Right Ventricular Structure and Function in Elite Athletes in Relation to Pre-Participation Screening

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Abstract

Cardiovascular adaptations to long-term high intensity causes physiological remodelling of the Right ventricle (RV) due to frequent exposure to elevated exercise intensity. Evidence suggests dynamic exercise training serves as the primarily stimulator for the RV adaptation. This cardiac adaption might exceed the cut off limit meeting structural criteria for arrhythmogenic right ventricular cardiomyopathy (ARVC) disease. Athlete pre-participation screening is focused on detecting pathological conditions like ARVC. Current issues include: indices that differentiated ARVC patients and healthy people; the impact of different levels of dynamic training exposure on the RV structure, function in elite male athletes; insight into the RV structural and functional in those athletes meet the structural TFC (MTFC) for ARVC and those that do not (NMTFC) via utilising 12-leads Electrocardiography (ECG) and echocardiography.

Study one is a systematic review and meta-analysis technique that employed a case-control design sought to determine the extent of the RV structural and functional ranges in ARVC. In second study, athletes were grouped according to their sporting discipline using the Mitchell Classification as Low Dynamic (LD), Moderate Dynamic (MD) or High Dynamic (HD) and underwent through traditional and novel echocardiography techniques with a focused and comprehensive assessment of the RV. In study 3, athletes were grouped to MTFC for ARVC and those NMTFC. Study four, retrospective study looking at the 12-lead ECG for athletes in study MTFC compared to NMTFC.

The key finding form the first study was a significant differences in a range of structural and functional echocardiographic parameters between ARVC patients and healthy control participants. Patients with ARVC had larger RV outflow tract (RVOT) diameter

at short-axis view (mean ± SD; 34 vs. 28 mm P<0.001) and RV end-diastolic area (23 vs. 18 cm^2 P<0.001) compared to healthy controls. ARVC patients also had lower value on conventional and global RV strain (ε) parameters. HD and MD sport disciplines in second study had generally larger absolute and scaled RV structural indices than LD group. There were no between group differences in conventional RV functional indices as well as global RV ε (LD: -23.4 ± 3.1 vs MD: -22.7 ± 2.7 vs HD: -23.5 ± 2.6, %) and strain rate (P>0.01). The base to apex ε gradient in the RV septum was lower in the MD athletes compared to HD and LD due to a lower apical septal ε which significantly correlated with absolute RV chamber size. In third study, MTFC had larger absolute and scaled RVOT diameter compared to NMTFC (P <0.05) but these athletes did not develop a proportional increase in the RV inflow dimensions. MTFC also had lower global RV ε, peak systolic and late diastolic tissue velocity compared to NMTFC. Study four, MTFC had generally normal ECG finding compared to NMTFC. The finding have important implication for cardiovascular screening of athletes.

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Preface

A number of the chapters in this thesis have resulted in joint authored peer reviewed publication:

Chapter 4:

Qasem, M., Utomi, V., George, K., Somauroo, J., Zaidi, A., Forsythe, L., Bhattacharrya, S., Lloyd, G., Rana, B., Ring, L., Robinson, S., Senior, R., Sheikh N., Sitali, M., Sandoval, J., Steeds, R., Stout, M., Willis J. and Oxborough, D. (2016). A meta-analysis for the echocardiographic assessment of right ventricular structure and function in ARVC. *Echo research and practice*, *3*(3), 95-104.

Chapter 5:

Qasem, M., George, K., Somauroo, J., Forsythe, L., Brown, B. and Oxborough, D. (2018) Influence of Different Dynamic Sporting Disciplines on Right Ventricular Structure and Function in Elite Male Athletes. *The International Journal of Cardiovascular Imaging*, PP:1-8

Chapter 6:

Qasem, M., George, K., Somauroo, J., Forsythe, L., Brown, B. and Oxborough, D. (2018). Right ventricular function in elite male athletes meeting the structural echocardiographic task force criteria for arrhythmogenic right ventricular cardiomyopathy. *Journal of sports sciences* 1-7.

Glossary of Terms and Abbreviations

AH= Athlete's heart

ARVC**=** Arrhythmogenic right ventricular cardiomyopathy

ASE= American society of echocardiography

BSA= Body service area

cMRI= cardiac magnetic resonance imaging

ECG= Electrocardiography

HD= High dynamic

LA= left atria

LD= Low dynamic

LV= left ventricle

MD= Moderate dynamic

MTFC= Athletes did meet echocardiographic structural TFC

NMTFC= Athletes did not meet echocardiographic structural TFC

PPCS= Pre-participation cardiac screening

RA= Right atrium

RBBB= Right bundle branch block

RV= Right ventricle

RV A'= late diastolic motion on TDI

RVD1= Basal RV diameter

RVD2= Mid RV diameter

RVD3= RV Base-to-apex length

RVDA= RV end-diastolic area

RV E'= early diastolic motion on TDI

RV EF= RV ejection fraction

RVFAC= Fractional area change

RVH= Right ventricular hypertrophy

RVOT= RV outflow tract

RVOT1= RV outflow tract diameter at the subpulmonary region

RVOT2= RV outflow tract diameter at the pulmonic valve annulus

RVOT-PLAX= RV outflow tract diameter at the parasternal long-axis view

RV S'= Peak systolic motion on TDI

RVSA= RV end-systolic area

RV SV= RV stroke volume

SCD= Sudden cardiac death

STE= Speckle tracking echocardiography

SR= Strain rate

SRE'= Strain Rate during ventricular early diastole

SRA'= Strain Rate during late ventricular diastole

SRS'= Strain Rate during ventricular systole

TAPSE= Tricuspid annular plane systolic excursion

TDI= Tissue Doppler imaging

TFC= Task force criteria

TWI= T-wave inversion

ε = Strain

2D= Two-dimension

Chapter 1- General Introduction

1.1 Introduction

An elite athlete is an individual who is performing at the highest level of their sporting discipline (Drezner et al., 2017). Alongside numerous physiological changes, elite athletes present with cardiac adaptations in response to high volumes of training that are referred to as the 'Athlete's Heart' (AH). The AH describes electrical, structural and functional adaptation of all the cardiac chambers (Utomi et al., 2013; Brown et al., 2017).

In clinical and scientific work the right ventricle (RV) and its character or phenotype in the athlete is often overlooked (Ionescu, 2012) and the available descriptive information has lagged behind that of the left ventricle (LV) (Voelkel et al. 2006; Sadeghpour and Alizadehasl 2015). This is primarily due to the geometric complexity of the RV and the challenges associated with non-invasive imaging (Ho and Nihoyannopoulos, 2006). Recently, more attention has been devoted to RV assessment based on advancements in non-invasive cardiac diagnostic tools such as electrocardiography (ECG), echocardiography and magnetic resonance imaging (MRI). These tools have been applied to the study of the RV and may play an important role in the differentiation of the AH from pathological disease states that affect the right heart (Voelkel et al., 2006; Ionescu, 2012).

Recent data has suggested a disproportionate RV adaptation to exercise training when compared to changes in the LV, that is potentially related to a greater relative increase in RV afterload with exercise (La Gerche and Claessen, 2015a). Exercise causes end systolic LV wall stress to increase by 14% whilst in similar conditions the RV wall

stress can increase by up to 125% (La Gerche and Heidbu, 2011). This acute stimulus may serve to drive chronic adaptation and results in RV structural, functional and electrical changes that can be documented by both echocardiography and ECG (Oxborough et al., 2012b; Lord et al., 2014; Utomi et al., 2014; Drezner et al., 2017).

It has been suggested that RV adaptation is primarily influenced by high dynamic sporting activity and some studies have highlighted the magnitude and nature of this adaptation using conventional echocardiography (Utomi et al., 2013; McClean et al., 2014; Oxborough et al., 2016; D'Ascenzi et al., 2017b). These data suggest that there is enlargement of the RV cavity with a disproportionate increase at the inflow. On-going advances in echocardiographic techniques including the development of speckle tracking echocardiography (STE) have allowed the assessment of myocardial strain (ε) and strain rate (SR) yet there is a lack of data pertaining to this novel assessment of RV global and regional mechanics in these athletes. In addition, the extent of any electrical remodelling and its association to RV structure in elite athletes is not well understood.

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a "primary" disease of the heart muscle affecting predominantly the RV, and to some extend the LV. It is characterised by fibrofatty replacement of the myocardial tissue and predisposes an individual to the risk of sudden cardiac death (SCD) possibly through the promotion of fatal arrhythmias. In the United Kingdom, it has been estimated that 14% of SCD in young athletes is attributed to ARVC (Finocchiaro et al., 2016). It has also been proposed that the true prevalence of ARVC may be higher than originally thought due to the complexities in diagnosing the disease (Sorrell, Kumar and Kalra , 2009). More controversially, an ARVC phenotype without genetic cause has been described in a

small number of endurance athletes (i.e. high dynamic) raising the possibility that forms of ARVC may be acquired through long-term intensive endurance exercise (Harper and Mottram, 2009; La Gerche et al., 2010).

The diagnosis of ARVC is made utilising a multi-disciplinary approach as described by the revised Task Force Criteria (TFC) (Marcus et al. 2010). This approach is used in pre-participation cardiac screening (PPCS) programmes around the globe to identify those athletes that may have underlying disease and an elevated risk for SCD. Both the echocardiogram and 12-lead ECG are considered to be fundamental in the TFC and their application is important during PPCS (Marcus et al., 2010). The revised TFC was written to improve the diagnostic yield of PPCS test compared to the original TFC (McKenna et al., 1994). Despite an apparent increase in specificity there are still improvements to be made with regards to its sensitivity (Vitarelli et al., 2013). This may in-part be explained by the revised TFC using only RV outflow tract measures to reflect chamber size whilst functional criteria are based on a global measure; fractional area change (RVFAC) as well as a subjective assessment of wall motion. Based on this it is clear that more studies are needed to determine the ranges of RV structure and function for conventional and STE derived echocardiographic indices in patients with ARVC. In addition, it is important to investigate the effectiveness of utilising the revised TFC for athlete populations.

In addition, athletes with RV enlargement might exhibit an increased prevalence of T-wave inversion (TWI) on 12-lead ECG which present a challenge in the differential diagnosis from ARVC (Zaidi et al., 2013b; Drezner et al., 2017). More data is required to help aid the differential diagnosis of the AH and ARVC with particular attention to

the upper limits of RV structural and functional adaptation in athletes alongside the potential role of STE. The addition of STE would provide insight into the mechanical function of the RV specifically as myocardial dysfunction leads us to acknowledge that specific muscle layers degrade prior to other areas, which in turn may become compensatory which means that heart works well enough that person do not notice any problems or the symptoms (Iacoviello et al., 2011). This is clearly highlighted in studies detecting early onset of RV dysfunction in small populations of patients with ARVC with normal fractional area change (FAC) (Teske et al., 2009a; Teske et al., 2012; Iacoviello et al., 2011).

1.2 Aim of this Thesis

The overarching aim of this thesis is to characterise the RV phenotype in elite male athletes using standard conventional echocardiography, STE and 12-lead ECG whilst determining any phenotypical presentation in those athletes that meet structural and functional TFC criteria for ARVC.

This broad aim can be achieved through careful assessment of the following specific objectives:

1. To interrogate existing literature to establish ranges for conventional and STE derived echocardiographic indices in patients with ARVC.
2. To determine the impact of sporting discipline, and its dynamic component, on RV structure and function as determined by conventional echocardiography and STE in a large sample of elite male athletes.

3. To assess RV structure and function in elite male athletes who present with extreme phenotypical expression of the AH (i.e. meeting structural TFC for ARVC) with those athletes who do not present with TFC measures.
4. To assess resting 12-lead ECG data in elite male athletes who present with extreme phenotypical expression of the AH (i.e. meeting structural TFC for ARVC) compared to those that don't meet the TFC.

These aims can be stated as the following null hypothesis:

- $H0_1$: Conventional indices of RV function will NOT be different between patients with ARVC and healthy controls.
- $H0_2$: STE derived indices of RV function will NOT be different between patients with ARVC and healthy controls.
- $H0_3$: There will be no difference in conventional indices of RV structure and function across different dynamic sporting disciplines in elite male athletes.
- $H0_4$: There will be no difference in STE derived indices of RV structure and function across different dynamic sporting disciplines in elite male athletes.
- $H0_5$: There will be no difference in conventional indices of RV structure and function between elite male athletes that meet TFC for ARVC and those athletes that do not meeting the structural TFC for ARVC.
- $H0_6$: There will be no difference in STE derived indices of RV structure and function between elite male athletes that meet TFC for ARVC and those athletes that do not meeting the structural TFC for ARVC.

- $H0_7$: There will be no difference in resting 12-lead ECG criteria between elite male athletes that meet TFC for ARVC and those athletes that do not meeting the structural TFC for ARVC.

1.3 Structure of the Thesis

Following this general introduction, the thesis provides a substantive literature review describing; firstly information pertaining to the physiology and assessment of cardiac structure and function, with specific attention to the RV. Secondly, the literature review develops to provide a discussion on the prevalence of SCD in athletes and the importance of pre-participation screening of competitive athletes as a means of lowering the risk of SCD from diseases such as ARVC. Particular attention is given to the advancement of echocardiographic technology and its role in cardiac screening. The review raises questions related to RV adaptation in elite athletes and the paucity of research on: 1) influence of different training stimuli on RV structure and function, 2) the most common echocardiographic indices used in the assessment of ARVC and 3) the role of echocardiography and ECG on the differentiation of ARVC from AH. The fundamental role of the literature review is to provide a sound scientific rationale for the subsequent empirical studies contained within this thesis.

Chapter three provides a clear description of the general methods that were adopted in the empirical studies in this thesis. This includes the echocardiographic and electrocardiographic procedures and measurements as well as collection of data pertaining to anthropometric assessment. Ethical and informed consent procedures are also documented.

Chapter 4 is the first empirical study and employs a systematic review and meta-analysis design to establish the extent and magnitude of conventional echocardiographic and STE measures of RV function in patients with ARVC. This provides the foundations for which the subsequent studies into the AH can be compared.

Chapter 5 introduces the AH and determines the nature of the RV phenotype in a large sample of elite male athletes. The study utilises a cross-sectional design attempting to elucidate any differences across athletes of varying sporting disciplines based on the specific dynamic component of their training and competition.

