Structural and Functional Adaptation of the Heart to Resistance Training in Combination with Anabolic Androgenic Steroid Use – Insights from Echocardiography and the 12 Lead Electrocardiogram

Harry Carpenter

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Abstract

The ‘Athlete’s Heart’ (AH) is a complex phenomenon that has been extensively researched in the modern era. It has been described as the chronic process of cardiac structural and functional remodelling that occurs as a result of regular exercise (Prior and La Gerche, 2012). The type and magnitude of adaptation that occurs is subject to various factors including age, gender, ethnicity, and type of exercise. Adaptations to both endurance (ET) and resistance training (RT) have been well documented (Spence et al., 2013a; Dores et al., 2015; Utomi et al., 2015). However, recent literature has refuted historic work that previously stated a dichotomy of adaptation between ET and RT athletes (Morganroth et al., 1975). Rendering the Morganroth hypothesis obsolete in the present day, illustrating a more complex relationship between the two disciplines, rather than a simple dichotomous one.

The use of anabolic-androgenic steroids (AAS) has increased significantly over the past decade, with their prevalence spreading across the world (McVeigh et al., 2021) (Baggish et al., 2017). This is due to their increased popularity as Image and Performance Enhancing Drugs (IPED’s) (McVeigh et al., 2021). The use of IPED’s has become widespread, from the recreational gym user to high profile and professional athletes.

Echocardiography has been used in previous work to assess the impact of RT in combination with AAS use (Angell et al., 2014; Baggish et al., 2017). Illustrating a significantly larger cardiac geometry in AAS users, with a concomitant decrease in ventricular function. Although research on this topic has become more prevalent in

recent years, the difficulty still remains in standardising these adaptations in such a wide and diverse population. This thesis explores structural and functional adaptation within non-using or 'pure' RT athletes. Additionally, this will be assessed in RT athletes that are both past and current users of AAS. The thesis will seek to highlight any differences in structural and functional adaptation between the three groups.

The first empirical study focuses on echocardiographic assessment of the heart, where that all mean values of both left ventricular (LV) and right ventricular (RV) parameters for non-using RT athletes, were within normal ranges for non-athletic individuals (Harkness et al., 2020b). Current users of AAS experienced significantly larger absolute and indexed values of LV mass (LVM) and mean wall thickness (MWT) compared to both past and non-users. Current users also demonstrated higher absolute values of LV dimension (LVIDd) and LV end diastolic volume (LVEDV) compared to non-users albeit these differences disappeared for indexed values to body surface area (BSA). There were no significant differences between past and non-users for any LV structural parameter. LV ejection fraction (EF) was significantly lower in current users compared to non-users and they also demonstrated significantly lower peak global longitudinal strain (GLS) and global circumferential strain (GCS) compared to both non-users and past users. Peak GLS was significantly lower in past users compared to non-users.

Current users had significantly larger absolute values of the proximal RV outflow tract ($RVOT_1$) than both non and past users and had significantly greater absolute values for $RVOT_{plax}$, $RVOT_2$, RV dimensions (RVD_1, RVD_2, and RVD_3) than non-users. These

differences disappeared when RV chamber dimensions were indexed to BSA. There were no significant differences between past and non-users for any RV structural measurements. Peak RV free wall strain was also significantly lower in current users compared to both past and non-users.

The second empirical study focused on the electrocardiogram (12-lead ECG) and demonstrated that non-users displayed a greater prevalence of 2 or more training related ECG changes (55%). Only current users (n=57) demonstrated borderline (n=4) and abnormal (n=2) findings. T wave axis was significantly lower in current users compared to both past and non-users. QRS duration and voltages for RVH were also significantly higher in current users compared to non-users.

To summarise, the main findings from the thesis are 1) non-using RT athletes display minimal adaptation to RT; with echocardiographic parameters within normal ranges for non-athletic individuals (Harkness et al., 2020b), 2) current users exhibit significantly larger hearts than their non-using counterparts, with a concomitant decrease in function, particularly systolic and 3) past users exhibit significantly smaller LV and RV size compared to current users. Additionally, they displayed non-significant differences between themselves and non-users. Suggesting that certain adaptations to AAS may be reversed with abstinence.

This thesis highlights some significant implications. First, these findings further refute the Morganroth hypothesis, highlighting minimal adaptation to RT alone, with no concentric hypertrophy amongst non-using RT athletes. Second, current users demonstrate a potential pathological pathway of adaptation, with significantly increased structural measurements, combined with a global reduction in systolic

function. Third, current users exhibit potential abnormal ECG changes, shown through a significantly reduced T axis, a novel finding. Finally, past users seem to exhibit a reverse in structural adaptation with abstinence. However, some functional parameters still remain significantly different to that of non-users. Suggesting a more permanent form of adaptation, shown through reduced function.

Declaration

No portion of the work within this thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

I declare that the work within this thesis is entirely my own.

This work has helped to support the submission of publications to peer-reviewed journals and conferences:

- The Impact of Image and Performance Enhancing Drugs on Atrial Structure and Function in Resistance Trained Individuals – Florence Place, **Harry Carpenter,** Barbara N. Morrison, Neil Chester, Robert Cooper, Ben N. Stansfield, Keith P. George & David Oxborough, Echo Research and Practice 2023.
- Regional Left Ventricular Longitudinal Strain in Resistance Trained Individuals using Anabolic-Androgenic Steroids - **Harry Carpenter,** Florence Place, Barbara N. Morrison, Neil Chester, Robert Cooper, Ben N. Stansfield, Keith P. George & David Oxborough, British Society of Echocardiography Annual Conference 2023. Echo Research and Practice 2024, 11(suppl 1):18
- The Longitudinal Impact of Image and Performance Enhancing Drugs on Left Ventricular Structure and Function: A Case Report - Florence Place, **Harry Carpenter,** Barbara N. Morrison, Neil Chester, Robert Cooper, Ben N.

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Chapter 1 General Introduction

Image and Performance Enhancing Drugs (IPED's) is an umbrella term used to describe substances which are taken for their image and performance enhancing benefits (Brennan, Wells and Van Hout, 2017). In the majority of sports, they are purely used for their performance enhancing element. A majority of which are classed as 'prohibited substances' and are banned by various professional bodies, such as the World Anti-Doping Agency (WADA). The most well-known type of IPED's are Anabolic-Androgenic Steroids (AAS). Throughout recent history, these types of drugs have been commonly used across sport to enhance performance, as well as improve body image in sports such as bodybuilding. However, over the past 20 years the use of AAS has increased significantly in the United Kingdom (McVeigh, Evans-Brown and Bellis, 2012), with greater prevalence in amateur and recreational sport (Piacentino et al., 2022). The combination of increased use with high profile cardiac events in the bodybuilder population, has raised particular concerns about the use of AAS by young men in the gym and fitness sector (UKAD, 2019). Previous studies have suggested that 34% (123) of gym-goers were aware of IPED use in their facilities. With 6% (21) of males and 1% (3) of females regularly attending the gym and using AAS (UKAD, 2019).

The concern around the recreational use of AAS, is substantiated by a lack of awareness by users of the potential adverse effects (McVeigh et al., 2021). A previous study discovered that 87% (5660) of British adults did not seek any advice from a healthcare professional prior to taking sports supplements (UKAD, 2024). In

comparison to professional athletes, recreational users have limited access to regular general health checks. With increased accessibility and popularity of these drugs, there is a combination of factors that pose a significant risk to public health.

A wide range of cardiovascular adverse effects related to AAS use have been reported. Cardiovascular disease such as coronary heart disease (CHD), hypertension, and cardiomyopathy have been previously reported in AAS users (Ganesan et al, 2023). More specifically, AAS use has been associated with a wide range of chronic cardiovascular adaptations; highlighted through echocardiographic evaluation. AAS users exhibit larger hearts in comparison to non-using counterparts. This is a consistent finding that has been documented by increased wall thicknesses and a subsequently greater left ventricular (LV) mass (LVM) with concentric LV geometry (Di Bello et al., 1999; Angell et al., 2014) . (Baggish et al., 2017). This larger geometry has been consistently coupled with a reduction in both systolic and diastolic function. Studies have demonstrated reduced LV ejection fraction (EF) and global longitudinal strain (GLS) (Baggish et al., 2010b; Hammoud et al., 2023) as well as reductions in isovolumetric relaxation time and impaired diastolic filling (Urhausen, Hölpes and Kindermann, 1989) (Hammoud et al., 2023). Other work has highlighted increased coronary artery (CA) plaque volume and CA calcification among AAS users (Santora et al., 2006; Baggish et al., 2017).

These findings raise concern, however, there is still a notable lack of detail across the literature in this population. Firstly, sample sizes among a multitude of the studies outlined are relatively small. In such cases, it is difficult to apply these findings across such a unique and diverse population. Additionally, true scaling to body size within

this population is often neglected or disparate. Various methods of scaling are used including the integration of scalars such as body surface area (BSA) and / or fat free mass (FFM) whilst not considering allometric relationships. These issues raise concerns regarding accuracy and standardisation.

There is also a lack of data pertaining to the right heart and yet it is clear that an assessment of the right heart in more detail would create a more conclusive picture as to the holistic cardiac adaptations. Similarly, there is no data in relation to the 12-Lead ECG within this population, leaving a significant gap in data that could otherwise provide valuable context to already known adaptations.

This thesis aims to provide evidence of the chronic adaptation to AAS use among a RT population; utilising echocardiography and the 12-lead ECG to both elucidate previous findings and generate novel data. The findings provide substance for future advice and guidance for the public, allowing for amateur and recreational athletes to make better informed decisions. Additionally, raising awareness within the clinical domain is of key importance to effectively treat this unique population.

Chapter 2 Literature Review

2.1 The Anatomical Heart and How We Assess It

Our ability to assess the heart is fundamentally based on our understanding of its anatomy and how it functions. The heart is made up of four chambers, these include the two chambers at the top (right and left atria (RA and LA)) and the two chambers at the bottom: the RV and LV. There are multiple methods that can be utilised to assess the heart's structure and function, including non-invasive, widely accessible techniques such as echocardiography and ECG. Echocardiography is a form of ultrasound imaging that provides an image of the heart's structures, that in turn, allows for the assessment of function (Omerovic S, 2022). The ECG measures the electrical activity of the heart using specially placed electrodes. This primarily provides information on the hearts rate and rhythm, as well as highlighting any ECG abnormalities (Ashley, 2004).

Anatomy of the LV

Assessing the structural and functional components of the ventricles can be challenging due to their complex anatomy. The LV can be seen as a cone shape (Figure 1.1). The normal LV is made up of an inlet portion that contains the mitral valve apparatus, an outlet portion which leads to the aortic valve and an apical portion comprising of fine trabeculations (Ho, 2009). The muscle fibres within the LV form a helical or spiral arrangement, with the outlet of the LV overlapping the inlet (Sengupta et al., 2007). The spiral arrangement of these muscle fibres within the LV are imperative to its functionality. The counter-directional movement of these

muscle fibres in the LV provide an efficient suction and expulsion force that can distribute stresses and strains efficiently (Sengupta et al., 2007).

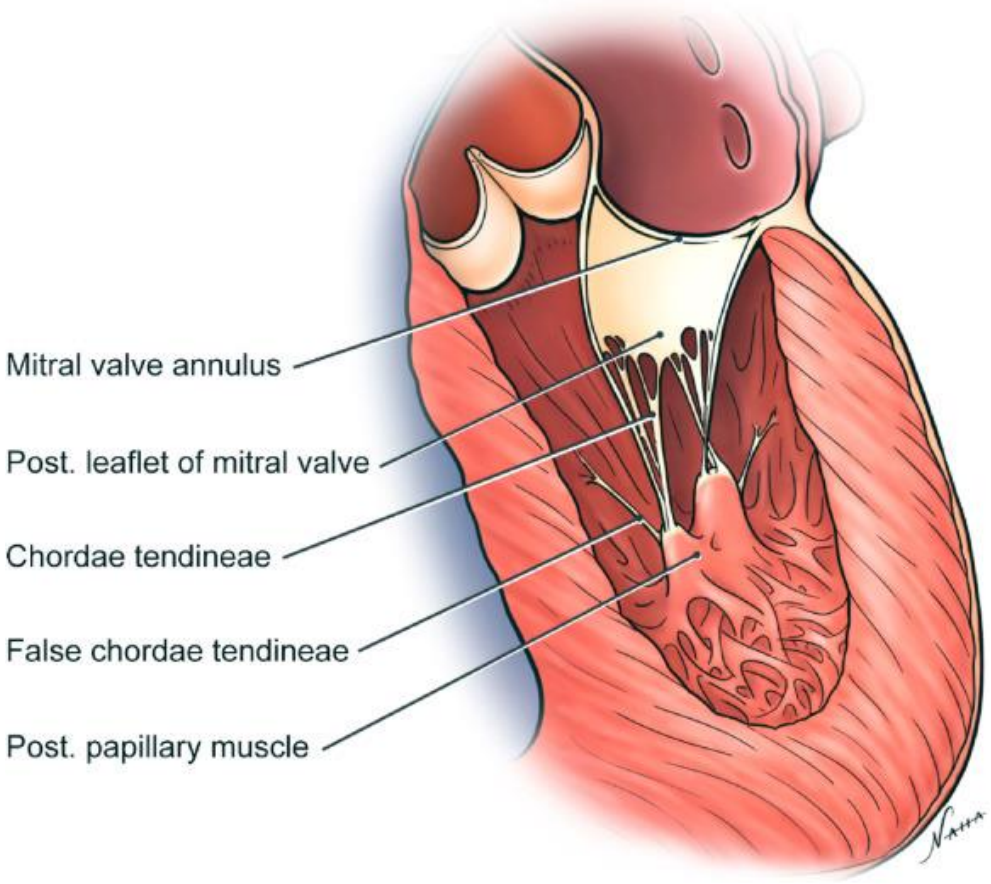

Figure 2.1 – *Image of the LV, displaying its cone-like shape and key physiological components (Whiteman et al., 2021).*

The LV wall has three different layers: superficial (subepicardial), middle, and deep (subendocardial). These different layers represent changes in the orientation of the myocardial strands transmurally (Ho, 2009). Within the superficial layer of the LV the strands run obliquely and descend toward the cardiac apex. The middle layer of the LV is the thickest occupying approximately 53-59% of the ventricles wall thickness (Ho, 2009). The strands in this layer are arranged more circumferentially. Within the deep layer of LV the myocardial strands are arranged longitudinally and insert into the aortic and mitral valves along with the membranous septum (Ho, 2009). The orientation of these fibres has been described in previous studies as chiral (Vendelin et al., 2002). This is where the right handed helical fibre arrangement in the subendocardial region moves into a left handed geometry in the subepicardial region (Sengupta et al., 2007).

Anatomy of the RV

The RV is located anterior in the thoracic cavity in relation to the LV. The RV is divided into three sections: the inflow tract, the infundibulum (outflow tract) and the apex (Horton, Meece and Hill, 2009). There are three muscular bands within the RV cavity: the parietal band, the septomarginal band, and the moderator band. The arrangement of fibres within the RV is similar to that of the LV. Within the sub-endocardial layer, fibres are arranged more or less circumferentially, in a direction parallel to the atrioventricular groove and encircle the sub pulmonary infundibulum (Ho and Nihoyannopoulos, 2006). In the normal RV, the muscular wall is 3-5mm thick, with a predominance of longitudinal and circumferential fibre orientations (Foale et

al., 1986; Ho and Nihoyannopoulos, 2006). Which is in contrast to the LV's obliquely arranged myofibres.

Assessment of the LV

Assessing the structural components of the LV is essential for enabling a comprehensive evaluation of its function. 2D echocardiography can be utilised to measure chamber dimensions and volumes within the LV cavity (Chengode, 2016). The most common method of assessing LV volumes is the Simpsons Biplane method. This uses the principle of summation of twenty cylindrical disks of equal height (Kim et al., 2022). These volumes are taken at end diastole and end systole and are subsequently used to calculate EF. Additionally, the calculation of the LV internal diameter (LVIDd) is taken either at or below the tips of the mitral valve leaflets or directly through the centre point of the LV cavity (Chengode, 2016).

Furthermore, there are alternative methods that can be used for the assessment of function within the LV. Pulse wave doppler (PWD) and tissue doppler imaging (TDI) are techniques that are used for the assessment of blood flow and myocardial velocities (Yu et al., 2007). PWD uses short bursts of ultrasound to analyse reflected sound waves. TDI utilises low velocity-high amplitude signals from the myocardium. This is commonly used in assessment of diastolic function (Russ et al., 2023).

Assessment of the RV

Although anatomically and physiologically different, the RV is assessed in a similar way to the LV. 2D echocardiography can be utilised to provide a comprehensive evaluation of RV structure and function. This is usually done through the use of

multiple 2D acoustic windows, including RV outflow tract (RVOT), parasternal short axis and apical views (Horton, Meece and Hill, 2009). RV free wall thickness is usually measured in the apical or subcostal four-chamber views (Ho and Nihoyannopoulos, 2006). Measurements of RV chamber dimensions include the diameters above the tricuspid valve (TV) and in the mid-RV cavity, as well as the distance from the TV annulus to the RV apex (Horton, Meece and Hill, 2009). RV systolic function can be assessed through RV fractional area change (RVFAC). This represents a 'surrogate' measurement of RV EF. This is expressed as the percentage change in RV chamber area from end-diastole to end-systole (Horton, Meece and Hill, 2009). Pulsed wave TDI can also be utilised in the assessment of myocardial velocities, much like within the LV.

Speckle Tracking Echocardiography and Strain

These different fibre arrangements provide both ventricles with their own specific functions. We can assess this function using a specific type of echocardiography known as two-dimensional (2D) speckle tracking echocardiography (STE).

2D STE is a novel technique in the assessment of cardiac function. The different fibre arrangements within the LV perform longitudinal shortening and lengthening movements around the long axis, along with thickening and thinning movements around the transverse axis (Kurt, Tanboga and Aksakal, 2014). Additionally, there is continuous thickening-thinning of the radial axis and lengthening-shortening of the circumferential axis (Johnson et al., 2019). As the heart contracts, the fibres within the LV shorten longitudinally, therefore causing a compensatory thickening transversely. This movement and displacement of the LV is achieved through

deformation of muscle fibres within the walls, through different segments and at different velocities. Within the RV there are three key mechanisms that contribute to its successful pump function. Firstly, there is a shortening of fibres in the longitudinal axis. There is also inward (radial) movement of the RV free wall, which is commonly known as the 'bellows effect'. Finally, there is a bulging of the interventricular septum into the RV during LV contraction. There is also stretching of the free wall, which causes shortening in the anteroposterior direction (Kovács et al., 2019).

The most frequently used measurement of this deformation (Figure 1.2) is known as strain. Strain measures the fractional change in length of a myocardial segment, relative to its baseline length. 2D STE is used to track the different segments within the LV and RV walls to calculate strain (Schumann, Jaeger and Kramer, 2019). Global strain is calculated as an average of all segments. Providing an assessment of global function. This measurement is usually displayed as a negative percentage (for longitudinal and circumferential) whilst radial strain is represented as a positive percentage due to radial thickening (Johnson et al., 2019). We can also use 2D STE to calculate measurements of twist. Twist is a measurement of the difference in angles of rotation between the base and apex of the LV (Sengupta et al., 2008). Throughout systole, when the LV is examined from the apex, the basal segments rotate clockwise, whereas the apical segments rotate anticlockwise, thus causing a 'twisting' effect.

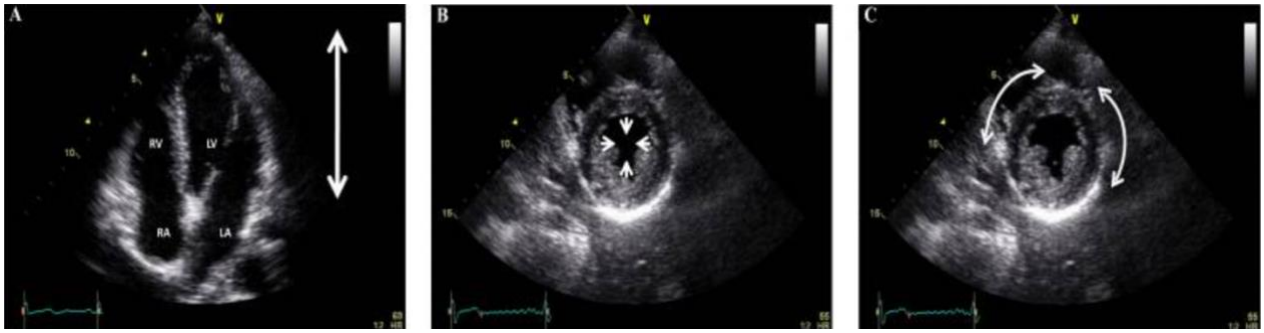

Figure 2.2 – *Apical four chamber view demonstrating where longitudinal deformation would occur (left), a short axis view at the papillary muscle level showing radial displacement towards the centre (middle), and a short axis view demonstrating circumferential deformation at the papillary muscle level (right) (Lopez-Candales and Hernandez-Suarez, 2017).*

Assessing Electrical Activity in the Heart

Aside from assessing structure and function via echocardiography, we can also assess electrical activity within the heart. The heart contracts using an electrical conduction system that begins at the sino-atrial node (SAN) (Bhattacharyya and Munshi, 2020). The excitation signal that is created, travels down to the atria, which causes them to contract. The atrio-ventricular node (AVN) then delays this signal until the atria are empty of blood (Arshad and Atkinson, 2022). This signal is then transferred to the bundle of His. The bundle of His comprises of a right and left bundle branch which subsequently carry the signal through the Purkinje fibres to the right and left ventricle, causing them to contract (Bhattacharyya and Munshi, 2020).

The ECG can be utilised to assess this conduction pathway. It represents an electrical tracing of the heart that is recorded non-invasively from the surface of the body (Figure 1.3). This is done using electrodes that are specially placed across the chest, arms and legs. These are connected to an ECG machine that produces this tracing (Informed Health, 2023). The P wave represents atrial depolarisation, which is initiated by the SAN in the right atrium. The Q wave represents depolarisation of the interventricular septum, with the R wave representing the electrical stimulus that passes down the ventricles during depolarisation. The S wave then demonstrates the final depolarisation of the Purkinje fibres. These three components make up the QRS complex. This is followed by the T wave that represents ventricular repolarisation (Sattar and Chhabra, 2023). All of these components can be pulled together in the 12 Lead ECG.

As well as allowing for a comprehensive assessment of the normal conduction pathway, the 12 Lead ECG can be sensitive in detecting abnormal electrical activity (Zhu et al., 2020). For example, a prolonged PR interval could indicate first degree AV block (slower conduction from atria). T wave morphology can be used to indicate a wide range of pathologies, shown through T wave inversion, biphasic T waves, or flat T waves. Increased R and S waves can also be used to identify criteria for both right and left ventricular hypertrophy (Sattar and Chhabra, 2023).

