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Peer-reviewed author version

D'Ambrosio, P; DE PAEPE, Jarne; Rowe, SJ; Janssens, Kristel; Mitchell, AM; Van Puyvelde, T; Spencer, LW; Bogaert, Jan; GHEKIERE, Olivier; PAUWELS, Rik; HERBOTS, Lieven; Robyns, T; Kistler, PM; Kalman, JM; HEIDBUCHEL, Hein; Willems, Rik; CLAESSEN, Guido; La Gerche, A; BEKHUIS, Youri; HANSEN, Dominique & OP 'T EIJNDE, Bert (2025) Mechanistic Insights Into Reduced Arrhythmia Prevalence in Female Endurance Athletes. In: JACC. Clinical electrophysiology, 11 (10) , p. 2225 -2237.

DOI: 10.1016/j.jacep.2025.05.023
Handle: http://hdl.handle.net/1942/49329

Mechanistic insights into reduced arrhythmia prevalence in female endurance athletes

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Formatting: JACC
Structured Abstract: 283
Manuscript (incl Fig legends): 4666
References: 79
Figures & Tables: 7

Abstract

Background: Lower rates of atrial fibrillation (AF) and sudden cardiac death (SCD) have been reported in female athletes, but the mechanisms underpinning the sex disparity in arrhythmia risk remain poorly defined.

Methods: We analysed Holter monitors in a cohort of 397 current and former endurance athletes enriched with prevalent AF. Echocardiography and cardiac magnetic resonance were used to detail cardiac structure and function. Athletes with overt cardiomyopathies, channelopathies, pre-excitation and/or myocardial infarction were excluded.

Results: Female athletes (*n*=125, 27[18-47] years) had a lower prevalence of AF (6% vs 32%, $p<0.001$) and non-sustained ventricular tachycardia (NSVT: 2% vs 11%, $p=0.004$) than males (*n*=272, 44[22-61] years). Despite comparable age-adjusted exercise volume (MET hrs/wk: 77[74-111] vs 87[72-131], $p=0.499$) and duration of sports practice (15[5-35] years vs 24[6-35] years, $p=0.570$), females had lower VO_2 Max (48[38-55]ml/kg/min vs 52[40-62], $p<0.001$). Female athletes had smaller age-adjusted left atrial (40[34-47]ml/m^2 vs 44[37-52]ml/m^2, $p=0.007$) and ventricular volumes (LVEDV*i*: 98±16ml/m^2 vs 109±21ml/m^2, $p<0.001$; RVEDV*i*: 109±20ml/m^2 vs 123±23ml/m^2, $p<0.001$). Age-adjusted hinge (12% vs 22%, $p=0.125$) and non-hinge-point fibrosis (11% vs 18%, $p=0.952$) was equally prevalent between the sexes. Lower LV Mass, similar native T1 times and higher extra-cellular volume in females suggested less cardiomyocyte hypertrophy than males. Compared to age-matched male athletes (*n*=125), females had a similar prevalence of atrial and ventricular ectopy. Less bradycardia and lower resting & peak exercise blood pressure in females suggested additional modulating factors.

Conclusions:

Lower rates of AF and NSVT in female athletes may be attributed to smaller atrial and ventricular volumes and reduced cardiomyocyte hypertrophy, though there are likely additional modulating factors. A comparable prevalence of ectopy suggests that the disparity in arrhythmia risk may be more attributable to differences in underlying substrate than arrhythmogenic triggers.

Condensed Abstract (88 words)

Using Holter monitoring and multi-modal cardiac imaging in a cohort of 125 female and 272 male endurance athletes enriched with prevalent AF, we observed a comparable rate of atrial and ventricular ectopic triggers between the sexes, despite a reduced prevalence of AF and NSVT in females. Fewer arrhythmias and a lower risk of SCD in female athletes may be secondary to smaller atrial and ventricular volumes and reduced cardiomyocyte hypertrophy compared to males, though differences in bradycardia burden and blood pressure suggest the influence of additional modulating factors.

Clinical Perspective

What is new?

- *Female athletes have a similar rate of atrial and ventricular ectopic triggers, despite a lower prevalence of AF and NSVT.*
- *Female athletes with comparable exposure to endurance exercise have smaller atrial and ventricular volumes and less cardiomyocyte hypertrophy than males.*

What are the clinical implications?

- *The female endurance athlete's heart appears to be less arrhythmogenic than the male endurance athlete's heart.*
- *The observed sex disparity in arrhythmia and SCD risk may be more attributable to differences in underlying substrate than arrhythmogenic triggers.*

Key Words

Endurance athletes
Females
Arrhythmias
Atrial fibrillation
Non-sustained ventricular tachycardia

Abbreviations

AA	Atrial arrhythmia
AF	Atrial fibrillation
ARCV	Arrhythmogenic right ventricular cardiomyopathy
BMI	Body mass index
BP	Blood pressure
BSA	Body surface area
Ca^{2+}	Calcium
CM	Cardiomyopathy
CMR	Cardiac magnetic resonance
CPET	Cardiopulmonary exercise testing
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECV	Extracellular volume
GLS	Global longitudinal strain
HR	Heart rate
ICD	Implantable cardioverter defibrillator
LA	Left atrium
LAV*i*	Indexed left atrial volume
LBBB	Left bundle branch block
LGE	Late gadolinium enhancement
LV	Left ventricle
LVEDV*i*	Indexed left ventricular end-diastolic volume
LVESV*i*	Indexed left ventricular end-systolic volume
LVSV*i*	Indexed left ventricular stroke volume
LVEF	Left ventricular ejection fraction
MET	Metabolic equivalent task
MI	Myocardial infarction
NSVT	Non-sustained ventricular tachycardia
PAC	Premature atrial complex
pAF	Paroxysmal atrial fibrillation
PVC	Premature ventricular complex
RA	Right atrium
RBBB	Right bundle branch block
RV	Right ventricle
RVEDV*i*	Indexed right ventricular end-diastolic volume
RVESV*i*	Indexed right ventricular end-systolic volume
RVSV*i*	Indexed right ventricular stroke volume
RVEF	Right ventricular ejection fraction
SBP	Systolic blood pressure
SCD	Sudden cardiac death
SNS	Sympathetic nervous system
SR	Sarcoplasmic reticulum
SVT	Supraventricular tachycardia
TTE	Transthoracic echocardiography
TWI	T wave inversion
VO_2 Max	Maximal oxygen consumption
VT	Ventricular tachycardia

Introduction

Female participation in sport has significantly increased in the past 4 decades with nearly equal numbers of women and men now competing in the United States(1,2) and gender parity at the 2024 Paris Olympics(3). Despite this, females remain significantly under-represented in sports cardiology literature. Data on arrhythmia prevalence and athletic cardiac remodelling in female endurance athletes in sparse, though existing studies suggest a lower prevalence of atrial fibrillation (AF)(4,5) and sudden cardiac death (SCD)(6-10) than their male counterparts. This biological difference in arrhythmia risk is thought to be due to a variety of factors including younger age, fewer comorbidities, shorter duration of exposure to vigorous exercise, less pronounced atrial structural remodelling, lower sympathetic tone and lower blood pressure (BP) in females(5,11,12). In this study, we aimed to evaluate the mechanisms underlying the sex disparity in arrhythmia prevalence by analysing the relationship between arrhythmias, fitness and athletic cardiac remodelling in a cohort of female and male endurance athletes enriched with prevalent AF.

