed of a combination of fast twitch and slow twitch muscles.¹¹ An athlete's overall fitness and response to physiological stress is dependent upon a number of factors that go far beyond the scope of this paper. Simply stated, there is a great deal of individual variation in how people respond to any one type of exercise training or prescribed plan. Some individuals may respond positively to a given regimen, undergoing the physiological and aesthetic benefits associated with that training plan, whereas others might respond quite poorly to that very same routine, even after taking into consideration factors such as gender, age and ethnic background.¹²

Cardiac Remodeling

Significant structural changes can take place over time in the heart due to various stressors being imposed upon it. These changes are typically the result of cardiac disease or cardiac injury and are known collectively as cardiac remodeling. The definition has evolved throughout the years since the term "remodeling" was first coined in a 1982 study analyzing acute myocardial infarction.¹³ The currently accepted definition, established in 2000, designated cardiac remodeling as a group of molecular, cellular and interstitial changes that clinically manifest as alterations in size, shape and function of the heart resulting from cardiac injury.¹⁴ Cardiac remodeling, in any of its various forms, is a universal phenomenon and its prevalence is, therefore, dependent upon the specific precipitating cause.¹⁵

In practice, if this remodeling is due to injury to the heart muscle, it is referred to as pathological remodeling (a maladaptive process).¹⁶ Remodeling of this type is associated with the development and progression of ventricular impairment, irregular heart rhythms and an overall poor prognosis.¹⁷ Conditions that could cause this include myocardial infarction, chronic hypertension, congenital heart disease and valvular heart failure.¹⁶ However, cardiac remodeling can also arise as a result of high intensity exercise in otherwise healthy athletes. This is referred to as physiological remodeling (an adaptive process). In athletes, the result of physiological remodeling due to the demands of exercise is known as athlete's heart syndrome.

Athlete's Heart

Athlete's heart, sometimes referred to as athlete's heart syndrome or athletic heart syndrome, is a non-pathological cardiac adaptation to long-term, high-intensity training characterized by an increase in three principal cardiac metrics: heart cavity diameter, wall thickness and left ventricular mass.¹⁸ Clinically, there are no symptoms, at least initially, though maximal stroke volume and cardiac output both increase, thereby contributing to a resting heart rate under 60 bpm (known as bradycardia) and a longer diastolic filling time.¹⁹ Ventricular remodeling resulting from physical activity is a physiological process due to both diastolic and systolic functions of the heart remaining normal or even improving following remodeling.²⁰ Thus, those stressors would likely trigger the same physiological process on the left atrium of the heart.²⁰

Evidence is currently mixed on whether strictly physiological remodeling increases one's risk for negative health outcomes, such as arrhythmias and embolic events. Of note, one important distinction between the two types of remodeling is that physiological remodeling tends to be reversible, while pathological remodeling, though modifiable, is largely an irreversible process.²¹ Despite the fact that the structural changes seen in athlete's heart resemble those seen in various cardiac disorders, these changes (along with the accompanying bradycardia) typically regress completely with detraining. However, one study found that substantial left ventricular chamber dilatation actually persisted in approximately 20% of elite athletes.^{22,23} Treatment for athlete's heart is currently deemed unnecessary, although a deconditioning period of 3 months with regular follow-up may be advisable in order to track left ventricular regression to discriminate the syndrome from a pathological process, such as hypertension or cardiomyopathy.²²

Research remains sparse with regard to the potential impact of top-level training on the left atrium, though this chamber is widely believed to be involved as one of the components of athlete's heart.¹⁸ One major study defined the upper ranges of left atrial enlargement in a large athlete cohort (determined to be a left atrial diameter of 46 mm in women and 50 mm in men).²⁴ As a result, transverse left atrial dimensions exceeding those thresholds in trained athletes (either endurance or resistance) were deemed more likely to represent the physiological sequelae of a primary pathologic condition rather than the benign physiological adaptation of the heart to intensive exercise training.²⁴

It is imperative that we have standardized and accurate values for what defines the normal ranges of heart chamber dimensions since the clinical consequences can be

considerable. For instance, increased left ventricular cavity dimensions in many elite athletes fall within the same range as those of patients with known pathological conditions, such as primary dilated cardiomyopathy.²⁵ Subjects with athletic backgrounds possessing left ventricular dimensions which fall within this overlapping range are, therefore, more difficult to diagnose as additional testing must be done to determine the root cause of the cardiac remodeling: athlete's heart or structural heart disease.²⁶ Moreover, the implications for professional athletes can range from serious to utterly catastrophic. For instance, an athlete could be incorrectly disqualified from a competition due to an erroneous diagnosis of primary cardiac disease. Or in a terrifying worst case scenario, an athlete could be mistakenly diagnosed with athlete's heart while concealing primary cardiac disease, such as hypertrophic cardiomyopathy, which would subsequently remain undiagnosed, thus putting the patient at risk for grievous adverse outcomes.²⁷

The most commonly cited mechanism of physiological left atrial dilation in athletes is increased volume load, as opposed to increased left ventricular filling pressure as observed in pathologic left ventricular hypertrophy.²⁴ In practice, alterations in atrial size can be detected after approximately 3 to 4 months of intensive exercise training.²⁸ As this adaptation is reversible following a period of detraining, there is a direct causal relationship between intense exercise and resultant atrial enlargement.²⁸ Physical exercise also directly influences cardiac growth through the activation of both circulating and tissue-specific cardiac progenitor cells, as well as instigating the formation of new cardiomyocytes.²⁹ Physiological remodeling may take several forms, largely dependent

upon the type and intensity of exercise training. For instance, certain types of sports have the most significant effect in enlarging left ventricular cavity dimensions.²⁶ Furthermore, both left atrial and left ventricular remodeling in trained athletes is a manifestation of a global adaptation of the heart to the elevated preload accompanying intensive and chronic dynamic training.²⁶

These mechanisms have been found to exist in animal models as well. For instance, swim training in rats was found to induce a different response when compared to running on a treadmill. Swim training led to a greater resting bradycardia, as well as increased adrenaline and noradrenaline concentrations in cardiac tissue, when compared to running.^{30,31} Swimming is generally considered both an aerobic and anaerobic sport, whereas running is largely deemed to be aerobic. Despite this study not being done on human subjects, it nonetheless supports the hypothesis that there is a detectable difference in how the heart responds and adapts to various types of exercise training.