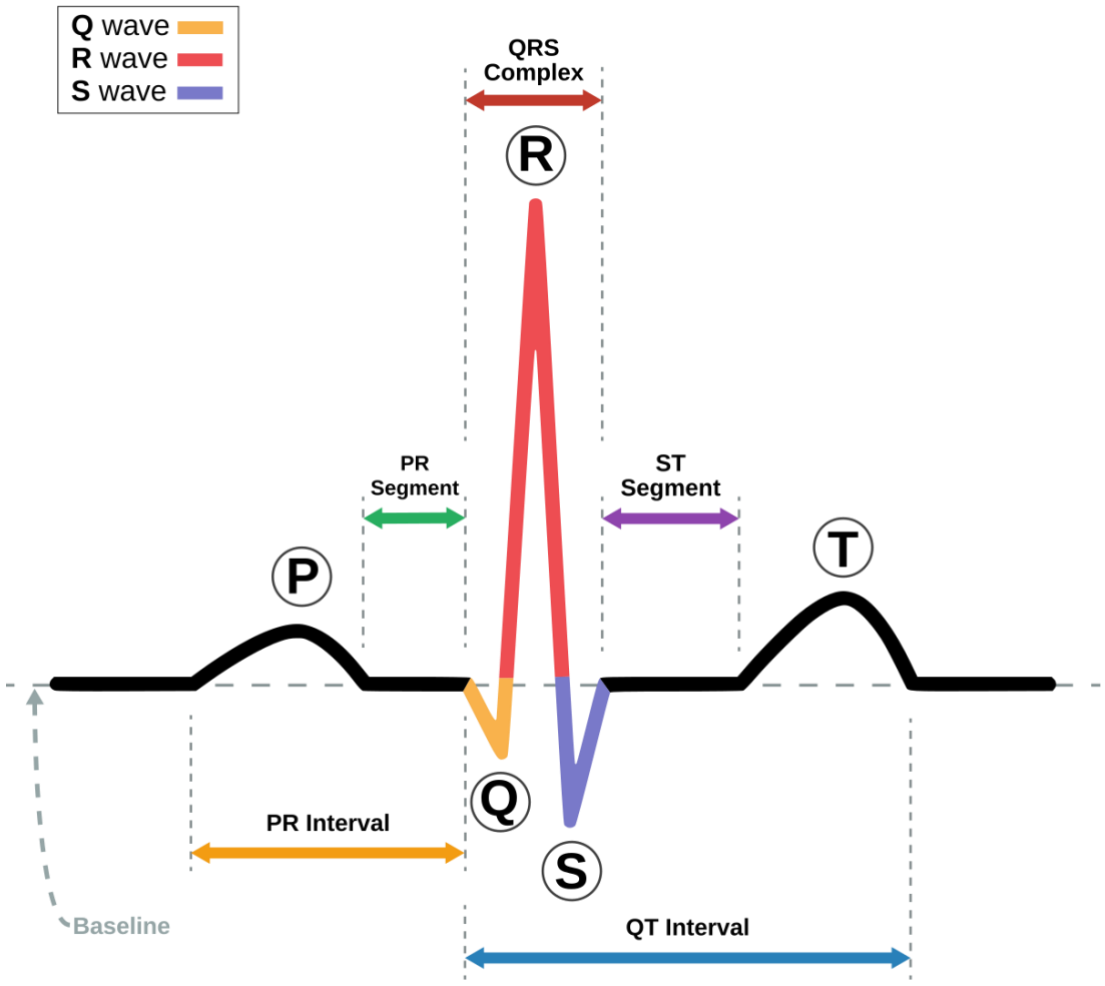

Figure 2.3 – *Image demonstrating the key components of the heart's conduction pathway via ECG. Illustrating the P wave, PR interval, PR Segment, QRS Complex, QT interval, ST segment, and the T wave.*

2.2 Advancing imaging technology

Echocardiography itself has changed over the past 45 years from simple M-mode tracing to various techniques including 2D, 3D, MRI and tissue doppler imaging that is utilised in the present day (Nagueh and Quiñones, 2014). This multitude of techniques allows for the extensive evaluation of the AH. Allowing for the concise exploration of both cardiac structure and function, providing us with more accurate data and therefore more definitive conclusions (Gillam and Marcoff, 2024). The switch from analogue to digital signal processing is one of the main reasons that ultrasound has developed so profoundly. This allowed for smaller instruments along with improved image resolution. One of the most important advancements was the ability to store a digital image, in order to quantify data and compare it with previous studies more accurately. This contributed to the development of transducer technology and digital image processing, creating new techniques such as automated border detection and quantification, along with speckle tracking. (Nagueh and Quiñones, 2014).

The major advancement in ultrasound technology came through two-dimensional (2D) echocardiography (2DE). This technique allowed us to produce real time images of the heart. These images are created using the ultrasound beam that is swept back and forth through an arc (Gowda et al., 2004). In the early 1970's (Bom et al., 1971) and (Griffith and Henry, 1974) developed a handheld transducer device which was used for scanning 2D images. From that the first 2D scanner was created, which then formed the backbone for current echocardiographic examination. Other advanced

techniques include doppler echocardiography, which analyses the effect of the observers motion, relative to the source of a wave on a perceived wave frequency, this is known as the Doppler effect (Gowda et al., 2004). It was originally used to measure valvular regurgitation, however, in the 1970's there was a major breakthrough where that Doppler ultrasound was used to quantify pressure drops across valvular stenosis. The measurement of aortic blood flow velocities came in the early 1970's, which was followed by colour flow imaging in the early 1980's. This allowed for the visualization of blood flow non-invasively. Pulsed wave Doppler recordings were introduced by (Kitabatake et al., 1982) which allowed for the assessment of diastolic filling in the LV. Doppler echocardiography is now the main clinical technique used for non-invasive measurement of diastolic filling patterns (Gowda et al., 2004).

LVM has been identified as one of the most important indicators of hypertrophy within patients (Foppa, Duncan and Rohde, 2005). It is therefore crucial that it is calculated accurately. Advances in technology have allowed for the combination of both M-mode and 2D echocardiography. Two-dimensionally orientated M—mode is utilised to obtain images perpendicularly from the longitudinal axis above the papillary muscle and is now widely employed in a clinical setting (Foppa, Duncan and Rohde, 2005). Two-dimensional M-mode has also improved due to more refined imaging technology. This, along with built in border detection software has allowed for the more accurate calculation of real-time volumes.

2.3 The Athletes Heart

The AH has been described as the process of cardiac structural and functional remodelling that occurs as a result of regular exercise (Prior and La Gerche, 2012). These adaptations can vary in magnitude and can occur as a result of both short and long-term exercise. As well as exercise, there are multiple factors that can also contribute to varying adaptations within the athlete's heart, such as age, gender or body size (La Gerche et al., 2022). This form of remodelling, however, can lead to an overlap in parameters which would commonly be associated with pathology, and in some cases related to sudden cardiac death (Dores et al., 2015). For example, it has been found that some athletes display measurements of LV wall thickness that overlap with that observed in patients with morphologically mild hypertrophic cardiomyopathy (HCM) (Rawlins, Bhan and Sharma, 2009). With one study finding that 1.5% of 3000 British athletes had an LV wall thickness of > 12mm (Basavarajaiah et al., 2008). Thus, highlighting the difficulty in distinguishing between normal physiological adaptations and pathology within the AH.

Sport related factors

The type and intensity of training is a paramount factor in the determination of cardiac adaptations (Martinez et al., 2021b). Isotonic exercise or endurance/dynamic exercise increases cardiac output and maximal oxygen consumption, with normal or reduced peripheral vascular resistance (Dores et al., 2015). Long-term isotonic exercise can also cause bradycardia (heart rate < 60pm), which can easily be detected via the ECG (Bahrainy et al., 2016). In sports such as long-distance running, cycling or

football, volume overload is predominant (Santoro et al., 2014). Volume overload relates to the increased volume of blood that the heart needs to pump in order to meet the requirements of the body during exercise (Allen et al., 2020). In contrast, isometric exercise such as RT and strength-based exercises, increases blood pressure and peripheral vascular resistance, with only a slightly increased cardiac output (Barauna et al., 2007). Previous work has indicated that during contraction, RT athletes do undergo a significant increase in systolic blood pressure (SBP) (Saunders, 2024). Example sports include bodybuilding, power lifting or wrestling. Endurance exercise overall induces a greater magnitude of cardiac remodelling (Maron and Pelliccia, 2006). Potentially due to the increased haemodynamic burden that is placed on the heart over a more sustained period of time (Santoro et al., 2014). However, it can be difficult to distinguish between adaptations as a result of training type. There are multiple sporting disciplines that include elements of both strength and endurance; therefore creating a level of ambiguity pertaining to cardiac remodelling (Mitchell et al., 2005). These sports will of course vary in the intensity and effort that is required to complete them, and thus differences in metabolic demand. Similarly, the combination of the two will cause specific haemodynamic effects that will determine the type and degree of cardiac adaptation (Martinez et al., 2021a). interestingly previous work has suggested that intensity and time of training may play an important role in adaptations. Previous work has suggested that after 9 months of continuous exercise, there was an initial rapid increase in adaptations, however past this point there seemed to be slower increased rate. Suggesting there may be approximation of limits in cardiac growth after a certain period of time (Arbab-Zadeh et al., 2014).

Structural adaptations and the Morganroth hypothesis

There has been uncertainty regarding the differences in type and magnitude of structural remodelling between RT athletes and ET athletes (Naylor et al., 2008). The Morganroth hypothesis suggests the level of cardiac remodelling that is observed, corresponds with the pressure that the ventricles endure with repeated bouts of exercise (Morganroth et al., 1975). The original study found that ET leads to an eccentric form of cardiac hypertrophy, defined as an increased cavity dimension and concomitant increase in wall thickness. The rationale is based on the large increase in cardiac output during training and competition. Thus, creating a haemodynamic burden due to the increased blood volume, which in turn causes increased wall stress. The Morganroth hypothesis describes a dichotomy with RT leading to concentric hypertrophy (Figure 1.4), with an increase in wall thickness and cavity size remaining unchanged. It is suggested that RT athletes are subjected to increased arterial pressure rather than a volume stress which subsequently causes this type of remodelling.

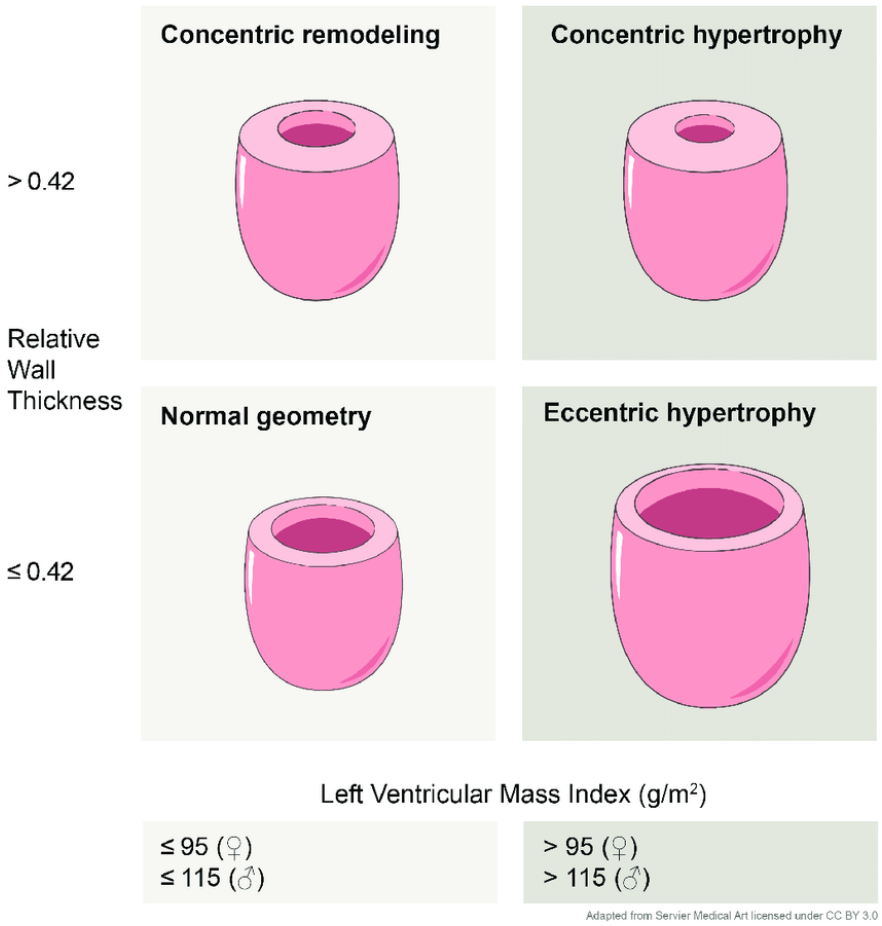

Figure 2.4 – *Different types of left ventricular geometry in comparison to normal geometry (bottom left) (Nauta et al., 2019)*

A study by (MacDougall et al., 1985) further backed up this hypothesis, highlighting significant increases in both systolic and diastolic blood pressure (DBP) during the lifting phase of a static leg press exercise. They stated that due to the contraction of a larger muscle mass the compression on the vasculature would be much greater. Therefore, the elevation in blood pressure that is observed within the lifting phase, is caused by the increased compression on the walls of the blood vessels. This would be proportional to the size of active muscle mass and the absolute force of the contraction. They stated however, that this could not be the sole reason of increased blood pressure as there would be a more direct relationship to increased muscle mass. Instead, as an individual increases the number of repetitions they complete and near fatigue, they may recruit additional motor units along with an increased involvement of accessory muscles. Resulting in a progressive increase in active muscle mass, which would account for the progressive elevation in SBP observed with each repetition.

Although these studies highlight the presence and potential mechanisms for concentric hypertrophy in RT athletes, there is debate regarding the Morganroth hypothesis. Since the publication of earlier work there have been a multitude of studies that suggest RT athletes who train for short (< 5 years) to long (> 18 years) periods of time, do not experience any changes in LVIDd, ventricular septal or posterior wall thickness (PWT), relative wall thickness (RWT) or LVM in either male or female athletes (Haykowsky et al., 2002) (Utomi et al., 2013) (Haykowsky et al., 2000). A paper by (Spence et al., 2011) studied untrained male participants and provided them with a 6-month training programme of either RT or ET. They found that after the 6-month period, ET individuals experienced an increase in LVM and

interventricular septum thickness (IVST). Whereas the RT group did not see any adaptations relating to cardiac structure. Concluding that concentric hypertrophy in this case was not a definitive adaptation of RT. Previous work suggests that the elevation of SBP seen during heavy lifting is not transferred to the LV and hence provides physiological evidence conflicting the common belief that systolic blood pressure loading is the cause of LV hypertrophy in RT athletes (Morganroth et al., 1975; Lentini et al., 1993; Haykowsky et al., 2001).

Furthermore, (Utomi et al., 2015), assessed LV geometry within the male AH, between ET and RT athletes. The main finding being that normal geometry was predominant across all groups. Where only 30% of ET athletes experienced eccentric hypertrophy, and no concentric hypertrophy was found within RT athletes. Also, they discovered that when indexed to BSA, LV wall thickness dimensions were increased in ET athletes when compared to RT athletes and controls (Utomi et al., 2014). These findings within ET athletes somewhat agree with the Morganroth hypothesis, where that ET is associated with an increase in LVM and volume, however with only 30% of ET athletes experiencing eccentric hypertrophy, this would suggest that the degree of hypertrophy varies between individual athletes (Utomi et al., 2014). On the contrary, discovering that no RT athletes experienced concentric hypertrophy, refutes the resistance training component of the Morganroth hypothesis. This agrees with the study by (Spence et al., 2011) albeit athletes in this study were assessed after a longer training period (11 – 12 years) compared to (Spence et al., 2011) (6 months). With this however, we could assume that the increase of LVM and IVST in ET in such a short space of time, and lack thereof within RT, would continue to increase and form a long term chronic adaptation, as seen in the study by (Utomi et

al., 2014) after 11-12 years of high level training. These findings render the resistance training component of the Morganroth hypothesis obsolete, as these measurements conflict with results from the original paper where that IVST was significantly increased in RT athletes, and not in ET. Whereas more recent studies have shown that on both smaller and larger time scales, we see the opposite in structural adaptation in comparison to the Morganroth study (training period of 3 years prior).

The study by (Spence et al., 2011) highlighted no changes in cardiac structure in RT athletes after a 6 month training period. However, a study by (Baggish et al., 2008) identified LV concentric hypertrophy in RT athletes after a 90-day training period. (Brown et al., 2017) suggested that these disparate findings could be due to differences in training volumes of the athletes between the two studies and different echocardiographic techniques (Spence et al., 2013b). Additionally, the 'strength athletes' group within the study by (Baggish et al., 2008) consisted of American football players. We could argue that this group uses a combination of both aerobic and strength training with their sport requiring both a high level of strength and aerobic fitness. Further research is required into the effects of different training volumes, as well as the effect of combining both ET and RT. This would allow for a greater understanding of the disparity observed.

The multitude of factors that can affect the size and shape of the heart do, however, create a difficulty for us to distinguish between normal physiological adaptation and pathology. It is unlikely that RT athletes will display concentric hypertrophy. However, there are mild phenotypes that can create a blurred line between pathology and physiological adaptation. The study by (Baggish et al., 2008) does

highlight this as they observed concentric hypertrophy in the strength athlete group after 90 days of training. Late stages of hypertension also display this level of increased wall thickness and concentric hypertrophy (Marwick et al., 2015). Indicating that we cannot use measurements of structure alone to diagnose a certain condition.

We can however use measures of function to distinguish between pathology and physiological adaptation. There are novel measurements of systolic function that can be utilised, including strain. It has been shown to be abnormal in individuals with HCM, whereas studies in athletes with left ventricular hypertrophy (LVH) demonstrate normal longitudinal, circumferential, and radial strain (Poulsen et al., 2007) (Richand et al., 2007) (Rawlins, Bhan and Sharma, 2009). Indicating that more sensitive measures of function can be used to distinguish between pathological or physiological LVH. The ECG is also a fundamental tool in the assessment of cardiovascular pathology, due to its high sensitivity to detect abnormalities (Sattar and Chhabra, 2023). ECG changes in athletes occur as a result of electrical and structural adaptations following repeated bouts of exercise. However, much like echocardiographic parameters, some of these findings overlap with that of pathology (Basu and Malhotra, 2018). However, recent guidelines such as the 'International Recommendations for ECG Interpretation in Athletes' (Sharma et al., 2017), has led to a significant reduction in false positives. Additionally, it has helped aid interpreters in their ability to distinguish between pathology and normal physiological remodelling in athletes

Additionally to this, previous work on the AH has identified increases in wall thicknesses, cavity size and LVM as a result of mixed and endurance sports training (Pelliccia et al., 2018). Although, LV geometry is predominately normal or eccentric (Utomi et al., 2014), with concentric remodelling being reported in a small percentage of young athletes (Finocchiaro et al., 2017). However, the methods in which these conclusions are determined are still under speculation (Oxborough et al., 2024). This paper raises concern around ratiometric scaling of LVM directly to BSA. This assumes that there is a linear relationship between the two , when in reality there is a lack of geometric similarity (Tanner, 1949). Most biological relationships are not linear, rather allometric, therefore, raising this particular concern around the method of scaling in previous work, as this could produce inaccurate results. Subsequently, the same study by (Oxborough et al., 2024) determined that ratiometric scaling to BSA does not produce a size independent index in mixed and ET athletes. With these athletes demonstrating a predominance for normal LV geometry, with a small percentage displaying eccentric hypertrophy and concentric hypertrophy/ remodelling, when allometrically scaled. These findings are important as they inform future interpretation of data and geometric classifications, specifically within athletes due to the unique nature of adaptation (Oxborough et al., 2024).

Disparity in findings

Potential reasoning for the disparity observed by more recent studies in comparison to previous work, could be due to older echocardiographic techniques used by the likes of (Morganroth et al., 1975) and (MacDougall et al., 1985). The first form of echocardiography that was used in 1973 was called M-mode echocardiography. M-

mode echocardiography used a single beam which was directed towards the heart and the signals that were reflected back were displayed on a strip chart or oscillograph (Gowda et al., 2004). However, M-mode echocardiography did not produce a clear image of the anatomy of the heart. Thus, making it difficult to accurately quantify measurements. Precise measurements were heavily reliant on time resolution (Maleki and Esmaeilzadeh, 2012). It is also stated in the study by (Morganroth et al., 1975) that they had to use the T-scan technique to visualize ventricular septum and the posterobasal LV wall. Highlighting the difficulty in visualizing the anatomy of the heart walls, and subsequently the ability to make precise measurements.

More advanced techniques in the present day, provide us with a greater understanding of the relationship between the mass of the LV and RWT. RWT increases where that there is an increased pressure load on the heart walls. The increase in wall thickness is a compensatory mechanism in response to the increased pressure, in an effort to maintain contractile forces and subsequently relieve wall stress. This, however, creates an increased stiffness in the ventricular walls causing increased diastolic ventricular pressure (Bornstein et al., 2019). RWT is calculated using: (PWT * 2 / LVIDd). This can be utilised in conjunction with the LVM index (LVM/BSA), allowing us to clearly categorize LVH into different types: either concentric or eccentric (Foppa, Duncan and Rohde, 2005). Identifying different types of hypertrophy is important to correctly diagnose individuals and highlight the origin of their condition.

Body size in athletes

The size of an athlete has been highlighted to have a profound effect on their cardiac structure (Dewey et al., 2008). Accounting for the size difference between athletes is of upmost importance as it could determine their diagnosis. The difficulty in differentiating between physiological and pathological adaptation to exercise is clear, and body size is a large contributor to the ambiguity that exists. In previous studies that have stated the normal range of cardiac morphological responses to training, between 1.7 – 2.5% of those athletes experienced LV wall thickness measurements that are compatible with a diagnosis of HCM (Whyte et al., 2004) (Dewey et al., 2008) (Nagashima et al., 2003). This highlights the difficulty of diagnosing an athlete based on their chamber morphology alone, and that body size and composition should always be considered. A previous meta-analysis by (Pluim et al., 2000) failed to account for the potential differences in body size and composition between athletes and controls, which could have negatively affected their interpretation of the AH. An issue that has been described in previous work (Utomi et al., 2013).

The difficulty however in accurately measuring body size and BSA in RT athletes is also clear. There are multiple methods that have been used to scale for body size in these athletes. The size of the LV and LVM are both related to body size and are commonly divided by BSA to account for differences in body size and improve clinical validity (Hayward et al., 2019). BSA is commonly used over FFM as accurate measurements of FFM are not widely available. This, however, would overestimate LVH in lean individuals and underestimate it in obese individuals. This is because BSA is affected by fat mass. A study by (Whalley et al., 2004) discovered that ratiometric scaling of LVM and LVIDd to FFM in athletes formed a stronger correlation than BSA

or height (Brown et al., 2017). They discovered that between athletes and non-athletes, LVM and LVIDd when indexed to FFM were similar between the groups. As both were predicted by FFM alone, it suggests that the greater FFM observed in athletes provides reasoning for the increased LVM and cardiac dimensions (Whalley et al., 2004). This highlights therefore that indexing to FFM can overcome limitations that are observed when indexing to BSA or height (Brown et al., 2017). This is because increases in LVM will also increase FFM.

2.4 The role of IPED's

IPED's are used extensively across the world. The reasoning behind the use of these drugs lends itself to the name, to improve body image and enhance performance. A recent review by (McVeigh et al., 2021) broadly highlights the role of these drugs within the UK. Some of the most common types of IPED's include drugs that increase an individual's lean muscle mass: AAS and human growth hormone (HGH) (McCullough et al., 2021). AAS are synthetic derivatives of the male hormone testosterone (Hartgens and Kuipers, 2004). Therefore, they are regularly prescribed to individuals with medical conditions related to low testosterone (Mullen et al., 2020). However, the increased recognition of these drugs and their potential performance enhancing capabilities over the years, has led to an increase in the abuse of AAS. The use of AAS lends itself towards the elite athlete/bodybuilding community due to their well-known benefits for performance and body image (Hattab et al., 2024).