Methods

Study Population

The study cohort included current and former endurance athletes from the Pro@Heart and ProAFHeart studies. The Pro@Heart study protocol has been previously detailed(13). The ProAFHeart study is a multicentre prospective trial aiming to determine the prevalence and 2-year incidence of arrhythmias and athletic remodelling in endurance athletes 16-85 years of age. Consecutive athletes are recruited through the national centre for sports cardiology via 1 of 2 pathways: 1) ostensibly healthy athletes sampled from the community and 2) athletes referred with known or suspected arrhythmias based on symptoms. The latter group is included to enrich the cohort with those who have (or are suspected to have) arrhythmias in an attempt to understand mechanisms of arrhythmogenesis in athletes. In both studies, athletes are comprehensively phenotyped at baseline using 12-lead electrocardiogram (ECG), 24-hour Holter monitoring, cardiopulmonary exercise testing (CPET), transthoracic echocardiography (TTE) and contrast-enhanced cardiac magnetic resonance (CMR). Athletes are then followed up at 2 years for repeat Holter. Athletes were recruited individually or through their sports federation or team, who were made aware of the study through advertisements, media and scientific presentations. Participants were enrolled to undergo study investigations at 1 of 5 medical research facilities: (1) St Vincent’s Institute of Medical Research, Melbourne, Australia; (2) Baker Heart and Diabetes Institute, Melbourne, Australia; (3) University

Hospitals, Leuven, Belgium; (4) Jessa Ziekenhuis, Hasselt, Belgium; and (5) University Hospital Antwerp, Antwerp, Belgium.

Athletes were eligible if they were ≥14 years old and compete (or formerly competed for a minimum of 5 years) in endurance sports at a national or international level, in which aerobic conditioning is a principal component of performance (e.g. triathlon, cycling, rowing, distance running ≥1500m and swimming ≥400m). Those with overt cardiomyopathies (CM), channelopathies, pre-excitation and/or myocardial infarction (MI) were excluded. Protocols (ProAFHeart: 484/16 & ACTRN12618000711213; Pro@Heart: S57241 & NCT05164328) were approved by the Human Research Ethics Committee at each of the recruiting sites in Australia and Belgium, and all participants provided informed written consent.

Exercise History

All participants completed a questionnaire which incorporated type of sport, number of years exercising and the frequency, duration and intensity of exercise sessions. Each sport was assigned a metabolic equivalent task (MET) score from the Compendium of Physical Activities(14) but using the reported level of performance (e.g. recreational vs national competition) and intensity (low, moderate or high) to choose the appropriate MET score from the Compendium since multiple options were available. Endurance exercise volume (MET hrs/wk) was calculated by multiplying the MET score by the reported weekly exercise hours as reported previously(15,16).

ECG & Holter monitoring

All participants underwent resting ECG and 24-72hour Holter monitoring. Athletes were instructed to perform normal physical activity including training during the Holter acquisition. All recordings were reviewed by 2 independent cardiologists. Minimum and average heart rate (HR) were those sustained for ≥30s. Bradycardia was defined as a heart rate (HR) <50/min and a cardiac pause as an interruption in ventricular rate ≥2s. Bradycardia burden was defined as % of time with HR <50/min divided by total analysed time. Those with cardiac devices or on negatively chronotropic medications were excluded from bradycardia and pause analyses. Atrial arrhythmias (AAs) included AF and all supraventricular tachycardias (SVT) ≥30s in duration. Non-sustained AAs were defined as those <30s in duration. Non-sustained ventricular tachycardia (NSVT) was defined as >3 consecutive ventricular beats >100/min and lasting <30s. Ventricular tachycardia (VT) was defined as >3 consecutive ventricular beats >100/min and lasting ≥30s and/or requiring intervention. Any sustained arrhythmia diagnosed prior to enrolment and/or detected on baseline or follow-up study Holters was recorded. Arrhythmias diagnosed prior to enrolment were verified with review of ECG and/or telemetry traces. All non-sustained arrhythmias, including NSVT, were recorded from baseline or follow-up study Holters only. Analysis of all parameters such as HR, pauses, bradycardia burden and premature atrial (PAC) and ventricular (PVC) complex burden was performed on baseline study Holters only.

CMR Imaging

CMR was performed using a 1.5T or 3.0T magnetic resonance imaging scanner (Magnetom Aera 1.5T, Prisma 3.0T or Skyra 3.0T, Siemens Healthineers, Erlangen, Germany; Ingenia, Achieva or Ambition 1.5T, Philips Medical Systems, Best, The Netherlands). A steady-state free precession dynamic echo-gradient sequence was used to obtain cine-loops during breath-hold in short axis and 4-chamber views. Left ventricular (LV) mass (not including papillary muscles and trabeculae) and biventricular volumes and function were quantified by two independent experienced cardiologists using customized analysis software (Circle Cardiovascular Imaging, cvi42, Calgary, Canada & SuiteHEART, Neosoft, Pewaukee, USA). Myocardial fibrosis was assessed by late gadolinium enhancement (LGE) imaging on breath hold phase-sensitive inversion recovery sequences 10 minutes after administration of gadolinium-DTPA. Hinge-LGE (H-LGE) was defined as LGE confined to the interventricular septum where the right ventricle (RV) attaches to the septum (hinge points). All other LGE was defined as non-hinge LGE (NH-LGE).

Echocardiography

TTE was performed (Vivid E9 or E95 ultrasound system, GE Healthcare, Horton, Norway) to assess atrial volumes and LV global longitudinal strain (GLS). Analysis of all TTE images were performed at 1 of 2 core laboratory facilities, both of which use the same software (EchoPAC^{TM}, GE Healthcare, Horton, Norway) and methods. All TTE and CMR measurements were indexed to body surface area where appropriate.

ECG Cardiopulmonary Exercise Test

CPET was conducted on an electronically braked cycle ergometer using a continuous ramp protocol. Respiratory gas exchange data was analysed using a breath-by-breath open circuit spirometry system. Maximal oxygen consumption (VO_2 Max) was determined as the highest

30s average oxygen consumption. Percentage of predicted VO_2 Max was calculated by dividing the relative VO_2 Max by age-predicted norms (using the FRIEND registry nomogram(17)).

Statistical Analysis

Data was collected and managed using REDCap and analysed with SPSS® version 29 (IBM Corporation, Armonk, NY). Normality was tested using the Shapiro-Wilk test. Continuous variables are presented as means (± standard deviation) or as medians [25th-75th percentile]. Between-group differences in continuous variables were assessed using independent t-test or Mann-Whitney U test as appropriate. Dichotomous variables were compared using a Chi-squared or Fisher exact test. All analyses were adjusted for age as a possible confounder using an analysis of covariates for parametric data, Quade's test for non-parametric data, and logistic regression for dichotomous data. Logistic regression was also used to assess for predictors of arrhythmias. A two-tailed p-value of <0.05 was considered statistically significant.

Results

Participant Characteristics

A total of 397 current and former endurance athletes aged 14-81 years were investigated. Table 1 shows the participant characteristics. Female athletes (n=125, 27[18-47] years) were significantly younger than male athletes (n=272, 44[22-61] years, p<0.001). Compared to males, female athletes exhibited lower height, weight, body mass index (BMI), body surface area (BSA), resting systolic blood pressure (SBP) and peak exercise SBP. Age-adjusted co-morbidities and medication use between the groups were well balanced, though fewer females had dyslipidaemia. Two athletes had implantable cardioverter defibrillators (ICD) and 4 permanent pacemakers (all symptomatic sinus node dysfunction). Compared to males, female athletes had a similar duration of sports practice and endurance exercise volume. Whilst females had a higher percentage of predicted VO_2 Max, relative VO_2 Max was significantly lower than male athletes. The majority of athletes in our cohort were rowers (43%), cyclists (33%) and runners (20%) with no sex-difference in the proportion participating in these sports.