Consequences of Remodeling

Lastly, atrial fibrillation has been consistently linked to physiological cardiac remodeling. Atrial fibrillation is an irregular heartbeat (arrhythmia) in which the atria of the heart beat ineffectively, thereby leading to an increased risk of blood clots.³² If left untreated, atrial fibrillation doubles the risk of heart-related deaths and is associated with a 5-fold increase in ischemic stroke risk.^{32,33} It is estimated that between 2.7 million and 6.1 million people in the United States alone have atrial fibrillation and this number is on the rise as our population ages.³⁴ While atrial fibrillation has a wide array of subtypes and

respective etiologies, the secondary focus of this paper will be on atrial fibrillation as a consequence of cardiac remodeling from long-term training in endurance and resistance athletes.

Interestingly, one study reported that in a large population of highly trained athletes competing in 38 different sports, left atrial enlargement was common with a prevalence of roughly 20%.²⁴ In another study involving 134 Swiss professional cyclists, despite left atrial dilatation in more than $\frac{3}{4}$ of athletes, the highest prevalence of atrial fibrillation was 10% in the 7th decade of life.² This suggests that left atrial enlargement by itself is not a good predictor of atrial fibrillation risk. Another study found that there might be some measure of overlap between physiological and pathological remodeling, such that the formation of fibrosis might accompany the remodeling from lifelong endurance training, which subsequently acts as a substrate for arrhythmias.³⁵ Thus, given the variety of forces at play and unique physiological attributes of each individual athlete, the long term implications of these processes remain largely speculative.

Existing Research

Left Atrial Enlargement in Young High-Level Endurance Athletes – Another sign of Athlete’s Heart?

This study was performed by Wojciech Król, et al. in Warsaw, Poland in 2016. The objective of this study was to further supplement the research around what constitutes athlete’s heart syndrome. The authors focused on left atrial enlargement, a major element of the syndrome, and sought to illustrate that this was a physiological adaptation related to fitness rather than the result of any pathological phenomenon. The cohort consisted of

114 international-level rowers with an average age of 17.5 years and 46.5% of whom were women. All subjects engaged in both cardio-pulmonary exercise testing and resting transthoracic echocardiography in addition to two-dimensional speckle tracking echocardiography to assess left atrial strain. Based on these measurements, researchers found that left atrial enlargement was present in almost half of all the athletes (43%). More specifically, left atrial enlargement was mild in 27.2%, moderate in 11.4% and severe in 4.4% of the athletes. They also detected a significant association between the left atrial volume index and maximal aerobic capacity ($R > 0.3$; $p < 0.001$). Lastly, left atrial strain was found to be independent of atrial size, left ventricle hypertrophy and left ventricle filling pressure. The authors, thus, concluded that left atrial enlargement was a common physiological adaptation found in healthy young endurance athletes and was correlated only with exercise capacity, thereby providing evidence to its classification as a physical manifestation of athlete's heart syndrome.

This study provides credible evidence to support left atrial enlargement as being a strictly physiological process and, thus, an integral component of athlete's heart syndrome due to its heightened frequency in healthy young endurance athletes and its marked association with exercise capacity. This is a descriptive cross-sectional study inspecting the prevalence of left atrial enlargement in a defined population at a specific period in time. This type of study is fairly straightforward to perform and inexpensive, when compared to other types of study designs such as a prospective cohort study. An extensive array of medical assessments was used to evaluate subjects, including clinical and physical examination, resting ECG, transthoracic echocardiography and finally, an

exercise cardiopulmonary test. Researchers also made sure to exclude any athletes with comorbidities, such as hypertension, valvular heart disease, cardiomyopathy, absence of sinus rhythm, and any subjects with a history of pulmonary, endocrine or renal disease. This was imperative because these conditions would all result in some measure of pathological cardiac remodeling. Thus, the inclusion of subjects with these conditions could have drastically influenced and potentially skewed the results. Crucially, all athletes provided informed consent and a research ethics committee was consulted to sign off on the study. The study authors also chose to perform the left atrial strain analysis using the approach of the most experienced echo labs specializing in athletes' assessment. The fact that they took this step not only lends additional credibility to the study but also ensures good study reproducibility.

Another strength of this study is their use of two-dimensional speckle tracking echocardiography, which was a new echocardiographic method that allowed for the evaluation of atrial function in a completely non-invasive manner. This helped to attain accurate measurements, while keeping distress to their subjects to a minimum. They found that the left atrial speckle tracking echocardiography derived strain was completely independent of left atrial size in a much larger sample size ($n = 114$) than in prior studies where $n < 25$. With a more highly powered study, the results are more reliable and, therefore, provide more convincing evidence to support their conclusions.

Lastly, they also studied left atrial strain parameters with respect to other echocardiographic signs of athlete's heart rather than simply assessing them in isolation. Medical assessments were performed in the mornings to guarantee there was at least a

12-hour gap since the last training session. This helped to avoid any residual, and potentially confounding, physiological factors at play which could be considered a direct consequence of the last training session. This was a key aspect that protected the integrity and accuracy of the resulting measurements.

With regard to the weaknesses of this study, as a descriptive cross-sectional study, it is possible that risk factors relevant to the remodeling processes taking place may not have been identified or recorded. Furthermore, even though athletes diagnosed with the aforementioned health conditions were excluded, certain participants might have had subclinical and therefore undiagnosed conditions thereby making the measurement of risk factors and outcomes less reliable. Moreover, the study looked exclusively at one specific population (Polish) and one specific sport (rowers). While Polish athletes undoubtedly share many traits and characteristics with athletes of other backgrounds, these findings are far less generalizable since the authors did not include any other athletes from other nationalities or cultural backgrounds. These specific results, therefore, only apply to a narrow segment of the population, since the subject pool was non-diverse. The same argument can be made for the use of a cohort of elite-level rowers rather than including a wide array of endurance athletes, which would help to better generalize the results across endurance competitors as a whole. Though rowing tends to be classified as an endurance sport, it also incorporates many aspects of resistance training and static exertion as well. This further narrows the focus of these findings as they are truly only applicable to elite level rowers.

Left Atrial Volume Index in Highly Trained Athletes

This study was performed by Antonella D'Andrea, MD, FESC, et al. in Naples, Udine, Salerno and Milan, Italy in 2010. The objective was to support the theory that the increase in left atrial diameter identified in trained athletes is indeed a component of athlete's heart. Another primary goal of the study was to define reference values for left atrial volume index within athlete populations. The study was a cross-sectional study in which a group of 615 elite athletes were assembled and underwent a comprehensive transthoracic echocardiography exam complete with physical, chest radiograph and doppler studies. A key feature of this study is that both endurance athletes (n = 370) and strength trained athletes (n = 245) were included so as to compare the two types of training. Through their results they defined left atrial volume index values of 29-33 mL/m² as equating to mild left atrial dilatation (found in 150 athletes or 24.3%), whereas moderate dilatation was defined as left atrial volume index values >34 mL/m² (found in only 20 male athletes or 3.2%). Strength trained athletes were found to have increased body surface area, wall thickness, left ventricular circumferential end-systolic stress and relative wall thickness. Conversely, left atrial volume index, left ventricular stroke volume and left ventricular end-diastolic volume were greater in endurance trained athletes. Left atrial volume index was found to be remarkably greater in endurance athletes.