Hence, there is now an increased amount of illegally manufactured AAS available on the market. Specifically developed through research or underground laboratories to optimise muscle growth (Mullen et al., 2020). These specific types of AAS have been outlined in a table by (Mullen et al., 2020) which describes the recommended dosages, pharmacology and formulation of each type of drug (Figure 1.4). Although the guidelines/recommendations for taking these drugs and their subsequent benefits seem to be clearly outlined. The negative physiological impact of taking these drugs, is something that is still not widely recognised by the general public.

				Recommended effective dose (online community)		
Chemical name	**Commercial name**	**Formulation**	**Pharmacology**	**Male**	**Female**	**Popularity**
Androisoxazol	Neo-Ponden	Oral	Cutting (fat loss)	15–40 mg·day^{-1}	5–10 mg·day^{-1}	
Bolasterone	Myagen	Oral	Bulking (muscle gain)	50–100 mg		
Bolazine caproate	Roxilon Inject	Injectable	Cutting	100–500 mg·week^{-1}	50–100 mg·week^{-1}	
Boldenone blend	Equilon 100	Injectable	All purpose	400–600 mg·week^{-1}		
Boldenone undecylenate	Equipoise®	Injectable	All purpose	200–600 mg·week^{-1}	50–100 mg·week^{-1}	a
Boldenone/methylandrostenediol blend	Drive®	Injectable	All purpose	300–600 mg·week^{-1}		
Calusterone	Methosarb	Oral	Cutting	200 mg·day^{-1}	200 mg·day^{-1}	
Chlorodehydromethylandrostenediol	Halodrol	Oral	Bulking and strength	100–150 mg·day^{-1}	Not recommended	
4-Chlorodehydromethyltestosterone	Oral Turinabol	Oral	Cutting	15–40 mg·day^{-1}	2.5–5 mg·day^{-1}	
Chloromethylandrostenediol	Promagnon	Oral	All purpose	50–100 mg	Not recommended	
Clostebol acetate	Megagrisevit-Mono®	Oral	Bulking	100–200 mg·day^{-1}		

Figure 2.5 – *A proportion of the table presented by (Mullen et al., 2020) outlining recommended dosages, pharmacology and formulation of specific types of AAS*

The different types, dosages, and frequencies of these steroids could have their own individual impact on the cardiac remodelling. The most common types of administration are injection (intravenous or intramuscular), or orally (Mantri et al., 2023). There are different methods that users can utilise when taking AAS. For example, users may use cycles of 6-12 weeks (known as the 'on' period) followed by 4 weeks to several months off. During this time users may combine several types of AAS along with other supplements in an attempt to enhance the effects of AAS, this is known as 'stacking'. Alternatively, some users utilise the pyramid approach, increasing dosages to a 'peak' and then reducing it thereafter (de Ronde and Smit, 2020). Some of the most common types of oral AAS include: Methandienone (Dianobol), Stanozolol (Winstrol), and Oxandrolone (Anavar). Whilst common injectable forms include: Nandrolone Decanoate ('Deca'), Trenbolone Acetate (Finajet or 'Tren'), and Methenolone Enanthate (Primobolan) (Davis K, 2023). It is well reported that the regular use of AAS can lead to an increased risk of cardiovascular issues, sudden cardiac death, and myocardial infarction (AlShareef, S, 2023). Although with the cocktail of different drugs and methods of administration utilised by users, it is difficult to determine the specific impacts in such use cases.

It is highlighted in the review by (McVeigh et al., 2021) that the wide range of subgroups that now use AAS in the UK, provide various characteristics, risk behaviours and levels of engagement with support services. The use of AAS is not a new phenomenon, although previously, they were more restricted to elite athletes/bodybuilders (Piacentino et al., 2022). However, due to the low-cost production and distribution that has developed in the modern day, AAS have become much more accessible for any population, including non-elite and recreational

athlete's using the gym on a day-to-day basis. (Evans-Brown and McVeigh, 2009). This is important to highlight as although there are relevant support services in place, such as needle and syringe programmes that provide sterile injecting equipment (Dunn, McKay and Iversen, 2014). The increasing accessibility of AAS through close contacts, or online services will begin to diminish the control that these support programmes have over the ever-increasing population of AAS users.

Due to the popularity of AAS use (Hoseini and Hoseini, 2024), it is important that users are made aware of relevant support programmes and potential abnormal physiological effects that can occur as a result of regular use. This elucidates the importance of future research and getting information into the wider public domain. This would help establish guidelines to support both clinicians and researchers who work with individuals in this population in their respective settings. Moreover, this would help to educate individuals on the potential impacts of AAS use and allow them to make their own informed decisions.

2.5 Negative impact of IPED's – What we know so far

Supraphysiological doses of AAS have been shown to induce both morphological and functional changes on the heart, with a tendency to produce myocardial hypertrophy (Vanberg and Atar, 2010). Potential mechanisms behind this have also been highlighted in previous work. AAS are likely to influence hypertrophy through actions on the androgen receptor. These are commonly found within skeletal muscle cells as well as cardiac myocytes (Payne, Kotwinski and Montgomery, 2004). There are also several lines of evidence to suggest that endogenous androgenic

pathways play a part in cardiac hypertrophy, through raised 5a reductase, aromatase, and AR expression in hypertrophic hearts of humans and mice (Liu, Death and Handelsman, 2003). Other previous work has highlighted the cardiotoxic effect that AAS use can have on the cardiovascular system (Baggish et al., 2017). Other work has also outlined that AAS can have a significant metabolic effect, increasing LDL by more than 20% in users, whilst decreasing HDL levels by 20-70% (Achar, Rostamian and Narayan, 2010).

Previous work has highlighted the impact of AAS misuse on the cardiac structure and function of athletes. A study by (Angell et al., 2014) evaluated 21 strength trained participants and split them into two groups. One group had been taking AAS for the past two years and were currently in a 'using cycle', the other group was made up of age and training matched controls. The two groups had been training for 9 ± 4 and 10 ± 6 years respectively. The key findings from the study were that the AAS group displayed a significantly greater LVM, along with reduced LV longitudinal strain, RV EF, and differences in diastolic function also. AAS users were also heavier and had a higher fat free mass than non-users. Higher fat free mass in AAS users has been elucidated in previous work from (Ferrando et al., 1998), who discovered an up-regulation of skeletal muscle protein synthesis as a result of AAS use when combined with RT. The significantly greater LVM observed in AAS users was highlighted through increased mean LV wall thickness and increased LV end diastolic volume (LVEDV). Interestingly, the between group differences in peak wall thickness and LVM did not persist after indexing for individual differences in fat-free mass. They suggested therefore, that increases in LV size occur in conjunction with skeletal muscle mass in AAS users.

These findings are similar in other previous work where that LVM was significantly greater in users compared to both non-using weightlifters and past-users (Urhausen, Albers and Kindermann, 2004). Conversely, however, after indexing for BSA and FFM these differences persisted between users and non-using weightlifters. Although, increased LVM in AAS users is a consistent finding among previous research (De Piccoli et al., 1991; Di Bello et al., 1999). This finding has also been accompanied by significantly increased wall thicknesses (De Piccoli et al., 1991; Sachtleben et al., 1993a). Increased structural parameters have been found with a concomitant decrease in diastolic function shown through impaired isovolumetric relaxation time and diastolic filling (Urhausen, Hölpes and Kindermann, 1989; Hammoud et al., 2023). With the reduction of systolic function also being a consistent and prominent finding among previous work (Baggish et al., 2010b; Angell et al., 2014; Hammoud et al., 2023). Shown mostly through a significantly reduced EF in both the LV and RV as well as longitudinal strain.

AAS users exhibit significantly larger hearts with increased wall thicknesses. This is interesting as previous work has highlighted that non-using RT athletes do not experience increased wall thickness and therefore no hypertrophy (Haykowsky et al., 2000; Spence et al., 2011). We could speculate therefore that the use of AAS in conjunction with RT directly induces an increase in wall thickness and subsequently contributes to an overall increase in LVM. The increased cardiac morphology of AAS users is accompanied with decreased systolic and diastolic function when compared with controls. This decreased systolic function is of concern, especially in conjunction with the increased wall thicknesses observed in AAS users. Previous work has highlighted reduced strain in individuals with HCM, however within athletes who had

physiological LVH it was normal (Rawlins, Bhan and Sharma, 2009). Indicating that increased wall thicknesses can be a normal physiological response to exercise. However, when coupled with decreased systolic function, it could be a pathological finding that is indicative of underlying disease.

A study by (Baggish et al., 2017) split participants into two groups, users and non-users. Users were then split into two subgroups: Users that were on cycle (on-drug users) and users that were off cycle (off-drug users). They found that AAS users as a whole displayed significantly decreased systolic function when compared to non-users, this was shown through decreased longitudinal strain and EF. Interestingly, systolic function was greater impaired in on-drug users compared to off-drug users. Suggesting that decreased systolic function may be related to user specific cycles. LV diastolic function however was impaired in both on and off-drug users, suggesting that potentially diastolic function is more permanently affected as a result of AAS use. A reduction in diastolic function within AAS users is apparent in previous work (Urhausen, Hölpes and Kindermann, 1989; Hammoud et al., 2023). However, this finding is equivocal, with other work suggesting no differences in diastolic function between users and non-users (Palatini et al., 1996; Di Bello et al., 1999). Elucidating the need for further assessment of this disparity as well as the effect of AAS use cycles on ventricular function.

Furthermore, they also discovered that AAS users displayed greater LV concentric geometry in comparison to non-users. This was reflected through LVM, where this pattern remained after indexing for both BSA and height. This finding is consistent with some previous work, (Urhausen, Albers and Kindermann, 2004) although

disparate from others (Angell et al., 2014). The level of LV hypertrophy seen in AAS users was also directly linked to the impairment of function seen, agreeing with multitude of previous work outlined above. One of the most important findings from the study by (Baggish et al., 2017) was that AAS users displayed a significantly higher coronary artery (CA) plaque volume (Figure 1.5) than that of non-users. Which was associated with increased coronary atherosclerosis. They also found that the severity of atherosclerotic disease was strongly associated with lifetime duration of AAS use. This finding is consistent with other work that highlighted increased CA calcification in AAS users, which was linked to coronary atherosclerosis (Santora et al., 2006). Suggesting that long term AAS use is associated with adverse cardiovascular phenotypes. Thus, highlighting a clinical health problem that may not otherwise be recognised.

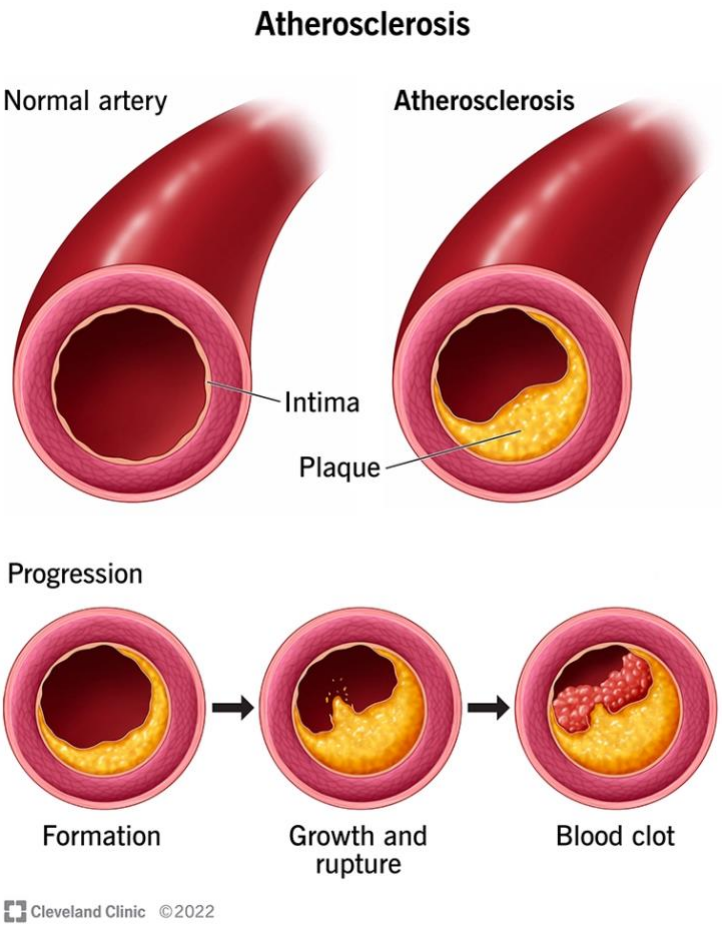

Figure 2.6 – *Image displaying the formation and progression of atherosclerosis within the arteries as a result of increased plaque volume (Cleveland Clinic, 2024).*

A review by (La Gerche and Brosnan, 2017) also highlighted the cardiovascular effects of AAS use in athletes. It was stated that AAS use can cause a 6 – 20-fold increase in mortality among users compared to non-users, of which one third of the deaths are a result of cardiovascular effects. The most common being myocardial infarction, dyslipidaemia, and coagulation abnormalities. They highlighted a series of post-mortem studies that used echocardiography and MRI. These studies found evidence of AAS-induced cardiomyopathy as a result of increased cardiac mass, LV wall thickness (LVH), prevalence of cardiac fibrosis and impaired systolic and diastolic function (Darke, Torok and Duflou, 2014). These studies highlight the increased risk of sudden cardiac death among AAS users, and that the direct cardiovascular effects of AAS should be explored further to highlight the cause of adverse phenotypes among this population.

Although there is a plethora of data on this population derived from echocardiography, there is a significant lack thereof pertaining to the 12 Lead ECG. With recent work finding no differences between users and non-users for any ECG measure, and only 9 (18%) of AAS users experiencing LVH (Fyksen et al., 2022). Additionally, a recent case report identified normal ECG and stress ECG findings in a male body builder, who had abused AAS for 4 years (Skorupska et al, 2023). This significant gap of data within research needs to be addressed in order to consolidate the abundance of evidence that has already been outlined via echocardiography.

Past users

Aside from current users of AAS, there is a phenomenon surrounding past users that has been reported in previous work. The study by (Baggish et al., 2017) highlighted

this, finding that systolic function was greater impaired in on-drug users compared to off-drug users. With other work highlighting a significantly reduced LVM and IVST in AAS users after being off-cycle for just 8 weeks (Sachtleben et al., 1993b). Suggesting that there may be a reversibility of adaptation with cessation of AAS use, even for a short period of time. Other work has highlighted significantly greater measurements of LVM within current users in comparison to past and non-using counterparts (Rasmussen et al., 2018). Another case study highlighted a reduction in LV wall thickness and chamber geometry after cessation of AAS use (Nieminen et al., 1996). This evidence elucidates the reversibility of adaptations to the use of AAS with cessation of use. With the potential for some adaptations to revert back to 'non-using levels'. Although evident, this phenomenon is not widely reported in the present day and therefore requires further research to explicate these findings.

2.6 Conclusion

To conclude, the importance of both echocardiography and electrocardiography in the assessment of cardiac structure and function is evident. Historic work has outlined a dichotomy of adaptations between ET athletes and RT athletes (Morganroth et al., 1975). Stating that ET athletes undergo an eccentric form of cardiac hypertrophy, whereas RT athletes experience concentric hypertrophy.

Advancing imaging technologies in the modern day, have developed a greater understanding of cardiac adaptations and LV geometry. Thus, a wide variety of research has since refuted the Morganroth hypothesis. Suggesting that RT athletes who train for short and long periods of time do not experience increases in wall thickness or LVM (Haykowsky et al., 2000; Haykowsky et al., 2002; Utomi et al., 2013).

This evidence alone would suggest that RT athletes do not experience concentric hypertrophy as a result of regular exercise, as stated by Morganroth.

Aside from physiological remodelling, there can be alternative contributors to the adaptations that occur within some RT athletes. AAS have become increasingly prevalent across the world due to their ability to increase lean muscle mass (McCullough et al., 2021; McVeigh et al., 2021). The cardiovascular effects of AAS use in combination with RT appear to be extensive, with multiple studies listing a vast range of abnormalities. The main pattern appears to be an increase in chamber geometry with a concomitant decrease in ventricular function. This data is of concern; promoting an increased risk of adverse cardiac events (Darke, Torok and Duflou, 2014; La Gerche and Brosnan, 2017).

Hence, the aims of the current thesis are: 1) to assess the impact of bi-ventricular structural and functional cardiac adaptation in non-using RT athletes, via both echocardiography and the 12-Lead ECG, 2) to determine the magnitude of bi-ventricular structural and functional cardiac adaptation in RT athletes who are currently using AAS, via both echocardiography and the 12-Lead ECG, 3) to determine significant differences or trends between non, past and current users of AAS and 4) to identify whether past users have residual bi-ventricular structural or functional adaptation as a result of previous AAS use.

It is hypothesized that: 1) Non-using RT athletes will exhibit minimal cardiac adaptation in comparison to their AAS using counterparts, 2) AAS users will exhibit significantly larger geometry with a concomitant decrease in function in comparison to non-users and 3) past users will exhibit a reduction in structural parameters in

comparison to current using counterparts, as well as a reversibility of functional deterioration.

Chapter 3 Biventricular adaptation to resistance training in combination with Anabolic-Androgenic Steroid Use

3.1 Introduction

The AH is a complex phenomenon that has been extensively researched in the modern era. Adaptations to both ET and RT have been well documented (Spence et al., 2013b; Dores et al., 2015; Utomi et al., 2015). The traditional view of adaptations to RT centred around the concept that an elevation in afterload causes concentric hypertrophy (Morganroth et al., 1975). Whereas the elevation in preload caused by ET resulted in eccentric hypertrophy. However, more recent studies have challenged this hypothesis demonstrating a lack of concentric hypertrophy in RT athletes (Bjerring et al., 2020).

These data highlight more complex adaptations that relate directly to the acute cardiac stimulus that is encountered during RT. The presence of a Valsalva manouvre counterbalances the elevation in blood pressure (and subsequent afterload) during RT (Lentini et al., 1993), by normalising LV wall stress due to a concomitant increase in thoracic pressures (Haykowsky et al., 2001). In addition, the exercise stimulus during RT is of short duration and together provide physiological support to refute the resistance limb of the Morganroth Hypothesis (Morganroth et al., 1975).

Biventricular adaptations to RT have been outlined in previous work, such as increased LVM (Green et al., 2024) and RV free wall thicknesses (Utomi et al., 2015), although differences were small. Primarily however, other work has discovered that RT athletes exhibit no changes in structural parameters, even after a 6 month training programme (Spence et al., 2011). More profound adaptations are apparent in ET athletes (Morrison et al., 2023), potentially due to a more prolonged exercise stimulus on the heart (Martinez et al., 2021a).

The prevalence of AAS use in combination with RT has increased significantly over the past decade (McVeigh et al., 2021). Previous studies have highlighted an increase in LVM and wall thicknesses in this population, along with reduced EF and GLS (Angell et al., 2014; Baggish et al., 2017; La Gerche and Brosnan, 2017; Grandperrin et al., 2021). Additionally, other work has highlighted significantly larger RV volumes (Luijkx et al., 2013), and reduced RV EF (Angell et al., 2014). There is also evidence of increased CA plaque volume within AAS using RT athletes (Baggish et al., 2017).

Aside from current use, the past and subsequent cessation of AAS use has been addressed in some studies. A case-report highlighted after cessation of AAS use, a RT individual demonstrated a reduction in LV wall thickness (Nieminen et al., 1996). Highlighting the potential for reverse remodelling. RT athletes who ceased use for 8 weeks during the AAS cycle have also shown significantly reduced LVM and interventricular septal wall thickness (Sachtleben et al., 1993a). That aside, these studies are small, utilise older technology and provide only a snapshot. It is, therefore, important to explore whether past users of AAS have residual iatrogenic adaptations.

In view of this, the aims of this current study are to: 1) Investigate bi-ventricular structure and function in RT athletes not using AAS, 2) determine the nature and magnitude of bi-ventricular structural and functional adaptation in RT athletes using AAS and 3) determine whether past users of AAS use have residual biventricular adaptations. It is hypothesised that 1) non-using RT athletes will demonstrate minimal adaptation in regard to chamber morphology compared to current users, 2) current users of AAS will exhibit larger bi-ventricular size combined with a reduction

in function compared to past and non-users and 3) past users will have smaller bi-ventricular size and better functional parameters compared to AAS using counterparts with no difference to non-users, highlighting the temporary nature of AAS induced cardiac adaptation.

3.2 Methods

3.2.1 Study Population and design

Male (n = 81) and female (n = 15) RT individuals (age 29 ± 5 years) with a training duration of >2 years and currently engaged in RT >3 hours per week were recruited into the study. Participants were grouped based on their self-reported AAS user status: current user defined as using AASs within 12 months of data collection (n=57), past user defined as a previous user of AASs > 12 months from data collection (n=19) and non-users defined as never using AASs (n=20). Participants were excluded if they had a history of cardiovascular disease, diabetes, renal or liver disease, were pregnant, smoked, or were over 80 years old. Participants provided written informed consent prior to participation. Ethics approval was obtained from the ethics committee of Liverpool John Moore's University (reference 21/SPS/078).

Athletes were recruited from all levels of a RT background, from recreational gym use to high level competitive athletes. All participants were advised 24 hours prior to data collection to abstain from alcohol and caffeine, and not to undergo any vigorous exercise. All athletes were asked to fast for 8-12 hours before testing.

A cross-sectional study was designed, with data acquired from each participant on one occasion in resting state where they completed the following procedures: a

health and AAS questionnaire, measurement of height, weight and brachial artery blood pressure, a 12-lead ECG and a full transthoracic echocardiogram (including 2D, Doppler and STE for strain).

3.2.2 Procedures

AAS Questionnaire

Prior to any testing, participants were asked to fill out an AAS questionnaire. The questionnaire determined AAS use characteristics and training schedules (Appendix 1). Those in the current and past using group also reported their AAS use history, including names of substances, dosages, administration method, duration of use and frequency of use.

Anthropometry

All participants underwent anthropometric assessment prior to cardiac assessment. Body mass (Seca 217, Hannover, Germany) and height (Seca Supra 719, Hannover, Germany) were recorded and body surface area (BSA) was calculated using the Mosteller equation (Mosteller, 1987).

Resting Blood Pressure

Resting blood pressure was obtained following a 5-minute seated rest using an automated blood pressure monitor (Seca, Hannover, Germany). Alternatively, due to increased muscle size on the upper arm, some participants exceeded the size of the cuff on the blood pressure monitor. Therefore, a manual blood pressure was taken in these specific cases.

12 Lead Resting ECG

Participants completed a 10-second, resting, supine 12-Lead ECG (CardioPad, Seca, Hannover, Germany) prior to echocardiographic assessment. Participants were asked to lay in a supine position on a bed with their chest area exposed. Electrodes were placed in the relevant positions (V1 – V6 and limb leads) before the ECG commenced. Participants lay still for 10 seconds whilst the ECG was being recorded. The ECG was stored electronically as well as printed on standard ECG paper.

Echocardiographic assessment

A standard transthoracic echocardiogram was performed by a single experienced sonographer in accordance with guidelines from the British Society of Echocardiography (BSE) (Robinson et al., 2020). Standard 2D, M-mode, Doppler, Tissue Doppler and STE were performed using a commercially available ultrasound system (Vivid E95, GE Medical, Horton, Norway) and a 1.5 – 4 MHz phased array transducer. All images were acquired with the subject in the left lateral decubitus position, echocardiographic images were obtained using a systematic approach (Robinson et al., 2020) and were stored digitally in raw DICOM format to an offline archive. Analysis was undertaken by the primary researcher using commercially available software (EchoPac, Version 203, GE Medical Systems, Horten, Norway).