ECG & Bradycardia

Table 2 shows results from ECG and Holter monitoring analysis. All ECG intervals were in the normal range with female athletes having shorter PR and QRS intervals, and longer QTc compared to males. More female athletes had T wave inversion (TWI) in V1 and V2 with a trend towards more TWI in V3 (p=0.068). There was no difference in the proportion of abnormal TWI according to international guidelines(18). All participants underwent baseline Holter monitoring with 70% undergoing repeat Holter at 2 years. There was no difference in analysed time (23.9[22.5-67.8]hrs vs 23.9[23.2-65.6]hrs, p=0.323) or number of repeat Holters between the groups (p=0.632). On baseline Holter analysis, excluding those with devices or taking negatively chronotropic medication (female, n=2; male, n=36), and adjusting for age, female athletes had higher average HR, higher minimum HR and lower bradycardia burden compared to males. Females also had a lower prevalence of pauses ≥2s. Minimum minutely HR negatively correlated with LVEDV (r=-0.521, p<0.001) and RVEDV (r=-0.499, p<0.001).

Atrial Arrhythmias

A total of 90 (23%) athletes had prevalent AF, with a lower prevalence in female compared to male athletes (6% vs 31%, p<0.001). Eighty-two percent of cases were classified as paroxysmal atrial fibrillation (pAF), with no sex difference in AF phenotype (pAF: 100% vs 81%, p=0.091). Five athletes (4 males and 1 female) were newly diagnosed with AF on study Holters. Compared to those without AF, athletes with AF were older (60[45-68] years vs 29[19-49] years, p<0.001) and exhibited greater height (1.81±0.75m vs 1.78±0.09m, p=0.003). After adjusting for age, those with AF also had higher resting SBP (134±16mmHg vs 124±14mmHg, p=0.011) and indexed left atrial (LA) volumes (LAV*i*: 47[39-56]ml/m^2 vs 42[35-49]ml/m^2, p=0.002), with the difference in absolute LA volumes more pronounced (94[80-121]ml vs 80[66-95]ml, p<0.001). There was no difference in age-adjusted peak exercise SBP (p=0.427) between these groups. A total of 22 (6%) athletes had other types of supraventricular tachycardia (SVT) with a similar prevalence between females and males (3% vs 7%, p=0.147).

Ventricular Arrhythmias

A total of 33 (8%) of athletes had NSVT recorded on study Holters with the prevalence significantly lower in female compared with male athletes (2% vs 11%, p=0.004). Episodes of NSVT were predominately monomorphic (87%), asymptomatic (95%) and not related to exercise. Compared to those without NSVT, athletes with NSVT were older (62[55-67] years vs 36[20-53] years, p<0.001), and the age-adjusted prevalence of NSVT between the sexes was not statistically significant (p=0.110). Seven athletes (1 female and 6 males) had a history of sustained VT prior to enrolment. Five of these (all male) had outflow tract VT successfully treated with catheter ablation. There were 2 cases of idiopathic cardiac arrest with secondary prevention ICDs implanted. Both of these athletes (1 female rower aged 40 years and 1 male cyclist aged 50 years) had athlete's heart on CMR without evidence of overt structural or electrical heart disease. No athletes had sustained VT recorded on study Holters.

Ectopic Triggers

To examine the relationship between ectopy and arrhythmias, accounting for the age difference between the sexes in our cohort and the age-related increase in PAC(19) and PVC(20) prevalence, we conducted a sub-analysis with female athletes age-matched 1:1 to male athletes. The results of this analysis are shown in Table 3. Paralleling the results of the primary analysis, females exhibited lower rest and peak exercise SBP and were well-matched in terms of duration of sports practice and endurance exercise volume. Relative VO_2 Max was significantly lower in females whilst percent of predicted VO_2 Max was similar. As shown in Figures 2 and 3, despite a significantly lower prevalence of AF and NSVT in age-matched female athletes, there was no difference in the prevalence of atrial ectopy, non-sustained AAs and ventricular ectopy, including PVC couplets and triplets.

Cardiac Imaging

Cardiac imaging results are shown in Table 4. TTE was performed in all, while CMR was performed in 91% of participants (115 females and 245 males). Female athletes had smaller LA volumes, with the difference in LA size even more pronounced when absolute LA volumes were compared (72[59-89]ml vs 87[72-103]ml, age-adjusted $p<0.001$). Female athletes also had smaller LV and RV end-diastolic volumes (LVEDV*i* & RVEDV*i*) and lower LV mass. Although males had a higher unadjusted prevalence of total and H-LGE, there was no sex difference in unadjusted NH-LGE or any type of scar when adjusting for age. Approximately 86% of NH-LGE was mid-myocardial/epicardial. On univariate and multivariate logistic regression (incorporating age and sex), no type of scar increased the odds of any arrhythmia. In a sub-analysis of 55 female and 166 male athletes with CMR performed on the same scanner and using the same analysis software, females had higher cardiac extracellular volume (ECV) with no difference in native T1 time. As shown in table 3, imaging results between age-matched groups were similar to the primary analysis.

Discussion

This study includes one of the largest cohorts of female endurance athletes, comprehensively phenotyped with Holter monitoring, CPET, TTE and multi-modal cardiac imaging. Inclusion of athletes with known or suspected arrhythmias (e.g. prevalent AF) was intentional to ensure a sufficient prevalence of arrhythmias and enable analysis of structural remodelling with CMR. Female athletes had a similar prevalence of comorbidities and exercise exposure to males, thereby addressing confounders present in prior studies, and all analyses were age-adjusted. Our main findings were: 1) atrial and ventricular ectopic triggers were similarly prevalent in both sexes, despite lower rates of AF and NSVT in female athletes, 2) females had smaller atrial and ventricular volumes and less cardiomyocyte hypertrophy than males, 3) non-hinge point fibrosis was equally prevalent between the sexes, and 4) potential sex-differences in autonomic tone and ion channel expression may further modulate the sex-differences in arrhythmia risk.

Arrhythmia Prevalence & SCD

In line with emerging evidence associating high-intensity endurance exercise with up to a 5-fold increased risk of AF(21), and lower rates of AF in female compared to male athletes(4,5), 24% of athletes in our cohort had AF, with a significantly lower prevalence in females. Whilst this high AF prevalence reflects selection bias, it is notable that 91% of those referred to our centre with AF were male. Further, among ostensibly healthy athletes sampled from the community, 94% of those with AF were also male. Selection bias may have similarly influenced the prevalence of NSVT in our cohort, which was higher than the 2-3% reported in previous studies(22-24). However, NSVT was detected only on study Holters and 95% of athletes with NSVT were asymptomatic, suggesting the true prevalence of NSVT in endurance athletes may be higher than previously reported. Whilst age-matched males had a significantly higher prevalence of NSVT than females (Figure 3), contrasting findings from prior studies(23,24), the age-adjusted *p*-value for NSVT in the overall cohort was not statistically significant. Therefore, further research is needed to clarify the potential sex-difference in NSVT prevalence amongst endurance athletes.

Reduced AF(4,5) and a potentially lower prevalence of NSVT, suggests that the female athlete's heart may be less arrhythmogenic than the male athlete's heart. This hypothesis is supported by a 5- to 10-fold lower incidence of SCD in young female athletic populations(6-10,25). Since this difference in SCD incidence is unlikely to be fully explained by the slightly lower phenotypic prevalence of conditions associated with SCD in athletes, such as hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy (ARVC)(25-27), it is likely that other factors are involved. These may include relative protection from arthrosclerosis in female athletes until after menopause and biological differences in cardiac electrophysiology properties due to substrate variations influenced by sex hormones during cell development, differences in autonomic tone, and the impact of circulating sex hormones before and after puberty(28).