This study possesses several major strengths. Not only did the authors include both endurance and strength trained athletes, in order to target the differences in how their training influences their physiology, but they included an array of different sports

within each subclass. Long- and middle-distance runners and swimmers, as well as soccer and basketball players, constituted the endurance athlete cohort, whereas the strength trained cohort was comprised of bodybuilders, weightlifters, martial arts fighters and windsurfers. Having this breadth of athletes for each subgroup provides a wider range of sport specific stressors that qualify for admission into a certain group. This also helps to augment the generalizability of the results as the conclusions of the study can now be applied to a much broader group of athletes. Furthermore, having a cohort of 615 athletes ensures the study was sufficiently powered and, therefore, collected enough data to detect a genuine effect. The authors of the study excluded any subjects suffering from diabetes mellitus, arterial hypertension and coronary artery disease, ensuring patients with hearts that might be remodeled by these conditions would not influence the results. The study authors also not only included both men and women in each study group to elucidate any differences attributable to sex, but they made certain that the mean age was comparable between both of the groups, thereby ensuring that that variable was properly controlled for. Finally, no extramural funding was secured in order to support the study; thus, the study authors were less susceptible to external pressures that might have otherwise influenced the direction of the study.

This study also had several weaknesses. To begin, while the authors attempted to categorize athletes as either endurance (aerobic training) or strength (anaerobic training) athletes, it is seldom, if ever, that a sport or activity can be qualified as either 100% aerobic or 100% anaerobic. Sport participation involves a complex chain of movements and reflexes relying on both fast twitch and slow twitch muscles. Consequently, any

given sport, whether it is classified as an endurance sport or resistance/strength training, will undoubtedly make use of a combination of both aerobic and anaerobic metabolism. As a result, a certain percentage of the cardiac adaptations being measured in endurance athletes could be the result of anaerobic mechanisms and vice versa.

This study also targeted left atrial diameter as one of the indicators of cardiac remodeling. Echocardiography was used to quickly and easily measure the diameter of the chamber; however, this is unlikely to be a reliable or useful measurement. Not only is the left atrium asymmetrical prior to any remodeling that takes place, but the process of left atrial enlargement itself does not take place uniformly, thereby limiting the usefulness of this particular cardiac value. To their credit, the study authors included left atrial volume as another (and more accurate) metric, which more accurately characterized the true size and, therefore, extent of remodeling of that chamber. Additionally, left atrial volume was characterized using a method (biplane area-length method) which is the most commonly used approach in prior clinical studies and research. However, they opted not to employ two other existing methods despite various other studies relying on those methods. It would have been interesting to see the potential impact on results using the other two accepted calculation methods.

Prevalence and Clinical Significance of Left Atrial Remodeling in Competitive Athletes

This study was performed by Antonio Pelliccia, MD, et al. in Rome, Italy and Minneapolis, MN in 2005. This study sought to evaluate the left atrial dimension and corresponding prevalence of supraventricular tachyarrhythmias in competitive athletes

from a wide array of sports. This allowed them to determine the distribution across various sports, as well as the clinical significance of left atrial size in the wider context of athletes' hearts. The study found a mild increase of left atrial diameter (≥ 40 mm) in 18% of athletes and a marked dilation (≥ 45 mm) in 2% of athletes. They also reported a close association between left atrial diameter and left ventricular cavity dimensions. Interestingly, a larger percentage of subjects with enlarged left atria had attained an international level of recognition in their respective sport (40% vs. 20% of athletes with normal-sized left atria; $p < 0.001$). Based on the results of this study, they were able to establish for the first time, the upper limits of left atrial diameters in athletes (defined as 45 mm for women and 50 mm in men).

The alterations in morphology of the left atria in these athletes was found to be shaped by the type of sport being practiced. Sports which combined dynamic and static exercise – namely rowing/canoeing (18% of athletes with enlarged left atria), cycling and ice hockey (10%), rugby and soccer (7%) -- exhibited the greatest impact on left atrial size. With these limits on left atrial diameters, the scientific community can better distinguish physiological cardiac remodeling from various pathological conditions. This study extended to the clinical implications of physiological remodeling and found that atrial fibrillation, along with other supraventricular tachyarrhythmias, as measured over a long-term follow-up, were not only uncommon but were comparable to the prevalence found in the general population ($<1\%$). This provided evidence that, while exercise induced left atrial enlargement was present in many athletes, it is actually a benign adaptation and is only minimally associated with adverse clinical consequences.

This study was widely cited throughout the existing literature due to its many strengths. First and foremost, this study is a prospective cohort study involving a substantial study population of 1,777 highly trained athletes across 38 different sporting disciplines. This is an extremely large subject pool comprised of both men and women with a wide range of ages (spanning from 11 to 56 years) with large variability in the types of sports they participated in. In addition, every one of the athletes had competed at the regional or national level with 390 (22%) competing at either the Olympic or World Championship level. Therefore, they were able to analyze precisely what happens to the heart in a population that stresses their hearts to the extremes in a variety of different physiological manners. Study authors also avoided the influence of any cardiovascular disease states, as these were controlled for by excluding any such participants from further analysis following abnormal findings on clinical and echocardiographic assessment. These attributes help to increase the broad generalizability of these results. Researchers also assessed interobserver variability by randomly selecting 90 of the subjects and asking two investigators to independently conduct measurements without knowledge of the subjects' identities. This level of blinded self-policing lends additional credibility to the results and establishes trust in their findings.

Electrocardiography was also used as another method of assessing left atrial enlargement (prolonged P-wave duration in leads I or II and/or inverted P-wave in V₁), thereby, providing further characterization and evidence of the remodeling process. Another strength of this study is the extensive clinical and echocardiographic follow-up they performed on the majority of athletes with an enlarged left atrium (318). In

conducting a 1 to 10-year follow-up, they were able to determine the longitudinal effects of left atrial enlargement and subsequent development of atrial fibrillation or other arrhythmias. This increases the clinical significance of this study's findings.