Conventional 2D Echocardiography

Left Ventricle

The parasternal views were used to provide images for measurements of LVM, LV wall thickness, and cavity size. LVM was calculated using the corrected American

Society of Echocardiography equation using LV linear dimensions (LVIDd and LV systolic diameter (LVISd)) acquired from a parasternal long axis view. To calculate LV wall thicknesses eight measurements were made from a parasternal short axis orientation at mid and basal levels from antero-septum, infero-septum, posterior wall and lateral wall. MWT was calculated from an average of these eight measurements. RWT was calculated using the formula: (2xMWT/LVIDd). Eccentric hypertrophy was classified as RWT ≤ 42mm with an LVM index ≥ 115 g/m^2 in men and ≥ 95 g/m^2 in women. Concentric hypertrophy was classified as RWT > 42mm and LVM index of > 115 g/m^2 in men and > 95 g/m^2 in women. Concentric remodelling was identified as normal LVM index (49-115 g/m^2 in men and 43-95 g/m^2 in women) and RWT > 0.42mm (Możdżan et al., 2013; Harkness et al., 2020a). Normal geometry was classified as an LVM index of 49-115 g/m^2 in men and 43-95 g/m^2 in women as well as RWT ≤ 0.42mm. The apical orientations were used to establish LV end systolic volume (LVESV) and LVEDV and were calculated using the Simpson's biplane method, with LV concentricity calculated as (LVM/LV EDV$^{0.667}$) (Kosaraju et al., 2023). Stroke volume (SV) and EF were calculated from LV EDV and ESV respectively. SV index was calculated as (SV/BSA$^{1.5}$). Pulsed-wave TDI was used to examine the septum and lateral walls, allowing for the calculation of systolic (S'), early diastolic (E') and late diastolic (A') velocities, with average values calculated from the two walls. Transmitral Doppler was used to determine E velocity, A velocity and subsequent calculation of the E/A ratio. Deceleration time was calculated from the peak of the E wave to its baseline. All structural and functional indices were presented as absolute values but were also allometrically scaled to BSA based on geometric similarities.

Linear dimensions were scaled to $BSA^{0.5}$, with areas scaled directly to BSA. Volumes were scaled to $BSA^{1.5}$ (Dewey et al., 2008).

Right Ventricle

To assess RV structure and function, an apical-four chamber (AP4CH) orientation was acquired in accordance with BSE guidelines (Robinson et al., 2020). The RV outflow tract was measured at three locations from a parasternal long axis view ($RVOT_{plax}$, $RVOT_1$ and $RVOT_2$). An AP4CH orientation was used to acquire measurements at the main body and base of the RV (RVD_1), mid-cavity (RVD_2), and RV length (RVD_3).

TAPSE was measured using M-mode echocardiography with the cursor positioned through the lateral aspect of the tricuspid valve annulus. Pulsed wave TDI was used to analyse the RV lateral wall with the sample volume placed within the tricuspid annulus. Peak systolic (S'), early-diastolic (E'), and late diastolic (A') myocardial velocities were measured.

Speckle Tracking Echocardiography

Left Ventricle

All images were acquired and optimised with 2D gain, compression and dynamic range to ensure maximal endocardial delineation, with a frame rate maintained between 40 and 90 frames per second. To calculate GLS, the apical four-chamber (4CH), two-chamber (2CH) and three-chamber (3CH) orientations were used. Providing a global value based on the average of 17 segments.

To measure LV global circumferential strain (GCS) a standard parasternal short axis (PSAX) orientation was used. This involved tilting the transducer for definition at the level of the mitral valve leaflet tips, papillary muscle level and the apical level. For GCS measurements, an average was taken from all 12 of the basal and mid-level regional segments. LV twist was determined by calculating the net difference between the apical and basal rotations.

Right Ventricle

RV longitudinal strain was measured using an RV focused AP4CH orientation. Images were optimised for depth, gain, compression, and sector width for optimal endocardial delineation, with a frame rate maintained between 40 and 90 frames per second. The region of interest was taken for the RV free wall and septum. RV longitudinal strain was calculated as an average of the basal, mid and apical free wall segments only.

LV and RV time to peak (TTP) strain were measured at the time point in which the maximum (peak) strain value occurred.

Statistical analysis

All Statistical analyses were performed using IBM SPSS (version 27, SPSS, Chicago, Illinois). All data are presented as mean ± standard deviation. All data are presented as mean ± standard deviation and were assessed for normal distribution using a Kolmogrov-Smirnov test and if present then a one-way ANOVA was performed across the three groups (non-user, past-user and current-user). For non-normally distributed data a Kruskal-Wallace test was used for the same group comparison.

Due to multiple testing a post hoc Bonferroni was used to establish specific differences. The mean difference was statistically significant at the 0.05 level.

3.3. Results

Participant demographics and AAS use

Current AAS users had a history of use of 6.8 ± 5.1 years, with a median dose of 1108mg per week^{-1} [range (40-4500)] (combined dosage of different AAS'). Current users were taking 3.4 ± 1.6 [range (1-6)] substances simultaneously. Administration was primarily through injection (81% injection, 19% oral tablet).

Athlete demographics are presented in Table 2.1. Current users were significantly older (30 ± 4 years) than both past (27 ± 5 years, P = 0.049) and non-users (27 ± 6 years, P = 0.020). Current users were also significantly taller (178 ± 9cm) than non-users (170 ± 9cm, P = 0.003). There were no significant differences between groups for training duration in years (P = 0.904) or training hours per week (P = 0.334). There was no significant difference between past and non-users for weight (P = 0.169). However, current users (102 ± 18kg) were significantly heavier than non-users (76 ± 14kg, P <.001), and past users (86 ± 16kg, P = 0.002). Current users also displayed a significantly higher heart rate (68 ± 11 bpm) than non-users (56 ± 9 bpm, P <.001), and past users (58 ± 11 bpm, P = 0.002). All athlete groups were predominantly of white Caucasian ethnicity (95%). Other groups included mixed / multiple ethnic groups (4%) and Asian / Asian British (1%).

Table 3.1. *Anthropometric data and baseline demographics for non-users, past users, and current users.*

Variable	**Non-user (n = 20)** *Mean ± SD*	**Past User (n = 19)** *Mean ± SD*	**Current user (n = 57)** *Mean ± SD*
Age (years)	27 ± 6	27 ± 5	30 ± 4[a,b]
Weight (kg)	76 ± 14	86 ± 16	102 ± 18[a,b]
Height (cm)	170 ± 9	173 ± 11	178 ± 9[b]
BSA (m^2)	1.89 ± 0.22	2.02 ± 0.24	2.24 ± 0.24[a,b]
Heart rate (bpm)	56 ± 9	58 ± 11	68 ± 11[a,b]
Systolic BP (mm Hg)	119 ± 11	122 ± 13	127 ± 10[b]
Diastolic BP (mm Hg)	72 ± 10	71 ± 8	74 ± 9
Training duration (years)	11 ± 9	12 ± 6	12 ± 7
Training hours (per week)	9 ± 3	9 ± 3	11 ± 3

[a] denotes significance <0.05 between current users and past-users

[b] denotes significance <0.05 between current users and non-users

[c] denotes significance <0.05 between past and non-users

Normal physiological adaptation

All data for non-users i.e. pure RT athletes are outlined in Tables 2.2 - 2.6 below. Non-users displayed entirely normal geometry, with almost all non-users within the normal ranges for non-athletic individuals (Harkness et al., 2020a).There were however some individual outliers: 5% of non-users were above the normal range for LVM, with 10% for LVIDd and 20% for LVEDV. 5% of non-users were outside the normal range for RVOT 2, with 55% outside the normal range for RVD3.

5% of non-users were below the cut-off values for peak GLS and 10% for peak GCS. 10% of non-users were below the normal cut-off value for EF with 5% for absolute SV.

AAS use

Left Ventricular Structure

All measurements for LV structure are displayed in Table 2.2. Current users displayed a significantly greater LVM (260.6 ± 94.5g) and MWT (9.9 ± 1.4mm) than both non-users (139.9 ± 38.0g; 7.5 ± 0.7mm, P <.001) and past users (178.8 ± 56.7g; 8.1 ± 1.0mm, P <.001), with this significant difference remaining after indexing for BSA (P <.001) (see Figure 2.1). Current users also displayed a significantly greater LVIDd (57.6 ± 6.0mm) and LVEDV (169.7 ± 37.4ml) than non-users (50.7 ± 4.0mm; 126.0 ± 29.9ml, P <.001). However, when allometrically scaled to body size, this significant difference disappeared (see Figure 2.2). Current users also had a significantly greater RWT (0.37 ± 0.05mm) and concentricity (8.4 ± 2.1) than both non-users (0.31 ± 0.03mm; 5.6 =

1.0, P <.001) and past users (0.32 ± 0.04mm; 6.6 ± 1.4, P <.001). There were no significant differences between past and non-users for any LV structural parameter.

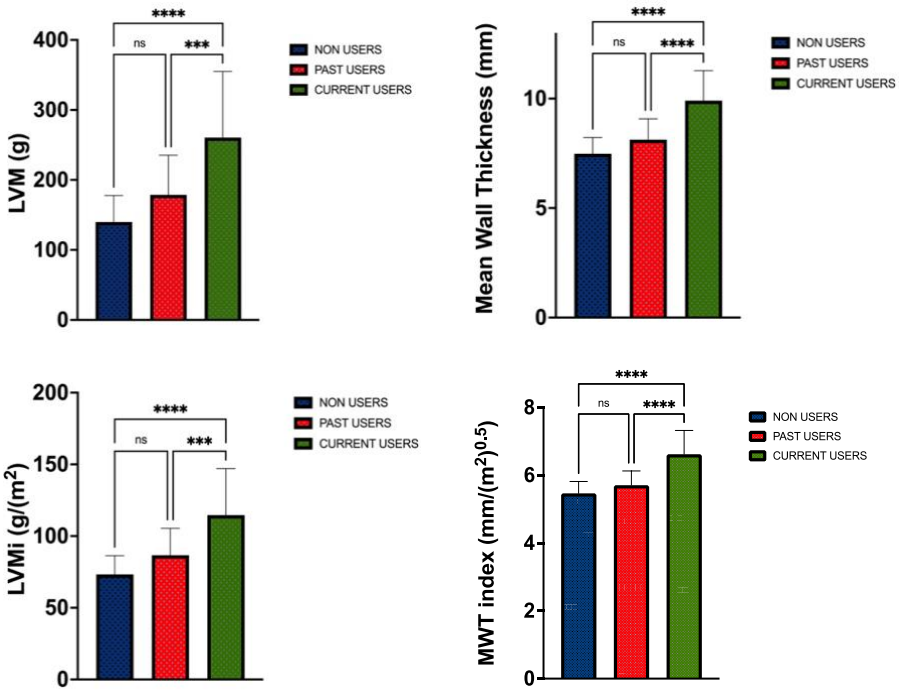

Figure 3.1 - *Absolute and indexed mean values for LVM and MWT across users, past-users, and non-users. With asterisk's detailing level of significance (* P < 0.05; ** P < 0.01; *** P < 0.001; **** P < 0.0001, ns = not significant).*

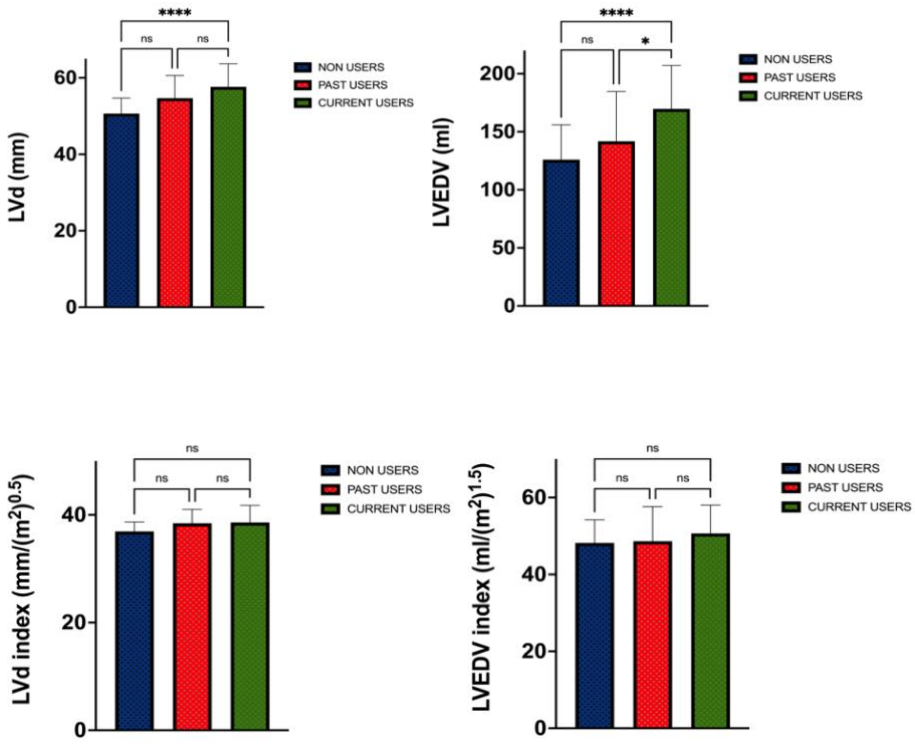

Figure 3.2 - *Absolute and indexed mean values for LVIDd and LVEDV across users, past-users, and non-users. With asterisk's detailing level of significance (* P < 0.05; ** P < 0.01; *** P < 0.001; **** P < 0.0001, ns = not significant).*

Left Ventricular Function

Systolic

All measurements for LV function are displayed in Table 2.3. Current users displayed a significantly lower EF (54.5 ± 5.7%) than non-users (60.6 ± 3.5%, P <.001), however the difference was not significant when compared to past users (56.6 ± 5.1%, P = 0.289). Current users also had a significantly greater SV (91.6 ± 18.2ml) than both non-users (76.6 ± 19.2ml, P = 0.008) and past users (79.4 ± 21.3 ml, P = 0.045) However, there were no differences between groups for SV index (See Figure 3). EF was significantly lower in past users (56.6 ± 5.1%) compared to non-users (60.6 ± 3.5%, P = 0.045). No other LV systolic functional parameters were significantly different between past and non-users.

Diastolic

Current users displayed significantly lower values of E (0.78 ± 0.20m/s), A (0.54 ± 0.10m/s) and E/A ratio (1.5 ± 0.5) compared to non-users (0.89 ± 0.20m/s, P = 0.018; 0.47 ± 0.09 m/s, P = 0.049; 1.9 ± 0.4, P <.001), with a significantly lower A and E/A ratio than past users (0.46 ± 0.10 m/s, P = 0.022; 1.8 ± 0.4, P = 0.039). There were no significant differences between groups for deceleration time (P = 0.693). None of the diastolic functional parameters were significantly different between past and non-users.

Speckle Tracking Echocardiography

All strain parameters are outlined in Table 2.6. Current users displayed a significantly lower peak GLS (-12.8 ± 5.3%) and GCS (-15.9 ± 7.0%) compared to both non-users (-

17.0 ± 5.6%; -20.6 ± 8.0%, P<.001) and past users (-15.5 ± 4.6%, P = 0.012; -18.8 ± 9.0%, P = 0.007). Peak GLS was significantly lower in past users (-15.5 ± 4.6%) compared to non-users (-17.0 ± 5.6%, P = 0.036). There was no significant difference between these two groups however for peak GCS (P = 0.338). TTP GCS was significantly higher in current users (0.40 ± 0.05s) compared to both non-users and past users (0.40 ± 0.05s, P<.001). There was no significant difference between groups for time to peak GLS (P = 0.132) or peak twist (P = 0.356). No other strain mechanics were significantly different between past and non-users.

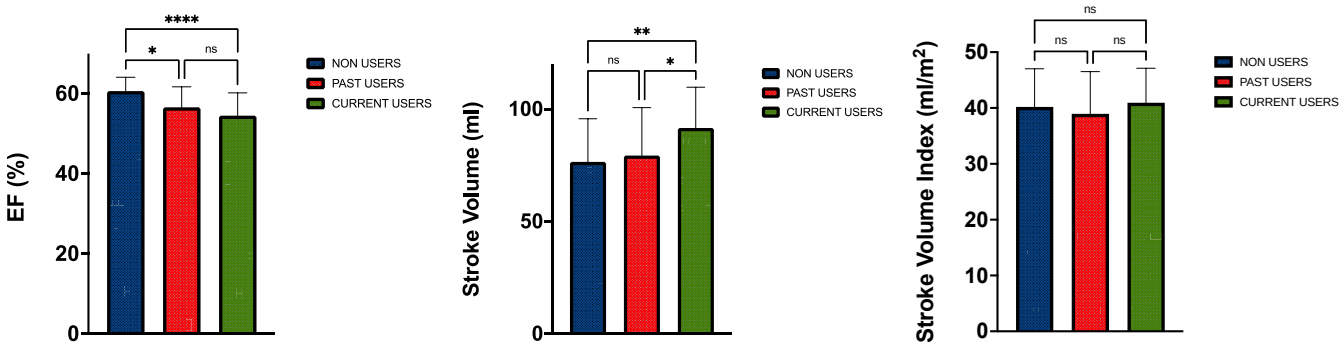

Figure 3.3 - *Absolute and indexed mean values of EF and SV across non-users, past users, and current users. With asterisk's detailing level of significance (* P < 0.05; ** P < 0.01; *** P < 0.001; **** P < 0.0001, ns = not significant).*

Left Ventricular Geometry

Proportion of LV geometry across groups is demonstrated below in Figure 2.4. Both current (Median = 9, IQR = 9) and past users (Median = 1.5, IQR = 1) demonstrated eccentric hypertrophy. Current users (Median = 2.5, IQR = 2) also displayed concentric hypertrophy with one individual demonstrating concentric remodelling. A median of 17.5 current users demonstrated normal geometry (IQR = 17). Past users demonstrated predominately normal geometry also with a median of 9 participants (IQR = 9). Non-users demonstrated entirely normal geometry.

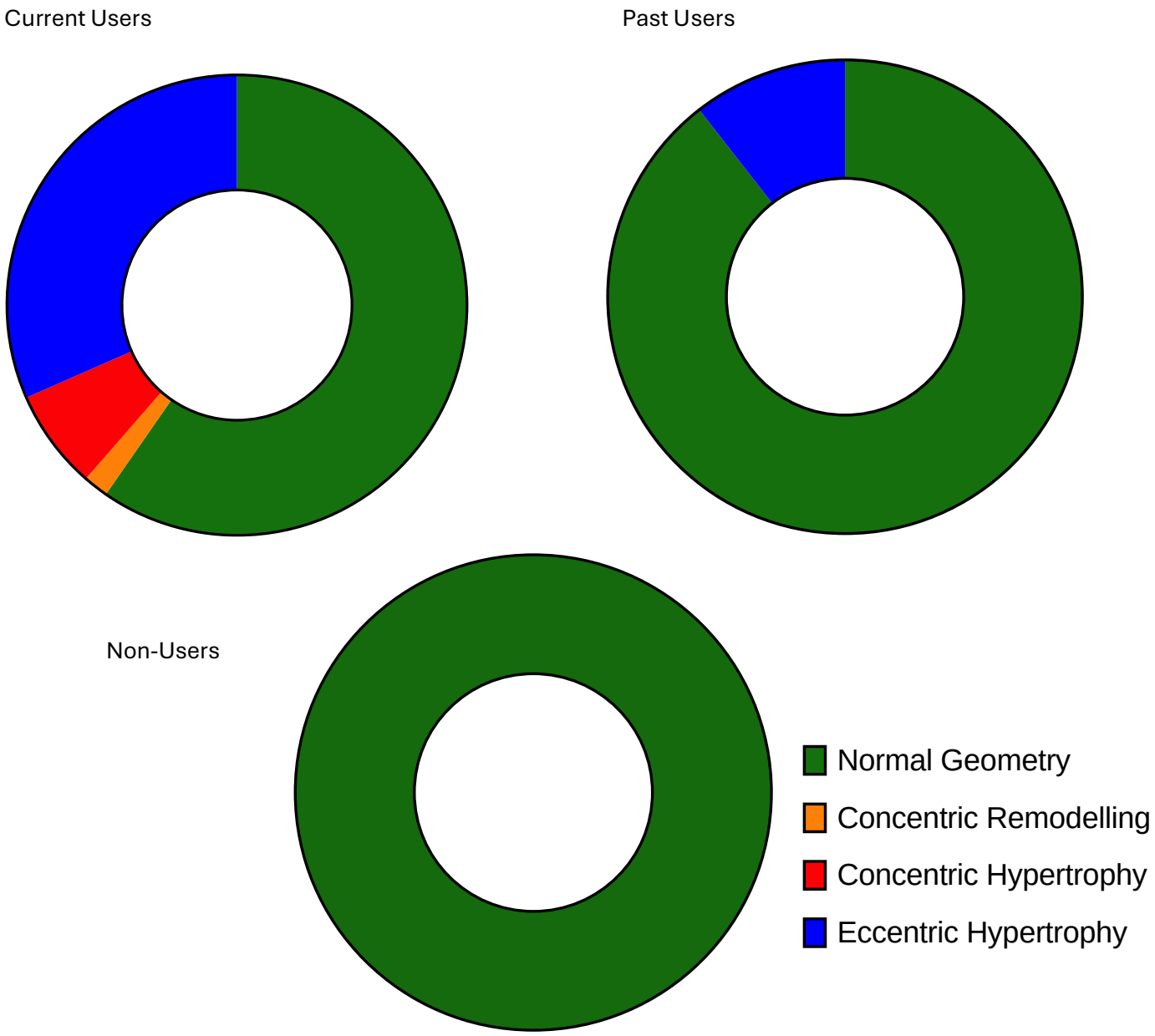

Figure 3.4 - *LV geometry (%) across current users, past users, and non-users. With a key representing each type of geometry.*

Table 3.2. *LV structural data for non-users, past users, and current users.*

Variable	**Non-user (n = 20)** *Mean ± SD*	**Past User (n=19)** *Mean ± SD*	**Current user (n=57)** *Mean ± SD*
MWT (mm)	7.5 ± 0.7	8.1 ± 1	9.9 ± 1.4[a,b]
MWT index	5.5 ± 0.4	5.7 ± 0.4	6.6 ± 0.7[a,b]
LVM (g)	139.9 ± 38.0	178.8 ± 56.7	260.6 ± 94.5[a,b]
LVM index (g/m^2)	73.3 ± 13.0	86.7 ± 18.7	114.6 ± 32.5[a,b]
LVIDD (mm)	50.7 ± 4.0	54.7 ± 6.0	57.6 ± 6.0[b]
LVIDD index ($mm/(m^2)^{0.5}$)	36.9 ± 1.8	38.4 ± 2.6	38.6 ± 3.2
LVEDV (ml)	126.0 ± 29.9	141.7 ± 42.9	169.7 ± 37.4[a,b]
LVEDV index ($ml/(m^2)^{1.5}$)	48.2 ± 6.0	48.7 ± 9.0	50.6 ± 7.4
RWT (mm)	0.31 ± 0.03	0.32 ±	0.37 ± 0.05[a,b]

Concentricity	5.6 ± 1.0	6.6 ± 1.4	8.4 ± 2.1[a,b]

[a] denotes significance <0.05 between current users and past users

[b] denotes significance <0.05 between current users and non-users

[c] denotes significance <0.05 between past and non-users

Table 3.3. *LV functional data for non-users, past users, and current users.*

Variable	**Non-user (n = 20)** *Mean ± SD*	**Past User (n = 19)** *Mean ± SD*	**Current user (n = 57)** *Mean ± SD*
EF (%)	60.6 ± 3.5	56.6 ± 5.1[c]	54.5 ± 5.7[b]
SV (ml)	76.6 ± 19.2	79.4 ± 21.3	91.6 ± 18.2[a,b]
SV index (ml/(m^2)$^{1.5}$)	40.2 ± 6.8	38.9 ± 7.6	40.9 ± 6.2
Medial S' (cm/s)	8.7 ± 1.2	8.5 ± 1.4	8.1 ± 1.3
Lateral S' (cm/s)	11.6 ± 2.6	10.7 ± 2.7	9.8 ± 2.4[b]
Average S' (cm/s)	10.1 ± 1.6	9.6 ± 1.6	9.0 ± 1.6[b]
Medial E' (cm/s)	12.8 ± 2.0	11.9 ± 2.9	10.2 ± 2.2[a,b]
Lateral E' (cm/s)	18.2 ± 4.2	17.5 ± 4.3	13.5 ± 3.4[a,b]
Average E' (cm/s)	15.5 ± 2.4	14.7 ± 2.8	11.8 ± 2.1[a,b]
E (m/s)	0.89 ± 0.20	0.79 ± 0.10	0.78 ± 0.20[b]
A (m/s)	0.47 ± 0.09	0.46 ± 0.10	0.54 ± 0.10[a,b]
E/A Ratio	1.9 ± 0.4	1.8 ± 0.4	1.5 ± 0.5[a,b]
DT (cm/s)	163.5 ± 34.5	165.5 ± 21.6	160.8 ± 32.9

[a] *denotes significance <0.05 between current users and past users*

[b] *denotes significance <0.05 between current users and non-users*

[c] *denotes significance <0.05 between past and non-users*

Right Ventricular Structure

Measurements for RV structure are displayed in Table 2.4. Current users had a significantly greater $RVOT_1$ (34.5 ± 4.3mm) than both non (30.2 ± 4.1mm, P <.001) and past users (31.2 ± 4.1mm, P = 0.010). They also had a significantly greater $RVOT_{plax}$ (32.7 ± 4.5mm, P = .005) and $RVOT_2$ (25.9 ± 4.3mm, P = .005) than non-users. However, they were not significantly greater when compared to past users (30.8 ± 3.7mm, P = 0.215; 24.1 ± 4.1mm, P = 0.230). These significant differences disappeared after allometrically scaling to BSA. Current users also displayed a significantly greater RVD_1 (43.2 ± 5.2mm), RVD_2 (29.5 ± 4.0mm), and RVD_3 (94.7 ± 9.1mm) when compared to non-users (38.1 ± 5.5mm, P = 0.001; 28.7 ± 4.3mm, P = 0.002; 90.8 ± 9.4mm, P <.001) which again, did not remain after indexing to BSA (P = 0.291; P = 0.193; P = 0.522) (Figure 2.4). There were no significant differences between past and non-users for any RV structural measurement.