Chapters 6 and 7 provide additional insight into the AH by assessing RV structure and function in elite athletes with extreme phenotypical presentation of RV dimensions (i.e those that meet the structural TFC for ARVC) in comparison to those athletes that do not meet structural TFC for ARVC. Chapter 6 focuses on echocardiographic assessment whilst chapter 7 raises the question as to whether the 12-lead ECG may be mediated by individual variance in RV presentation.

Chapter 8 presents an overarching general discussion of the issues raised across all of the studies. The discussion relates to pathological and physiological RV adaptation, the role of echocardiography (including STE) and the 12-lead ECG in the athlete PPCS setting. Furthermore limitations are discussed and directions for future research are introduced. An overall conclusion reflects on the aims and objectives for the thesis set out in this section.

Chapter 2- Literature Review

2.1 Human Heart

The human cardiovascular system is a closed-loop system in which the heart is the pump that inputs kinetic energy into the blood stream to ensure circulation to all parts of the body. What gets pumped out of the heart returns in the closed-loop system. The heart is a muscular organ that consists of two “priming” atria, which sit above the dual pumps of the ventricles. The LV supplies blood to the systemic circulation and the RV supplies blood into the pulmonary circulation. Because of the proximity of the LV and RV as well as the nature of the closed-loop system, any modifications in RV structure and function may have a serial and/or parallel impact on delivery of blood to the left atria (LA) and thus LV. In addition, any degradation in RV structure or function could affect venous return with a subsequent impact on RV filling. The studies contained within in this thesis focus on RV structure and function in athletes and those with cardiac disease. It is, therefore, pertinent to explore the anatomy of the RV as well as the mechanical processes that underpin RV function.

2.1.1 Right Ventricular Structure and Function

As the heart is rotated in the thoracic cavity, the RV lies just behind the sternum. The inlet to the RV is the tricuspid valve and the outlet is at the pulmonary valve (Figure 2.1).

Figure 2. 1: The three major chamber components: inflow tract (inlet/sinus), infundibulum (conus/outflow tract) and apex – TV is the tricuspid valve; PV is the pulmonary valve (adapted from Haddad et al., 2008)

The RV is composed of three areas: 1) the inlet (sinus) portion, which starts from the inlet point connecting between the chordae tendinae, the papillary muscles and the tricuspid valve, 2) the muscular trabeculations within the apex, and 3) the outlet (conus) portion of the infundibulum, which lies just below the pulmonary valve (Figure 2.1).

The myocardial wall of the RV is characterized by being thinner and more compliant than the LV and this is largely due to the fact that the RV works against a lower afterload and thus is a "lower pressure system" (Sadeghpour and Alizadehasl, 2015). The chamber appears as a crescent when viewed in cross-section at the basal level (Figure 2.2). In normal conditions, the RV is concave toward the LV enclosing and wrapping around the bigger ventricle (Haddad et al., 2008; Aneq, 2011; Sadeghpour and Alizadehasl, 2015).

Figure 2. 2: Cross-sectional view of the heart at mid-wall level - demonstrating the crescent shape of the right ventricle and conical form of the left ventricle. The obliquity of the septal muscle structure and its spiral arrangement is clear. Note the thickened septum and the wrap around basal loop (adapted from Buckberg and Hoffman, 2014)

There is also a muscular band termed the crista supraventricularis that separates the inflow section and the outlet portion and is continuous with the RV free wall. Furthermore, there is ventriculo-infundibular fold (a non-fibrotic continuity) between wall; the tricuspid and pulmonary valves. The RV wall is also often divided into 6 sections: 1) anterior, 2) lateral and 3) inferior wall, as well as 4) basal, 5) mid and 6) apical sections (Figure 2.3). (Haddad et al., 2008; Aneq, 2011; Sadeghpour and Alizadehasl, 2015).

Figure 2. 3: Echocardiography view. The lateral (red, blue and purple) and septal (yellow, ligh blue and green) wall of the RV is divided into 3 segments each: base (yellow and red), mid (blue and light blue) and apex (green and purple) (adapted from Aneq, 2011)

The arrangement and the architecture of the myofibres of both the RV and LV form a three dimensional network that gives each ventricle its own unique structure (Ho and Nihoyannopoulos, 2006). This myofibre arrangement serves to connect both ventricles as a helix with two loops. The apical loop provides a structure of the septum and the LV wall with ascending and descending oblique fibres and the basal loop structure supports the RV free wall and septum with transverse fibres (Figure 2.4).

Figure 2. 4: Fiber orientation relationship of the septum composed of oblique fibers that arise from the descending and ascending segments of the apical loop surrounded by the transverse muscle orientation of the basal loop that comprises the free right ventricular wall. Note the conical arrangement of the septum muscle and the basal loop wrap, forming the right ventricular cavity (adapted from Buckberg and Hoffman, 2014)

The myofibre arrangement in the RV septum is composed of both superficial and deep muscle layers. The superficial muscle fibres have a circumferential arrangement in a parallel direction to the inflow region (i.e. atrioventricular groove) and these then turn obliquely toward the cardiac apex continuing into the superficial myofibres of the LV (Figure 2.5). The deep muscle fibres are aligned longitudinally from base to apex and thus longitudinal shortening plays a predominant role in contributing to RV stroke volume (RV SV) (Haddad et al., 2008; Aneq, 2011; Brown et al., 2011; Sadeghpour and Alizadehasl, 2015). The RV free wall is thin and composed mainly of transverse myofibres with some longitudinal muscle fibres in the subendocardial layer (Figure 2.6) (Buckberg and Hoffman, 2014)**.**

Figure 2. 5: View of the intact heart demonstrating the transverse appearance of the right ventricular free wall and oblique fiber arrangement of the underlying anterior segment of the apical loop that covers the right ventricular septum and lower left ventricular free wall (adapted from Buckberg and Hoffman, 2014)

Figure 2. 6: Longitudinal view of the heart showing the thin RV free wall and the trabecular RV surface muscle , and thickness of the biventricular septum (adapted from Buckberg and Hoffman, 2014)

The RV and LV are connected by: 1) the septum, which presents as a shared wall for both ventricles, 2) reciprocal encircling epicardial fibres, 3) a shared pericardial space

and 4) attachment of the RV free wall to the anterior and posterior septum. This connection between both ventricles presents the anatomic basis of the free RV wall traction caused by the LV contraction. This also contributes to ventricular interdependence along with the interventicular septum and the pericardium.

The complex gross and myofibre structure of the RV leads to equally complex mechanical function with overall RV SV being dependent on specific muscle layers as well as LV contractility. Previous work has suggested four mechanisms that underpin RV systolic function. Initially, 1) there is the production of a bellow effect due to basal loop constriction with 2) concomitant movement of the tricuspid annulus toward the RV apex by longitudinal helical shortening. In late systole there is 3) infundibular contraction caused by apical loop contraction whilst throughout cardiac cycle the 4) LV assists RV contraction via contract of the interventricular septum.

What is important to remember is that in a closed loop system RV output and LV output must be equivalent. The fact that the heart achieves this, over a range of levels of metabolic activity, given the different size, shape and mechanics of the two ventricles is something of a scientific “marvel”. It is also important that both RV and LV can be effectively measured and assessed. The odd shape of the RV makes this quite a complex and demanding task that will be developed in the next section of the review. Allied to different shapes is the unique way in which each ventricle produces flow. This also must be measured as accurately as possible with knowledge it cannot simply imply LV functionality (globally or regionally) on the RV. Finally, it has noted that RV function is also dependent upon the specific electrical conduction system specific to its anatomical regions. This chapter will discuss the basic 12-lead ECG assessment of cardiac

electrical depolarisation in the next section as well. This underpins RV function but has a key role in athlete screening for the detection of disease.

2.2 Non-Invasive Assessment of Right Ventricular Structure and Function

2.2.1 Transthoracic Echocardiography

Echocardiography is as a non-invasive technique using ultrasound to image the heart in order to assess its structure and function. The technique provides information on chamber geometry, valve structure and function as well as myocardial function. Since its introduction and the first published study (Edler and Hertz, 1954), the advancement in technology has resulted in echocardiography being extensively used in the management and evaluation of the patient suffering from cardiac disease (Douglas et al., 2011). The development and evolution in echocardiography technology passed through various stages from two-dimensional (2D) echocardiographic images, M-mode, Doppler, tissue Doppler imaging (TDI) and STE (Edler and Hertz, 1954; Baker, 1970; Bom et al., 1973; Griffith and Henry, 1974; Isaaz et al., 1989; Bleeker et al., 2006). Collectively these modalities provide an all-inclusive quantitative evaluation of the heart. In addition, echocardiography also provides the capacity to comprehensively assess RV structure and function (Rudski et al., 2010).

2.2.1.1 Standard echocardiography techniques – 2D and M-mode

Since both 2D and M-mode echocardiography techniques have been introduced, it has been possible to develop a systematic approach to the assessment of the RV. RV structure and function is extremely complex with separate infundibulum and marked trabeculation making its assessment through echocardiography challenging (Levine et

al., 1984; Ho and Nihoyannopoulos, 2006). In this regard, it has been suggested that RV structure should be assessed at both inflow and outflow by providing specific dimensions from various acoustic windows (Foale et al., 1986). The work by Foale et al. (1986) provided RV data pertaining to a healthy population (Foale et al., 1986) and was used ubiquitously until a validation study was undertaken in 2008 using cardiac magnetic resonance imaging (cMRI) (Lai et al., 2008). Lai et al., (2008) demonstrated a very weak association between their dataset (i.e., cMRI) and the Foale's normal range and hence in 2010 the American Society of Echocardiography (ASE) presented a meta-analysis to provide RV echocardiographic normal ranges (Rudski et al., 2010). This data has been adopted by professional guidelines and provides a range of clinically useful indices of RV structure and function in a normal healthy population. While, few researchers highlighted the impact of physiological adaptation of the RV (Teske et al., 2009b; D'Andrea et al., 2011), there is no data identifying the impact of body size (Rudski et al., 2010).

A significant challenge has been the application of these techniques to the assessment of RV function (Jurcut et al., 2010). Numerous studies have attempted to obtain RV volumes and subsequent RV ejection fraction (RV EF) mathematically, but the introduction of cMRI provided more accurate gold standard techniques, thus it became clear that 2D echocardiography had significant limitations (Helbing et al., 1995; Sheehan and Redington, 2008). In view of this, fractional area change (FAC) was introduced as a surrogate of RV EF. RVFAC is a measurement of the percentage change in RV area between end diastole and end systole from a single plane acquisition (Foale et al., 1986). Therefore, the RVFAC provides an index of RV function and appears to correlate well with RV EF as determined by cMRI (Anavekar et al., 2007);

consequently the ASE recommended RVFAC as part of the assessment process (Rudski et al., 2010). Although RVFAC appears to correlate well with RVEF, RV function is primarily driven by longitudinal shortening. Based on this, M-mode echocardiography has been applied to assess the excursion of the tricuspid annulus (TAPSE). This different approach from the apical four chamber view has been shown to have an excellent correlation with RVEF when assessed by radionuclide angiography (Bleeker et al., 2006). That aside, these techniques are often limited by image quality and do not fully represent myocardial shortening and/or function. In order to overcome some of these limitations, newer techniques have been developed.

2.2.1.2 Tissue Doppler Imaging (TDI)

In 1989, utilization of the Doppler technique was used to assess myocardial tissue directly (Isaaz et al., 1989). Based on the examination of the high amplitude and low velocity signals, TDI works by expressing ultrasound signals from the myocardial Doppler signals. A pulsed-wave technique is applied to the annulus of the tricuspid valve and provides temporal data of the longitudinal movement of the myocardium and thus it can be recorded in both systole and diastole (Nagueh et al., 1997; D'Andrea et al., 2010). Pulsed-wave TDI provides measures of Systolic (S'), early diastolic (E') and late diastolic (A') myocardial velocities from the RV lateral wall (Pelliccia et al., 2017). TDI has been recognised as useful tool with good reproducibility and validity (Bleeker et al., 2006; Abraham, Dimaano and Liang, 2007; Sorrell, Kumar and Kalra , 2009; Lord et al., 2014). Research affirmed the practicality of TDI by exhibiting the potential for evaluation regional myocardial function (Abraham, Dimaano and Liang, 2007; Sorrell, Kumar and Kalra , 2009) and its usefulness in athlete's cardiac screening (Rudski et al., 2010; Lang et al., 2015; D'Ascenzi et al., 2017; Pelliccia et al., 2017)

2.2.1.3 Speckle Tracking Echocardiography (STE)

STE was introduced in 1991 (O'Donnell et al., 1994). It is based on the tracking of characteristic speckle patterns generated by destructive and constructive interference of ultrasound waves reflected from tissue structures (Amundsen et al., 2006; Geyer et al., 2010; Mor-Avi et al., 2011). This technique involves using a speckle tracking algorithm usually radio frequency based in order to record the uniform motion of a speckle producing objects (kernel) (Rappaport et al., 2006). STE is an offline and partly angle independent technique that can assess radial, circumferential and longitudinal deformation of the myocardium as well as providing a measure of lagrangian ε that can be applied to previously acquired 2D images files (Andersen et al., 2004; Geyer et al., 2010). Therefore, this technique provide a valuable information on measuring of tissue deformation and its change in length normalized to the original length (i.e. strain) and its rate of strain (SR) (see Figure 2.4). This technique has recently been applied to the RV and can assess longitudinal function only (Mor-Avi et al., 2011; Sengupta and Narula, 2013; La Gerche and Roberts, 2015b). Previous studies reported measurement of RV global and regional ε and SR data are feasible, comparable and reliable at rest (Bleeker et al., 2006; Kothari and Ramakrishnan, 2011; Oxborough et al., 2012a; Lord et al., 2014). Numerous clinical applications has been implemented in clinic providing a prognostic valuable information for various disease such as ARVC (Lang et al., 2015) and in sport cardiac screening studies (Oxborough et al., 2012b; Oxborough et al., 2016; D'Ascenzi et al., 2017b).

2.2.2 Electrocardiography

The electrical activity is the primary stimulus for mechanical function. It promotes cardiac muscle contraction which changes chamber and vessel pressure and thus generates the force for blood to flow down a pressure gradient. Consequently, blood flows and volume changes will occur.

The electrical signals in the heart are transmitted by a highly specialised anatomical structure: 1) the Sinoatrial (SA) node, 2) Atrio-Ventricular (AV) node, 3) AV bundle (i.e. Bundle of His), 4) right and left bundle branches and purkinjie fibres. This electrical signals are causing atrial and ventricular depolarization and repolarization which are represented on the ECG as a series of waves: the P wave followed by the QRS complex and the T wave (Fang, 2012; Hampton, 2013) (see Figure 2.7).