There were several areas in which this study was limited. For instance, for certain aspects of the research, echocardiograms were done on athletes while engaged in periods of intense exercise. However, due to what study authors refer to as "unavoidable practical considerations", the imaging did not always take place when athletes were at peak conditioning. As a result, the imaging used to evaluate the heart during said workouts would not reflect the athlete's heart in its state of peak performance and thus, potentially skew the detected values to some extent. ECG monitoring during follow up evaluations to detect various arrhythmias was also only done sporadically so that, while the occurrence of atrial fibrillation might actually have been 0.2% as detected in their study, the true incidence might also have been drastically higher had the ECG monitoring been performed more routinely. A set follow-up schedule should have been maintained to the greatest extent possible so as to ensure accurate detection of arrhythmias during follow up.

Training-Specific Changes in Cardiac Structure and Function: A Prospective and Longitudinal Assessment of Competitive Athletes

This study was performed by Aaron L. Baggish, et. al in Boston, MA in 2008. Study authors designed a prospective, longitudinal study with the objective of assessing the impact of various types of exercise training on cardiac structure and function.

Interestingly, this study followed a cohort of competitive college athletes across a single season (90 days). They also included cohorts of both competitive endurance athletes and strength athletes in order to identify any differences in remodeling of the various heart chambers between the two groups. The endurance athletes consisted of long-distance male and female rowers (n = 40), while the strength athlete group consisted of male American-style football players (n = 24). Each group was studied with echocardiography both at baseline, as well as following 90 days of team training. The study authors had hypothesized that marked structural and functional changes would occur over the training period and that both the nature and the magnitude of those changes would vary according to the training method. The results supported this hypothesis.

Left ventricular mass was 11% higher in endurance athletes and 12% higher in strength athletes by the end of the training period. Endurance athletes also saw an $8.0 \pm 4.2 \text{ ml/m}^2$ increase in left ventricular dilation, vastly improved diastolic function, and biatrial enlargement, whereas strength athletes were found to experience left ventricular hypertrophy with diminished diastolic function. The right ventricle was impacted as well with endurance athletes experiencing right ventricular dilation and enhancements in both systolic and diastolic function, whereas the right ventricle in strength athletes was left unchanged. In short, they found that a single season of competitive endurance athletics led to both biatrial enlargement and biventricular dilation with improved diastolic function, while one season of competitive strength training led to isolated, concentric left ventricular hypertrophy with decreased relaxation of the chamber during diastole

(decreased left ventricular diastolic function) and no changes in atrial dimensions or right ventricular parameters.

This study has a variety of strengths which help to support the conclusions that were gathered. To begin with, creating a prospective, longitudinal study helped to provide evidence of a cause-and-effect relationship while also ensuring that the negative influence of recall error was minimized as data was collected at regular time intervals. In addition, while it is more expensive and elaborate than many other study types, this is one of the most effective methods of determining variable patterns over time – ideal for assessing these types of cardiac changes, while allowing for follow-up across the study period. The authors chose to study university athletes rather than elite competitors so as to ensure the participants would enter the study in a relatively detrained state, after which they would exercise consistently at a high intensity, and thereby offer a clearly defined period in which they could accurately detect training-induced alterations. They also increased the generalizability of their study by including both male and female rowers in their cohorts. Moreover, echocardiography was performed by two trained sonographers, each of whom performed both baseline and post-study imaging on the same individual athletes, increasing accuracy and confidence in their results. The data analysis was also performed by two cardiologists who were blinded to the study time point. These factors lend credibility and provide further trust in their measurements.

There were several weaknesses in the study design which, unfortunately, likely impacted the results. The cohorts, while well-defined and specific to the various training types being studied, were composed of small sample sizes. Following only 64 athletes

across the two study groups makes it more likely that the wrong inferences could be drawn from this experiment. Ideally, much larger sample sizes would be used in the future if this study were to be reproduced. While one of the strengths was that both males and females were included in the study, this only held true for the endurance cohort as there were no female football players available to be studied and, as such, the female response to strength training could not be assessed. Study authors also made no efforts to control training regimens over the course of the study. While the endurance athletes were encouraged to use heart rate monitors and strength athletes worked under the supervision of dedicated strength coaches to ensure their training was at the required level, there was no possibility of controlling any activity that might have been done outside the scope of team training, which could potentially skew the results due to overtraining, improper technique or even exercise activity noncompliant with their respective exercise type. In addition, all subjects were asked about their use of anabolic steroids and were summarily, excluded if they had any positive history of use. This would have been a strength of the study; however, they did not perform serum testing to confirm the athletes' claims. As a result, there is less confidence that performance enhancing drugs did not play a role in the final data.

It is also worth noting that although the athletes in each cohort were age matched, they likely differed in the amount of formal athletic training they underwent prior to the study. This variability in lifelong training exposure could account for some differences in the subjects' baseline measurements and might have subsequently limited the degree of potential change observed during the 90-day study period. Finally, athletes in both the

endurance and strength cohorts were exposed to small amounts of crossover training stimuli, which could have served to decrease the magnitude and training specificity of the observed changes. However, since this study was deliberately designed to assess the cardiac response of genuine athletic team sport participation, this “weakness” actually works in their favor as it allows for a more accurate true-to-life assessment of the training type in question.

Left Atrial Size in Elite Athletes

This research study was carried out in 2015 by Aline Iskandar, MD, et al. in both CT and MA in the United States. Researchers conducted a systematic literature review and meta-analysis which investigated the association between high levels of various types of exercise training in elite-level athletes and left atrial size. After scanning major research databases and manually searching references from prior studies, review articles and meta-analyses, study authors were able to compile data from 54 studies which met their inclusion criteria. They obtained values for reported absolute left atrial diameter in 2,626 endurance-trained athletes; 411 strength-trained athletes; 875 combined endurance- and strength-trained athletes; 3,106 athletes for whom pure exercise classification was not possible (labeled “mixed trained athletes”); and 1,044 controls. They also compiled data on left atrial volume corrected for body surface area in 552 endurance-trained athletes, 255 strength-trained athletes, 185 combined trained athletes as well as 426 controls. The mean age of the athletes and controls in each study spanned from 18.9 to 36 years.

Through meta-regression analysis, they found that pooled mean left atrial diameter was 4.1 mm (corresponding to 13%) greater in athletes overall when compared with sedentary controls, while left atrial volume index was 7.0 ml/m² (corresponding to 30%) greater in athletes than in controls. More specifically, left atrial diameter was 4.6 mm greater in endurance-trained athletes, 2.9 mm greater in strength-trained athletes, 3.5 mm greater in combined trained athletes, and 4.2 mm greater in mixed trained athletes when compared to controls. They were unfortunately unable to complete a similar breakdown analysis by category for indexed left atrial volume, since the number of studies reporting that particular measurement was so small. Due to the extremely large sample sizes involved, these data provide highly credible upper limits for both left atrial size and volume in elite athletes, which can enable clinicians to accurately differentiate the physiological remodeling of athlete's heart syndrome from pathological heart disease; values surpassing those set limits are much more likely to represent a pathological condition than any adaptations to elite level exercise training.