Athletic Remodelling

In endurance athlete populations, sex-differences in cardiac remodelling may also contribute to the observed disparity in arrhythmia risk. In this study, female athletes had ventricular end-diastolic volumes approximately 10-15% smaller than those of male athletes. Whilst male athletes exhibited lower LVEF and RVEF, this may be due to a greater difference in LVEDV and RVEDV compared to their respective stroke volumes. In addition, consistent with prior studies(29), LA volumes were also 10-15% smaller in females. This almost certainly contributes to the reduced AF prevalence in female athletes, as increased LA size is associated with a higher risk of AF in both longitudinal(30) and cross sectional studies(31). The shorter stature of female athletes may further reduce their risk, as height correlates with absolute left atrial size(32) and both are independent risk factors for lone AF(33). Athletes with AF in our cohort were taller and had greater absolute LA volumes compared to those without AF. Notably, the sex difference in absolute LA volume was more pronounced compared to indexed LA volume. Whilst reduced LA volumes may protect against AF by reducing the risk of LA fibrosis, there are likely other mechanisms at play. For example, mechanical stretch of the atrial and ventricular myocardium, both acutely and chronically, may trigger arrhythmias. This is hypothesised to be via activation of mechano-sensitive ion channels, enhanced sodium and calcium (Ca^{2+}) influx via non-selective ion channels, and altered gene expression leading to hypertrophic remodelling(34).

Biological differences in the geometric pattern of remodelling may also play a role. Consistent with prior studies(35,36), female athletes in our cohort had lower LV mass, higher ECV and similar native T1 times compared to males, suggesting less cardiomyocyte hypertrophy. In general, greater muscle-mass (sex-related or training-induced) by itself creates a higher propensity for arrhythmias(37). Mild hypertrophy can result in non-uniform prolongation of the cardiac action potential and refractoriness(38,39), while also altering cardiomyocyte sarcoplasmic reticulum (SR) gene expression, impairing intracellular Ca^{2+} handling and increasing the likelihood of triggered activity(38,40,41). When these pro-arrhythmogenic effects are combined with observed sex differences in cardiomyocyte SR Ca^{2+} release(42,43), and evidence of sex-differences in ion channel expression, both dependant(44-47) and independent(48,49) on circulating sex hormones, it becomes more evident why male endurance athletes may be at higher risk of arrhythmias. Moreover, increased mechanical stretch and myocardial hypertrophy likely act synergistically in male athletes, as hypertrophy may contribute to electrical instability by increasing the sensitivity of mechano-electric feedback(34).

Ectopic Triggers

Interestingly, despite a lower prevalence of AF and NSVT in female athletes, we found no sex-differences in the rate of atrial or ventricular ectopy (Figures 2 and 3). Whilst one may expect the opposite given the effects of mechanical stretch and cardiomyocyte hypertrophy discussed above, these findings align with prior studies that report equal distribution of atrial(12) and ventricular ectopy(24) in both sexes among athletes. In non-athletic populations, some studies report PVCs are more common in males(50,51), whilst others indicate a higher prevalence in females(52). Although equal rates of ectopy does not rule out an increase in arrhythmogenic triggers contributing to higher arrhythmia rates in male athletes per se, it does suggest that the disparity in arrhythmia risk between female and male endurance athletes may be more influenced by differences in underlying arrhythmogenic substrate than ectopic triggers. Further, PVC burden may be a poor surrogate for ventricular arrhythmia risk in female athletes, though contemporary risk-prediction algorithms(53) suggest focusing more on PVC morphology (amongst other characteristics), and less on burden.

Myocardial Fibrosis

Whilst assessment of atrial fibrosis was outside the scope of our study, CMR analysis revealed a similar age-adjusted prevalence of total-LGE, H-LGE and NH-LGE between female and male athletes. Whilst the majority of previous studies report that male athletes have a higher prevalence of ventricular fibrosis compared to females(54-57), one study of 93 highly-trained endurance athletes found an equal prevalence (35-41%) of H-LGE between the sexes(58). To our knowledge, this is the first study to report an equal prevalence of NH-LGE (86% mid-myocardial/epicardial) between the sexes, which is significant given NH-LGE has been associated with life-threatening VAs and SCD(59), though prognosis in athletes with this often incidental finding remains variable(60). In comparison, H-LGE has not been associated with ventricular arrhythmias and SCD in studies to date(61-63). Whilst further work is needed to clarify the prognostic significance of both H-LGE and NH-LGE, it is notable that neither H-LGE or NH-LGE increased the odds of any arrhythmia in our study.

Arrhythmia Modulators

Although not formally assessed, we observed potential sex differences in autonomic tone. Consistent with other athlete studies(35,64), and non-athlete studies demonstrating that females can more effectively regulate the sympathetic nervous system (SNS) and, subsequently, arterial pressures, providing relative protection against hypertension(65), female athletes in our cohort had lower resting and peak exercise SBP than males. This indirect evidence of lower SNS tone and/or tighter SNS regulation in females is further supported by studies analysing heart rate variability, which indicate lower SNS activity in female athletes compared to males(12). Higher SNS tone may increase the risk of adrenergic-mediated AF and elevate both resting and peak exercise BP in male athletes. However, elevated resting BP might be more critical for AF risk, as we observed no difference in peak exercise BP between athletes with and without AF. We also observed that male athletes in our cohort were more bradycardic, had more pauses and longer PR intervals than females. Similar sex-differences have been observed in non-athletic populations(28), with changes in HR during menses implying a role of circulating sex hormones(66,67). Currently, it remains under debate as to whether endurance training-induced bradycardia is secondary to higher parasympathetic modulation of the sinus node(68,69) or atrial electrical remodelling(70). Consistent with previous studies(68), we found moderate negative correlations between minimum resting HR and ventricular end-diastolic volumes, indicating that ventricular remodelling may also play a role. This may be due to baroreflex regulation, which lowers resting HR in response to cardiac enlargement to mitigate the risk of arterial hypertension(71,72). Irrespective of the aetiology, biological differences in bradycardia burden and both rest and peak exercise BP suggests there are other modulating factors, such as autonomic tone and ion channel expression, which contribute to the sex disparity in arrhythmia risk.

ECG

Aligning with previous studies(73-75), female athletes exhibited a prevalence of normal, training-related ECG changes similar to that of males athletes, despite the observed differences in degree and pattern of athletic remodelling. Shorter QRS duration and longer QTc are also well described in female athletes(73-75). Consistent with existing data(73,74,76), a higher percentage of female athletes (9%) had TWI in V2, with a trend towards significance for TWI in V3 (5%). Unsurprisingly, the overall prevalence of inferior and lateral TWI was low, as these are rarely seen in White athletes of either sex(73,75,77,78). There was also no difference in the prevalence of abnormal TWI as defined by international guidelines(18). The aetiology of increased anterior TWI in otherwise healthy female endurance athletes remains unclear. However, factors such as differences in lead placement due to breast tissue and more lateral RV displacement owing to smaller thoracic size, as previously observed by our group(79), may play a role. This sex difference in anterior TWI has significant clinical implications, as anterior TWI remains part of the diagnostic criteria for ARVC.