Figure 2. 7: ECG Structure (Pappano and Wier, 2012)

The 12-lead ECG is able to detect activity from the right side of the heart by providing information from the early precordial leads (V1-V3) which lie close to the right side of the heart expressing mainly the electrical conductivity of the RA and the RV. In addition, RA enlargement, RV hypertrophy, right sided axis deviation and RV repolarisation abnormalities can be detected.

Based on these non-invasive developments it is clear that both echocardiography and the 12-lead ECG can provide insight into RV structure, function and electrical integrity. It is apparent that the application of both these techniques is important when considering the diagnosis of disease or when trying to differentiate physiological from pathological adaptation.

2.3 Sudden Cardiac Death (SCD) in athletes:

SCD in athletes is defined as unexpected death occurring during or after exercise with the true incidence remaining uncertain. In Italy, they suggested that SCD is three-times higher in athletes compared to non-athletes (Corrado et al., 2003), whilst SCD rates in females are recognised to be 2-25 times lower than in men. In addition, the incidence of SCD increases with age, being higher in athletes over 35 years old compared to younger athletes. Although certain demographics may predispose and athlete to SCD there is not a clear correlation between type of sports (Mont et al., 2016). In the UK, the causes of SCD in the athletic population have been summarised in figure 2.8 highlighting relevant conditions from the UK registry of young athletes (Finocchiaro et al., 2016). In view of this, PPCS is mandatory in many sporting disciplines to identify those athletes at risk of SCD.

The prevalence of cardiovascular disorders is estimated at 0.3% of the athletic population and ARVC is responsible for approximately 4,3% of the cases (Maron, 2007; Harmon et al., 2015). In addition, It has been estimated that ARVC is the cause of SCD in 4-23% of cases in the athletic population (Chandra et al., 2013; Mont et al., 2016) (see Figure 2.8) and is the most frequent pathology in Italian studies (Corrado et al., 2005). It was demonstrated to be present in 10% of all sudden cardiac arrest victims in France (Nava et al., 1988; Sorrell, Kumar and Kalra , 2009) and most common below the age of 40 years (Ferreira et al., 2003; Wang et al., 2010). Accuracy of prevalence data is debated due to the complexities in diagnosing the disease and the unexplained genotype-phenotype expression.

Figure 2. 8: Causes of sudden cardiac death in athletic population**:** sudden arrhythmic death syndrome (SADS), Hypertrophic cardiomyopathy (HCM), Left ventricular

hypertrophy (LVH), Arrhythmogenic right ventricular cardiomyopathy (ARVC) and Dilated cardiomyopathy (DCM) (adapted from Oxborough et al., 2018)

2.4 Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

ARVC is a genetic disease of that affects desmosomal dysfunction within the cardiomyocyte (Basso et al., 1996) Desmosomes are protein structures in the cell membrane premitting cell-to-cell adhesion. They occur in almost all solid tissue, but disease related to mutation in these proteins are manifested only in the heart muscle cells causing the protein and gap junction to develop a gradual disruption of the myocardial cells and to degenerate due to excess mechanical stress/forces which alter the biomechanical and biochemical behaviour of cells. As a result of these changes in the myocytes the normal myocardium is replaced by fibro fatty scar tissue (Basso et al., 1996). ARVC will cause global cellular disruption and atrophy of the myocardium and can lead to aneurysmal dilation and wall motion abnormalities with end-stage ARVC resulting in heart failure and subsequently death (Sen-Chowdhry et al., 2008; Marcus et al., 2009). ARVC is a predominantly RV disease, but occasionally it may involve LV myocytes (Sen-Chowdhry et al., 2008; Basso et al., 2009).

The natural history of ARVC is variable with various clinical presentations. Four clinical phases have been proposed: 1) concealed form of structural abnormalities and unnoticeable symptoms reported. In this phase, SCD might be the first manifestation (Corrado et al., 1997; Tabib et al., 2003; Merner et al., 2008; Sarvari et al., 2011; Romero et al., 2013; Gaido et al., 2017) and usually the diagnosis at this stage is based on family screening through genetic testing (Romero et al., 2013), 2) overt electrical anomalies usually occurs in young patients and are associated with ventricular

arrhythmia and SCD, 3) RV failure caused by progressive loss of myocardium with severe dilation and systolic dysfunction with pump failure (Sarvari et al., 2011; Romero et al., 2013; Gaido et al., 2017) and 4) biventricular failure described as the late and progressive phase of the ARVC disease. Importantly, it has been suggested that the existence of life-threatening arrhythmia or electrical changes can precede structural changes (Marcus et al., 2010; Sarvari et al., 2011) or any clinical evidence of myocyte loss and RV dysfunction (Gaido et al., 2017). There are however some other studies that have reported normal electrical activity in these patients (Bauce et al., 2010; Marcus et al., 2010; Zaidi et al., 2013b), exacerbating the diagnostic challenge in this condition.

Currently, the diagnosis of ARVC is established in accordance with the revised TFC (Marcus et al., 2010). It involves a multivariant model and tools from ECG, echocardiography, cMRI, tissue characterisation and family history. These categories contain major and minor criteria and include global and/or regional dysfunction and structural alterations, tissue characterisation of the wall, repolarisation abnormalities, depolarisation/conduction abnormalities, arrhythmias and an adverse family history. Based on TFC, it is required that 2 major criteria or 1 major criteria and 2 minor criteria or 4 minor criteria from different categories in order to give a definitive ARVC diagnosis (see Table 2.1). Consequently, various types of evaluation should be conducted for diagnosing ARVC, especially when a patient has a suspicious physical examination and family history.

Table 2.1 : Modified Task Force Criteria 2010 (adapted from Marcus et al., 2010)

	1. Global or regional dysfunction and structural alterations	
	Major	**Minor**
Original TFC	❖ Severe dilatation and reduction of RV ejection fraction with no (or only mild) LV impairment ❖ Localized RV aneurysms (akinetic or dyskinetic areas with diastolic bulging) ❖ Severe segmental dilatation of the RV	❖ Mild global RV dilatation and/or ejection fraction with normal LV ❖ Mild segmental dilatation of the RV ❖ Regional RV hypokinesia
Reviseted TFC	**By 2D Echo:** Regional RV akinesia, dyskinesia or aneurysm and 1 of the following (end diastole): ❖ PLAX RVOT ≥32mm ❖ PSAX RVOT ≥36mm ❖ Or fractional area change ≤33% **By MRI:** Regional RV akinesia, dyskinesia or aneurysm or dyssynchronous RV contraction and one of the following: ❖ Ratio of RV end-diastolic volume to BSA ≥110 mL/m2 (male) or ≥100 mL/m2 (female) ❖ Or RV ejection fraction ≤40% **By RV angiography:** ❖ Regional RV akinesia, dyskinesia or aneurysm	**By 2D Echo** Regional RV akinesia, dyskinesia or aneurysm and 1 of the following (end diastole): ❖ PLAX RVOT ≥29 to <32mm ❖ PSAX RVOT ≥32 to <36mm ❖ Or fractional area change >33% to ≤40% **By MRI** Regional RV akinesia, dyskinesia or aneurysm or dyssynchronous RV contraction and one of the following: ❖ Ratio of RV end-diastolic volume to BSA ≥100 to <110 mL/m2 (male) or ≥90 to <100 mL/m2 (female) ❖ Or RV ejection fraction >40% to ≤45%

	2. Tissue characterization of wall	
	Major	Minor
Original TFC	❖ Fibrofatty replacement of myocardium on endomyocardial biopsy	
Reviseted TFC	❖ Residual myocytes <60% by morphometric analysis (or <50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy	❖ Residual myocytes 60% to 75% by morphometric analysis (or 50% to 65% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy

	3. Repolarization abnormalities	
	Major	**Minor**
Original TFC		Inverted T waves in right precordial leads (V2 and V3) (people age >12 years, in absence of right bundlebranch block)
Reviseted TFC	❖ Inverted T waves in right precordial leads (V1, V2 and V3) or beyond in individuals >14 years of age (in the absence of complete right bundle-branch block, QRS ≥120 ms)	❖ Inverted T waves in leads V1 and V2 in individuals >14 years of age (in the absence of complete right bundle-branch block) or in V4, V5, or V6 ❖ Inverted T waves in leads V1, V2, V3, and V4 in individuals >14 years of age in the presence of complete right bundle-branch block

	4. Depolarization/conduction abnormalities	
	Major	**Minor**
Original TFC	❖ Epsilon waves or localized prolongation (>110 ms) of the QRS complex in right precordial leads (V1 to V3)	❖ Late potentials (SAECG)
Reviseted TFC	❖ Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V1 to V3)	❖ Late potentials by SAECG in ≥1 of 3 parameters in the absence of a QRS duration of ≥110 ms on the standard ECG ❖ Filtered QRS duration (fQRS) ≥114 ms ❖ Duration of terminal QRS <40 microV (low-amplitude signal duration) ≥38 ms ❖ Root-mean-square voltage of terminal 40 ms ≤20 microV ❖ Terminal activation duration of QRS ≥55 ms measured from the nadir of the S wave to the end of the QRS, including R′, in V1, V2, or V3, in the absence of complete right bundle-branch block

	5. Arrhythmias	
	Major	**Minor**
Original TFC		❖ Left bundle-branch block–type ventricular tachycardia (sustained and nonsustained) (ECG, Holter, exercise) ❖ Frequent ventricular extrasystoles (>1000 per 24 hours on Holter).
Reviseted TFC	❖ Nonsustained or sustained ventricular tachycardia of left bundle-branch morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)	❖ Nonsustained or sustained ventricular tachycardia of RV outflow configuration, left bundle-branch block morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis ❖ >500 ventricular extrasystoles per 24 hours (Holter)

2.4.1 Electrocardiography in ARVC

The ECG is considered to be one of the most important tools in cardiovascular screening for detecting ARVC. The disease is characterized by progressive replacement of the myocardium by fibrous and fatty tissue in the free wall of the RV which is the final part of the heart to depolarise (Durrer D et al., 1970; Marcus 2009). In this setting, when there is damage to the musculature of the RV free wall, there may be fragmentation and selective slowing and prolongation at the end of the QRS complex in the anterior precordial leads. The delay in depolarization may be extremely prolonged and may be visible as low frequency, low amplitude waves that extend beyond the QRS complex and before the T wave; known as epsilon waves (Fontaine et al., 1978; Marcus 2009). In addition, T wave inversion is often a manifestation of myocardial injury such as in patients with an anterior myocardial infarction, Likewise, this is an ECG feature in patients with ARVC where the RV free wall musculature has been replaced by fibrous-fatty tissue (Marcus 1986, 2009).

In this condition, T-wave inversion (TWI) in the anterior leads (in the absence of right bundle branch block) has been reported to have a sensitivity of up to 81% (Nava et al., 2000; Marcus et al., 2009), with a specificity of 97% in young adults without the disease (Marcus, 2005). The presence of a combination of both TWI and ectopic ventricular beats of RV origin increases the likelihood of making a diagnosis of ARVC. In the absence of right bundle branch block (RBBB), up to 76% of ARVC cases presented with prolongation of conduction and depolarisation of the QRS complex exceeding 110ms in V1-V3 (Nasir et al., 2004; Piccini et al., 2005). Also, up to 71% of ARVC cases were presented with prolongation of the S-wave duration (Peters et al.,

2007). The most distinct feature of ARVC disease on ECG is the presence with epsilon wave which is considered to be a major criteria but it is present in only 30% of cases (Hurst, 1998; Biernacka et al., 2017). That aside, even in marked structural / functional phenotypes of the disease there may still be the presence of a normal ECG (Marcus et al., 2010; Zaidi et al., 2013b). In addition, ECG sensitivity for detection in the concealed phase of the disease is poor (Sorrell, Kumar and Kalra, 2009).

Furthermore, A positive signal average electrocardiogram (SAECG) is another minor TFC for ARVC diagnosis. The test involves the use of special ECG equipment to markedly increase the amplitude of the QRS complex in order to accurately measure the duration of the QRS complex as well as to observe and measure the small electrical potentials that may occur after the end of the QRS complex (Marcus et al., 2010) (see Table 2.1).

2.4.2 Echocardiography in ARVC

In view of this, the echocardiogram has been shown to provide added value for the diagnosis of ARVC (Marcus et al., 2009). Although, the 2010 Task Force revision has improved specificity of the technique it appears to have had less impact upon diagnostic sensitivity (Vitarelli et al., 2013). The possible explanation for this is based on the dependence on two RV anatomical measures (i.e. RV outflow tract from a parasternal long [RVOT-PLAX] and short axis [RVOT1] or [RVOT-SAX] and one functional measure (i.e. RVFAC). RV structure and function are complex and therefore it is pertinent to speculate that in order to increase its diagnostic sensitivity specifically in ARVC where phenotype expression is variable (Sorrell, Kumar and Kalra , 2009; Aneq et al., 2012) a more substantive assessment of RV structure and function is required.

Therefore, it is necessary to develop a more comprehensive echocardiographic assessment (Zaidi et al., 2015) to improve the diagnostic accuracy whilst conforming to standardised guidelines (Lang et al., 2015; Wharton et al., 2015)

2.5 Pre-participation cardiac screening (PPCS) of Competitive Athletes

PPCS is employed within the athletic population to identify those individuals who may be predisposed to SCD through an inherited cardiac condition such as ARVC. Italian data from Corrado et al., (2006) presented an 89% reduction in the annual incidence of SCD in screened athletes compared to an unscreened non-athlete population (Corrado et al., 2006) (see Figure 2.9). That aside, Van Brabandt et al., (2016) suggest that this study should be interpreted with caution, as it fails to prove that the reduction in SCD could be attributed directly to pre-participation screening (Van Brabandt et al., 2016). In addition, Corrado et al 2009 did not utilise a randomised study design with an unscreened control group to further justify the effectiveness of cardiac screening. It could also be argued that a randomised study design was not feasible due to the ethical implications as screening is compulsory by law in Italy (Corrado et al., 2016). However, despite the critique around Corrado et al. 2009 study and its figure 2.9, a recent study by Malhotra et al, (2018) screened 11,168 adolescent athletes From 1996 through 2016 in the English Football Association (FA) and stated that deaths are three times greater than expected and up to 70% players with serious diseases can be tested which raising awareness of the importance of routine cardiac screening to save young lives (Malhotra et al, 2018) and thus demonstrates the importance of PPCS.