Study authors provided associations aiming to describe the mechanisms responsible for left atrial enlargement. They theorized that enlargement of both the left atrium and the left ventricular cavity are closely linked and may in fact represent the physiological sequela of chronic left ventricular volume overload and/or pressure overload resulting from long-term intensive training. Furthermore, they cited a meta-analysis of six case-control studies comprised of 655 athletes and 895 controls, that found overall risk for atrial fibrillation was significantly elevated in athletes compared to controls. The mechanisms behind this were attributed to bradycardia, which is

exceedingly pervasive in athletes and has been associated with an increased incidence of atrial fibrillation in those with structurally normal hearts. Inflammatory changes arising from excessive training were also proposed to be a precipitating cause.

This meta-analysis had a wide array of strengths, which helped to substantiate its claims. The authors took great care in initially extracting the data upon which their entire analysis was based. Two reviewers independently worked to compile the data, thereby providing checks on each other and ensuring the quality of their numbers. Discrepancies, if and when they did arise, were resolved by consensus. The sheer quantity of data involved in this analysis is another major strength of this study—so much so that this is considered the single largest compilation of studies to demonstrate that the left atrium of highly trained athletes, regardless of whether they are involved in endurance, strength or both types of exercise, is enlarged in comparison to controls. Moreover, this study explored a feature of remodeling rarely considered in other studies. Left atrial enlargement in the AP (anterior-posterior) frame of reference is confined anteriorly by the aortic root and posteriorly by the rigid tracheal bifurcation, thereby forcing the chamber to expand along a different unrestrained axis. This changes the geometry such that its dimensions don't accurately represent its true size. As a result, left atrial volume is a far more accurate measure of quantifying atrial size. This is important because left atrial volume has been found to have a stronger association with negative cardiovascular events than left atrial area or diameter.

With regard to limitations, this meta-analysis could only make use of the data that they were able to uncover and include. As a majority of the studies were cross-sectional

studies, they were unable to analyze participants over time and, thus, had weaker evidence to establish cause and effect. It is, therefore, possible that the sizes of the athletes' left atria were inherently larger than those found in the sedentary control subjects, even prior to exercise training. In addition, the included studies all used a wide variety of different statistical tools to analyze their results. This meta-analysis attempted to control for this by using multivariate meta-regression analysis, which allowed them to pool all the studies together for additional power while simultaneously adjusting for the wide range of differing characteristics. However, it is highly unlikely that they were able to adjust for all of the potential confounding factors within the chosen studies.

In summary, prior research in this domain is focused in large part on characterizing the unique features and determining the limits of physiological remodeling in order to distinguish it from pathological remodeling. Regrettably, the two processes share so many overlapping features that it can be difficult to decipher whether the root cause is of physiological or pathological origin. Through analysis of the alterations and adaptations in cardiac structure and function that occur following various types of high intensity training in athletes across the sporting spectrum, researchers have succeeded in creating reference values to help refine the clinical diagnosis of athlete's heart syndrome. They have homed in on measures such as left atrial volume, diameter and wall thickness. These indexes are key to differentiating adaptive remodeling from pathological cardiac states. Athletes focused on strength training exhibit increased cardiac wall thickness and relative wall thickness as well as left ventricular end-systolic stress. Alternatively, endurance trained athletes sustain larger increases in left atrial volume, left ventricular

stroke volume and left ventricular end-diastolic volume. Furthermore, research supports that these training-specific changes can occur rapidly, as detected following a single season of either competitive resistance or endurance training.

Left atrial enlargement is a common finding in endurance athletes and is one of the primary physical manifestations of athlete's heart syndrome. While some studies found that the subsequent risk of arrhythmias was equivalent to that of the general population, these studies were often either hampered by small sample sizes or relied on questionable follow-up monitoring to detect effects. Despite such research, the scientific community is in agreement that high intensity endurance training is linked to potentially harmful, albeit reversible, left atrial enlargement, along with a resulting increase in the overall risk of atrial fibrillation relative to non-athlete controls. Further study is required to determine if this phenomenon holds equally true for resistance athletes.

By measuring anatomical and functional changes in the hearts of athletes using transthoracic echocardiography, we can accurately track the changes taking place over time across various training regimens. This will provide insight into not only how the chamber remodels but also the pace at which the remodeling process takes place. As a result, we will be able to assess the true differences in left atrial remodeling occurring in endurance trained hearts vs resistance trained hearts. Ultimately, this data will shed light on the association of exercise type with specific left atrial remodeling patterns predisposing athletes to atrial fibrillation.

METHODS

Study Design

This study will be a prospective cohort study performed using students and student athletes from schools within the PAC 12 collegiate athletic conference, who will be recruited to assess how the pattern of left atrial remodeling differs between high intensity endurance athletes, high intensity resistance athletes and non-athletes. As a secondary objective, the incident risk of atrial fibrillation will be assessed for each of the three separate cohorts on a yearly basis for a follow-up period of 10 years.

Study Population and Sampling

The PAC 12 is a collegiate athletic conference operating in the Western United States participating in 24 sports at the NCAA Division 1 level. The schools making up the conference include the University of Arizona, Arizona State University, University of California, Berkeley, University of California, Los Angeles, University of Colorado Boulder, University of Oregon, Oregon State University, University of Southern California, Stanford University, University of Utah, University of Washington and Washington State University³⁶. At the Division 1 level, college sports teams possess anywhere from 30 active players on a soccer team to upwards of 125 active players in a football squad. To ensure a consistent number of players are recruited from each program, our “resistance” sample will include 25 male football players, 25 male weightlifters, and 50 female weightlifters. Our “endurance” sample will include 25 male cross-country athletes, 25 female cross-country athletes, 25 male soccer players and 25

female soccer players. Our control group will consist of 50 non-athlete male students and 50 non-athlete female students. In total 100 students for each of the 3 cohorts will be selected from each of the 12 universities for a total project population of 3,600 students.

In order to qualify for this study, students must be between the ages of 18 and 23 at the time of recruitment, enrolled as full-time students at their respective universities (regardless of athletic status), and free from any pre-existing cardiac conditions (any evidence of structural cardiac abnormalities following clinical and echocardiographic assessment will preclude any such applicants). These include abnormalities such as congenital heart defects, mitral valve prolapse, mitral valve regurgitation, ventricular septal defects, aortic valve stenosis, cardiomyopathy, myocarditis and any pre-existing cardiac arrhythmias. Participation will also be restricted to students with BMIs between 18.5 and 29.9 so as to rule out students within either the underweight or obese range³⁷. Lastly, drug testing will be performed to assess the use of performance enhancing drugs and other illicit substances as per NCAA regulations. Detection of any of the substances using the NCAA year-round on-campus drug testing throughout the duration of the study and summarily reported to the coaching staff, will result in removal of the participant in question. A participant's data will also be excluded from the final analysis if they underwent any break in training of ≥ 3 consecutive days across the 120-day study period.