Limitations

The current analysis relies primarily on cross-sectional data, limiting conclusions on the prognosis of those with myocardial scar and arrhythmias. The demographic profile of the athletes in our cohort was exclusively White, which limits the applicability of our findings to athletes of other ethnicities. Although we divided ventricular scar into H-LGE and NH-LGE, we did not report the extent of NH-LGE as a proportion of total LV mass, which may have better uncovered a sex difference in ventricular scar burden and better correlated with arrhythmias. We also did not assess for LA fibrosis which limits conclusions regarding sex differences in atrial remodelling and AF risk. Whilst similar native T1 times, lower LV mass and higher ECV in females suggests less cardiomyocyte hypertrophy compared to males, higher ECV in females may also be due to extracellular matrix expansion. Finally, 3-lead Holter monitoring does limit assessment of QRS morphology and conclusions regarding prevalence of ‘common’ (i.e. outflow tract or fascicular) and ‘uncommon’ PVCs/NSVT between female and male athletes, which may have prognostic significance.

Conclusion

Lower rates of AF and NSVT in female athletes may be attributed to smaller atrial and ventricular volumes and reduced cardiomyocyte hypertrophy. However, other modulating factors, such as biological differences in autonomic tone and ion channel expression, may also play a role. A similar prevalence of ectopic triggers between sexes suggests that the disparity in arrhythmia risk may be more attributable to differences in underlying substrate than arrhythmogenic triggers.

Acknowledgements

The authors would like to specifically acknowledge the work of Sofie Van Soest (Department of Cardiovascular Sciences, KU Leven, Belgium; Departmnt of Cardiovascular Sciences, University Hospitals Leuven, Belgium) as well as other members of the Pro@Heart Consortium: Youri Bekhuis; Peter Hespel, MSc, PhD; Steven Dymarkowski, MD, PhD; Tom Dresselaers, PhD; Hielko Miljoen, MD, PhD; Kasper Favere, MD; Bernard Paelinck, MD, PhD; Dorien Vermeulen; Isabel Witvrouwen, MD, PhD; Dominique Hansen, MSc, PhD; Bert Op't Eijnde; Daisy Thijs; Peter Vanvoorden; Kristof Lefebvre, MD; Elizabeth Paratz, MD, PhD; Maria J. Brosnan, MD, PhD; David L. Prior, MD, PhD. Department of Cardiovascular Sciences (Y.B.), Department of Movement Sciences (P.H.), Department of Imaging and Pathology (S.D.), KU Leuven, Belgium. Department of Cardiovascular Diseases (Y.B.), Department of Radiology (S.D., T.D.), University Hospitals Leuven, Belgium. Faculty of Medicine and Life Sciences, LCRC, UHasselt, Biomedical Research Institute, Diepenbeek, Belgium (Y.B., D.H.). Department of Radiology, Hartcentrum Hasselt (D.T., P.V.), Jessa Ziekenhuis, Belgium. Department of Cardiovascular Sciences, University of Antwerp, Belgium (H.M., K.F., B.P., D.V., I.W.). Department of Cardiology, University Hospital Antwerp, Belgium (H.M., K.F., B.P., D.V., I.W.). REVAL/BIOMED, Hasselt University, Diepenbeek, Belgium (D.H., B.O.E.). Department of Cardiology, Algemeen Ziekenhuis Nikolaas, Sint-Niklaas, Belgium (K.L.). Department of Medicine, University of Melbourne, Parkville, Australia (E.P., D.L.P.). HEART (Heart Exercise and Research Trials) Lab, St Vincent's Institute of Medical Research, Fitzroy, Australia (E.P.). Cardiology Department, St Vincent's Hospital Melbourne, Fitzroy, Australia (E.P., M.J.B., D.L.P.). National Centre for Sports Cardiology, Fitzroy, Australia (M.J.B., D.L.P.).

Funding

This work was supported by the National Health and Medical Research Council of Australia (ID: APP1130353).

Paolo D'Ambrosio is supported by a Royal Australian College of Physicians Research Entry Scholarship (ID: 2023RES00039), The National Health and Medical Research Council Postgraduate Scholarship (ID: 2031119) and a Heart Foundation PhD Scholarship (ID: 107659). Luke Spencer and Kristel Janssens are supported through and Australian Government Research Training Program Scholarship. Rik Willems is supported as postdoctoral clinical researcher by the Fund for Scientific Research Flanders. Andre La Gerche is supported by a National Health and Medical Research Council of Australia Investigator Grant (ID: APP2027105).

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Figure Legends

Central Illustration legend: *Abbreviations – AF: atrial fibrillation; CM: cardiomyopathy; MI: myocardial infarction; VO_2 Max: maximal amount of oxygen the body can utilise per kg per minute; BP: blood pressure; Vol: volume; Vent: ventricular; NSVT: non-sustained ventricular tachycardia. Athletes with devices or on negatively chronotropic medications were excluded from bradycardia & pause analysis. Image created with BioRender.com.*

Figure 2 legend: *Abbreviations – PAC/24hr: premature atrial complexes per 24-hours; SVT: supraventricular tachycardia; AF: atrial fibrillation.*

Figure 3 legend: *Abbreviations – PVC/24hr: premature ventricular complexes per 24-hours; NSVT: non-sustained ventricular tachycardia: VT: sustained ventricular tachycardia.*

Table 1 legend: *Abbreviations – BMI: body mass index; BSA: body surface area (Mosteller); SBP: systolic blood pressure; DBP: diastolic blood pressure; Vol: volume; MET: metabolic equivalents; VO_2 Max: maximal amount of oxygen the body can utilise per kg per minute; % Predicted VO_2 Max: percentage of VO_2 Max relative to predicted VO_2 max (derived from the FRIEND registry(17)); RER: respiratory exchange ratio; HTN: hypertension; CAD: coronary artery disease; PCI: percutaneous coronary intervention; TIA: transient ischaemic attack; PPM; permanent pacemaker; ICD: implantable cardioverter defibrillator; Anti-HTN: anti-hypertensive medication (ACE-inhibitors, Angiotensin II antagonists and/or Angiotensin receptor/neprilysin inhibitors); Ca: calcium; OAC: oral anticoagulation (all direct-acting oral anticoagulants); 'p value (Unadjusted)' represents comparison between the groups and 'p value (Adjusted)' represents comparison between the groups after adjusting for age.*

Table 2 legend: *Abbreviations – QTc: corrected QT using Bazett's formula; T Wave Inversion is in the absence of incomplete RBBB and complete RBBB/LBBB (female, n=24; male, n=46); Abnormal TWI: according to international guidelines(18) - ≥1mm in depth in ≥2 contiguous leads (excluding aVR, III and V1) in the absence of incomplete RBBB and complete RBBB/LBBB; HR: heart rate; PAC/24hr: 24-hour premature atrial complex burden; AF: atrial fibrillation; SVT: supraventricular tachycardia; PVC/24hr: 24-hour premature ventricular complex burden; NSVT: non-sustained ventricular tachycardia; VT: ventricular tachycardia; *Analyses exclude athletes taking negatively chronotropic medications (including anti-arrhythmics) and/or with intra-cardiac devices (female, n=2; male, n=36); 'p value (Unadjusted)' represents comparison between the groups and 'p value (Adjusted)' represents comparison between the groups after adjusting for age.*

Table 3 legend: *Abbreviations - BMI: body mass index; BSA: body surface area (Mosteller); SBP: systolic blood pressure; DBP: diastolic blood pressure; Vol: volume; MET: metabolic equivalents; VO_2 Max: maximal amount of oxygen the body can utilise per kg per minute; % Predicted VO_2 Max: percentage of VO_2 Max relative to predicted VO_2 max (derived from the FRIEND registry(17)); LAVi: left atrial volume indexed to BSA area; RAVi: right atrial volume indexed to BSA; CMR: cardiac MRI; LVEDVi: left ventricular end-diastolic volume indexed to body surface area (BSA); LVESVi: left ventricular end-systolic volume indexed to BSA; LV: left ventricle; LVEF: left ventricular ejection fraction; RVEDVi: right ventricular end-diastolic volume indexed to BSA; RVESVi: right ventricular end-systolic volume indexed to BSA; RVEF: right ventricular ejection fraction; LGE: late gadolinium enhancement; ECV: extracellular volume; *CMR scans performed in 51 females and 65 males using same CMR scanner and analysis software.*