Figure 2. 9: Annual incidence rates of sudden cardiovascular death among screened competitive athletes and unscreened non-athletes 12–35 years of age in the Veneto Region of Italy, from 1979 to 2004 (adapted from Corrado et al., 2011)

The application of specific criteria for 12-lead ECG interpretation during PPCS has been shown to reduce abnormal ECGs and false positives results and consequently the ration of athletes excluded per life saved is likely to be high (Sheikh et al., 2014; Kumar, Kalman and La Gerche, 2017; Drezner et al., 2017; Sharma et al., 2017). The PPCS utilises a range of investigations (see Figure 2.10).

Figure 2. 10: Flow diagram illustrating the modality of pre-participation cardiovascular screening recommended by the European Society of Cardiology section of Sports Cardiology (adapted from Corrado et al., 2011)

PPCS is recommended by both the American Heart Association and the European Society of Cardiology. In the United States of America, only a family history and a physical examination is recommended, whereas in Europe a 12-lead ECG is mandatory (Grazioli et al., 2014). Different countries also within Europe apply different regulation regarding the methods of PPCS and there are a number of sporting organisations that advocate echocardiography as a primary investigation (Corrado et al., 2011; Mont et al., 2016).

Specific sporting/screening organisation also will decide whether athletes require a routine transthoracic echocardiogram (TTE) as a first line investigation within the standard screening protocol (Mont et al., 2016; Oxborough et al., 2018) (see Table 2.2).

Table 2.2: Major international sporting federations with a pre-participation cardiovascular screening policy for elite or professional athletes (adapted from Mont et al., 2016)

Sporting Federation	Mandatory or recommended	Screening protocoScreening protocol	Primary screening methodology			
			Physical examination	Personal symptom and FH	12-lead ECG	Echocardiography
International Olympic Committee	Recommend	IOC	✓	✓	✓	
International Paralympic Committee	Recommend	IOC	✓	✓	✓	
Fédération Internationale de Football Association	Mandate	Self-imposed	✓	✓	✓	✓
Union of European Football Associations	Mandate	Self-imposed	✓	✓	✓	✓
Union Cycliste Internationale	Mandate	Self-imposed	✓	✓	✓	✓
Fédératoin Internationale de Motocyclisme	Mandate	Self-imposed	✓	✓	✓	✓
Fédération Internationale de l'Automobile	Mandate	Self-imposed	✓	✓	✓	✓
International Association of Athletic Federations	Recommend	IOC	✓	✓	✓	
National Basketball Association (USA)	Recommend	AHA	✓	✓	✓	
National Football League (USA)	Recommend	AHA	✓	✓		

Major League Baseball (USA)	Recommend	AHA	✓	✓		
National Hockey League (USA)	Recommend	AHA	✓	✓		
World Rugby	Recommend	Self-imposed	✓	✓	✓	
Fédération Internationale de Natation	Recommend	Self-imposed	✓	✓	✓	
World Boxing Federation	Recommend	Self-imposed	✓	✓	✓	
International Handball Federation	Recommend	IOC	✓	✓	✓	
International Triathlon Union	Recommend	IOC	✓	✓	✓	
Fédération Internationale de Ski	Recommend	IOC	✓	✓	✓	
Fédération International des Sociétés d'Aviron	Mandate	IOC	✓	✓	✓	

2.6 Athlete's Heart

In order to accurately differentiate AH from ARVC, it is important to understand normal physiological adaptation in RV structure and function to a regular exercise stimulus. With this in mind, the following section provides a critical review of the literature pertaining to RV adaptation in the athlete.

2.6.1 Right Ventricle

The human heart adapts to chronic training due to the high demand for blood flow to the body during training. Its structural response manifests through augmented chamber size and ventricular walls caused by signalling events in the cardiac myocyte that leads to protein synthesis (George et al., 2011). Traditionally, the RV has received less attention than the LV, however due to developments in imaging technology and high-profile

cardiac events, more recent studies have been driven to further explore RV structure and function (Brown et al., 2017).

The RV is an essential component of the cardiovascular system. It is responsible for receiving blood from the right atrium and for pumping blood into the pulmonary circulation. As the oxygen demand increases during exercise, the RV has to meet this demand by supplying an adequate stroke volume through pulmonary system and hence RV adaptation is important in providing the athlete with this capacity (George et al., 2011; Duncan, 2012). Numerous studies have utilised echocardiography to describe RV adaptation secondary to various types of exercise training such as strength (static) (i.e. as body builders and weightlifters) (D'Andrea et al., 2013; Utomi et al., 2013; Oxborough et al., 2016; D'Ascenzi et al., 2017a), endurance (dynamic) (i.e. long-distance runners, swimmers, and cross-country skiers) (D'Andrea et al., 2013; Oxborough et al., 2012b; Utomi et al., 2013; D'Ascenzi et al., 2017a) and combined (i.e. rowers, cyclist and speed skaters) (D'Ascenzi et al., 2017b). Based on this, a recent meta-analysis has attempted to provide normal values for 2D echocardiographic indices in the assessment of RV structure and function among elite athletes (see Table 2.3- 2.5).

Table 2. 3: Demographic characteristics of echocardiographic studies assessing RV structure and function in competitive athletes (adapted from D'Ascenzi et al. (2017b))

First author	Year	Type of sport	*n*	Gender	First author	Year	Type of sport	*n*	Gender
Douglas	1990	Combined	41	M, F	Pagourelias	2013	Mixed	80	M
Henriksen	1996	Endurance	127	M			Strength	28	
Henriksen	1999	Endurance	42	F	Schmied	2013	Endurance	210	M
Erol	2002	Mixed	36	M	Simsek	2013	Endurance	44	M, F
D'Andrea	2003	Endurance	32	M	Vitarelli	2013	Endurance	35	M
		Endurance	26				Strength	35	
Kasikcioglu	2005	Mixed	52	M			Strength	35	
Neilan	2006	Endurance	20	M, F	Zaidi	2013	Mixed	300	M, F
Koc	2007	Mixed	60	M, F			Mixed	375	
Baggish	2008	Combined	20	F	Zaidi	2013	Mixed	627	M, F
		Combined	20	M	D'Ascenzi	2014	Endurance	24	F
		Combined	24	M	Esposito	2014	Combined	40	M
La Gerche	2008	Combined	27	M, F	Gjerdalen	2014	Endurance	553	M
Poh	2008	Combined	24	M, F	Leischik	2014	Combined	54	M
Teske	2009	Combined	24	M, F			Combined	33	F
Baggish	2010	Mixed	58	M, F	Giraldeau	2015	Mixed	45	M
		Mixed	63				Mixed	45	F

		Mixed	54		Grunig	2015	Endurance	395	M, F
Bauce	2010	Endurance	40	M, F			Strength	255	
D'Andrea	2010	Endurance	50	M	Hedman	2015	Mixed	46	F
D'Andrea	2011	Endurance	370	M, F	Jongman	2015	Combined	24	M
		Strength	245		Major	2015	Mixed	52	M
Krol	2011	Combined	38	M, F	Malmgren	2015	Endurance	33	F
La Gerche	2011	Endurance	39	M, F	Utomi	2015	Endurance	19	M
Popovic	2011	Combined	21	M			Strength	21	
		Strength	16		D'Ascenzi	2016	Endurance	35	M, F
D'Andrea	2012	Endurance	220	M, F	D'Ascenzi	2016	Endurance	29	M, F
		Strength	210		D'Ascenzi	2017	Mixed	262	M, F
Karlstedt	2012	Endurance	25	M, F			Strength	277	
Oxborough	2012	Mixed	102	M, F			Mixed	216	
Bernheim	2013	Combined	38	M, F			Mixed	254	
D'Ascenzi	2013	Endurance	100	M, F					
King	2013	Combined	18	M					
		Endurance	24						
Moro	2013	Endurance	17	M					
		Endurance	19						
		Endurance	21						

Table 2. 4: Suggested normal values for 2D echocardiogc parameters of RV structure in male competitve athletes (Data are mean (95% CI) (adapted from D'Ascenzi et al. (2017b))

RVOT-PLAX (mm)		RV end-systolic area (cm^2)	
Endurance	29 (26-33)	Endurance	13 (10-15)
Combined	29 (26-33)	Combined	17 (14-20)
Mixed	29 (26-33)	Mixed	13 (8-18)
Strength	29 (26-33)	Strength	10 (8-13)
RVOT-PLAX index (mm/m^2)		RV end-systolic area index (cm^2/m^2)	
Endurance	17 (15-18)	Endurance	9 (7-10)
Combined	17 (15-18)	Combined	9 (7-10)
Mixed	17 (15-18)	Mixed	9 (7-10)
Strength	17 (15-18)	Strength	9 (7-10)
RVOT1 (mm)		RV basal diameter (mm)	
Endurance	34 (32-35)	Endurance	40 (38-42)
Combined	34 (32-35)	Combined	44 (39-49)
Mixed	34 (32-35)	Mixed	43 (41-44)
Strength	34 (32-35)	Strength	38 (31-45)
RVOT1 index (mm/m^2)		RV basal diameter index (mm/m^2)	
Endurance	18 (16-20)	Endurance	23 (19-26)
Combined	18 (16-20)	Combined	23 (19-26)
Mixed	18 (16-20)	Mixed	23 (19-26)
Strength	18 (16-20)	Strength	23 (19-26)
RVOT distal diameter (mm)		RV midcavity diameter (mm)	
Endurance	31 (27-34)	Endurance	29 (27-30)

Combined	31 (27-34)	Combined	41 (37-46)
Mixed	31 (27-34)	Mixed	36 (35-37)
Strength	31 (27-34)	Strength	26 (23-29)
RVOT distal diameter index (mm/m^2)		RV midcavity diameter index (mm/m^2)	
Endurance	16 (15-18)	Endurance	18 (14-22)
Combined	16 (15-18)	Combined	18 (14-22)
Mixed	16 (15-18)	Mixed	18 (14-22)
Strength	16 (15-18)	Strength	18 (14-22)
RV end-diastolic area (cm^2)		RV wall thickness (mm)	
Endurance	23 (20-27)	Endurance	4.2 (3.9-4.4)
Combined	32 (29-35)	Combined	7.0 (5-8)
Mixed	30 (28-31)	Mixed	nd
Strength	21 (17-25)	Strength	4.0 (3-5)
RV end-diastolic area index (cm^2/m^2)			
Endurance	15 (14-16)		
Combined	15 (14-16)		
Mixed	15 (14-16)		
Strength	15 (14-16)		

RV outflow tract (RVOT) diameter at the parasternal long-axis view (RVOT-PLAX), RV outflow tract diameter at the subpulmonary region (RVOT1)

Table 2. 5: Suggested normal values for 2D echocardiogc parameters of RV function in male competitve athletes (Data are mean (95% CI) (adapted from D'Ascenzi et al. (2017b))

RV FAC (%)	
Endurance	35 (32-38)
Combined	36 (32-40)
Mixed	43 (36-51)
Strength	41 (32-49)
TAPSE (mm)	
Endurance	25 (22-28)
Combined	25 (22-28)
Mixed	25 (22-28)
Strength	25 (22-28)
TDI s’ velocity (m/sec)	
Endurance	0.17 (0.13-0.20)
Combined	0.11 (0.09-0.13)
Mixed	0.14 (0.10-0.19)
Strength	0.17 (0.13-0.22)
TDI e’ velocity (m/sec)	
Endurance	0.18 (0.14-0.22)
Combined	0.12 (0.10-0.14)
Mixed	0.16 (0.12-0.20)
Strength	0.18 (0.16-0.20)
Strain (%)	
Endurance	—24.7 (22.9-26.4)
Combined	—24.7 (22.9-26.4)
Mixed	—24.7 (22.9-26.4)
Strength	—24.7 (22.9-26.4)

Tricuspid Annular Plane Systolic Excursion (TAPSE), RV Fractional Area Change (RVFAC), Peak systolic motion on Tissue Doppler Image (TDI RV S') , early diastolic motion (TDI RV E') ,

It has been reported that there is no difference in RV dimension between resistance (i.e. static) athletes and sedentary healthy control group (D’Andrea et al., 2013). Endurance athletes however, have demonstrated an increased RV inflow and outflow tract dimensions compared to resistance (i.e. static) athletes group (D’Andrea et al., 2013;

Oxborough et al., 2016). Oxborough et al (2012) also demonstrated that endurance athletes have larger RV dimensions at the RV outflow tract (RVOT) and RV inflow tract exceeded normal cut-off values (57% and 40%, respectively) (Oxborough et al., 2012b). The primary stimulus for this adaptation is speculative with La Gerche and Claessen (2015a) documenting the effects of increased wall stress (La Gerche and Claessen, 2015a) whilst others demonstrating the importance of an increased preload (Duncan, 2012). The concept that the RV adapts in response to a disproportionate wall stress (afterload) suggesting that during exercise a greater stroke work load and pulmonary artery pressure will be placed on the RV (La Gerche and Heidbu, 2011) leading to a coping mechanism that elevating the RV contractility and wall stress to overcome this afterload at least for a while (D'Andrea et al., 2015). However, the RV myocardium is unable to sustain exercise duration for prolonged period of time due to its characteristic of having thin wall so a reduction in its contractility occurs followed by a reduction in the RV stroke volume (Oxborough et al., 2010; La Gerche et al., 2010; Elliot and La Gerche, 2014), subsequently impacting on LV filling (Oxborough et al., 2010; La Gerche et al., 2010). Oxborough et al., (2011) and La Gerche et al., (2012b) reported RV dilation and reduced RV ε and SV with reduction in LV end diastolic volume, LV filling and LV preload in prolonged endurance exercise (Oxborough et al., 2011; La Gerche et al., 2012b). In support of this, Oxborough et al., (2012) demonstrated an increased RV/LV ratio consistent with alternative mechanisms of adaptation (Oxborough et al., 2012b). In agreement with this, other studies reported increased RV cavity dimension in endurance athletes after completing 6 months (Spence et al., 2013; Arbab-Zadeh et al., 2014) and after 12 months associated with an elevated RV/LV ratio (Arbab-Zadeh et al., 2014). Different cardiac physiological adaptation to training depends on the various factors and is summarized in Figure 2.11.