Specifics of the training plans, as well as assessment of the level of commitment shown by their players in completing each work out, will be left to the discretion of coaching staff. The assumption is that the training regimen for each respective sport will reflect the elite level training plans found at other top college programs across the country

and, as a result, will coincide with both the type and frequency of endurance or resistance work-outs necessary to excel at the sport in question.

The large population size involved in this study ($n = 3600$), assuming an alpha value of 0.05 and a power of 80%, is sufficiently powered to detect an effect size (f) of 0.0517545. This is a very small effect size as defined by Cohen which was generated using an online clinical calculator (www.gpower.hhu.de). Cohen's f statistic is the appropriate effect size index to use for the one-way ANOVA test which will be relied upon to determine if there are any statistically significant differences between the means of our study groups. Thus, the benefit to the large population size is that the study will be sufficiently powered to be able to detect subtle changes, which may arise in the architecture of the heart.

Exposure Groups

Participants will be assigned to one of three separate cohorts:

1. Non-athletes (NA) – Full-time male and female students not currently engaged in organized competitive sports. They will be excluded from the study if they engaged in 30 minutes or more of exercise (endurance or resistance) three or more times a week, as reported on a weekly self-reported email exercise survey. This will serve as the study control group.
2. Endurance athletes (EA) – Active full-time male and female student members of Division 1 college soccer and cross-country distance running teams.

3. Resistance athletes (RA) – Active full-time male and female student members of Division 1 college football and weightlifting teams.

Each student will be assigned to a cohort based upon the sport (or lack thereof) that they participate in. The student will be required to submit proof of their status as an active member on the official roster of the sports team they belong to.

Study Variables and Measures

Participants will be required to click on a link to fill out an extensive “Introductory Survey,” which will include a range of demographic and subjective information including name, age, gender, university, exercise type, frequency, intensity, sleep quality and duration, diet, academic challenges, stress/anxiety levels, emotional wellbeing and prior sporting experience, as well as a declaration that they will adhere to the specific guidelines of the study.

The extent of left atrial remodeling will be assessed through the measurement of four distinct variables: left atrial size, volume, function, and strain (a measurement used to evaluate myocardial deformation) (Table 1). Speckle Tracking Echocardiography (STE), also known as two-dimensional strain imaging, can provide feedback on conduit function, reservoir function and atrial kick.

Those participants who opt to remain in the study for phase two will be required to undergo a series of 12-lead electrocardiograms (ECG). Detection of variability in intervals between QRS complexes (an irregularly irregular ventricular rate) along with the absence of discrete P waves and fibrillatory (f waves) at rates of 350 and 600

beats/min will be the markers used to confirm the presence of atrial fibrillation on ECG.

(See Appendix 1 for full criteria).

Table 1 – Study Variables and Measures

Study Variables	Measurement
1. Left atrial size 2. Left atrial volume	Echocardiography
3. Left atrial function	Doppler Echocardiography (transmitral peak A wave velocity)
4. Left atrial strain/deformation	Speckle Tracking Echocardiography

Recruitment

Participants will be recruited on a voluntary basis using an email blast message sent to all relevant PAC 12 university athletic departments (for the two exercise cohorts) and research study student interest boards (for the control group). A second blast email will be sent out a week after the first should we require additional participants. This sequence will be repeated until all three cohorts are full. Participant adherence to the study guidelines will be improved by monetary compensation awarded upon completion of the study.

Participants will be informed that one of their coaches (without specifying which one) will be providing study researchers with feedback in regard to their attendance at training sessions and their perceived level of intensity. The participants will be made

aware from the first email blast that they will be compensated with \$100 should they complete all steps of the study, while adhering to the provided guidelines. Payment will be mailed to the address they provide 6-8 weeks following the conclusion of the study.

All five appointments for cardiac assessment will be scheduled and confirmed within the allotted time periods and will be provided free of charge to the participants at a local and convenient facility within a 10-mile radius of their respective university campus. The majority of schools will likely possess the necessary equipment in the medical department of the university athletics complex. Both the control and exposure groups will engage in consent discussions during which they will be informed of all potential risks and benefits secondary to their participation in this study, in addition to the extent to which participant confidentiality will be protected.

Data Collection

Data collection will begin with the collection and organization of all completed and returned electronic surveys. Cohorts will be filled on a first come-first serve basis, assuming they meet all qualifying criteria for a particular cohort. All surveys will be transferred to spreadsheets and stored securely in a digitally encrypted manner for further analysis. In order to ensure adequate participant adherence to their respective school's training regimen, a member of the coaching staff will be solicited to fill out a brief weekly "Progress Survey" in which they will be asked to confirm the attendance of each participant, as well as the perceived intensity (five categories ranging from minimal to maximum) of their effort during training across a given week. Any break in training for a

period of ≥ 3 consecutive days, or a report of ≥ 3 total days at moderate intensity or below in any given week, will result in disqualification from the study.

Participants in the control group will be responsible for completing a weekly “Self-Reported Progress Survey” to indicate whether or not they engaged in ≥ 30 minutes of either endurance or resistance exercise ≥ 3 times a week. Two or more responses in the affirmative will result in disqualification from the study. All surveys used in the study will be disseminated by email and offered electronically through SurveyMonkey in a multiple-choice format with clear and coherent instructions. Participants will be provided with a phone number and email to contact should they have any questions or concerns throughout the course of the study.

Participants will undergo initial cardiac testing by trained sonographers within 5 days of the beginning of the 120-day study period in order to establish a baseline against which a comparison can be made throughout and following the training period. Echocardiographic studies will be performed every 30 days following the start of the study with the final scan to take place within a 5-day period following the end of the 120-day study period using commercially available equipment (Sonos 2500 and 5500, Philips Technologies). Measurements of cavity dimensions and wall thicknesses will be obtained from the M-mode echocardiogram consistent with the recommendations of the American Society of Echocardiography. Images will be obtained after 20 minutes of quiet rest between 2 and 5 PM and will be separated from the previous training session by a minimum of 24 hours. Two-dimensional, pulsed-Doppler, and color tissue-Doppler imaging from standard parasternal, apical, and subcostal positions will be performed. The

two-dimensional frame rate will be 25–75/s and the tissue Doppler frame rate will be >100/s for all images. All echocardiography will be performed by the same trained sonographers who will complete all five scans (baseline, month one, month two, month three and poststudy imaging) on the same athlete to which they have been assigned. Definitions of normalcy have also been adopted from the most recent American Society of Echocardiography guidelines.