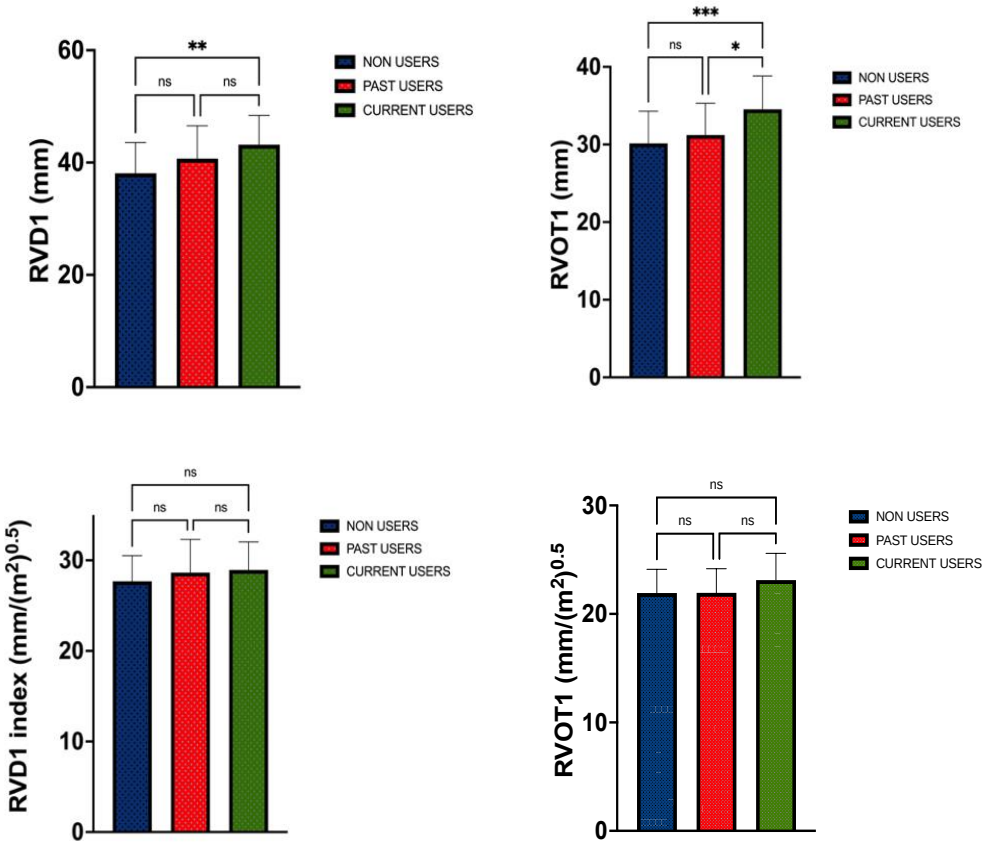

Figure 3.5 - *Absolute and indexed mean values of RVD_1 and $RVOT_1$ across non-users, past users, and current users. With asterisk's detailing level of significance. (* P < 0.05; ** P < 0.01; *** P < 0.001; **** P < 0.0001, ns = not significant).*

Table 3.4. *RV structural measurements across non- users, past users, and current users.*

Variable	**Non-user (n = 20)** *Mean ± SD*	**Past User (n = 19)** *Mean ± SD*	**Current user (n = 57)** *Mean ± SD*
$RVOT_{plax}$ (mm)	29.1 ± 4.0	30.8 ± 3.7	32.7 ± 4.5[b]
$RVOT_{plax}$ Index ($mm/(m^2)^{0.5}$)	21.2 ± 2.1	21.7 ± 1.8	21.9 ± 2.6
RVOT 1 (mm)	30.2 ± 4.1	31.2 ± 4.1	34.5 ± 4.3[a,b]
RVOT 1 Index ($mm/(m^2)^{0.5}$)	21.9 ± 2.2	21.9 ± 2.2	23.1 ± 2.5
RVOT 2 (mm)	22.4 ± 3.7	24.1 ± 4.1	25.9 ± 4.3[b]
RVOT 2 Index ($mm/(m^2)^{0.5}$)	16.3 ± 2.0	16.9 ± 2.4	17.3 ± 2.4
RVD 1 (mm)	38.1 ± 5.5	40.7 ± 5.9	43.2 ± 5.2[b]
RVD 1 Index ($mm/(m^2)^{0.5}$)	27.7 ± 2.8	28.6 ± 3.7	28.9 ± 3.1
RVD 2 (mm)	25.7 ± 4.6	28.7 ± 4.3	29.5 ± 4.0[b]
RVD 2 Index ($mm/(m^2)^{0.5}$)	18.6 ± 2.6	20.2 ± 2.4	19.7 ± 2.4
RVD 3 (mm)	85.2 ± 7.5	90.8 ± 9.4	94.7 ± 9.1[b]

RVD 3 Index (mm/(m^2)$^{0.5}$)	62.1 ± 4.0	63.8 ± 3.9	63.4 ± 5.2

[a] *denotes significance <0.05 between current users and past users*

[b] *denotes significance <0.05 between current users and non-users.*

[c] *denotes significance <0.05 between past and non-users.*

Right Ventricular Function

All measurements for right ventricular function are displayed in Table 2.5. Current users had a significantly lower RV E' (12.4 ± 2.7 cm/s) than non-users (14.2 ± 2.7 cm/s, P = 0.033). There were however no significant differences between current and past or past and non-users. There was no significant difference between groups for RV A', RV E/A', RV S' or TAPSE. There were no significant differences between past and non-users for any RV functional measurement.

Speckle Tracking Echocardiography

Current users displayed a significantly lower RV longitudinal strain (-17.3 ± 5.6%) than both non (-23.1 ± 5.0%) and past users (-23.1 ± 5.1, P<.001). This difference was not significant between past and non-users (P = 0.975). There was no significant difference between groups however for TTP longitudinal strain (P = 0.760). There were no significant differences between past and non-users for RV strain mechanics.

Table 3.5. *RV functional measurements across non- users, past users, and current users.*

Variable	**Non-user (n = 20)** *Mean ± SD*	**Past User (n = 19)** *Mean ± SD*	**Current user (n = 57)** *Mean ± SD*
RV E' (cm/s)	14.1 ± 2.7	12.5 ± 2.6	12.4 ± 2.7[b]
RV A' (cm/s)	11.0 ± 2.6	9.8 ± 2.4	10.4 ± 2.8
RV E'/A'	1.4 ± 0.4	1.3 ± 0.4	1.2 ± 0.3
RV S' (cm/s)	13.5 ± 2.1	12.7 ± 2.2	13.3 ± 2.4
TAPSE (mm)	21.2 ± 3.3	20.4 ± 3.9	21.8 ± 3.9

[a] *denotes significance <0.05 between current users and past users*

[b] *denotes significance <0.05 between current users and non-users.*

[c] *denotes significance <0.05 between past and non-users*

Table 3.6. *Strain and Rotational measurements across non-users, past users, and current users for both the LV and RV.*

Variable	**Non-user (n = 20) Mean ± SD**	**Past User (n = 19) Mean ± SD**	**Current user (n = 57)Mean ± SD**
GCS Peak strain (%)	-20.6 ± 8.0	-18.8 ± 9.0	-15.9 ± 7.0[a,b]
GCS - Time to Peak (s)	0.40 ± 0.05	0.40 ± 0.05	0.40 ± 0.05[a,b]
GLS Peak strain (%)	-17.0 ± 5.6	-15.5 ± 4.6[b, c]	-12.8 ± 5.3[a,b]
GLS - Time to Peak (s)	0.4 ± 0.1	0.4 ± 0.1	0.4 ± 0.2
Peak Twist (degrees)	15.6 ± 6.2	14.4 ± 4.5	13.8 ± 5.0
Time of peak Twist (s)	0.37 ± 0.06	0.35 ± 0.05	0.33 ± 0.05[b]
RV Peak LS (%)	-23.1 ± 5.0	-23.1 ± 5.1	-17.3 ± 5.6[a,b]
RV LS - TTP (s)	0.40 ± 0.03	0.40 ± 0.04	0.40 ± 0.05

[a] *denotes significance <0.05 between current users and past users*

[b] *denotes significance <0.05 between current users and non-users.*

[c] *denotes significance <0.05 between past and non-users.*

3.4 Discussion

The main findings from the current study are: 1) non using RT athletes display a significantly lower magnitude of wall thickening and LVM, compared to current users and subsequently do not display concentric hypertrophy, 2) current users displayed significantly larger cardiac size than that of non-users and past users. Demonstrated through significantly increased LV and RV structural parameters. 3) current users demonstrated a significantly reduced LV and RV systolic function and 4) past users exhibited significantly reduced LV and RV size compared to current users. Additionally, structural parameters were not significantly different to that of non-users. Thus, displaying evidence of regression of structural remodelling with abstinence. Conversely, some functional parameters were significantly different to that of non-users, suggesting a more permanent form of adaptation in relation to function.

Normal Echocardiographic Adaptation

The common belief for many years outlined that RT athletes exhibit greater wall thicknesses in comparison to ET athletes and controls (Morganroth et al., 1975). The Morganroth hypothesis also highlights that RT athletes display parameters that conform with concentric hypertrophy. However, more recent work has highlighted the significantly lower magnitude of remodelling within RT athletes (Haykowsky et al., 2002; Spence et al., 2011), compared to that illustrated by (Morganroth et al., 1975).

Within the current study non-using RT athletes demonstrated a significantly lower magnitude of cardiac remodelling in comparison to their AAS using counterparts. None of these athletes met the criteria for concentric hypertrophy, with all of them displaying normal geometry. Previous work has highlighted this difference in magnitude of adaptation does not only exist as a result of AAS use, but also a consequence of sporting discipline directly.

(Spence et al., 2013a) discovered after six months of RT that athletes exhibited smaller RV morphological adaptations to that of ET athletes. These minimal RV adaptations that were observed, may be explained by the intermittent nature of RT in comparison to ET (Utomi et al., 2015). Previous work has also highlighted that the haemodynamic stimulus that is thought to promote cardiac adaptation through an increased end-systolic wall stress, may not even exist during RT (Haykowsky et al., 2001). ET athletes experience chronic volume and pressure overload that results in increased cardiac output, due to prolonged sub-maximal intensity exercise (Santoro et al., 2014). Causing subsequent chamber enlargement and wall thickening to cope with the increased overload (Maron and Pelliccia, 2006). Hence, it is important to challenge the resistance element of the Morganroth hypothesis. Most importantly, whether the haemodynamic stimulus needed in order to induce this magnitude of cardiac adaptation, even exists within RT athletes.

The Structural Impact of Anabolic Steroid Use

Left Ventricle

Current users demonstrated significantly larger hearts than their non using counterparts. More specifically, significantly greater measurements of MWT and LVM, which remained so after scaling to BSA. On the contrary, cavity dimensions such as LVIDd and LVEDV normalised after scaling. We could speculate that this increase in cavity size is a primary adaptation for

increased SV at rest and during exercise. An increase in cavity size is said to be a normal adaptation to exercise training, although more prominent in ET athletes (Bletsa et al., 2023). Due to increased body size of AAS users, however, naturally stroke volume would need to increase. Subsequently inducing a greater volume overload within the LV cavity, causing it to increase in size as a physiological response (Barauna et al., 2007). Other literature, however, highlighted no significant differences in LVIDd or LVEDV between AAS users and non-users (Baggish et al., 2017; Fyksen et al., 2022).

In contrast to this, differences in MWT and LVM in current users remained after scaling to BSA. We could suggest therefore, that there is an alternative pathway to this adaptation, which we could assume to be a direct result of AAS use. The growth promoting effects of androgens on muscle cells are currently well known (Wyce et al., 2010). More specifically, there are several lines of evidence that implicate endogenous androgenic pathways in the development of cardiac hypertrophy (Payne, Kotwinski and Montgomery, 2004). This includes the demonstration of raised 5α reductase, aromatase, and AR expression in hypertrophic hearts of humans.

Supra-physiological doses of AAS have been shown to induce pathological cardiac hypertrophy after just 8 weeks in animals (Pirompol et al., 2016). There is also evidence that elucidates similar findings within humans. (Baggish et al., 2017) identified a significantly increased LVM in AAS users, that remained after indexing for BSA and height. Allometric scaling here is of key importance to understand whether differences observed are a result of increased body size in AAS users. However, much like the current study they identified that LVM was significantly larger irrespective of increased body size, suggesting an alternative pathway of adaptation. Furthermore, current AAS users demonstrated a greater prevalence

of concentric geometry compared to non-users. These findings support the evidence that AAS's induce an anabolic effect on cardiac muscle mass. Furthermore, demonstrating that AAS use is associated with adverse cardiovascular phenotypes, categorised by pathological cardiac remodelling.

Other work has also highlighted significant increases in LV wall thicknesses and subsequently LVM in current users compared to non-users (Angell et al., 2014). Interestingly however, they stated that the differences between the groups did not persist after indexing for FFM. Suggesting that LV size increases in conjunction with body size in AAS users. The current study however found the opposite where that differences between LVM and MWT remained after indexing for BSA. Firstly, the study by (Angell et al., 2014) used cardiovascular magnetic resonance (CMR) to assess for structural parameters. Previous work has highlighted significant disparity between echocardiography and CMR, suggesting that echocardiography significantly overestimates LVM (Supe-Markovina et al., 2016). This may relate to greater visualisation of the blood-endocardial border, as well as better quality images acquired through CMR (Valente et al., 2013). Secondly, the current study scaled to BSA, which is affected by fat mass. Thus, scaling to BSA could over overestimate LVH in lean individuals and underestimate it in obese individuals (Whalley et al., 2004). Previous work has discovered that ratiometric scaling of LVM and LVIDd to FFM in athletes formed a stronger correlation than BSA or height (Whalley et al., 2004; Brown et al., 2017).

Right Ventricle

The current study observed significantly greater absolute RV structural measurements in current users when compared to non-users. However, these differences did not remain after scaling to BSA. On the contrary, some previous work has highlighted significantly larger RV

EDV in AAS using athletes compared to non-using athletes, even after scaling (Luijkx et al., 2013). Conversely, other previous work identified that significant differences in RV structure did not remain after scaling (Angell et al., 2014). This evidence, however, in line with the current study suggests that RV morphology increases proportionally with body size. RT athletes display similar chamber dimensions to that of sedentary individuals (D'Andrea et al., 2013). Suggesting that the increased body size of RT athletes promotes little difference in RV chamber dimensions. This evidence in part conflicts with the current study where that current using RT athletes, who had a significantly larger body size, still seem to exhibit greater RV morphology in comparison to non-using counterparts.

The growth promoting effects of androgens on muscle cells is well known (Wyce et al., 2010). Myocardial cells contain androgen receptors, that have been shown to have a high affinity for androgens (McGill et al., 1980). The study by (Angell et al., 2014) suggested due to their findings that the adaptations to AAS were similar in both the RV and LV. These findings however contradict other work as well as the current study that suggested LV structural parameters increase beyond the proportion of body size, and remain significant even after indexing (Rasmussen et al., 2018; Fyksen et al., 2022). Suggesting there may be a more exaggerated anabolic effect on cardiac muscle within the LV. Although differences in magnitude of adaptation to AAS are evidenced between the two ventricles, the anabolic mechanisms behind this are not understood and require further investigation.

The Functional Impact of Anabolic Steroid Use

EF in current users was significantly lower compared to non-users. However, they displayed a significantly greater absolute value of SV which then normalised when indexed to BSA,

suggesting that the increase in stroke volume, may be a manifestation of larger cavities at rest. This therefore creates speculation as to whether this paradoxical relationship between EF and stroke volume is 'normal' within this population.

Current users sit in the 'borderline low' range for EF, which was significantly lower than their non-using counterparts (Harkness et al., 2020b). This finding seems to be consistent among other echocardiographic studies that assessed current AAS users (Baggish et al., 2017; Fyksen et al., 2022). Interestingly, in the study by (Baggish et al., 2017) EF was greater reduced in athletes who were 'on cycle'. Suggesting that LV dysfunction may be directly related to specific use cycles. Reduced EF has been highlighted in previous work as a potential sign of systolic dysfunction (Golla, Hajouli and Ludhwani, 2024). Although this finding is fairly common among high level ET athletes (Claessen et al., 2024). With it being expressed as a more benign physiological adaptation. In these cases, more sensitive measurements of systolic function showed normal or even supranormal strain or strain rate with normal values of GLS (Grazioli et al., 2015). However, these values have been shown to be reduced in patients with sub-clinical dilated cardiomyopathy (DCM) (Lakdawala et al., 2012). AAS users within the current study experience widespread reduction in systolic function, with impaired global contractility, shown through markedly reduced strain. There is an apparent overlap with measurements that are consistent with cardiovascular disease (Pinamonti et al. 2019). Although, SV is significantly greater within current users. Suggesting that regardless of the paradoxical relationship with EF, there is a physiological adaptation to the need for increased SV due to increased cavity size. Which seems to be unaffected by the otherwise impaired systolic function.

Interestingly in the study by (Angell et al., 2014) LV EF and stroke volume were not significantly different between current users and non-users, a disparate finding to the current study. All of the evidence we have found indicates that RT athletes experience an increase in cavity size to compensate for increased body mass and in combination the need for increased stroke volume. However, the study by (Angell et al., 2014) suggests that although the AAS user group were heavier and had a higher fat free mass, their SV did not increase and their EF was also maintained. Other work has agreed with the current study where that AAS users had a significantly reduced EF compared to non-users (Baggish et al., 2017). However, they found that there was no significant difference between the groups for absolute LVEDV, which disagrees with the current study. As described above there is disparity between measurements made by CMR and echocardiography. Previous work has highlighted the significant differences between the two in measuring EF and ventricular volumes (Clark et al., 2023). Suggesting that the agreement between CMR and 3D echocardiography is significantly higher than that of 2D echocardiography, the technique used in the current study (Nazir et al., 2024). Highlighting potential reasoning behind the disparity between the current study and previous work that utilised CMR.

In the current study, we see a global reduction of peak strain at all levels that were assessed in both the LV and RV (GLS, GCS and RV longitudinal strain). This, in combination with a significantly reduced EF in the AAS using group, provides no evidence to suggest a compensatory increase in circumferential strain to maintain it. Rather, a global impairment of systolic function, particularly evidenced in the LV. It is difficult to elucidate similar findings within the RV, as we did not assess for RV EF or RV circumferential strain. Although previous work has highlighted a significant reduction in RV EF in current AAS users compared to non-users (Luijkx et al., 2013; Angell et al., 2014). As well as reduced RV diastolic function in other

work (Kasikcioglu et al., 2009). With the current study finding a significantly reduced RV longitudinal strain in AAS users. Suggesting there could be parallel impairment of RV systolic function also. The clinical implications of this, however, are currently difficult to determine. Future work is needed to further highlight the impact of AAS use on global bi-ventricular impairment of systolic function.

Previous studies have suggested that regions of the heart can go into 'hibernation' if there is a lack of sufficient blood supply from the coronary arteries (Kloner, 2020). The concept suggests that a region of the heart is being supplied with blood from an atherosclerotic CA. This therefore supplies the region of the heart with enough blood to maintain its function at the lowest level, but not enough to maintain normal contractility of the region (Ryan and Perera, 2018). A previous study by (Baggish et al., 2017) found that RT athletes who use AAS, display a significantly larger coronary artery plaque volume than that of non-users. This finding has previously been linked to dyslipidaemia, with elevated low-density lipoprotein (LDL) and lowered high-density lipoprotein (HDL) concentrations (Hartgens et al., 2004). Additionally, they identified that AAS users had experienced prior myocardial infarctions due to underlying atherosclerotic disease. Although, in the current study we did not assess for atherosclerotic disease, this previous evidence may suggest potential mechanisms behind the global reduction of function observed in the current study, shown through strain measurements. However, future work is needed to assess specific regions of the heart to determine whether specific regions are more negatively affected than others, and whether this described pathology exists within this population.

Past Users

Past users within the current study experienced significantly reduced structural parameters of both the LV and RV, compared to current users. Thus, suggesting that upon cessation of AAS use there seems to be a reversibility of morphological adaptations. This is also apparent in previous work; where that with cessation of AAS use or during an off-drug cycle, structural parameters were significantly reduced in comparison to when they were using (Nieminen et al., 1996).