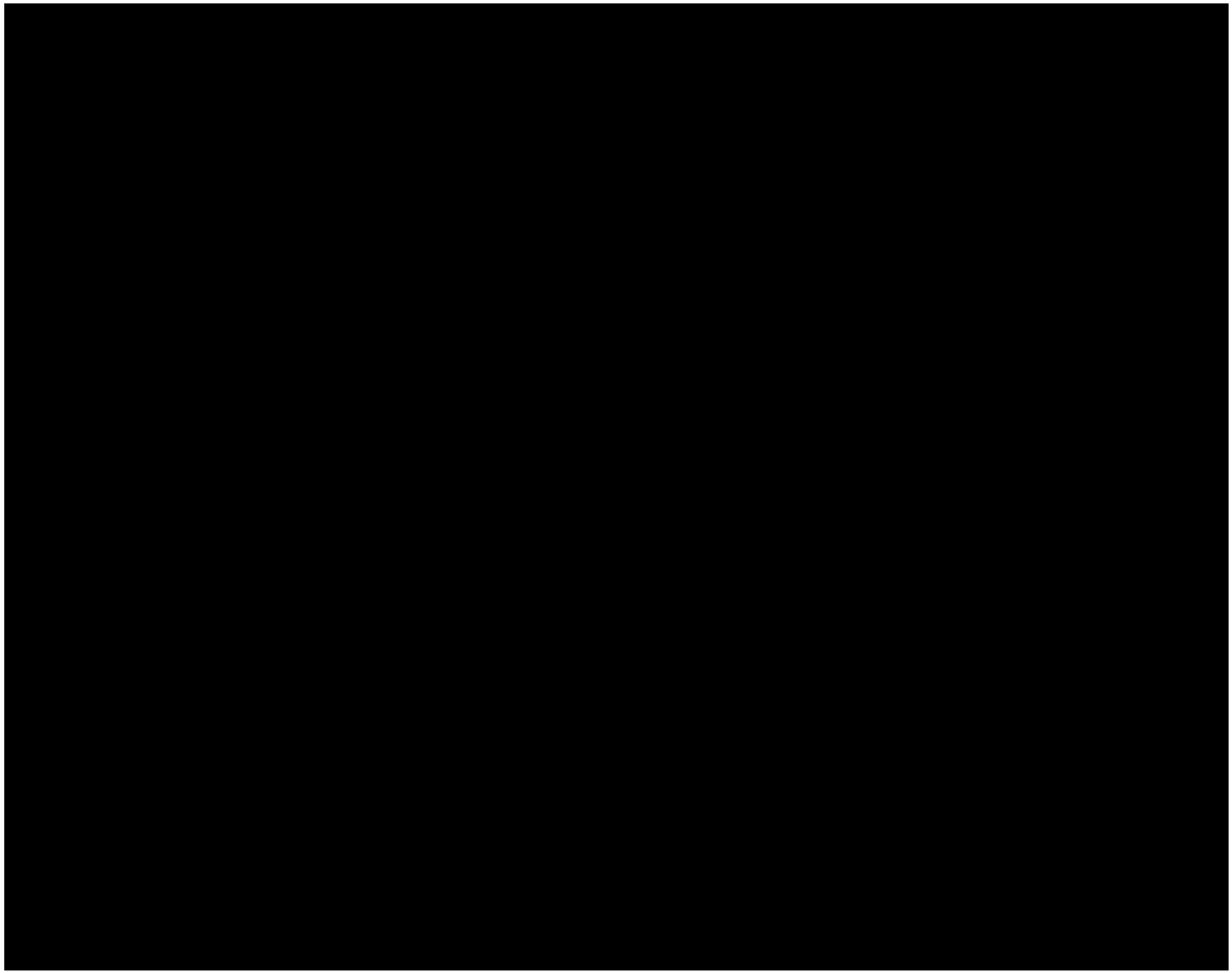

Figure 2. 11: The multifactorial impact of cardiac adaptation in the athletes (adapted from Brown et al., 2017)

The Mitchells classification serves as a guide to the relative dynamic and static components to specific sporting disciplines (Mitchell et al., 2005; Levine et al., 2015). Dynamic exercise training is defined as low (<50% maximal oxygen uptake ($maxO_2$)), moderate (50-75% maximal oxygen uptake ($maxO_2$)) and high (>75% maximal oxygen uptake ($maxO_2$)). Static exercise training is classified to low (<10% maximal voluntary contraction (MVC) that defined as the greatest amount of tension the relevant muscle (groups) can generate and hold), moderate (10-20% MVC) and high (>30% MVC) (Levine et al. 2015). Nevertheless, the majority of sports have a combination of both dynamic and static due to that cardiac adaptations determined by the degree of combination of intensity, duration and frequency induced by individual sports and exercise training (Beaudry et al., 2016; Beaumont et al., 2016; Brown et al., 2017).Therefore, Mitchells classification classified sporting disciplines into 9 groups providing information on varies sporting disciplines relative to the static and dynamic components which serve as a useful guide in this regard (Mitchell et al., 2005; Levine et al., 2015; Oxborough et al., 2018) (Figure 2. 12). However, many researchers have questioned this classification which is based on sport disciplines and not on athletes' fitness level related to their underlying training load (intensity and duration). It has been well established that there is a strong association between cardiac structure and function with exercise training and not sport discipline (Beaudry et al., 2016; Haykowsky et al., 2018). Although fitness level is important, the Mitchell classification is considered an important contribution to the medical field with healthcare professionals utilising it to decide whether cardiac patients can participate in sport.

Figure 2. 12: Mitchells classification (adapted from Levine et al., 2015)

In a recent meta-analysis, athletes were classified into four categories: 1) strength (i.e. bodybuilder), 2) endurance (i.e. long distance runners, swimmers), 3) combined (i.e. rowers, cyclist) and 4) mixed (i.e. groups of athletes of different sports classification) (D'Ascenzi et al., 2017b). There was no difference in RVOT dimension between the four groups, however, the combined group, (which by definition includes high dynamic exercise training), demonstrated the greatest RV dimension and RV inflow tract (D'Ascenzi et al., 2017b). In support, a study comparing 92 male athletes from mixed sport disciplines and were split into groups according to the Mitchells Classification demonstrating that the high static and high dynamic group had larger RVOT and RV inflow tract compared to the high static and lower dynamic group. These studies

demonstrated that dynamic exercise training is the primary motivator for RV adaption (Oxborough et al., 2016). However, more work needed to be done exploring the influence of different dynamic component levels only based on Mitchells Classification on RV morphology and function by utilising novel echocardiography technique with myocardial regional assessment.

Right ventricular mechanics are unique due to the predominance of longitudinal fibres in a thin walled chamber and thus there is significant contribution of longitudinal ε to RV SV (Kukulski et al., 2000; Pellerin et al., 2003; Rudski et al., 2010). RV ε is heterogenously dispersed compared to the LV (Weidemann et al., 2002). RV ε shows a reverse base to apex gradient reaching the highest values in the outflow tract and apical segments (Teske et al., 2009b; Mor-Avi et al., 2011) which has been attributed to the RV structure and geometry i.e. the thin walled crescent shape and less homogenously distribution of regional wall stress (Rudski et al., 2010; Mor-Avi et al., 2011). A study by Oxborough et al., (2012b) reported normal longitudinal RV ε value in endurance athletes, but Teske et al., (2009b) reported lower values of global longitudinal RV ε in elite endurance athletes as well as lower basal regional ε compared to non-athletes and controls group. This reduction in the basal region has been explained by different curvature shape that RV apex and basis take in order to control the wall stress during exercise. In addition, RV dilation occurrence as a result of exercise primarily involves both the RV basal (inflow tract) to lesser extent the outflow tract (Bauce et al., 2010). La Gerche et al., (2012a) also explained this reduction due to that the volume is greatest at the RV base so a lesser degree of deformation needed to generate the same amount of stroke volume.

Furthermore, Pagourelias et al., (2013) stated no association between RV size and RV function impairment. Previous studies demonstrated a preserved global longitudinal RV ε in highly trained athletes (Oxborough et al. 2016; D'Andrea et al. 2013; Brown et al. 2017) providing evidence that function at rest remains within the normal range in athletes, regardless of sport discipline, training volume and morphological remodelling.

In clinical bases, RV ε imaging has demonstrated the fundamental ability to identify regional wall motion abnormalities in ARVC patients (Teske et al., 2009a) and in asymptomatic ARVC patient mutations carriers (Teske et al., 2012). Therefore, the ability to quantify regional RV dysfunction objectively by STE may increase the sensitivity to distinguish between physiological adaptation and pathology such as ARVC.

2.6.2 12-lead ECG in athletes

Chronic exercise training is usually associated with unique electrical presentation on the ECG that reflects on the cardiac changes in its nervous system and chambers size and that makes the differential diagnosis from ARVC in athletes more complicated. Therefore, an international group of experts in sports cardiology presented a list of normal, borderline and abnormal ECG finding that does or does not need further investigation if athletes presented with one of these criteria (Drezner et al., 2017; Sharma et al., 2017) (see Figure 2.13).

Figure 2. 13: International consensus standards for ECG interpretation in athletes (adapted from Drezner et al. 2017)

Chronic exercise training is usually associated with unique electrical presentation on the ECG that reflects on the cardiac changes in its increased vagal tone including: 1) early repolarisation, 2) sinus bradycardia, 3) sinus arrthymia, 4) ectopic atrial rhythm, 5)1st degree atrioventricular (AV) block and 6) Mobitz type I 2nd degree AV block, that considerd to be normal ECG finding related to exercise training (Drezner et al., 2017; Sharma et al., 2017). Besides, regular long-term exercise training is also associated with increased RV chamber size causing physiological increase in cardiac mass from athletic cardiac remodelling presented by voltage criteria for left venticular hypertrophy and for right ventricular hypertrophy (RVH), incomplete RBBB (Drezner et al., 2017; Sharma et al., 2017).

Many factors can affect the QRS voltage criteria such as gender, sex and age (Drezner et al., 2017). Elite athletes often persuade QRS voltage criteria with up to 13% for RVH of athletes meeting the Sokolow-Lyon index. RVH and incomplete RBBB used to reflect the increase in RV size from athletic cardiac remodelling, but, in a study carried out by Zaidi et al., (2013) consisted of 627 athletes and 68 patient with ARVC demonstrated that athletes might present with isolated QRS voltages for RVH without correlating with underlying pathology and also none of the athletes with isolated QRS voltage criteria for RVH had any RV pathology on cMRI. They also reported that none of the ARVC patients present voltage criteria for RVH in the absence of additional ECG abnormality. In addition, RVH showed to have poor correlation with increased RV wall thickness on echocardiography (Zaidi et al., 2013b). Apart from QRS voltage criteria for RVH, Kim et al., (2011) stated in their study, which consisted of 510 athletes, that incomplete RBBB in athletes considered to be normal physiological adaptation to exercise in which the mildly delayed RV conduction, which is measured by QRS duration is caused by RV remodelling associated with augmented RV cavity size and thus increase its electrical conduction time instead than being an intrinsic delay within the HIS-Purkinjie system (Kim et al., 2011). Therefore, RVH by voltage criteria appears to be a benign phenomenon among male elite athletes unless it associated additional abnormal ECG finding such as TWI and/or right-axis deviation (i.e. borderline criteria) to elicit further investigation.

Athletes may exhibit abnormal ECG finding that mimic those documented in ARVC such as T-wave inversion (TWI). Although, the presence of TWI in ARVC patients is

well demonstrated, Brosnan et al., (2014) compared in their study between 1010 non-endurance athletes and 251 endurance athletes and reported that TWI in anterior lead were more common in endurance athletes than non-endurance athletes (1.1 vs 4.0%, P<0.0001) (Brosnan et al., 2014). Higher TWI in the anterior leads were presented in elite athletes (27%) and lower compared with mixed sport cohort endurance athletes (10%) and in other heterogeneous athletes group (2-5%). In a study involving 2958 athletes aged 16-35 years, a prevalence of 2.3% with TWI in anterior leads and importantly none of them were diagnosed with RV pathology (Malhotra et al., 2016). Based on this, TWI in anterior leads is recognised to be predominant among endurance athletes (Brosnan et al., 2014; Wasfy et al., 2014) which also might suggests that TWI inversion is presenting for a higher degree of RV remodelling as consequences of the high hemodynamic load placed on the RV (Wasfy et al., 2014; Malhotra et al., 2016) and thus increase the "grey zone" for differentiating normal RV remodelling from RV pathology predominantly in endurance athletes. In addition, TWI in the anterior leads V1-V3 is considered to be a normal ECG finding in black athletes and in all athletes aged <16 years (Dreazner et al., 2017; Sharma et al., 2017).

Furthermore, athletes may exhibit TWI in the inferior leads. Although TWI in the inferior leads is uncommon, its prevalence among Caucasian elite athletes is about 2% and it gets higher among black/African athletes about 8-10% (Drezner, 2012). Brosnan et al., (2014) reported 0.4% of endurance athletes to have TWI in the inferior leads compared with non-endurance athletes 0.2% which was not significantly different between both groups (P=0.49). Although, TWI in the inferior leads is uncommon, its existence alone does not indicate RV cardiomyopathy and also it cannot attribute to physiological remodelling (Drezner et al., 2017) and thus further studies are needed.

In view of this, ECG and echocardiography play pivotal roles in the diagnosis or exclusion of inherited cardiac diseases like ARVC with any missed diagnosis having serious implications for the athlete (Marcus et al., 2010; Drezner et al., 2017).

2.7 Summary

It is clear even from the limited databases that physiological adaptation in RV morphology may mimic the pathological changes observed in ARVC, which makes the differentiation of physiological and pathological remodelling a diagnostic challenge. Besides, the specificity of the TFC for diagnosis of ARVC (Marcus et al., 2010) is only applicable to the general population and sensitivity reduces significantly when dilatation and a reduction in regional contractility occur as a physiological consequence of exercise training (Teske et al., 2009b). RV dilatation in endurance trained athletes (i.e. high dynamic) met TFC for the diagnosis of ARVC in 40% of elite athletes in absolute terms and 6% when accounting for body size (Oxborough et al., 2012b). The evidence base describing the RV function in the athletic population is equivocal with some studies demonstrating normal RV systolic function (Oxborough et al., 2012b; D'Andrea et al., 2013) and others highlighting regional dysfunction at rest (Teske et al., 2009b; La Gerche et al., 2012a). A false positive diagnosis of ARVC has the prospect of severe consequences, where the removal from competition is mandatory, and brings about associated psychological, social, and physical consequences (Rawlins et al., 2009) as well as being associated with significant direct and indirect health care costs (Sorrell, Kumar and Kalra , 2009).