All data from cardiac measurements will be de-identified and assigned a 7-digit signature code, which will ensure study authors are unable to identify individual participants based on their codes. The information will then be encrypted and stored securely until the poststudy results are available, at which point the data will be combined into a single spreadsheet and prepared for analysis.

The secondary objective of this study is to determine the incident risk of atrial fibrillation across a span of 10 years following the conclusion of the study period. All participants who successfully complete the first phase of the study will be eligible to continue on to phase two. Those who decide to remain in the study will be required to undergo a 12-lead electrocardiogram (ECG) once a year for 10 subsequent years at a facility within 10 miles of their residence. All cardiac testing will be provided free of charge and all study participants will receive an additional award of \$30 within 6-8 weeks following each yearly ECG. The maximum award a participant will therefore receive following the successful completion of all 10 yearly ECGs in phase two will be \$300. All ECGs will be sent electronically to investigators upon completion of the test, where they

will be compiled and analyzed to assess for incidence of atrial fibrillation for each of the three cohorts.

Data Analysis

Poststudy data analysis will be performed by one of several study cardiologists blinded to the study time point. In phase one, all data from the control and exposure groups will be analyzed by determining the means and standard deviations of each of the four continuous variables for each cohort. Our primary focus will be on the overall change observed in each of the four variables from the start of the study period to the maximum difference detected across the 120-day follow-up. These data will then be compared using a one-way ANOVA to assess the differences in cardiac remodeling between the three cohorts. In phase two, the proportions reported from the yearly serial ECGs will be compared using a chi-squared test in order to determine if a statistically significant difference in the incidence of atrial fibrillation is detected among the exposure cohorts and controls.

Timeline and Resources

We predict it will take approximately two to four weeks to recruit all 3,600 participants. This process will largely be managed by our primary investigator as well as the study coordinator. The 120-day study period will begin following a five-day span in which all baseline cardiac assessments will be completed by our team of trained sonographers. The same sonographers will complete each subsequent assessment culminating with the final

post-study assessment. Student workers and additional clerical assistance will be available to manage the workflow and ensure timely completion of the assessments. Finally, the statistical analysis will be completed within a seven-day period by a qualified statistician in conjunction with a licensed cardiologist to ensure the accuracy of all prior assessments. Lastly, phase two will involve a medical team to carry out and interpret 12-lead electrocardiograms yearly across the 10-year follow-up after which these will then be compiled and analyzed over a seven-day period to ascertain our final results. (Table 2)

Table 2 - Timeline and Resources

	Intervention	Timeline	Resources
Phase 1	Recruitment of student athletes and non-athletes	2-4 weeks	Human resources: <ul style="list-style-type: none"> - Primary investigator - Study coordinators Materials: <ul style="list-style-type: none"> - Introductory Surveys
	Baseline cardiac assessment	5 days	Human resources: <ul style="list-style-type: none"> - Trained sonographers available at each facility - Clerical assistance Equipment: <ul style="list-style-type: none"> - Cardiac ultrasound machines
	Training study period	120 days	Human resources: <ul style="list-style-type: none"> - Trained sonographers available at each facility - Study coordinators - Student workers - Clerical assistance Equipment & Materials: <ul style="list-style-type: none"> - Cardiac ultrasound machine - Progress Surveys (EA + RA) and Self-Reported Progress Surveys (NA)
	Poststudy cardiac assessment	5 days	Human resources: <ul style="list-style-type: none"> - Trained sonographers available at each facility - Clerical assistance Equipment: <ul style="list-style-type: none"> - Cardiac ultrasound machines

	Statistical analysis	7 days	Human resources: <ul style="list-style-type: none"> - Primary investigator - Cardiologists - Statisticians - Clerical assistance Equipment: <ul style="list-style-type: none"> - Microsoft excel to aid in statistical analysis
Phase 2	Long-term follow-up with yearly ECGs	10 years	Human resources: <ul style="list-style-type: none"> - M.D./Nurse/ECG Technicians - Study coordinators - Student workers - Clerical assistance Equipment: <ul style="list-style-type: none"> - 12-lead electrocardiograms
	Statistical analysis	7 days	Human resources: <ul style="list-style-type: none"> - Primary investigator - Cardiologists - Statisticians - Clerical assistance Equipment: <ul style="list-style-type: none"> - Microsoft excel to aid in statistical analysis

Institutional Review Board

The protocol and guidelines of this research study will be submitted to the Boston University Medical Campus Institutional Review Board for expedited review under Category 4. The study will be considered minimal risk to patients due to the non-invasive nature of the echocardiographic/doppler imaging, the negligible risk of exposure of personal health information due to encryption and safe storage, and the knowledge that the participant will not be required or incentivized to alter their baseline college athletics

training regimen in any way. Their participation and commitment to fulfilling the duties set forth by the school's coaching staff had already been agreed upon prior to their recruitment into this study. We can reasonably conclude that there will be no added risk above that which they have already accepted by joining their respective team in the first place. A full and complete IRB protocol will summarily be submitted if the expedited status is not granted approval by the IRB.

CONCLUSION

Discussion

The results of this study have the potential to strengthen our understanding of how the human heart responds to various forms of high intensity exercise. The dynamic forces at play with regard to cardiac physiology are not always evident but the physiological consequences of those forces can be remarkable. While this study can help elucidate these processes, it also suffers from several limitations that must be acknowledged.

There is a vast array of factors that contribute not only to the overall health of an individual but to their ability to successfully participate in sport. Factors such as sleep quality, diet, academic challenges, stress levels, anxiety and emotional wellbeing can all play a significant role in impacting a student's ability to train properly. While we have endeavored to take these into consideration in our surveys, many of these variables are highly subjective and susceptible to substantial recall bias which unquestionably have an impact on our results. While there are undoubtedly overlaps between Division 1 schools in the types of drills, duration of rest periods, intensity, and frequency of both practices and official games, there is no way to ensure that the training regimen will be standardized across all study participants without designing and implementing a new regimen to be offered to and adopted by all 12 universities. This variability will undeniably have an impact on the process of cardiac remodeling in participants from one school to the next, in addition to the individual nuances that exist within each sport, ranging from which position on the team is being played, confidence in one's overall abilities or even an individual's propensity to push themselves to or past their "limits".

Lastly, the outcome and length of the season itself could potentially have a sizeable impact on the intensity and commitment displayed by participants; a school with a poor record would not only be excluded from playoff games but would also likely not be as motivated to train and play at the same intensity as one that was competitive nationally. These are some of the variables that unfortunately cannot be controlled for in the current study.