Table 4 legend: *Abbreviations –TTE: transthoracic echocardiogram; LAVi: left atrial volume indexed to BSA area; RAVi: right atrial volume indexed to BSA; CMR: cardiac MRI; LVEDVi: left ventricular end-diastolic volume indexed to body surface area (BSA); LVESVi: left ventricular end-systolic volume indexed to BSA; LV: left ventricle; LVEF: left ventricular ejection fraction; RVEDVi: right ventricular end-diastolic volume indexed to BSA; RVESVi: right ventricular end-systolic volume indexed to BSA; RVEF: right ventricular ejection fraction; LGE: late gadolinium enhancement; ECV: extracellular volume; *CMR scans performed in 55 females and 166 males using same CMR scanner and analysis software; 'p value (Unadjusted)' represents comparison between the groups and 'p value (Adjusted)' represents comparison between the groups after adjusting for age.*

Figures & Tables

Figure 1: Central Illustration

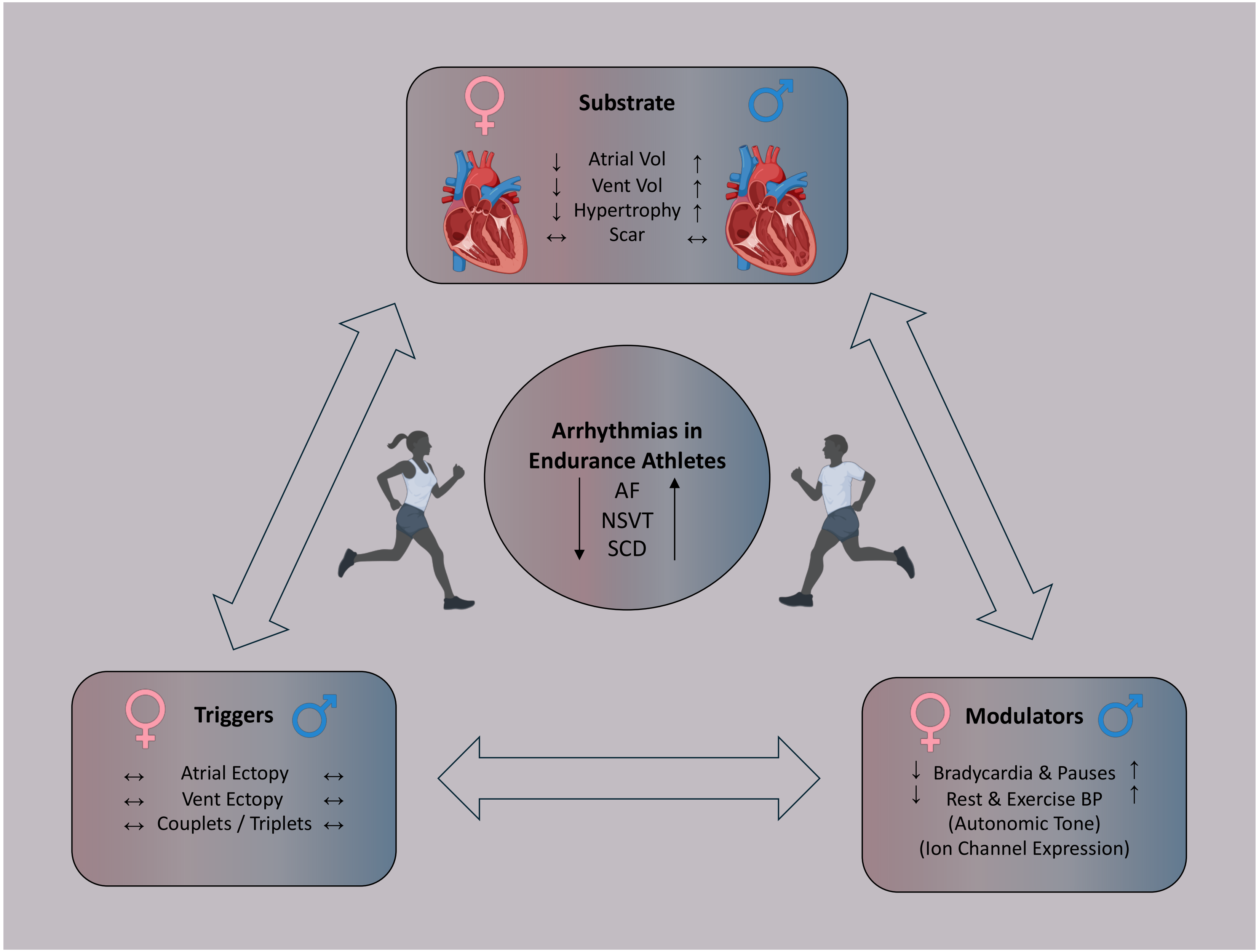
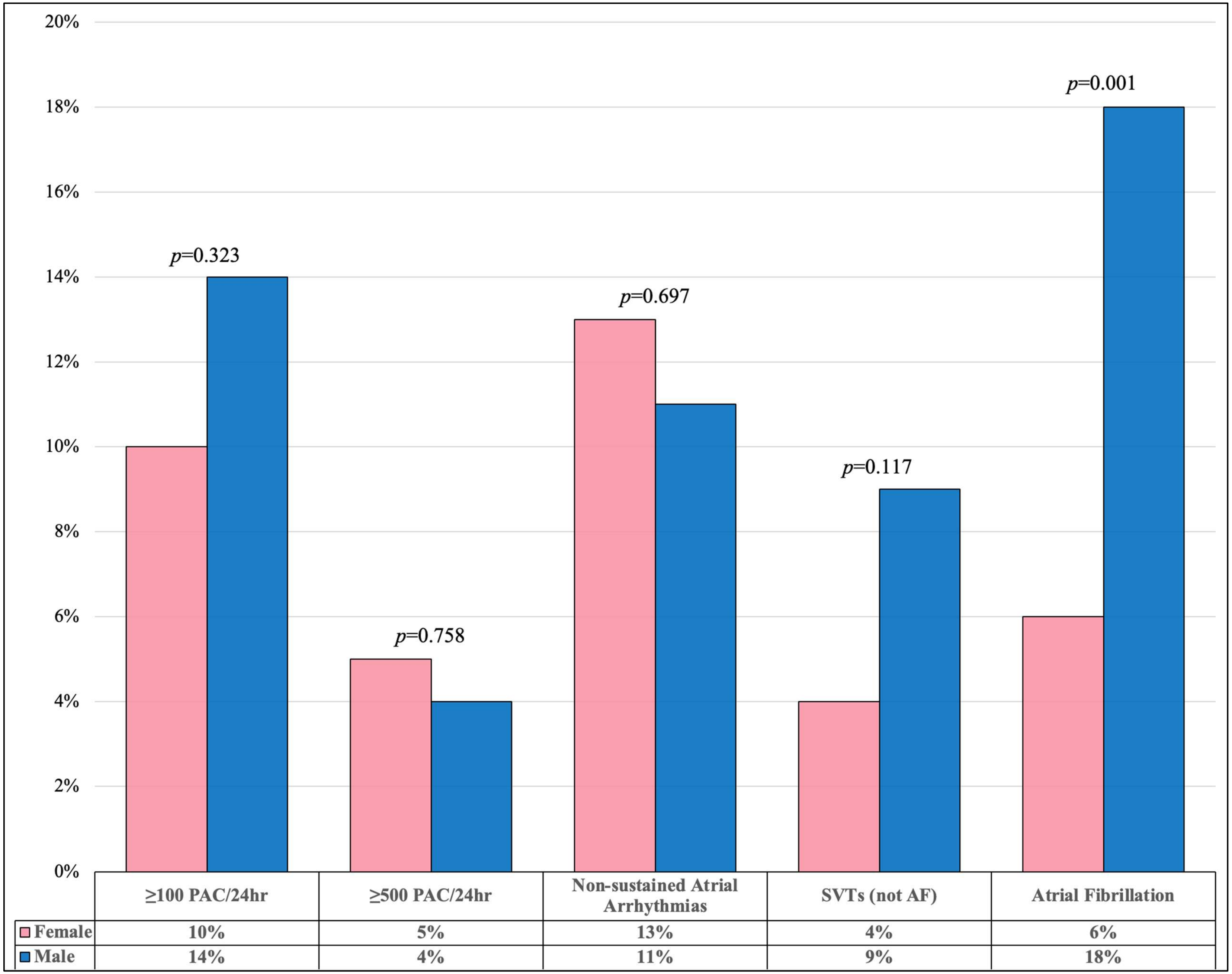
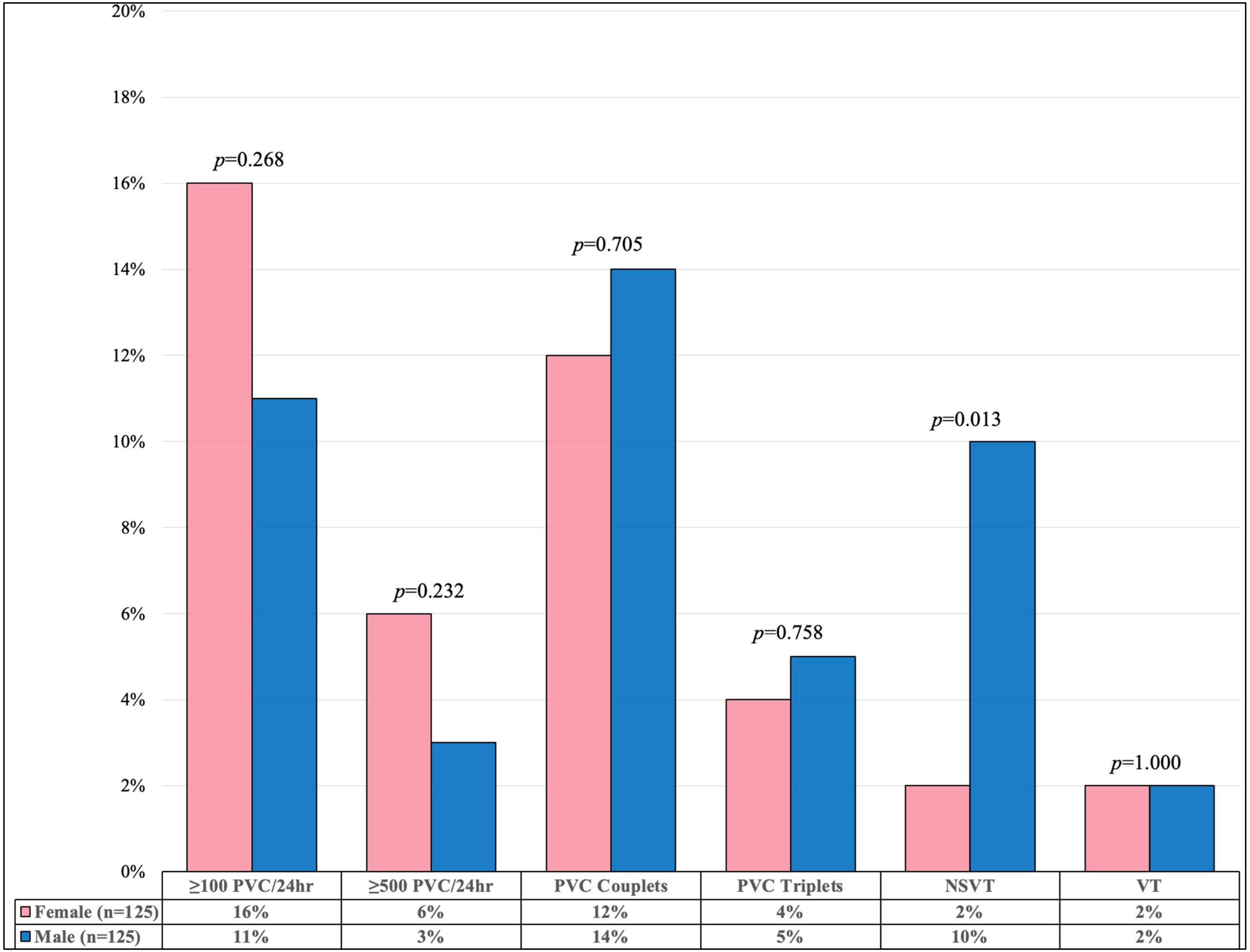