The development in medical technology has improved and helped researchers and scientists to shed light on a lot of fields. On particular interest, the development in echocardiography and its new mode of imaging have evolved the understanding of the cardiovascular system and on the cardiac structure and function. New and novel echocardiographic tools, such as myocardial ε studies, may well provide more insight into the differences between the AH and ARVC (Teske et al., 2009a; D'Andrea et al., 2010). In addition, the physiological nature of cardiac mechanics in the AH is not fully understood with only a handful of small studies assessing absolute values (Richand et al., 2007; Baggish et al., 2008; D'Andrea et al., 2008) so more studies assessing RV structure based on absolute and scaled values and utilising this myocardial ε technique will enhance the understanding on RV adaptation to exercise.

Chapter 3- General Methods

This chapter describes the common methods to the four studies in this thesis and when different methods are applied, they are described in the relevant chapters. Initially, the chapter starts with preliminary information and then particular attention is paid to echocardiographic assessment.

3.1 Preliminary Information

A prospective cross-sectional study design was performed. Ethics approval for research in this thesis was obtained by the Ethics Committee of the Liverpool John Moores University. Participant information sheets were provided to all athletes and full written informed consent was obtained prior to all data collection. All athletes provided written informed consent prior to data collection and cardiac screening. Information pertaining to the procedures was discussed prior to any investigation and where appropriate, familiarisation of specific measurements and techniques was established (see Appendix 1- 4).

Athletes attended the echocardiography laboratory for a single visit, ensuring that they had not undertaken any exercise training at least 6 hours prior to assessment as previous works have highlighted that any transient change in cardiac function is likely to have normalised within 6 hours post-recovery (Lord et al., 2015; Lord et al., 2016) and also ensuring that they had not consumed alcohol and caffeine for the previous 24 hours. The athletes initially completed a personal and family medical history questionnaire and had anthropometric assessment of height and weight, measurement of brachial artery blood pressure, a 12-lead ECG and a transthoracic echocardiogram performed. Male elite

athletes were included if they were; (1) competitive at National level in their specific sporting discipline and (2) no personal or early family history of cardiovascular, respiratory, renal and/or metabolic disease. Athletes were excluded if; (1) they were currently taking prescribed medication and/or (2) had non-training related ECG findings upon screening. Athletes were excluded if after the completion of a health questionnaire, consultant examination, 12-lead ECG, full echocardiographic examination and/or any other clinically relevant follow-up test they had a definitive or suggestive diagnosis of cardiovascular disease (Drezner et al., 2017; Sharma et al., 2017).

3.2 Procedures

3.2.1 Anthropometric Assessment

All athletes were assessed for height (HT, m) and body mass (BM, kg) using a standard scale and stadiometer (SECA 764, Birmingham, UK). Body surface area (BSA) was calculated by using a standardised formula (Mosteller, 1987):

$$BSA = \sqrt{\frac{([\text{subj\_ht}]\text{x}100) * [\text{subj\_wt}])}{3600}}$$

Systolic and diastolic blood pressures were recorded using an automated sphygmomanometer (DINAMAP 300, GE Medical System, Milwaukee, Wisconsin, USA) after at least 5 minutes of quiet seated rest due to the logistical challenges of screening at a club / sports organisation are such that this study were limited to this so that this is a limitation in our studies. Diastolic and systolic blood pressure was recorded as the average of three successive measurements.

3.2.2 12-Lead ECG

A standard resting 12-lead ECG (CardioExpress SL6, Spacelabs Healthcare, Washington US) specifically placed on the chest (leads V1-V6), both forearms and the left leg (leads I, II, III, aVF, aVR and aVL) in accordance with the American heart Association (Mason, Hancock and Gettes, 2007) and its interpretation in agreement with the international criteria for electrocardiographic interpretation in athletes (Drezner et al., 2017; Sharma et al., 2017).

3.2.3 Echocardiographic Assessment

Echocardiographic examination was performed using a Vivid Q ultrasound machine (GE Healthcare, Horten, Norway) with a 2.5-5 MHz transducer with the subject in the left lateral decubitas position (Henry et al., 1980). All acquisitions were made by two experienced sonographers using an echocardiography protocol in accordance with the American Society of Echocardiography (Rudski et al., 2010; Lang et al., 2015). Offline analysis was performed, after storing the images in a raw Digital Imagine and Communications in Medicine format and exported, using commercial available software (EchoPAC V.110.0.2; GE Helathcare, Horten, Norway). All measurements were made in accordance with American Society of Echocardiography guidelines (Lang et al., 2015) by the same sonographers.

3.2.3.1 Conventional 2D and Tissue Doppler measures

Harmonic images were used to perform the M-mode and 2D echocardiography so as to make the most of temporal and spatial resolution. This entails the adjustment of various

ultrasound parameters such as frame rate, gain, angle width, dynamic range, frequency and depth. 2D images were achieved in accordance with the ASE (Lang et al., 2015).

The size of the RV outflow tract dimension was assessed at 3 specific locations. The proximal aspect was measured from a parasternal long and short axis orientation (RVOT-PLAX and RVOT1, respectively) and the distal level from a parasternal short axis view (RVOT2) (see Figure 3).

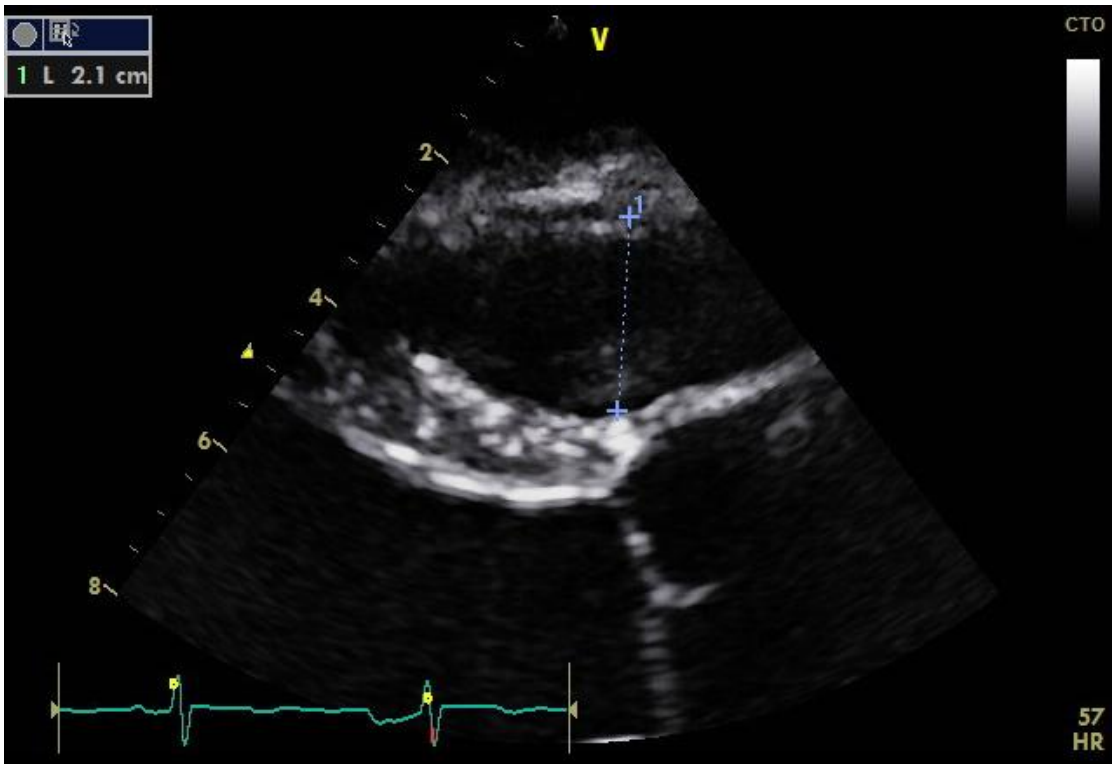

Figure 3. 1: RV outflow tract diameter at the parasternal long-axis view (RVOT-PLAX)

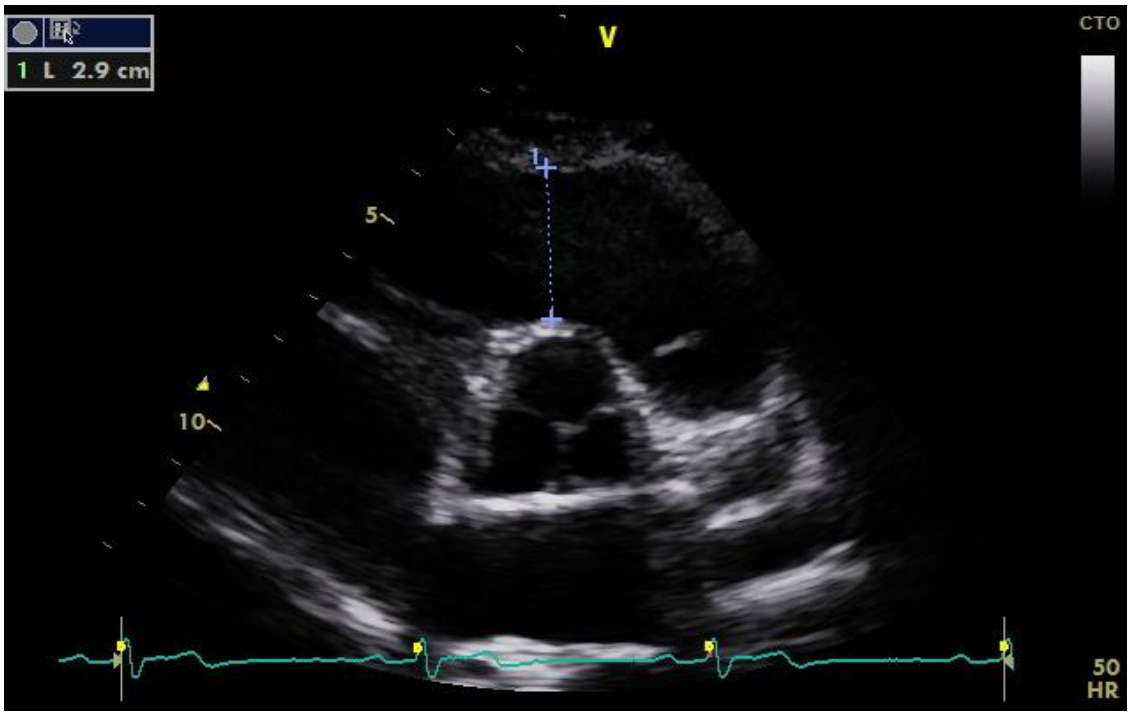

Figure 3. 2: RV outflow tract diameter at the subpulmonary region (RVOT1 or RVOT-SAX)

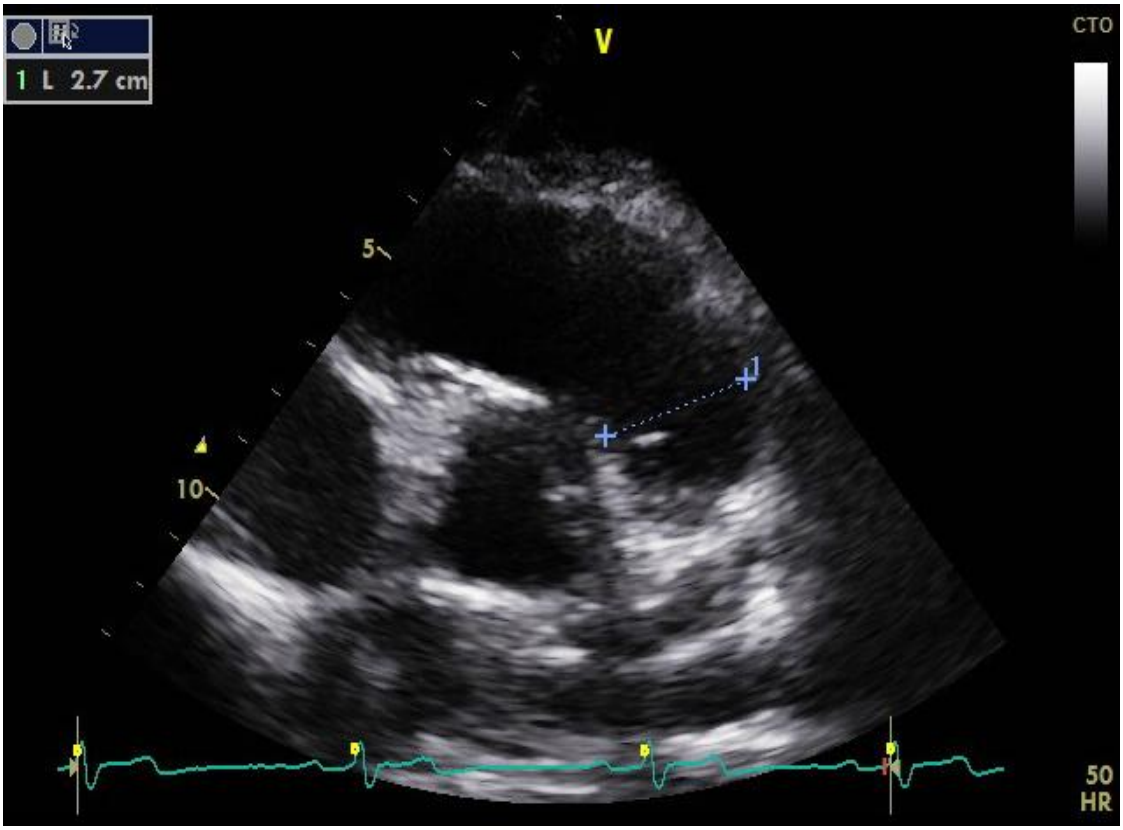

Figure 3. 3: RV outflow tract diameter at the pulmonic valve annulus (RVOT2)

The RV inflow was assessed using a modified apical four chamber orientation (Rudski et al., 2010), with minor dimensions taken at the basal and mid-levels (RVD1 and RVD2 respectively). The RV basal diameter described as the maximal short axis in the basal of the RV. RV mid-cavity diameter measured at the mid third of the RV at the LV papillary muscle level. RV length was measured from apex to the tricuspid annulus (RVD3) (see Figure 3.4).