Interestingly in the current study, past users experienced no significant differences for structural parameters of both the LV and RV compared to non-using counterparts. Thus, suggesting that cessation of AAS use, leads to a reversibility in adaptation back to that of a non-using RT athlete. Although structural parameters did not differ, there were some functional parameters that were still significantly different between past and non-users, those being global peak strain and EF. Previous work has also discovered that reduced EF and GLS were more prominent in AAS users who were on cycle compared to those who were off (Baggish et al., 2017). Suggesting that LV dysfunction may be directly linked to specific use patterns. Evidently, some cardiovascular phenotypes seem to be reversible with the cessation of drug use. However, according to this study and previous work, some factors may be more irreversible (ventricular dysfunction and coronary atherosclerosis). Hence, further longitudinal examination on this phenomenon would be beneficial.

3.5 Limitations

There are several methodological limitations associated with this study. First, with measurements taken in resting state, there is lack of understanding as to the effect that

exercise has on function within these individuals. As exercise is a large part of their lifestyles, it would be important to understand whether function is still markedly reduced or further reduces when exercising. Second, the current study scaled to BSA, which is affected by fat mass. Previous work has highlighted that scaling to BSA could over overestimate LVH in lean individuals (Whalley et al., 2004), with others discovering stronger correlations with FFM (Whalley et al., 2004; Brown et al., 2017). Hence, as the majority of our population were lean with low fat mass, there could be overestimation of chamber morphology in these athletes. Finally, and secondary to this, the current study utilised echocardiography, which although commonly used in the assessment of ventricular structure, has been shown to overestimate LVM in comparison to CMR imaging (Supe-Markovina et al., 2016). There is potential therefore, for LVM to be overestimated in the current study. Hence why we see significantly larger measurements in current users even after scaling for BSA.

3.6 Conclusion

In summary, non-using RT athletes display normal structural and functional parameters that sit within normal ranges for non-athletic individuals. Highlighting the significant lack of adaptation these athletes undergo as a result of RT exercise.

RT athletes who take AAS on the other hand, undergo significant morphological and functional changes. Significantly increased LVM and wall thickness measurements are observed in users, even after indexing for BSA and height. Suggesting that this adaptation is not purely related to increases in body size, but rather another, potentially pathological adaptation. Past users, however, seem to exhibit a reversibility of structural adaptations with cessation of AAS use.

Bi-ventricular function was reduced in the AAS using group, shown through significantly reduced EF and strain parameters. Past users also had significantly reduced function compared to non-users. Potentially demonstrating a more irreversible form of adaptation. Further research is required to assess the impact of exercise on bi-ventricular function within this unique population.

Chapter 4 The 12 Lead Electrocardiogram in resistance trained athletes using anabolic androgenic steroids

4.1 Introduction

Alongside structural and functional adaptation there are also concomitant changes in the electrical activity of the heart (Brosnan et al., 2014) with the ECG being an important diagnostic tool to detect such adaptation (Basu and Malhotra, 2018). Training related changes include but are not limited to; sinus bradycardia, isolated criteria for LVH, 1st degree AV block, early repolarisation and sinus arrhythmia and have been clearly outlined by the International Criteria for Assessment of the Athletes Electrocardiogram (Sharma et al., 2017). The more profound training-related changes have been identified from ET athletes (Brosnan et al., 2014) and is likely associated with the magnitude of physiological cardiac adaptation (Santoro et al., 2014). There is however a paucity of data pertaining to RT athletes and hence normal ECG adaptation in these individuals warrants further exploration.

The ECG is used frequently due to its high sensitivity and specificity, cost-effectiveness and ease of use (Rafie, Kashou and Noseworthy, 2021). Alongside identifying physiological changes, it is important for the detection of muscle disease such as HCM or dilated cardiomyopathy (DCM) (Bernardini et al., 2023). AAS are frequently used by RT athletes in an attempt to increase muscle mass, improve strength and improve their perceived body image (McVeigh et al., 2021). Within Chapter 2 of this thesis, we identified phenotypical structural and functional changes associated with AAS use in combination with RT. Current users of AAS displayed significantly increased LVM and MWT (both normal and scaled) and LV and RV dilatation compared to non and past users, along with significantly reduced systolic function. These findings in non-users (non-athletes) are commonly associated with LVH criteria (including increased QRS duration and amplitude and left axis-deviation) and repolarisation abnormalities on the 12-lead ECG (Seko et al., 2021). Other work in this field have also

demonstrated increased wall thickness's and LVM in combination with reduced systolic function in AAS users (Angell et al., 2014), as well as increased CA plaque volume associated with increased coronary atherosclerosis (Baggish et al., 2017). These data highlight the potential contribution of AAS use to the development of myocardial disease. The findings from Chapter 2 also highlighted that past users exhibited significantly reduced chamber geometry when compared to AAS using RT athletes, suggesting transient remodelling following a period of abstinence. As highlighted, findings from Chapter 2 are associated with structural remodelling, that can also be detected on the 12 Lead ECG. It would be important for us to understand therefore, whether there is a direct correlation between these measurements, to determine specific CV changes in this population.

There have been few studies, primarily cellular and animal models, that have attempted to elucidate the 12 lead ECG in AAS users (Alizade et al., 2015; D'Andrea et al., 2016). These data demonstrate repolarisation abnormalities with an impact on the QT interval and abnormalities associated with calcium handling. There have been no studies that have solely focused on standard ECG criteria (both training and abnormalities) in AAS users or RT athletes. More so there is no evidence to demonstrate any changes (if present) would persist following cessation of use.

In view of this the main aims of the current study are to determine: 1) the normal 12-lead ECG findings in RT athletes, 2) to establish the impact of AAS use in combination with RT on the 12-lead ECG and to highlight any differences between non, past and current users of AAS and 3) to determine the presence of any correlations between echocardiographic measurements observed in Chapter 2 and the current results. It is hypothesised that: 1) RT athletes (non-users) will present with minimal training related criteria on the 12-lead ECG, 2) AAS users will

present with more marked ECG changes than both past and non-users, with significant correlations to measurements observed in Chapter 2 and 3) cessation of AAS use (i.e. past-users) will demonstrate some residual changes on the 12-lead ECG.

4.2 Methods

4.2.1 Study Population and design

The detailed methods for this study are presented in Chapter 2 with the study population remaining the same and the 12-Lead ECG performed as part of the procedural methods. RT athletes were allocated into groups based on self-reported AAS user status from questionnaires provided (Non = 20 (never used AAS) , Past = 19 (used AAS previously but not within 12-months of the examination) and Current = 57 (currently using AAS)).

All participants self-reported through cardiac screening health questionnaires, to be healthy without any history of cardiovascular disease and did not have a current illness.

4.2.2 Procedures

All standard procedures are detailed in Chapter 2.

12 Lead Resting ECG

A 10-second, resting, supine 12-Lead ECG (CardioPad, Seca, Hannover, Germany) was undertaken in accordance with American Heart Association guidelines (Hancock et al., 2009). Participants were asked to lay in a supine position on a bed with their chest area exposed. Hair was shaven on the chest area if this was necessary. Electrodes were then placed in the required positions (V1 – V6 and limb leads). Participants lay still for 10 seconds whilst the ECG

was being recorded. The ECG was then printed onto standard ECG paper and stored in PDF format to allow data extraction.

ECG Assessment Criteria

Each 12-lead ECG was interpreted in accordance with the International Criteria for Assessment of the Electrocardiogram in Athletes (Sharma et al., 2017) to determine the prevalence of training and non-training related findings (see Figure 3.1). The other extracted ECG parameters included heart rate, P wave duration, PR interval, QRS complex duration, QTc duration, P wave axis, QRS complex axis, T wave axis and voltage criteria for LV and RV hypertrophy. These parameters were utilised to determine presence of chamber enlargement, rhythm abnormalities or delays in conduction.

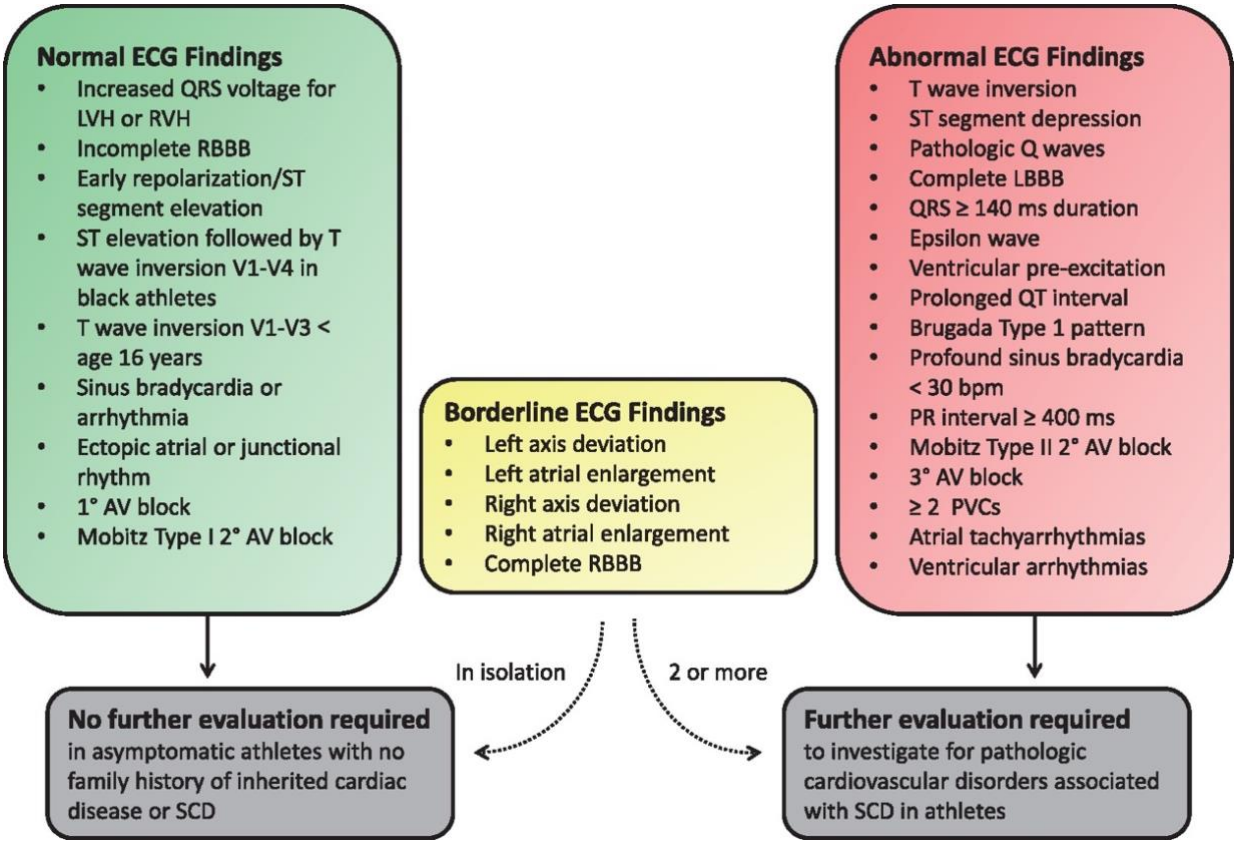

Figure 4.1 – *Training and non-training related findings, separated into normal, borderline and abnormal (Sharma et al., 2017).*

Statistical analysis

All data are presented as mean ± standard deviation and were assessed for normal distribution using a Kolmogrov-Smirnov test and if present then a one-way ANOVA was performed across the three groups (non-user, past-user and current-user). For non-normally distributed data a Kruskal-Wallace test was used for the same group comparison. Due to multiple testing a post hoc Bonferroni was used to establish specific differences. The mean difference was statistically significant at the 0.05 level. Nominal data pertaining to criteria for (non)training related adaptation were presented as median and interquartile range (IQR). Correlations were performed between current ECG data and echocardiographic data from Chapter 2 using a Pearson's Correlation (two-tailed). All Statistical analyses were performed using IBM SPSS (version 27, SPSS, Chicago, Illinois).

4.3 Results

Participant demographics

All participant demographics are presented in Chapter 2 (Table 2.1).

Training and non-training related findings

Training related ECG findings are presented in table 3.2. Sinus bradycardia was the only finding that was significantly different between groups (P = 0.004). A median of 22 individuals displayed 2 or more training related ECG changes (IQR = 22) with the most common training related ECG findings being sinus bradycardia (Median = 21.5, IQR = 21), early repolarization (Median = 17, IQR = 17.5) and increased QRS voltage for LVH (Median = 11.5, IQR = 11). Non-users displayed a greater prevalence of 2 or more training related ECG changes (Median = 6, IQR = 6) than that of both past users (Median = 4.5, IQR = 4) and current users (Median = 11.5, IQR = 11) albeit with no significant difference (P = 0.552). Only the current users presented with borderline findings; two had isolated left axis deviation, one had isolated left atrial enlargement, and one had complete RBBB. There were non-training related findings of T wave inversion in two of the current users. In one of the participants this was present in both the inferior and lateral leads, and in the other participant, it was constrained to the inferior leads.

Table 4.1 *Normal and borderline training related ECG changes within non, past and current users.*

Training related ECG changes	Non-users (n = 20, n (%))	Past users (n = 19, n (%))	Current users (n = 57, n (%))
Increased QRS voltage for RVH	0	2 (11)	2 (4)
Increased QRS voltage for LVH	4 (20)	3 (16)	15 (26)
Incomplete RBBB	0	1 (5)	3 (5)
Early Repolarisation	10 (50)	8 (42)	17 (30)
Sinus arrhythmia	0	2 (11)	5 (9)
Sinus bradycardia	15 (75)	9 (47)	18 (32)[a,b]
Ectopic atrial rhythm	1 (5)	0	4 (7)
First degree AV block	0	0	1 (2)
Mobitz type I 2nd Degree AV block	0	0	0
2 or more training related ECG changes	11 (55)	9 (47)	23 (40)

Borderline ECG changes			
Right axis deviation	0	0	0
Left axis deviation	0	0	2 (4)
Left atrial enlargement	0	0	1 (2)
Complete RBBB	0	0	1 (2)

[a] denotes significance <0.05 between current users and past users

[b] denotes significance <0.05 between current users and non-users

[c] denotes significance <0.05 between past and non-users

Parametric ECG variables

All parametric data is presented in table 3.3. T axis was significantly lower in current users (8.8 ± 19.5 degrees) compared to both past (22.3 ± 11.2 degrees, P = 0.009) and non-users (32.7 ± 10 degrees, P < 0.001). QRS duration and voltages for RVH were also significantly higher in current users (101 ± 9 ms and 5.8 ± 2.3 mm) compared to non-users (90 mm ± 11 ms and 3.9 ± 2.2, P <0.05), see Figure 3.2.

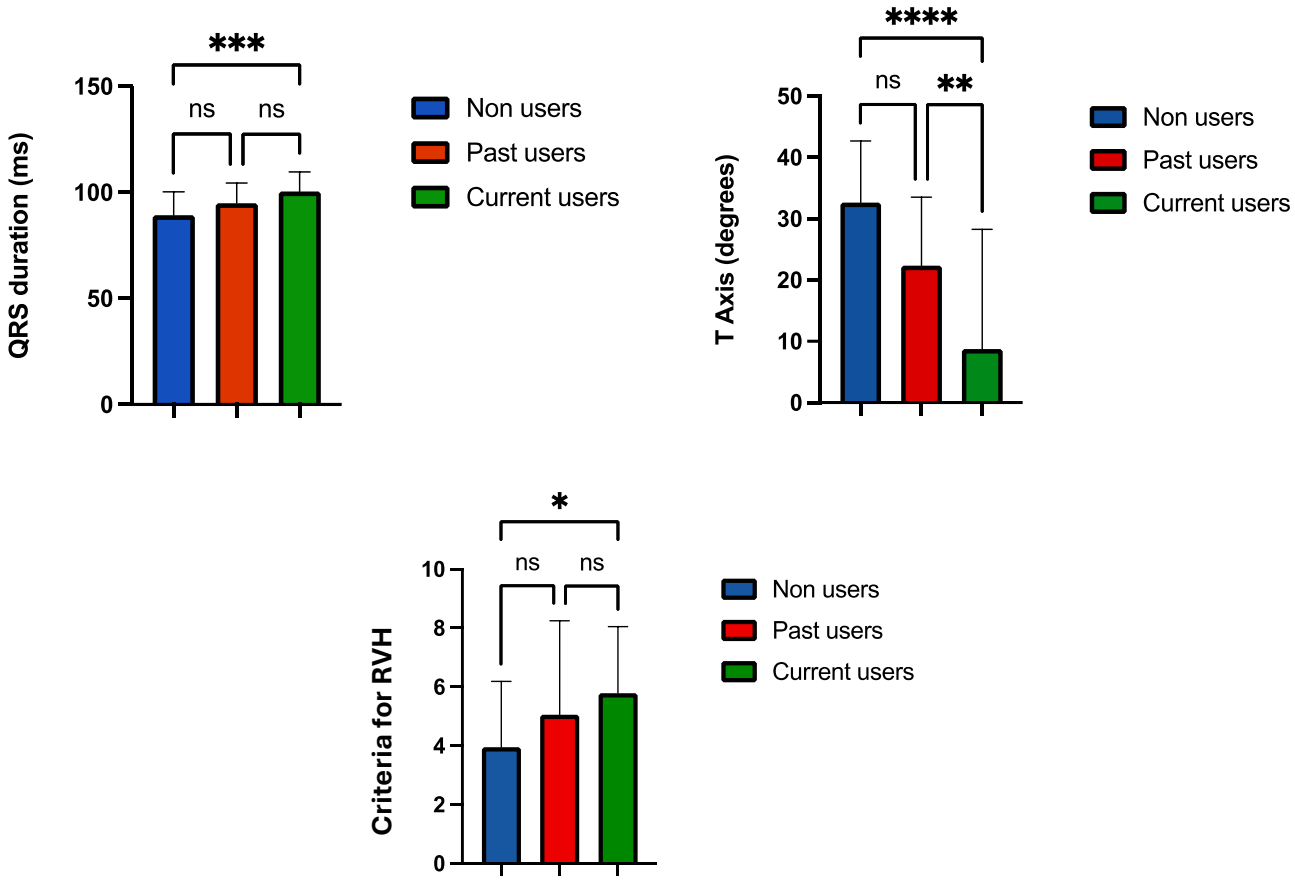

Figure 4.2 – *Absolute mean values of QRS Duration, T Axis and Voltage Criteria for RVH across non-users, past users, and current users. With asterisk's detailing level of significance. (* P < 0.05; ** P < 0.01; *** P < 0.001; **** P < 0.0001, ns = not significant).*

Table 4.2. *ECG data for non, past and current users.*

Variable	**Non-user (n=20)** *Mean ± SD*	**Past User (n=19)** *Mean ± SD*	**Current user (n=57)** *Mean ± SD*
Heart rate (BPM)	55.8 ± 7.4	56.8 ± 11.1	66.9 ± 11.2[a,b]
P duration (ms)	96.7 ± 11.6	101.6 ± 17	104 ± 11.9
PR interval (ms)	149.2 ± 23.8	159.9 ± 25.9	159.5 ± 21.6
QRS duration (ms)	89.7 ± 10.8	94.9 ± 9.5	100.5 ± 9.2[b]
QTc (Bazett)	402.3 ± 22.6	393.8 ± 31.2	398.8 ± 19.9
P axis (degrees)	41.4 ± 22.8	39.5 ± 27.9	40.6 ± 23.3
QRS axis (degrees)	56.3 ± 25.4	44.2 ± 30.8	41.2 ± 35.7
T axis (degrees)	32.7 ± 10	22.3 ± 11.2	8.8 ± 19.5[a,b]
Voltage: R in V_1	3.95 ± 2.2	5.1 ± 3.2	5.8 ± 2.3[b]

Voltage: S in V_1 + R in V_5 (mV)	26.2 ± 8.1	27.3 ± 8.3	30.4 ± 8.8

[a] *denotes significance <0.05 between current users and past-users*

[b] *denotes significance <0.05 between current users and non-users*

[c] *denotes significance <0.05 between past and non-users*

Correlations

All correlations are outlined in table 3.4. There were no significant correlations between isolated criteria for RVH found on the ECG and RV size (RVD 1, RVD 2 and RVD 3) ($P > 0.05$).There was, however, a significant positive correlation found between QRS duration and LVd index ($P < 0.01$, $R = .356$). There were also significant positive correlations identified between T axis and LVM ($P < 0.01$, $R = -.381$), MWT ($P < 0.01$, $R = -.431$) and EF ($P<0.01$, $R = .388$).

Table 4.3 Correlations between ECG findings and echocardiographic measurements observed in Chapter 2. With the R value representing the type of correlation, and the P value representing whether there is a significant correlation.