Figure 2: Atrial Ectopy & Arrhythmias in Age-Matched Athletes



	≥100 PAC/24hr	≥500 PAC/24hr	Non-sustained Atrial Arrhythmias	SVTs (not AF)	Atrial Fibrillation
Female	10%	5%	13%	4%	6%
Male	14%	4%	11%	9%	18%

Figure 3: Ventricular Ectopy & Arrhythmias in Age-Matched Athletes



	≥100 PVC/24hr	≥500 PVC/24hr	PVC Couplets	PVC Triplets	NSVT	VT
■ Female (n=125)	16%	6%	12%	4%	2%	2%
■ Male (n=125)	11%	3%	14%	5%	10%	2%

Table 1: Participant Characteristics

Variable	Female Athletes *n*=125	Male Athletes *n*=272	*p* value (Unadjusted)	*p* value (Adjusted)
Age (yr)	27 [18-47]	44 [22-61]	<0.001	-
Height (m)	1.71 ± 0.06	1.82 ± 0.07	<0.001	<0.001
Weight (kg)	63 [55-72]	78 [71-87]	<0.001	<0.001
BMI (kg/m^2)	22 [20-24]	24 [22-26]	<0.001	0.001
BSA (m^2)	1.74 [1.61-1.86]	1.99 [1.88-2.12]	<0.001	<0.001
SBP (mmHg)	118 ± 14	131 ± 14	<0.001	<0.001
DBP (mmHg)	66 ± 10	71 ± 11	<0.001	0.114
Fitness & Exercise				
Duration Sport Practice (yr)	15 [5-35]	24 [6-35]	0.054	0.570
Endurance Exercise Vol (MET hrs/wk)	77 [74-111]	87 [72-131]	0.539	0.499
VO_2 Max (ml/kg/min)	48 [38-55]	52 [40-62]	0.004	<0.001
% Predicted VO_2 Max	132 ± 21	123 ± 20	<0.001	<0.001
Peak RER	1.27 [1.20-1.34]	1.27 [1.22-1.32]	0.899	0.385
Peak Exercise SBP (mmHg)	200 ± 23	217 ± 28	<0.001	<0.001
Peak Exercise DBP (mmHg)	86 ± 13	84 ± 16	0.334	0.020
Comorbidities				
Arrhythmias:				
AF	7 (6%)	83 (31%)	<0.001	<0.001
Other SVTs	4 (3%)	18 (7%)	0.147	0.322
VT	1 (%)	6 (2%)	0.323	0.484
HTN	3 (2%)	29 (11%)	0.005	0.181
Dyslipidaemia	2 (2%)	44 (16%)	<0.001	0.015
Diabetes	0 (0%)	2 (1%)	0.218	0.996
Smoking:				
Current	0 (0%)	2 (1%)	0.218	0.996
Ex	13 (10%)	33 (12%)	0.616	0.068
Non-obstructive CAD	0 (0%)	14 (5%)	0.001	0.996
PCI	0 (0%)	8 (3%)	0.013	0.996
Stroke / TIA	0 (0%)	7 (3%)	0.021	0.996
PPM	1 (1%)	3 (1%)	0.774	0.747
ICD	1 (1%)	1 (1%)	0.586	0.490
Medications				
Anti-HTN	3 (2%)	27 (10%)	0.004	0.240
Statins	1 (1%)	29 (11%)	<0.001	0.064