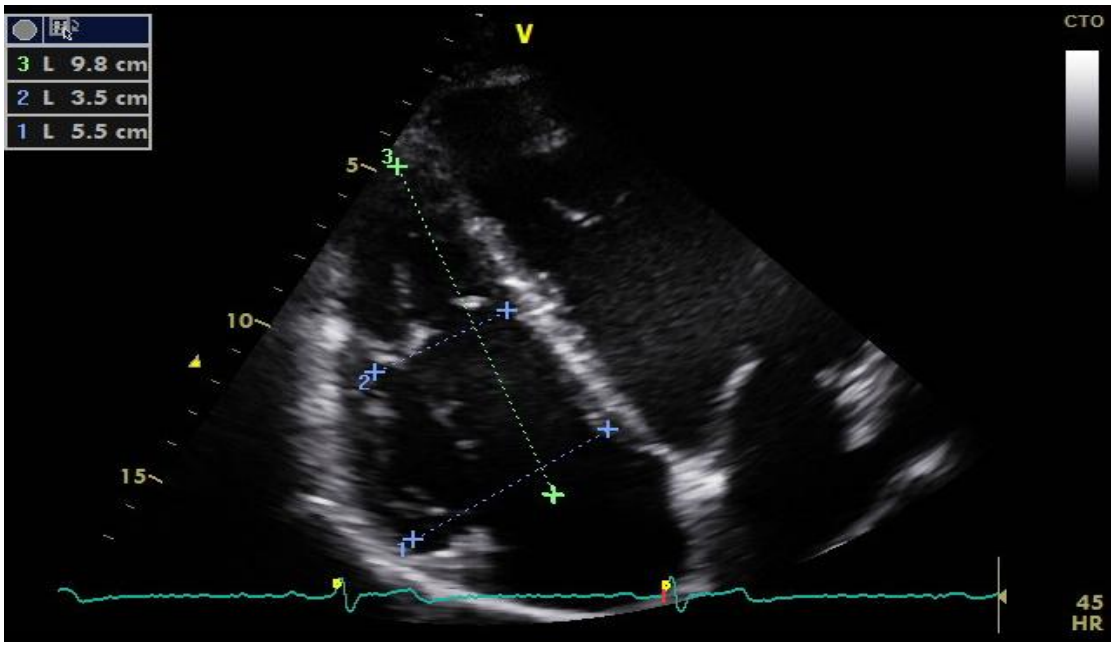

Figure 3. 4: Basal RV diameter (RVD1), Mid RV diameter (RVD2), Base-to-apex length (RVD3)

To establish relative outflow and inflow dimensions the ratio RVOT1/RVD1 was calculated. RV area was measured in diastole (RVDA) and systole (RVSA) by tracing the RV endocardium using the same modified apical four chamber view and RVFAC was calculated by this equation below: (RVFAC (%) = (RVDA – RVSA) / RVDA) (see Figure 3.5 and 3.6).

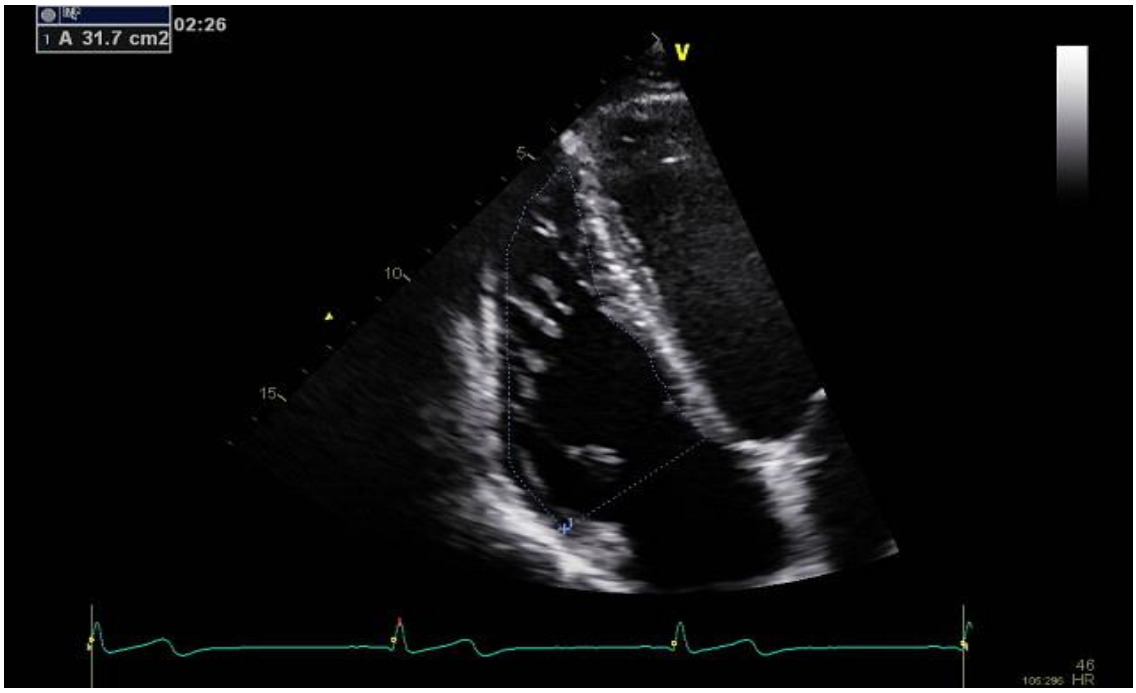

Figure 3. 5: RV end-diastolic area (RVDA)

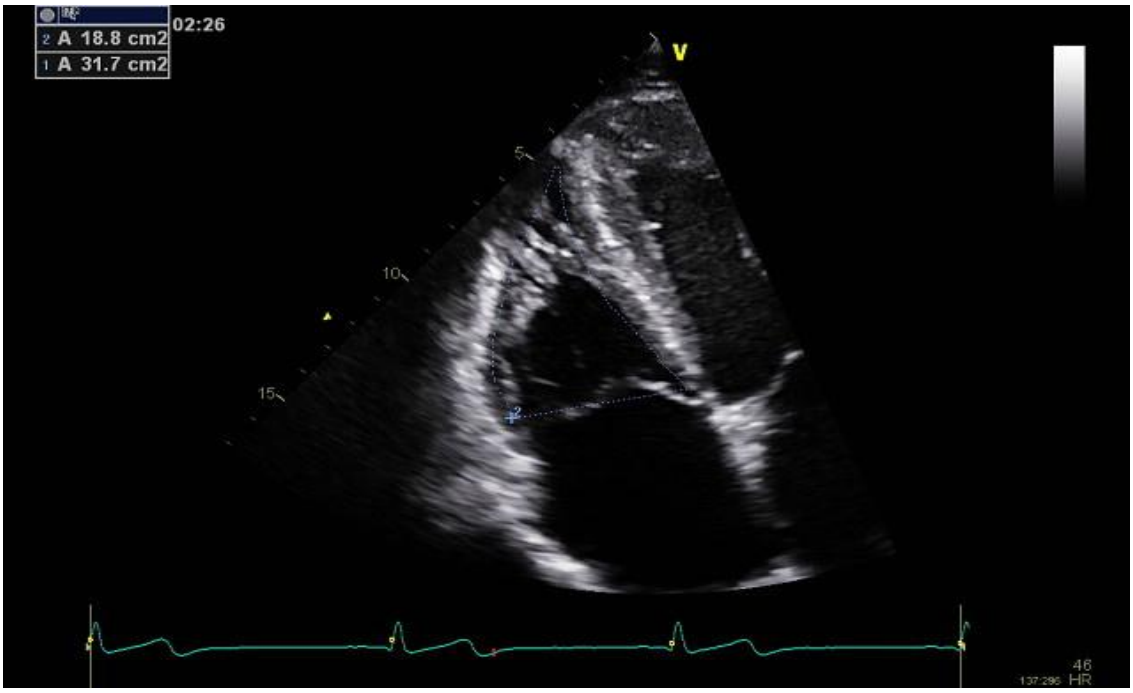

Figure 3. 6: RV end-systolic area (RVSA)

From a subcostal view, RV wall thickness (RVWT) was measured at mid wall level (see Figure 3.7).

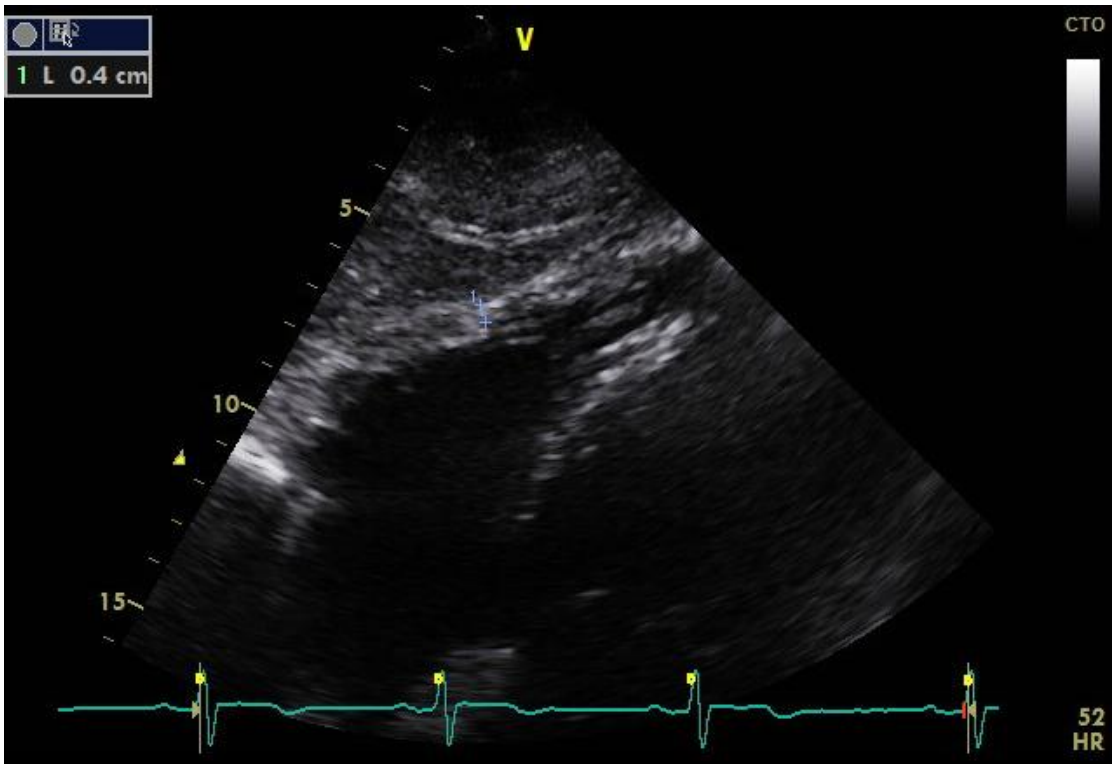

Figure 3. 7: RV wall thickness (RVWT)

For clinical utility, all structural variables were scaled to individual differences in BSA using a standard linear model. That aside, it is well established that biological systems follow a non-linear relationship and hence all indices were also scaled allometrically according to the laws of geometric similarity. This data provides size independent values that allow direct comparison across athletes of different body composition and involves scaling linear dimensions to $BSA^{0.5}$ and area measurements directly to BSA (Batterham et al., 1999).

RV longitudinal function was assessed using pulsed wave TDI and M-mode derived TAPSE of the RV lateral wall. This allowed the derivation of peak myocardial velocities in systole (S'), early diastole (E') and late diastole (A'). Pulsed wave Doppler

of the RVOT allowed the assessment of RV velocity time interval (RVOT VTI) (see figure 3.8).

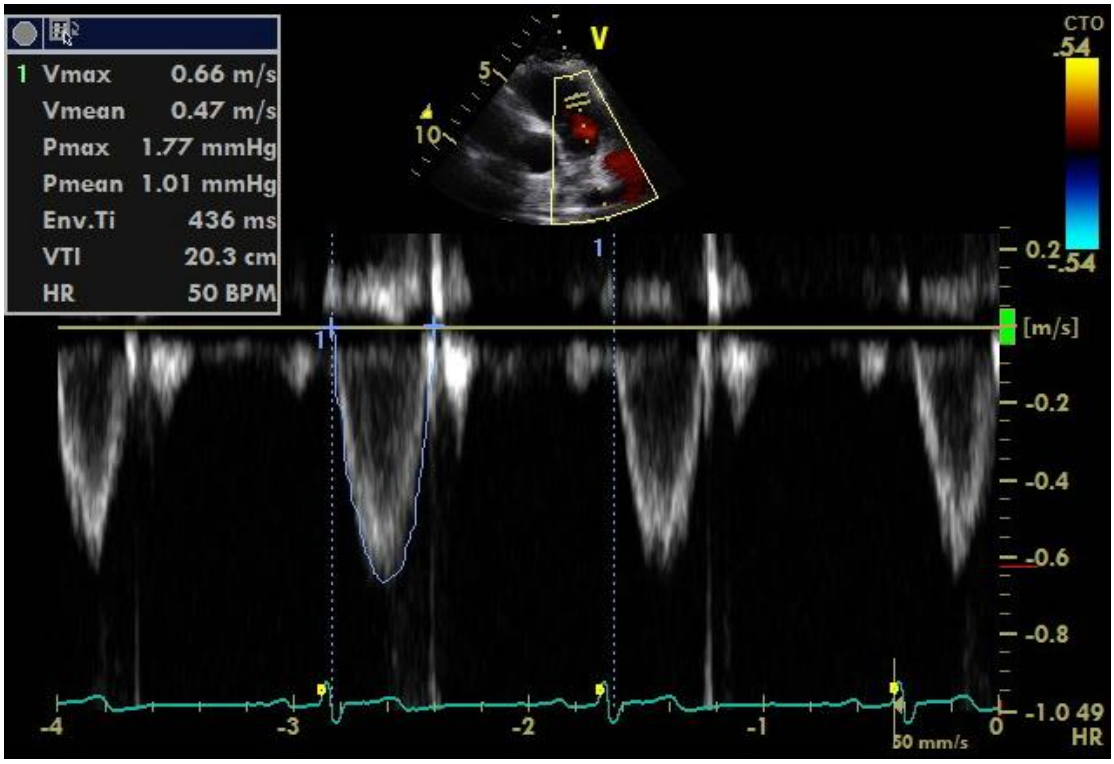

Figure 3. 8: RV velocity time interval (RVOT VTI)

3.2.3.2 Speckle tracking echocardiography measures

The modified apical four-chamber view was used for the assessment of longitudinal RV lateral wall and septal ε and SR. To provide optimal endocardial delineation, images were optimised using depth, gain, compression and sector width. Frame rates were set between 80 and 90 frames per second (Artis et al., 2008) and the focal point was positioned mid cavity to reduce the impact of beam divergence. For offline analysis, pulmonary valve closure (PVC) was obtained from the pulsed wave Doppler signal at the RVOT. A region of interest was placed around the RV basal lateral wall through to basal septum encompassing the mid and apical wall segments (see Figure 9).