Correlation	R Value	P Value
RVH criteria / RVD 1	.047	.729
RVH criteria / RVD 2	.079	.563
RVH criteria / RVD 3	.015	.912

RVH criteria / RVOT Plax	-.032	.816
RVH criteria / RVOT 1	-.125	.358
RVH criteria / RVOT 2	.001	.995
LVH criteria / MWTi	-.113	.418
LVH criteria / LVMi	-.036	.734
LVH criteria / LVdi	.045	.742
QRSd / LVdi	.356**	< 0.01
QRSd / LVMi	.167	.219
QRSd / MWT	.007	.958
QRSd / EF	.010	.942
QRSd / LVEDVi	.101	.459
QRSd / LV GLS	-.191	.162
QRSd / SVi	.124	.363
T axis / LVM	-.381**	< 0.01
T axis / MWT	-.431**	< 0.01
T axis / EF	.388**	< 0.01

** *Significant at the 0.01 level.*

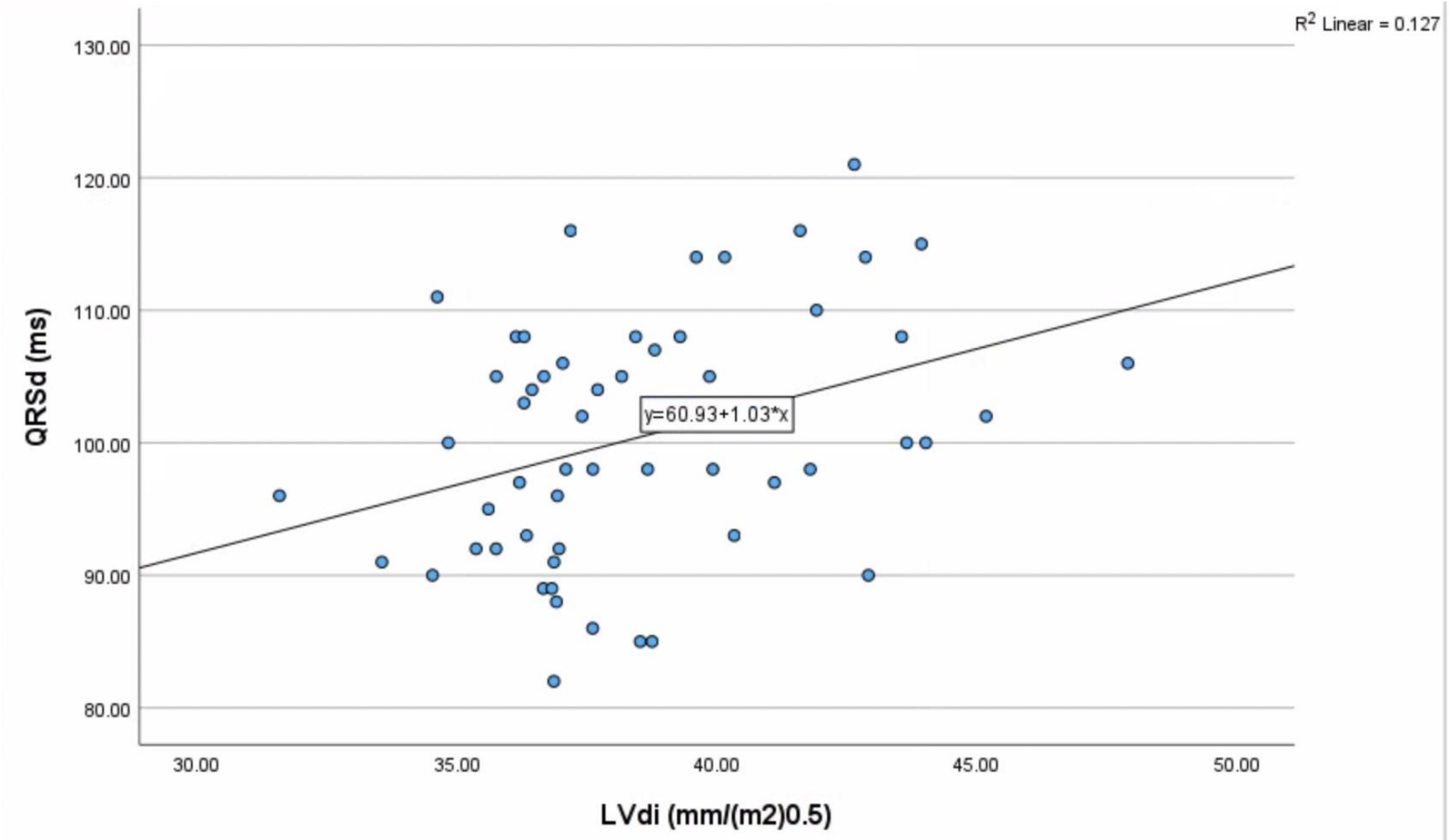

Figure 4.3 – *Scatter Plot demonstrating the correlation between QRS duration and LVDi, with individual data points plotted in blue and the fit line in black.*

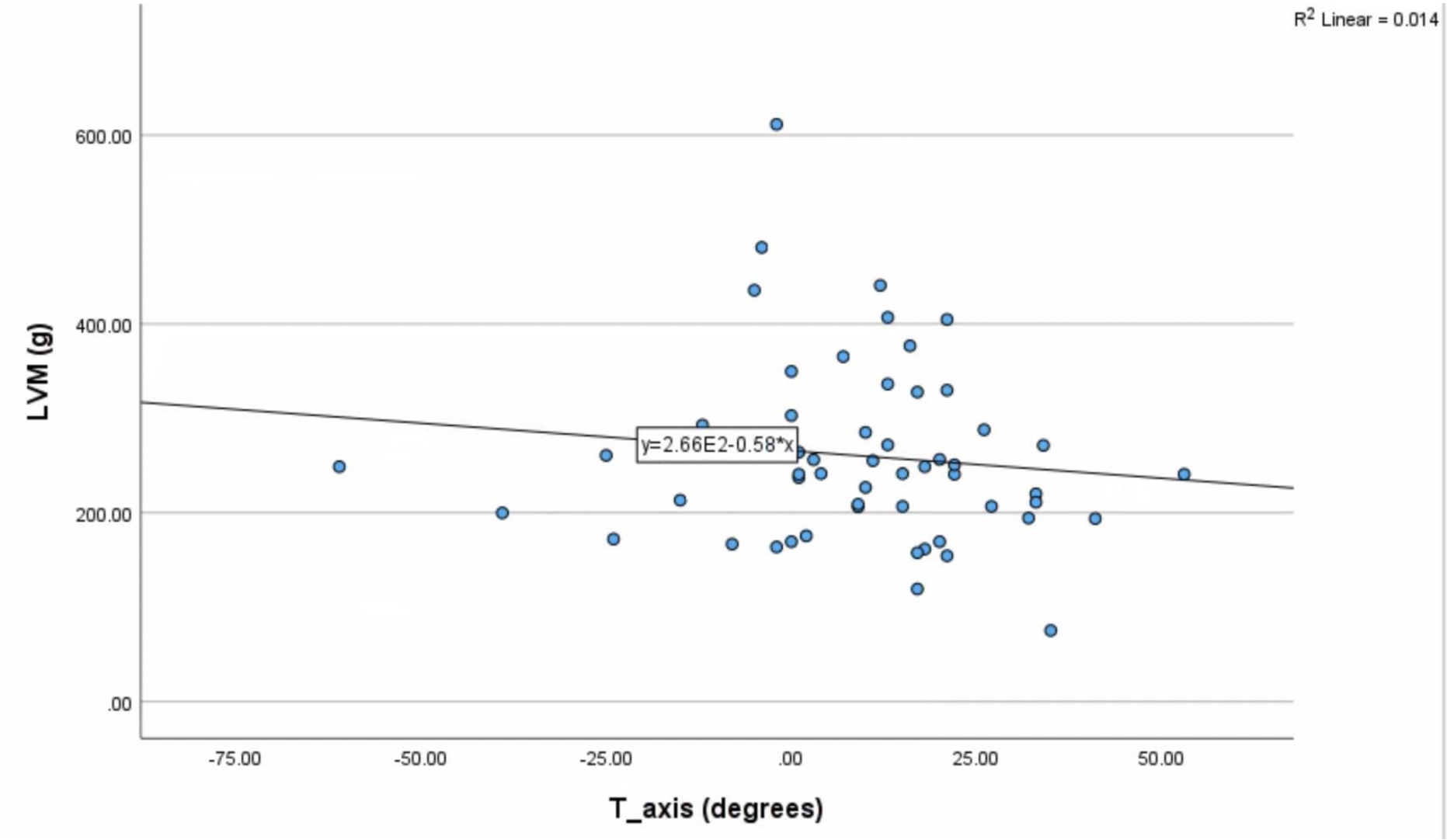

Figure 4.4 – *Scatter Plot demonstrating the correlation between LVM and T axis, with individual data points plotted in blue and the fit line in black.*

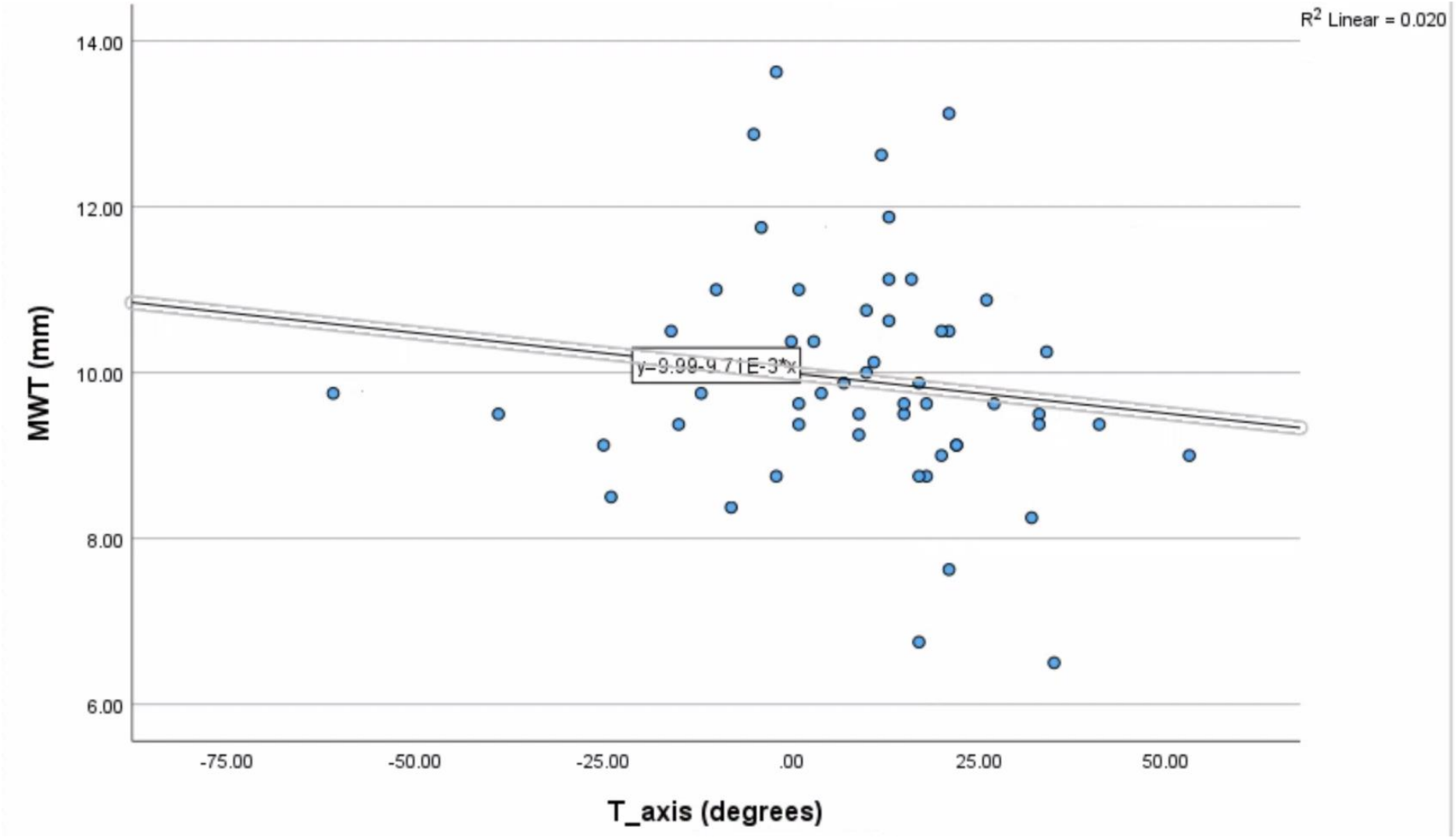

Figure 4.5 – *Scatter Plot demonstrating the correlation between MWT and T axis, with individual data points plotted in blue and the fit line in black .*

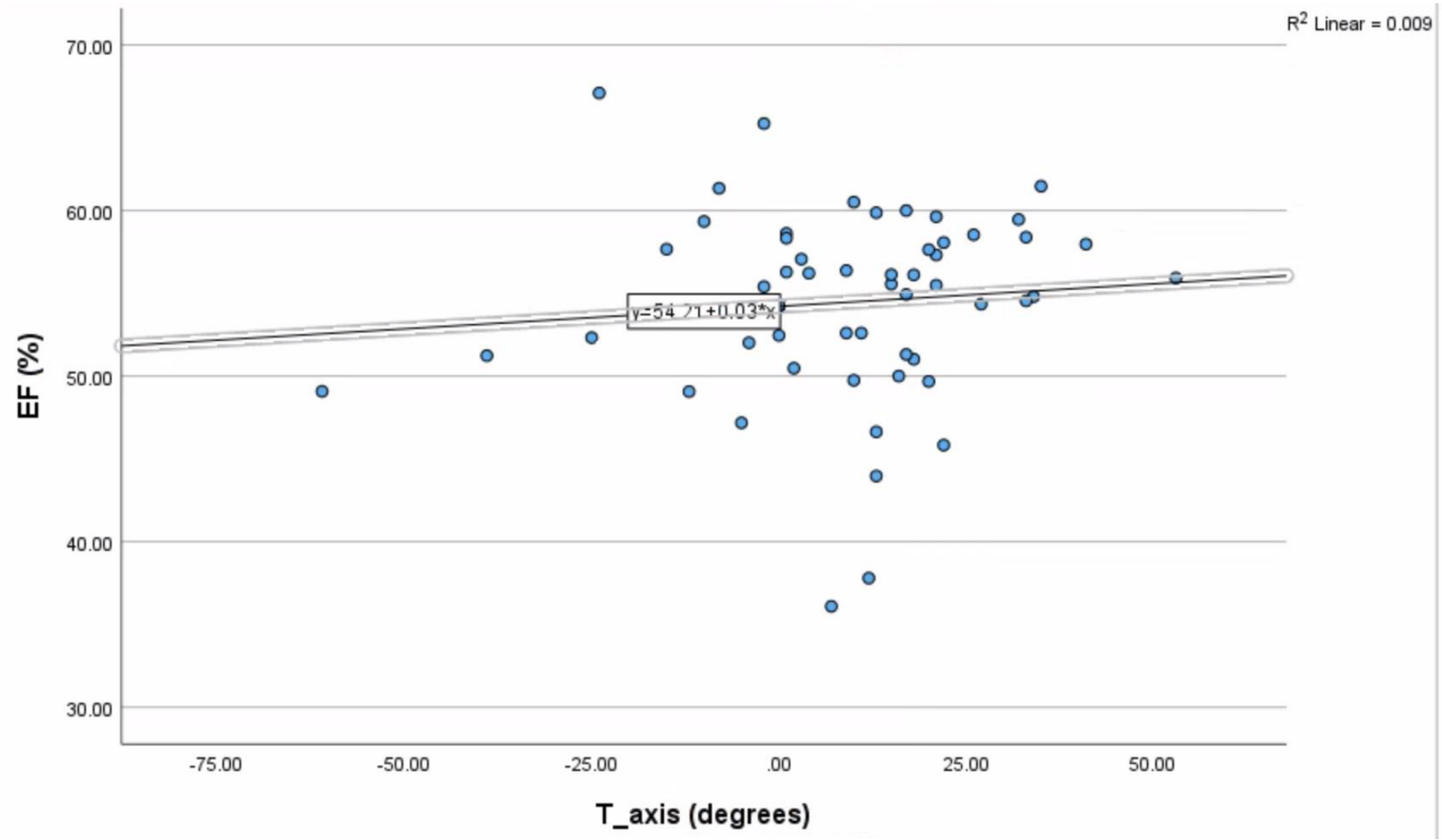

Figure 4.6 - *Scatter Plot demonstrating the correlation between EF and T axis, with individual data points plotted in blue and the regression line in black.*

4.4 Discussion

The main findings from the current study were: (1) RT athletes (non-users) had a greater percentage of 2 or more training related findings compared to the other groups, however, the findings were minimal and generally not significant, 2) current users presented with significantly higher QRS duration and voltage criteria for RV hypertrophy, along with a significantly reduced T wave axis when compared to non-users, 3) there were significant correlations found between T wave axis and LVM, MWT and EF (as observed in Chapter 2) and 4) findings outlined above in current users, were not significantly different between past and non-users, suggesting ECG changes may be reversed with abstinence.

Normal Electrocardiographic Adaptation

RT non-users presented with minimal training related findings on the ECG with the most common being sinus bradycardia and early repolarization, which were also common across past and current users. The third most prominent was an isolated criteria for LVH which was found in four of the non-users. The International Recommendation for ECG Interpretation in Athletes has stated that these findings are normal within highly trained athletes (Sharma et al., 2017). Due to an increased vagal tone, there is a reduction in heart rate (sinus bradycardia) and increased chamber size (LVH). Additionally, an early repolarisation pattern followed by concave ST segment elevation is seen in 25-40% of highly trained athletes and therefore does not warrant further investigation in asymptomatic athletes.

These, as well as abnormal ECG findings can be found across a wide range of athletes. Other work has identified abnormal changes such as T wave inversion, RBBB and RVH in endurance athletes (Malhotra et al., 2015). These findings are often benign and are a result of physiological adaptation to extreme levels of exertion, however, additional follow up would

be recommended. The same study also found that endurance athletes display a significantly higher presence of training-related findings than RT athletes. These most commonly being sinus bradycardia, sinus arrhythmia, early repolarization and criteria for LVH. These findings relate to our study where these factors were also the most common training related findings. However, according to the study above it seems the actual magnitude of electrical adaptation within endurance athletes is significantly greater than resistance athletes. Within their study, 24% of ET athletes experienced LVH compared to 3% of RT athletes (P = 0.004), similarly in sinus bradycardia (42% to 0% respectively, P = N/A) and early repolarization (64% to 21%, P<.001 respectively) (Malhotra et al., 2015). These cardiac characteristics in ET athletes, are due to the chronic volume and pressure overload that is associated with an increased cardiac output, due to prolonged sub-maximal intensity exercise (Santoro et al., 2014). Thus, causing chamber enlargement and wall thickening to cope with this increased overload during exercise (Maron and Pelliccia, 2006). Hence, sports with greater dynamic and lower static components (e.g. running, cycling, rowing etc.) display a greater magnitude of cardiac remodelling in comparison to RT athletes. Mainly, due to the greater static component of RT that does not induce a prolonged and consistent burden on the heart unlike the endurance exercises outlined above (Maron and Pelliccia, 2006).

Significance of T-Axis

Current users displayed a significantly lower T wave axis than that of both past and non-users with the mean value sitting within the 'borderline' range. This has been described previously as 15° to -15° (Salles et al., 2004). A previous study by (Kors et al., 1998) highlighted the link between T axis deviation and cardiac death in individuals aged over 55. This data suggests that the T axis may be an independent indicator of risk for cardiac events. This risk remained

after adjusting for age, sex and other ECG variables, with an abnormal T axis still being associated with a three-fold risk of cardiac death.

A further study demonstrates CHD risk in CHD-free men and women in association with T axis deviation (Rautaharju et al., 2001a). They discovered that T axis deviation was a subclinical sign of cardiac abnormalities and a marker for risk of future CHD events. CHD event rates were increased with each T axis group; where that the 'marked deviation' group showed the most significant number of CHD events as well as greater event rate, compared to normal and borderline T axis deviation groups. This was in agreement with the study by (Kors et al., 1998) where individuals with both abnormal and borderline T axis deviation, displayed significantly greater risk of CHD events and CHD death than those with normal T axis deviation.

These findings highlight a potential link between a reduced T wave axis (or T axis deviation) and negative cardiac health outcomes, in their respective populations. Within the current study we have identified this significant reduction in T wave axis in current users. With significant correlations between T wave axis and echocardiographic measurements observed in Chapter 2. Where T axis was lower, LVM and MWT were greater, and where EF was lower T Wave axis was also lower. Within Chapter 2, current users had significantly increased LVM and MWT irrespective of body size, suggesting there may be an alternative pathway to this adaptation, which we speculated to be the use of AAS. Other work has demonstrated that a reduced T-wave axis is associated with markers for sub-clinical cardiovascular disease in specific populations (Scherer et al., 2009). Further research is needed to determine whether current users exhibit an abnormal pathway of adaptation associated with cardiovascular disease, which may be detectable through deviations in T wave axis. Previous work has sought to elucidate the potential mechanisms behind T axis deviation. Some work has outlined that

primary repolarisation abnormalities may cause alterations in T wave axis. Secondary to this, action potential duration shortening or prolongation in ventricular regions could influence T wave axis also. T axis deviation therefore, could be a sensitive indicator in the disruption of ionic mechanisms, and the generation of electrical impulses as a result (Rautaharju et al., 2001b).

Many studies have highlighted the negative impact of AAS on lipid metabolism. It has been highlighted that AAS consumption can cause a reduction in HDL and an increase in LDL (Stergiopoulos et al., 2008). Indicating that the increase in cardiac risk could be as high as three-fold amongst individuals who use AAS (Stergiopoulos et al., 2008). High LDL and low HDL are universally accepted to be markers of atherosclerosis and cardiovascular disease, respectively (Li, M et al., 2018). Therefore, the adverse effect that AAS use has on lipid levels, may be a key mechanism in the underlying cause of myocardial infarction or stroke, that has been observed within these individuals (Li, M et al., 2018). With a previous case study presenting a 26 year-old male amateur athlete, who suffered from a posterior territory ischemic stroke (Santamarina et al., 2008). No abnormalities were discovered during angiography or echocardiography, or in haemostatic profile. The only risk factor highlighted was the use of AAS. These findings highlight the potential for sub-clinical disease from AAS use and a potential mechanism for differences in T-wave axis.

T wave inversion within athletes is uncommon. With a study demonstrating that from a population of over 40000 young (≤ 35 years) adult Caucasian athletes, less than 5% exhibited T wave inversion (Pelliccia et al., 2007). With the prevalence of T wave inversion in the inferior and lateral leads being even less common at 1.5 - 1.8% of adult and Caucasian athletes (Papadakis et al., 2009). Pathological T wave inversions have been associated with multiple

diseases that cause SCD in athletes, including HCM and DCM (Schnell et al., 2015). Interestingly, both of the individuals in the current study that experienced T wave inversions, also experienced voltage criteria for LVH. Which is a finding in 75% of patients with HCM, with repolarisation changes consisting of T wave inversions being present in over 90% of cases (Wilson et al., 2011) (Maron et al., 2005). Although this is the case, it was only observed in two athletes within the current study and therefore we can't suggest that this is fitting of a cardiomyopathic process as a whole within AAS users. These athletes were however referred onwards for a cardiac MRI with a consultant cardiologist, to further explicate these findings.

Ventricular Hypertrophy and QRS Duration

Current users displayed significantly increased criteria for RV enlargement compared to non-users, which was not significantly different from past users. Similarly in Chapter 2 of the current study, users displayed significantly greater RV diameters at the base and mid-level as well as increased longitudinal dimension. With both the diameter at the base and the longitudinal dimension exceeding that of recent 'normal' guidelines (Lang et al., 2015), suggesting RV dilatation and enlargement (Gripari et al., 2015). These differences however did subside after scaling.

Other athletic populations have been shown to have a significantly greater criterion for RVH than sedentary counterparts (Zaidi et al., 2013). Whilst demonstrating similar structural and functional parameters to that of athletes with normal ECG's. Further CMR imaging indicated no signs of RV pathology in any athlete. Again, suggesting this adaptation may not be pathological but is perhaps enhanced by the use of AAS. Interestingly, there was a significant lack of correlation between criteria for RV enlargement on the ECG and RV measurements

taken via echocardiogram in Chapter 2. Demonstrating that the electrical adaptation is not linked to structural adaptation.

The sensitivity of the echocardiogram to detect changes in RV structure and function has previously been questioned, due to the complex geometry of the RV (Tsipis and Petropoulou, 2022). In contrast to the LV there is no exact geometric model that exists for the RV. It is therefore difficult to make volumetric assumptions by 2D echocardiography. Hence, the size of the RV is underestimated in 2D echocardiography as opposed to cardiac MRI (Schneider and Binder, 2018). This especially applies to individuals with RV volume overload and congenital heart disease (Lai et al., 2008). This is potentially why we see a lack of correlation between the ECG and echocardiographic findings observed in Chapter 2.

Similarly, criteria for LVH within the current chapter did not have any correlation with measurements taken for LVM, MWT or LVd within Chapter 2. This could highlight the lack of sensitivity for the ECG to detect LVH within this current population of users. .

Past Users

There were no significantly different parameters between past and non-users, suggesting cessation of AAS use may result in a reverse of electrical adaptation back toward 'non-using' levels.

Interestingly, previous work has also highlighted this phenomenon. A study investigated a patient with heart failure and a history of significant AAS use in combination with RT. After cessation of AAS use, it was found that their LV wall thickness reduced quickly from 12 to 10.5mm (Nieminen et al., 1996). Other work has found that one AAS user showed constant ST segment depressions in leads II, III, aVF and V4-V6 at rest and during exercise. However,

after discontinuing AAS use these ECG changes were no longer present six months later (Urhausen, Albers and Kindermann, 2004). These are only individual cases, that could therefore not be applied to a whole population. However, this evidence suggests that there is some element of reversibility with cessation of AAS use and therefore, elucidating the need for further longitudinal work to further assess this phenomenon.