Anti-Arrhythmics:				
Beta-blockers	0 (0%)	12 (4%)	0.002	0.996
Ca-channel Antagonists	0 (0%)	7 (3%)	0.021	0.996
Flecainide	0 (0%)	11 (4%)	0.004	0.996
Sotalol	1 (1%)	2 (1%)	0.945	0.759
Amiodarone	0 (0%)	1 (1%)	0.497	0.996
Antiplatelets	2 (2%)	17 (6%)	0.027	0.428
OAC	0 (0%)	20 (7%)	<0.001	0.995

Table 2: ECG & Holter Monitoring

Variable	Female Athletes *n*=125	Male Athletes *n*=272	*p* value (Unadjusted)	*p value* (Adjusted)
ECG				
*PR (ms)	156 [137-172]	180 [160-199]	<0.001	<0.001
QRS (ms)	94 [88-102]	101 [96-106]	<0.001	<0.001
*QTc (ms)	415 [398-430]	393 [380-410]	<0.001	<0.001
T Wave Inversion:				
V1	73 (70%)	94 (42%)	<0.001	<0.001
V2	9 (9%)	5 (2%)	0.010	0.093
V3	5 (5%)	3 (1%)	0.068	0.194
Abnormal TWI	6 (5%)	5 (2%)	0.108	0.269
Holter				
*Average HR (bpm)	69 [63-75]	65 [59-70]	<0.001	<0.001
*Min HR (bpm)	44 [40-49]	43 [38-48]	0.037	0.001
Max HR (bpm)	155 [133-170]	148 [122-167]	0.038	0.219
*Bradycardia Burden (%)	2.6 [0.2-21.6]	10.4 [0.6-28.7]	0.008	<0.001
*Pauses ≥ 2s	19 (15%)	64 (26%)	0.016	0.023
PAC/24hr (n)	9.2 [3.0-31.3]	21.1 [6.0-97.7]	<0.001	0.015
Non-sustained Atrial Arrhythmias	18 (14%)	69 (25%)	0.014	0.393
Sustained Atrial Arrhythmias:				
AF	1 (1%)	26 (10%)	<0.001	0.069
Other SVTs	2 (2%)	4 (2%)	0.922	0.341
PVC/24hr (n)	1.4 [0.0-16.2]	3.2 [0.0-25.5]	0.207	0.243
PVC Couplets	15 (12%)	46 (17%)	0.207	0.838
PVC Triplets	5 (4%)	16 (6%)	0.425	0.912
NSVT	3 (2%)	30 (11%)	0.004	0.110
VT	0 (0%)	0 (0%)	-	-

Table 3: Age-matched Female vs Male Athletes

Variable	Female Athletes *n=125*	Male Athletes *n=125*	*p* value (Unadjusted)
Age (yr)	27 [18-47]	24 [18-47]	0.841
BMI (kg/m^2)	22 [20-24]	23 [21-24]	0.032
BSA (m^2)	1.74 [1.62-1.87]	1.92 [1.83-2.07]	<0.001
Rest SBP (mmHg)	118 ± 14	128 ± 12	<0.001
Rest DBP (mmHg)	68 ± 10	66 ± 10	0.204
Fitness & Exercise			
Duration Sport Practice (yr)	14 [8-18]	14 [5-20]	0.739
Endurance Exercise Vol (MET hrs/wk)	113 [65-159]	120 [90-160]	0.237
VO_2 Max (ml/kg/min)	48 [38-55]	60 [51-67]	<0.001
% Predicted VO_2 Max	133 ± 22	129 ± 15	0.178
Peak SBP (mmHg)	200 ± 23	219 ± 31	<0.001
Peak DBP (mmHg)	86 ± 13	80 ± 17	0.004
TTE	*n*=125	*n*=125	
LAV*i* (ml/m^2)	41 [34-47]	44 [37-52]	0.002
RAV*i* (ml/m^2)	28 [22-35]	29 [23-40]	0.101
CMR	*n*=110	*n*=113	
LVEDV*i* (ml/m^2)	98 ± 17	117 ± 17	<0.001
LVESV*i* (ml/m^2)	41 ± 10	51 ± 11	<0.001
LVSV*i* (ml/m^2)	57 ± 11	66 ± 12	<0.001
LV Mass (g/m^2)	60 ± 11	77 ± 16	<0.001
LVEF (%)	59 ± 5	56 ± 6	0.002
RVEDV*i* (ml/m^2)	109 ± 20	130 ± 20	<0.001
RVESV*i* (ml/m^2)	52 ± 13	64 ± 14	<0.001
RVSV*i* (ml/m^2)	57 ± 11	66 ± 13	<0.001
RVEF (%)	53 ± 6	51 ± 7	0.031
Total LGE	19 (17%)	30 (26%)	0.102
Hinge LGE	14 (13%)	24 (21%)	0.097
Non-Hinge LGE	14 (13%)	17 (15%)	0.636
*Native T1 time (ms)	1131 [1109-1161]	1139 [1117-1166]	0.419
*ECV (%)	27 [25-28]	24 [22-26]	<0.001

Table 4: Cardiac Imaging

Variable	Female Athletes	Male Athletes	*p* value (Unadjusted)	*p value* (Adjusted)
TTE	*n*=125	*n*=272		
LAV*i* (ml/m^2)	40 [34-47]	44 [37-52]	<0.001	0.007
RAV*i* (ml/m^2)	28 [22-34]	31 [24-43]	<0.001	0.050
CMR	*n*=115	*n*=245		
LVEDV*i* (ml/m^2)	98 ± 16	109 ± 21	<0.001	<0.001
LVESV*i* (ml/m^2)	41 ± 9	48 ± 11	<0.001	<0.001
LVSV*i* (ml/m^2)	57 ± 10	61 ± 14	0.003	<0.001
LV Mass (g/m^2)	60 ± 11	72 ± 15	<0.001	<0.001
LVEF (%)	59 ± 5	56 ± 6	<0.001	0.004
RVEDV*i* (ml/m^2)	109 ± 20	123 ± 23	<0.001	<0.001
RVESV*i* (ml/m^2)	52 ± 13	62 ± 15	<0.001	<0.001
RVSV*i* (ml/m^2)	57 ± 10	61 ± 14	0.005	<0.001
RVEF (%)	52 ± 8	50 ± 7	0.001	0.075
Myocardial Fibrosis				
Total LGE	19 (15%)	77 (28%)	0.005	0.114
Hinge LGE	15 (12%)	60 (22%)	0.017	0.125
Non-Hinge LGE	14 (11%)	49 (18%)	0.084	0.952
*Native T1 time (ms)	1139 [1098-1171]	1149 [1119-1173]	0.254	0.366
*ECV (%)	26 [24-28]	25 [23-27]	<0.001	<0.001