One potential obstacle to successfully carrying out this study lies in the ability to incentivize NCAA college athletes' participation in this study. While players are currently unable to accept any type of extra benefit for playing their respective sport³⁸, it is unclear whether providing monetary compensation for a research study would be allowed.

Despite the potential for residual confounding inherent to this study, the strengths are many. The sample size of 3,600 students from various genetic backgrounds, sexes, universities, and sporting backgrounds provides a substantial and highly diverse population that we can use to detect subtle physiological and functional changes, which could otherwise go undetected were the study insufficiently powered. This large and diverse population comprised of students from a wide array of universities helps to increase the generalizability of our results and sets this study apart from much of the existing research. With few exceptions, much of the current literature relies on much smaller sample sizes ranging from under 100 to several hundred participants in their study populations. Finally, this study also recruits an equal proportion of men to women, a unique characteristic to this study. This will further reinforce the generalizability of

these results and provide valuable insight into gender differences, which might account for some of the processes taking place but would otherwise have gone unnoticed.

Summary

The human heart is an essential organ tasked with maintaining cardiac output to the rest of the body. It must be able to adapt to and compensate for a wide range of metabolic and physical demands placed on the body, through a variety of mechanisms. The pattern and degree of adaptation found in various heart chambers will differ depending on the nature of the forces acting upon it. The focus of this study is the left atrium, which is implicated in the development of atrial fibrillation. In fact, atrial fibrillation can be both a cause and a symptom of left atrial enlargement. To date, existing research is sparse with regard to the adaptations of the left atrium secondary to high intensity resistance exercise, as well as its long-term sequelae.

By focusing on two main categories of physiological stressors, high intensity endurance exercise and high intensity resistance exercise, this study attempts to illuminate the effects these forces have on the heart over time. Endurance training induces cardiomegaly predominantly through submaximal muscle contractions, which allows for an increased stroke volume accompanied by an enhancement in the ability of muscle fibers to use oxygen. In contrast, resistance training induces changes to the size of the heart largely through maximal muscle contractions, which thicken the walls of the heart chambers to increase the contractile force that the muscle fibers are able to exert.

While both of these non-pathological adaptations result in athlete's heart syndrome, it is crucial to understand that in the long-term these processes are inherently divergent.

In this study we will quantify the changes taking place in the hearts of collegiate athletes through the use of various echocardiographic modalities to assess the size, volume, function and strain of their left atria over the course of a four-month training period. Echocardiograms are one of the most standard, easily attainable and least invasive methods to assess left atrial size and function. By assessing each of these metrics throughout the study, we can closely track what changes occur and when. Moreover, in phase two of the study, we will follow the three cohorts and compare their rate of developing atrial fibrillation. By determining the extent to which various metrics of cardiac remodeling change based on exercise type, we can distinguish which physiological changes are the most detrimental. We can then subsequently investigate which features of each training type have the greatest potential for harm in the long term. While this study cannot determine the defining cause of atrial fibrillation in college-age athletes, it will go a long way in identifying at least one modifiable contributing factor.

Clinical and/or Public Health Significance

The results of this study can better equip medical providers and athletic trainers to educate athletes on the adaptations they can expect to see as a direct result of their specific training regimen, as well as the potential consequences that may arise further down the line. Moreover, such an understanding will provide necessary information on how to properly guide an athlete to maximize athletic gains, while minimizing the risks

associated with left atrial enlargement and atrial fibrillation. Most importantly, expanding the breadth of knowledge in this sphere will enable the athletes themselves to more accurately and completely understand the short- and long-term risks they are incurring by opting to participate in a given sport. On a broader scale, this study could have significant impact on the fitness and athletic training industry as a whole, since fitness professionals would now have an even more sound basis for developing new exercise regimens and workouts catering specifically to athletes in their respective fields.

APPENDIX I

Per UpToDate, the full breakdown of criteria used to confirm the diagnosis of atrial fibrillation is as follows:

Note: For the purposes of this study, the presence of both underlined criteria alone is sufficient to confirm diagnosis.

FINDINGS

AF is associated with the following changes on ECG:

- Lack of discrete P waves
- Ventricular response follows no repetitive pattern; variability in intervals between QRS complexes is termed "irregularly irregular."
- Fibrillatory or f waves may be present at rates of 350 and 600 beats/minute (or unmeasurable); the f waves vary continuously in amplitude, morphology, and intervals.
- The ventricular rate (especially in absence of AV nodal blocking drugs or intrinsic conduction disease) usually ranges between 90 to 170 beats/min.
- The QRS complexes are narrow unless AV conduction through the His Purkinje system is abnormal due to functional (rate-related) aberration, pre-existing bundle branch or fascicular block, or ventricular preexcitation with conduction via an accessory pathway. Episodic prolonged runs of wide QRS complexes can be due to concealed perpetuated aberration, and the diagnosis is made by the classic long, short intervals before the episode initiates and the irregularly irregular pattern during the wide QRS.

UNCOMMON FINDINGS

Uncommon electrocardiographic findings include:

- A regular (rather than an irregularly irregular) ventricular rate due to a junctional (narrow or bundle branch block) or ventricular (wide QRS complex) escape rhythm if there is complete heart block but the presence of AF.
- A regular (wide QRS complex) ventricular rhythm due to ventricular pacing after atrioventricular junctional ablation or with spontaneous complete heart block; otherwise, after pacemaker placement.
- A regular wide QRS complex ventricular rhythm during ventricular tachycardia in the presence of AF.
- Variable QRS complexes with atrioventricular conduction during AF with conduction in lieu of ventricular pacing. There may be fusion beats.

LIST OF JOURNAL ABBREVIATIONS

Am Heart J	The American Heart Journal
Am J Cardiol	The American Journal of Cardiology
Arq Bras Cardiol	Arquivos Brasileiros de Cardiologia
Clin Sports Med	Clinical Journal Sports Medicine.
Curr Sports Med Rep	Current Sports Medicine Reports
Eur Heart J	European Heart Journal
Front Cardiovasc Med	Frontiers in cardiovascular medicine
JAMA	The Journal of the American Medical Association
J Am Coll Cardiol	Journal of the American College of Cardiology
J Am Soc Echocardiogr	The Journal of the American Society of Echocardiography
J Appl Physiol	The Journal of Applied Physiology
J Hum Kinet	The Journal of Human Kinetics
J Physiol	The Journal of Physiology
Mamm Genome	Mammalian Genome
Nutr Metab	Nutrition & Metabolism
Res Pharm Health Sci	Research in Pharmacy and Health Sciences
Sports Med Auckl NZ	Sports Medicine (Auckland, N.Z.)

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