4.5 Limitations

There were some limitations to this study. First, the sample sizes of the groups were significantly uneven, making it difficult to effectively compare the magnitude of ECG findings between the groups. For example, 4 (20%) of non-users had isolated criteria for LVH, whilst this was prevalent in 15 (26%) of current users. It would be interesting to see, had there been an increased sample size of non-users (same as current users) would there be a parallel increase in prevalence in non-users. Or alternatively, the percentage of current users with isolated criteria for LVH would remain greater. Second, we had no sedentary control group within the current study. This would have allowed us to assess the impact of RT on cardiovascular adaptation in non-using athletes. Which would have shown us the true extent of adaptation in RT athletes to RT alone, and also how much this is extenuated in anabolic steroid users. Allowing us to greater highlight the sensitivity of the ECG to detect adaptations in comparison to echocardiography.

4.6 Conclusion

Non-using RT athletes displayed minimal training related criteria. This has been highlighted in previous work showing that ET athletes seem to have a greater magnitude of electrical

adaptation in comparison to RT athletes. Perhaps due to the greater magnitude and intensity of training that they undertake.

RT individuals who take AAS, seem to exhibit greater criteria for chamber enlargement shown through a significantly increased voltage criteria for RVH and QRS duration. They also display a significantly reduced T wave axis, in comparison to non-users. Although a reduced T wave axis has been associated with sub-clinical markers for disease in other populations. The meaning of this within the current population is unknown and we cannot assume there is a direct link to cardiovascular disease. Past users demonstrated a reversibility of adaptation with cessation of AAS use. This is evident where changes that were significantly different between current and non-users, were not between past and non-users. Indicating that with abstinence, structural and functional remodelling seems to revert back to 'non-using' levels.

In summary, this study highlights differences in ECG findings between current users, past users, and non-users, which corresponds with Chapter 2. However, the mechanisms behind these measurements needs to be further investigated to elucidate whether some findings may be of an abnormal nature.

Chapter 5 General Discussion

5.1 Summary of Key Findings

The chapters within this thesis sought to address these specific aims: 1) to assess the impact of structural and functional adaptation in non-using RT athletes, via both echocardiography and the 12-Lead ECG, 2) to determine the magnitude of structural and functional adaptation in RT athletes who were currently using AAS, via both echocardiography and the 12-Lead ECG, 3) to determine significant differences or trends between non, past and current users of AAS and 4) to identify whether past users have residual structural or functional adaptation as a result of previous AAS use. A summary of the key findings is outlined in Figure 4.1 below.

Both Chapter 2 & 3 outline minimal adaptation within non-using RT athletes. Specifically, Chapter 2 highlights a significantly lower magnitude of structural remodelling in comparison to AAS using counterparts. Subsequently finding that none of the non-using athletes exhibited concentric hypertrophy. Furthermore, non-users in Chapter 3 demonstrated minimal training related ECG findings. Firstly, these findings agree with a multitude of previous work that highlights a significant lack of structural adaptation within RT athletes even after a sustained period of training (Haykowsky et al., 2002; Spence et al., 2011). Secondly, these findings refute that of previous work by Morganroth, demonstrating that RT athletes exhibit minimal structural adaptation. The intermittent nature of RT does not seem to provide a significant and prolonged haemodynamic stimulus in order to induce adaptation that aligns with concentric remodelling (Maron and Pelliccia, 2006).

Both Chapter 2 & 3 presented findings detailing the significantly greater magnitude of adaptation within AAS using RT athletes in comparison to their past and particularly non-using counterparts. Specifically, Chapter 2 detailed the significantly larger cardiac structure of AAS users. This was illustrated through greater LVM and MWT, as well as absolute values of both LVEDV and LVIDd. The significant increases in LVM and MWT were sustained after indexing for body size, whereas differences in LVEDV and LVIDd were not. Suggesting an alternative pathway to an increase in LVM and MWT which we would assume to be influenced by the use of AAS. The increased size of LVEDV and LVIDd on the other hand could be due to the requirement for a larger SV, as a result of increased body size in AAS users. Absolute SV was in fact significantly greater in AAS users, which then normalised after indexing for BSA. Further affirming that this seems to be a primary adaptation to increased body size. Due to the significantly increased size of AAS users, there is subsequently a greater amount of metabolically active tissue. Therefore, there is a requirement for increased blood volume, to ensure adequate oxygen delivery to contracting skeletal muscle (Hargreaves and Spriet, 2020). Hence, the need for an increased SV and cavity size as a result.

Chapter 2 also highlighted functional impairment in AAS users, shown through significantly reduced measurements of EF and strain. Absolute SV was significantly greater in AAS users, which then normalised after scaling. With a lower EF, this creates a paradox where that we could assume this is a manifestation of larger cavities at rest. Although, the combination of both reduced function and significantly increased structure could represent underlying disease. Chronic AAS use can lead to myocardial hypertrophy through various pathways, with one being androgen receptors on cardiac myocytes (Liu, Death and Handelsman, 2003). Furthermore, literature describes complex mechanisms related to the disruptions in the Renin-Angiotensin-Aldosterone System (RAAS) (Fadah et al., 2023). The RAAS can cause LV

hypertrophy and cardiac fibrosis through various mechanisms, including increased blood pressure and direct action on androgen receptors. AAS use and the resultant cardiac hypertrophy has been shown to derange electrical conduction properties. Creating a prolonged action potential duration, which is a common finding in myocardial hypertrophy (Fadah et al., 2023). Resulting electrophysiological disruption results in weaker contractility and increased arrhythmogenicity (Hart, 1994). Hence, chronic AAS use is associated with hypertrophic and fibrotic cardiac tissue changes, resulting in impaired contraction and subsequent reduction in pump function (Fadah et al., 2023).

Current users experienced significantly lower measurements of GLS and GCS. Reduced strain values have been highlighted as a common finding in patients who also have cardiovascular disease (Gil et al., 2019). Strain abnormalities have been linked to pathological disease such as HCM in previous work (Correia et al., 2011). The results of this thesis show a combination of both significantly increased structure and markedly reduced function in current users, suggesting an abnormal pathway of adaptation. To say this represents that of pathological disease at this stage is purely speculative. However, AAS are a synthetic derivative of the hormone testosterone (Hartgens and Kuipers, 2004). Testosterone is the preferred ligand of the androgen receptor within the myocardium and therefore directly modulates transcription, translation and enzyme function (Sullivan et al., 1998). These alterations in cellular pathology are similar to that seen in individuals with heart failure and cardiomyopathy. With hypertension, ventricular remodelling, myocardial ischemia, and sudden cardiac death all being associated with anabolic steroid use in humans (Ferenchick and Adelman, 1992; Santora et al., 2006; Baggish et al., 2017). Highlighting the cardiotoxic effect of chronic AAS use, and the subsequent pathological findings.

Chapter 3 also identified significantly increased electrical criteria for chamber enlargement in current users compared to non-users. This was shown through an increased QRS duration and voltage criteria for RVH. This was found in combination with a significantly reduced T axis. Which in fact had significant correlations with LVM, MWT and EF observed in current users in Chapter 2. An abnormal T axis has been linked in multiple previous work to an increased risk of cardiac death and more specifically related to CHD (Kors et al., 1998; Rautaharju et al., 2001a). CHD event rates increased by T axis group, where that the most significantly reduced T axis had the greatest rate of event. Interestingly, current users have also been shown to have significantly greater CA plaque volume (Baggish et al., 2017). It is however difficult to say whether there is a direct link between a reduced T axis and increased CA plaque volume, as we did not provide any direct data of the coronary arteries.

Both Chapters 2 and 3, found structural parameters that were significantly different between current and non-users, were not between past and non-users. Suggesting that there is a reversibility of structural adaptation with cessation of AAS use. This is backed up by other previous work that has highlighted the rapid reduction of structural parameters with cessation of AAS use (Nieminen et al., 1996). However, functional parameters such as EF and peak strain still remained significantly different between past and non-users. Potentially suggesting that some parameters may be more irreversible, such as reduced ventricular function. Other work has also highlighted severely impaired function within long term AAS-users (Baggish et al., 2010a). Toxin-induced cardiac dysfunction has been well documented in relation to other drug use (Felker et al., 2000). With data from the current study and previous work suggesting AAS use may be another contributor towards toxin-mediated myocardial impairment (Baggish et al., 2010a). This could have a significant impact through aging, even in past using athletes, with apparent elements of irreversible adaptation. Normal

cardiovascular aging is said to have a significant impact on the heart's response to an increased workload. Shown through reduced contractility, prolonged systolic contraction, and prolonged diastolic relaxation (Strait and Lakatta, 2012). Making the aging population more susceptible to cardiovascular disease and heart failure (Strait and Lakatta, 2012). Highlighting that past AAS users may have an ever-increasing risk of adverse cardiovascular affects. Due to a potential irreversible impairment of cardiac function, prior to normal cardiovascular changes with age.

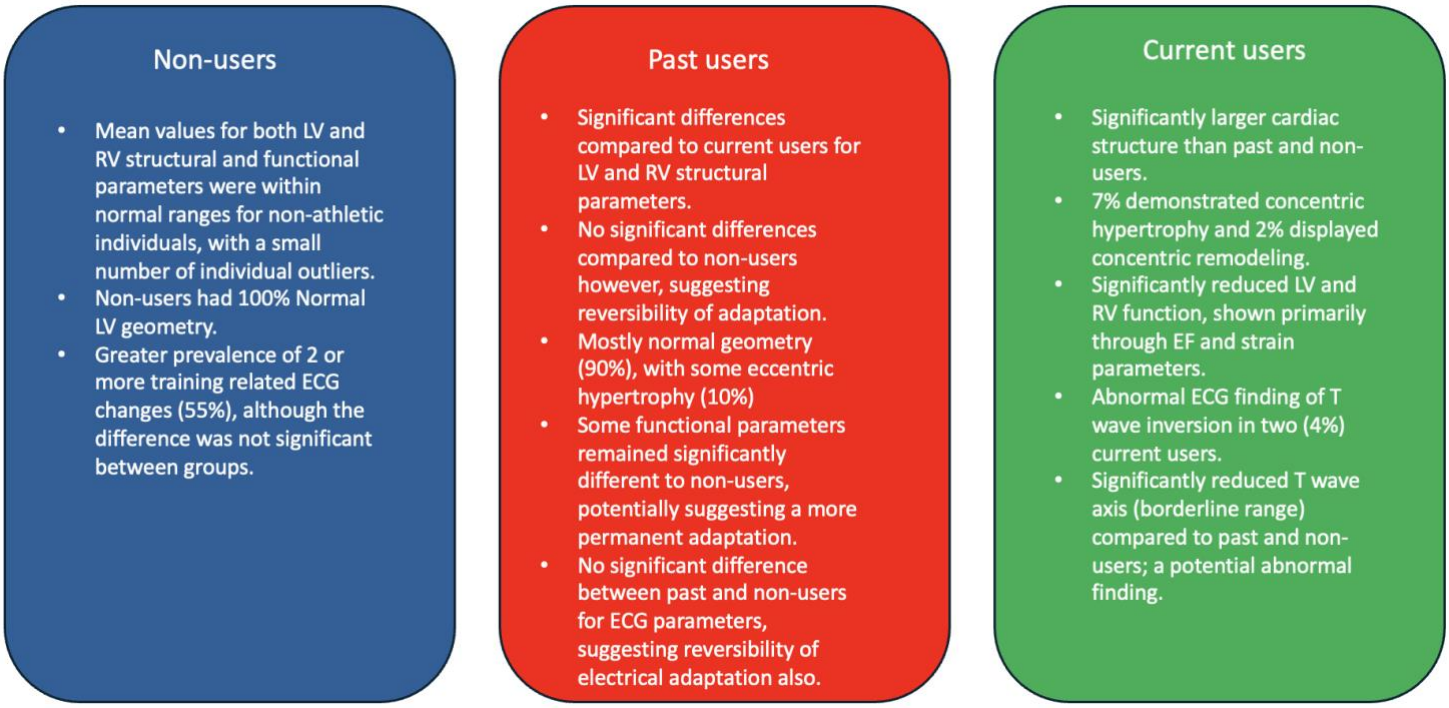

Figure 5.1 – *Summary of key findings across non, past and current users.*

5.2 General limitations

There were some general limitations in regard to both studies. First, participants were measured on a single occasion using a cross-sectional approach. The current study, therefore, does not highlight the implications that AAS use has on this population over a period of time. Exaggerating the need for further longitudinal work with these athletes.

Second, although there was demographic diversity within the current study, those of white Caucasian ethnicity (95%) were overrepresented, with the majority of participants being males (84%). Therefore, it is difficult to apply these findings to an entire population of these athletes. Thus, elucidating the need for the expansion of this study to recruit a wider and more diverse population in the future.

Third, AAS use, and training volumes were self-reported and are therefore potentially subject to bias. Participants were however fully aware of the aims of the study and as a result were open about their use of AAS. Although this was the case, the authenticity of self-reporting, specifically in the case of AAS use is still a recognised issue.

Fourth, we did not correlate AAS dosages or specific AAS substances to adaptations. Rather, we assessed individuals purely based off the combination of AAS taken and the impact that had on cardiac adaptations. It may be prudent for future work to assess the impact of specific AAS as well as dosages, on the adaptations observed within this study. Secondary to this, although there were no differences in training duration (years) or training hours (per week) there may have been differences in training intensity or type that have not been accounted for. This could have had an impact on cardiac demand between participants and hence differences in adaptation. Larger scale research that this work has informed, will look to use covariate adjustment to help identify important sub-group effects. This is not limited entirely

to AAS types/dosages and training but will also identify potential gender differences across the data, as well as other variables.

5.3 Future Implications

Although this thesis answers some questions, it also highlights many more that need to be addressed. Naturally, this lends itself towards the need for future work.

First, both studies were carried out in a cross-sectional manner, assessing athletes on one occasion. This firstly, gives us no insight into the progression of adaptations over time, as a result of AAS use. Firstly, for AAS users, and the potential worsening impact over a longer time period, that could create potentially irreversible effects. Secondly, for past users and the rate at which the apparent reversibility of adaptations occurs. It would be important therefore, for future work to assess the longitudinal impact of AAS use on RT athletes. As well as repeat examinations of past users in order to determine the timeline of reversibility that occurs.

Second, the concept of 'hibernating myocardium' may be a prevalent factor among this population. Although this is speculative, future research involving exercise could allow us to explore this further. As at rest, this adaptation provides a sufficient response to the lack of blood available for certain regions of the heart. However, it is unknown whether exercise would cause a too significant demand in this current population. It would be prudent therefore, to determine whether exercise has a further negative effect on function for current users. Or whether function remains the same, but their ability to exercise is significantly affected.

Third, although this study used 'AAS' as a blanket term to address their impact on the heart. There are differences in type, dosage and frequency of drug administered by individuals.

Whether this has a specific impact, we do not know at this stage. However, future work is required to understand the impact of specific types, dosages, and frequencies of AAS use on the heart. Previous work has assessed the impact of 'on and off' cycles in RT athletes (Baggish et al., 2017). Highlighting a greater negative functional impact in users who were on cycle. Suggesting impaired ventricular function may be directly related to AAS using patterns. Moreover, further work may be necessary to explicate this phenomenon.

Finally, current users exhibit findings that are also apparent in multiple cardiovascular diseases. Mainly, that of CHD and HCM. However, the ability for us to quantify what is 'normal' within this unique population through research alone remains a difficulty. From a clinical perspective, further follow up is required to determine the pathological nature (if any) of these adaptations.

5.4 Conclusions

This thesis provides many important insights into the effects of RT on athletes. As well as the effect of combining RT with AAS use. Firstly, non-users expressed minimal adaptation to RT in comparison to AAS using counterparts. Shown through significantly smaller echocardiographic structural parameters and minimal training related ECG criteria. Furthermore, AAS users demonstrate bi-ventricular adaptation, shown through significantly larger LV and RV structural measurements than that of their past and non-using counterparts. As well as greater criteria for chamber enlargement, shown through the ECG. Importantly, this was combined with significantly reduced function, particularly systolic. Shown predominately through reduced strain and EF. Additionally, a more novel parameter, T axis, was markedly reduced in the current user group. Past users on the other hand, seem to

experience a reversibility in adaptations with the cessation of AAS use, closer to 'non-using' levels.

Although findings in AAS users present signs of pathological adaptation, the mechanisms and relation to cardiovascular disease are not fully understood. With increased coverage of sudden cardiac deaths in professional bodybuilders over recent years, this provides significant clinical importance. Highlighting the need for further work to be undertaken with clinicians, in order to assess the potential pathological impact in this unique population.

Appendix

Appendix 1

PERFORMANCE AND IMAGE ENHANCING SUPPLEMENT AND DRUG USE QUESTIONNAIRE

Project title: **Anabolic steroid use and practices as image and performance enhancing drugs amongst resistance-trained individuals and their impact on cardiac health**

This questionnaire is to be completed anonymously – please do not include your name. Please take as much time as necessary and answer the questions as honestly and accurately as possible. Remember that you have the option of not answering any question that you do not wish to.

The questionnaire should be returned to the research team using the envelope provide.

Participant code: ……

1. Please state your age in years and months: ……

2. For how long would you consider yourself to be a gym user?

   Please include the date (as accurately as possible)

   ……

3. What is your primary reason/motivation for your gym use?

   ……

   ……

Supplement use

4. Do you use any sport supplements? *Please circle the appropriate answer.*

Yes No

If you answered yes please specify what supplement/s you use (i.e. protein, branch-chained amino acids, creatine, L-carnitine, omega-3 etc.)

……

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……

5. How would you describe yourself? *Please tick the appropriate box.*

Current user of anabolic steroids ☐

Past user of anabolic steroids ☐

Non-user of anabolic steroids ☐

6. If you consider yourself a past user, when did you stop taking anabolic steroids?

Please include the date (as accurately as possible)

……

……

7. If you have indicated from question 5 that you consider yourself to be either a current user or a past user of anabolic steroids, please indicate when you first started using them?

Please include the date (as accurately as possible)

……

……

8. If you have indicated from question 5 that you consider yourself to be either a current user or a past user of anabolic steroids and other image and performance enhancing drugs (IPEDs), please include in as much detail as possible, the type, the dose and the cycle that you have administered during the last 12 months.

*Please provide specific details (on the subsequent page) of the **anabolic steroids and other image and performance enhancing drugs (IPEDs)** used – stating the type, how it was administered (e.g. injection, oral or gel/cream), dose used and when in the last 12 months they were administered.*

Name of Anabolic Steroid or other IPED used:…….

……

How was the Anabolic Steroid or other IPED administered? …….

……

When did you administer the Anabolic Steroid or other IPED in the last 12 months?

……

What dose of Anabolic Steroid or other IPED did you administer?

……

When was the last dose of the Anabolic Steroid or other IPED administered?

……

Name of Anabolic Steroid or other IPED used:…….

……

How was the Anabolic Steroid or other IPED administered? …….

……

When did you administer the Anabolic Steroid or other IPED in the last 12 months?

……

What dose of Anabolic Steroid or other IPED did you administer?

……

When was the last dose of the Anabolic Steroid or other IPED administered?

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Name of Anabolic Steroid or other IPED used:……………………………………………………………………………………………………

………

How was the Anabolic Steroid or other IPED administered? …………………………………………………………………………

………

When did you administer the Anabolic Steroid or other IPED in the last 12 months?

……

What dose of Anabolic Steroid or other IPED did you administer?

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When was the last dose of the Anabolic Steroid or other IPED administered?

………

Name of Anabolic Steroid or other IPED used:……………………………………………………………………………………………………

………

How was the Anabolic Steroid or other IPED administered? …………………………………………………………………………

………

When did you administer the Anabolic Steroid or other IPED in the last 12 months?

……

What dose of Anabolic Steroid or other IPED did you administer?

……

When was the last dose of the Anabolic Steroid or other IPED administered?

………

Name of Anabolic Steroid or other IPED used:……………………………………………………………………………………………………

………

How was the Anabolic Steroid or other IPED administered? …………………………………………………………………………

………

When did you administer the Anabolic Steroid or other IPED in the last 12 months?

……

What dose of Anabolic Steroid or other IPED did you administer?

……

When was the last dose of the Anabolic Steroid or other IPED administered?

………

Name of Anabolic Steroid or other IPED used:…….

……

How was the Anabolic Steroid or other IPED administered? …….

……

When did you administer the Anabolic Steroid or other IPED in the last 12 months?

……

What dose of Anabolic Steroid or other IPED did you administer?

……

When was the last dose of the Anabolic Steroid or other IPED administered?

……

9. If applicable, please list any other dietary supplements (e.g. whey protein, BCAA (branch-chained amino acids), creatine monohydrate, multivitamins, omega-3, L-carnitine etc.) and/or drugs used for therapeutic purposes or otherwise that you have taken in the past 12 months, providing details of dose/amount and when administered if possible.

Please continue on another sheet if necessary.

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10. Considering your current use (past 12 months) is this different to how you have used them in the past? *Please tick the appropriate box.*

Increased use ☐

Decreased use ☐

Stayed the same ☐

Please provide specific details of how your use has changed below. (E.g. What did you previously take, how much did you take, when did you take it, when did you stop taking them, why did you change etc.)

Please continue on another sheet if necessary.

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11. What are your motivations for taking anabolic steroids or other IPEDs? (Improve lifting performance, occupational performance, increase body confidence etc.) Please specify any motivations you may have below.

- Improve lifting performance/strength ☐
- Improve strength/musculature for job/occupation ☐
- Improve musculature for participation in bodybuilding/fitness competitions ☐
- Increase body confidence ☐
- Hormone replacement therapy/medical reasons ☐
- Retaining youthfullness ☐
- Aid recovery from injury ☐
- Other (Please specify below) ☐

……

……

……

12. Where did you obtain the anabolic steroids or other IPEDs from? (Online, close friends, family member, personal contact etc.)

……

……

……

……

13. Have you ever experienced any of the following negative effects following anabolic steroid/IPED use?

	Past 12 Months		Ever	
Acne	Yes	No	Yes	No
Increased Irritability	Yes	No	Yes	No
Mood changes	Yes	No	Yes	No
Increased aggression	Yes	No	Yes	No
Increased feelings of anxiety	Yes	No	Yes	No
Difficulty sleeping	Yes	No	Yes	No
Testicular atrophy	Yes	No	Yes	No
Sexual dysfunction	Yes	No	Yes	No
Nausea	Yes	No	Yes	No

If you have experienced any other negative effects, please specify below:

……

……

……

……

……

……

14. Please indicate how much you agree, or otherwise with the following statement:

"I consider my drug use to be safe and risk free"

1- Strongly disagree 2- Disagree 3- Neither agree nor disagree 4- Agree 5- Strongly agree

15. Do you consult anyone for advice regarding use of anabolic steroids/IPEDs? i.e. type, dose, cycling etc.

Yes ☐ No ☐

If yes, who do you consult?

- GP/Doctor ☐

- Training partner ☐
- Partner/friend ☐
- Health care professional (other than GP e.g. nurse, physiotherapist ☐)
- Other (Please specify below ☐)

……
……
……
……

16. If you are concerned about your health in relation to your drug use who would/ do you consult?

- Training partner ☐
- Trainer/gym owner ☐
- Partner/friend ☐
- GP/Doctor ☐
- Other health care professional (e.g. nurse, physiotherapist) ☐
- Needle exchange/harm reduction programme ☐
- Other (Please specify below ☐)

……
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……

Training

17. On average, how many hours per week do you resistance train? ……..

18. On average, how many hours per week do you do aerobic-based activity (i.e. running, cycling, elliptical)? ……..

19. How long have you been strength training? …….years.

20. What is your current 1 repetition maximum (1RM) for the following exercises:

a. Barbell squat: ……. kg

b. Barbell bench press: …….. kg

c. Barbell deadlift: ……. kg

21. How many sets and reps do you do for each major muscle group during one training session?

Number of sets: ……

Number of reps: ……

Many thanks for completing this questionnaire

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