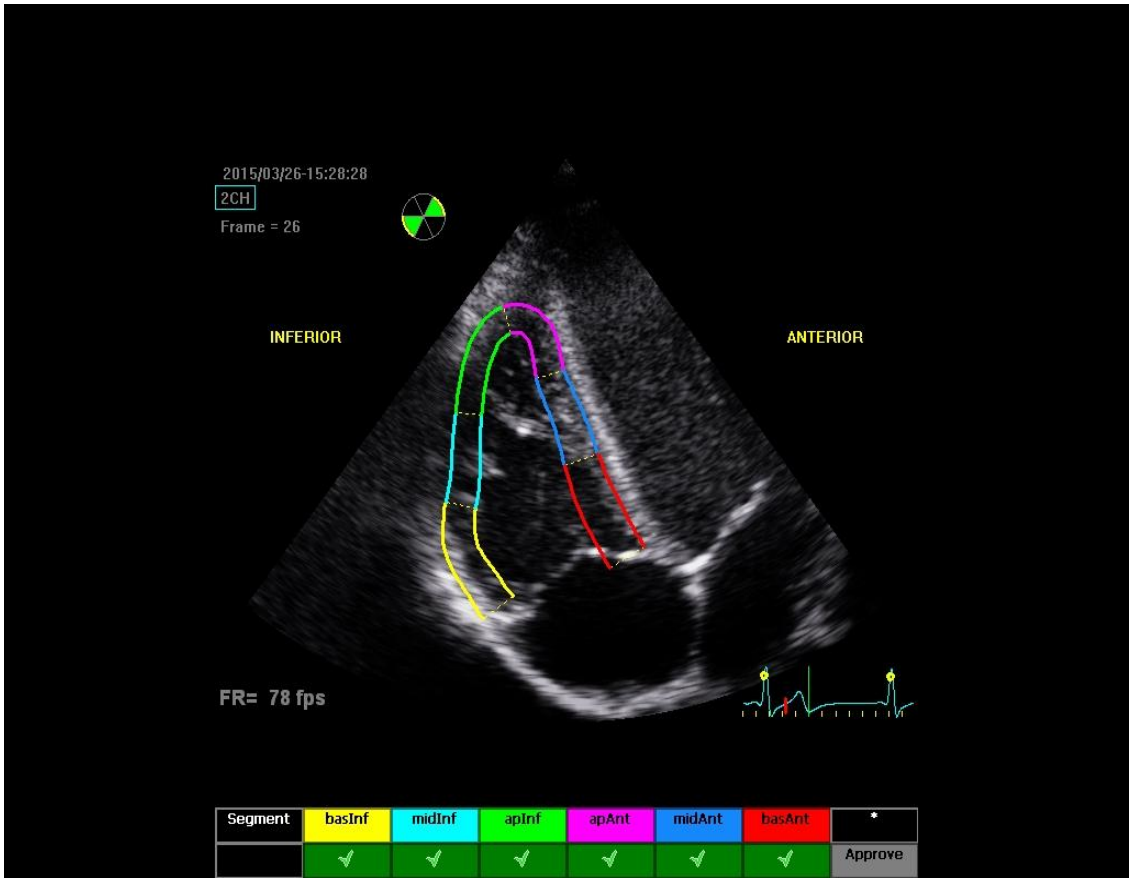

Figure 3. 9: Region of Interest placed down the RV wall

By tracking the continuous frame-by-frame of the 'natural acoustic market', the myocardial deformation was established (Korinek et al., 2005) and ε were determined from the change in length normalised to the original length, while the SR is the rate of displacement (Hein and O Brien, 1993). The analysis software comprises of better averaging abilities that enhance signal to noise ratio (Modesto et al., 2006) in addition to the automatic software grading of the tracking quality the base, mid and apical segments and presented an assessment of tracking quality with segments being excluded if deemed unacceptable.

Regional peak and time to peak RV ε, peak systolic SR (SRS'), peak early diastolic SR (SRE') and peak late diastolic SR (SRA') were obtained for each of the 6 myocardial segments and a global value was determined as an average of the base, mid and apical wall segments. A base to apex ε gradient was calculated for both the septum and the lateral wall as the difference between the peak values at both sites (see Figure 3.10 and 3.11).

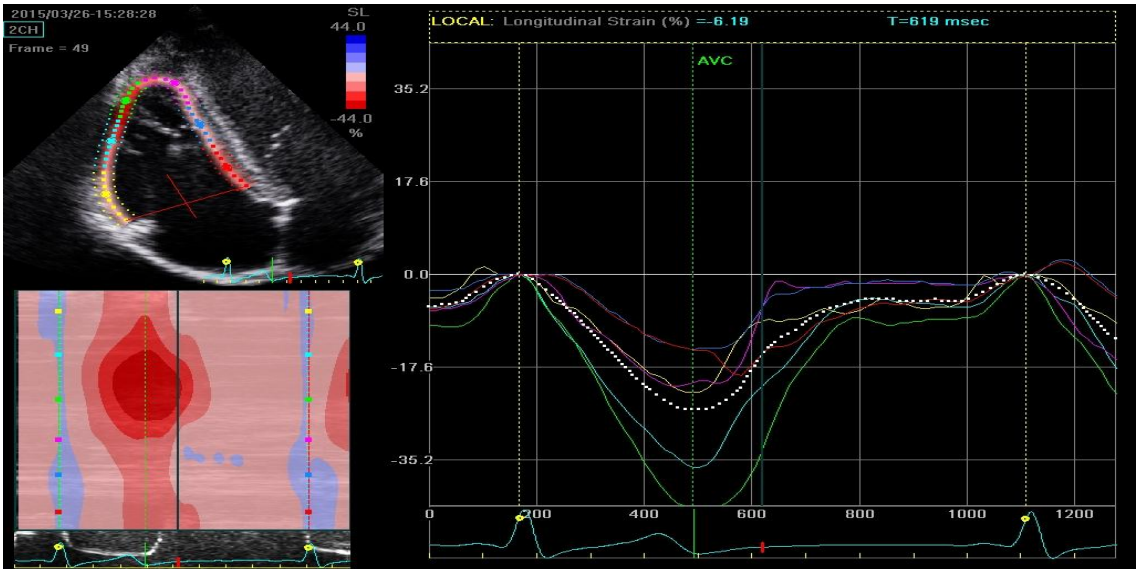

Figure 3. 10: Longitudinal ε Curves for the RV

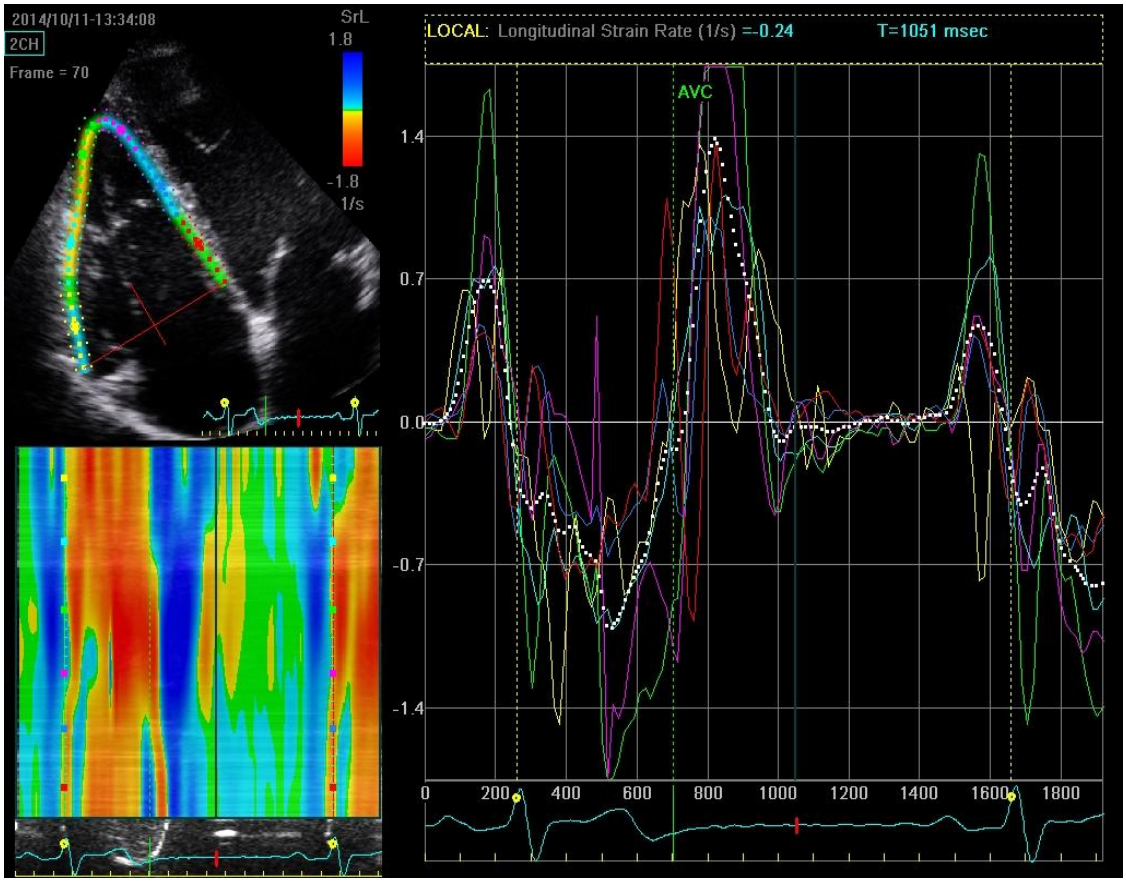

Figure 3. 11: Longitudinal SR Curves for the RV

In addition to the peak data, the raw data was exported to an excel spreadsheet (Excel, Microsoft Corp, Washington, US), where it underwent cubic spline interpolation to correct for variations in heart rates (Burns et al., 2010; Stohr et al., 2010) providing 300 ε and SR points in systole and 300 points in diastole. Normalization was realized by transferring the raw data to specialized graph software (San Diego, GraphPad Prism, and California). This data was then split into 5% increments to provide a comprehensive temporal assessment of RV ε across the cardiac cycle.

In order to establish intraobserver variability of blood pressure and conventional and strain imaging, the measurements from 10 athletes were repeated and the coefficient of variation presented (see tables 3.1 to 3.4).

Table 3.1: Intra-observer reliability and absolute mean± S.D. values for measurements in two times with Coefficient of variations (CoV) for the systolic blood pressure (SBP) and diastolic blood pressure (DBP)

	Scan 1	**Scan 2**	**CoV (%)**
Systolic blood pressure (mmHg)	132 ± 9	129 ± 12	2
Diastolic blood pressure (mmHg)	75 ± 6	76 ± 5	2

Table 3. 2: Intra-observer reliability and absolute mean± S.D. values for measurements in two times with Coefficient of variations (CoV) for the RV structure

	Scan 1	**Scan 2**	**CoV (%)**
RVOT-PLAX	30±4	31±4	4
RVOT1	30±3	31±3	7
RVOT2 (mm)	26±2	25±2	7
RVD1 (mm)	46±6	46±5	6
RVD2 (mm)	31±6	33±5	8
RVD3 (mm)	91±8	90±8	5
RVDA (cm^2)	31±5	27±4	5
RVSA (cm^2)	17±2	16±2	9

Table 3. 3: Intra-observer reliability and absolute mean± S.D. values for measurements in two times with Coefficient of variations (CoV) for the RV function and longitudinal **ε** and SR

	Scan 1	**Scan 2**	**CoV (%)**
TAPSE (mm)	25±4	26±4	8
TDI RV S' (cm/s)	13±2	14±2	9
TDI RV E' (cm/s)	16±3	17±2	8
TDI RV A' (cm/s)	9±3	9±2	8
Peak Strain (%)	-24 ± 3	-23 ± 4	6
Time to Peak Strain (s)	0.4 ± 0.03	0.4 0.05	2
Peak SRS' (l/s)	-1.1 ± 0.1	-1.1 ± 0.2	3
Peak SRE' (l/s)	1.6 ± 0.2	1.6 ± 0.4	9

Table 3. 4: Intra-observer reliability and absolute mean± S.D. values for measurements in two times with Coefficient of variations (CoV) for the temporal **ε** from base to apex gradient (%) and SR (l/s)

Base to apex ε gradient (%) and SR (l/s)	**Scan 1**	**Scan 2**	**CoV (%)**
lateral Wall:			
Basal ε	-24.5 ± 6.1	-26.6 ± 6.4	18

Basal SRS'	-1.5 ± 0.3	-1.8 ± 0.7	17
Basal SRE'	2.1 ± 0.6	2.5 ± 1.4	18
Basal SRA'	0.9 ± 0.4	1.1 ± 0.3	19
Mid ε	-29.3 ± 6.5	-29.5 ± 7.4	8
Mid SRS'	-1.4 ± 0.3	-1.4 ± 0.4	10
Mid SRE'	1.9 ± 0.7	2.0 ± 0.5	9
Mid SRA'	0.9 ± 0.3	0.9 ± 0.4	9
Apical ε	-34.0 ± 5.3	-31.7 ± 4.9	19
Apical SRS'	-2.1 ± 0.4	-1.7 ± 0.3	20
Apical SRE'	2.9 ± 0.7	2.5 ± 0.8	29
Apical SRA'	1.4 ± 0.5	1.1 ± 0.6	31
Septal Wall:			
Basal ε	-18.4 ± 2.2	-17.3 ± 3.5	16
Basal SRS'	-1.1 ± 0.2	-1.2 ± 0.3	17
Basal SRE'	1.4 ± 0.2	1.5 ± 0.2	10
Basal SRA'	0.7 ± 0.2	0.6 ± 0.2	22
Mid ε	-16.9 ± 3.2	-16.9 ± 3.1	7
Mid SRS'	-0.9 ± 0.2	-0.9 ± 0.2	5
Mid SRE'	1.4 ± 0.3	1.5 ± 0.2	9
Mid SRA'	0.5 ± 0.1	0.5 ± 0.2	17
Apical ε	-22.3 ± 2.2	-18.9 ± 6.8	33
Apical SRS'	-1.9 ± 0.4	-1.4 ± 0.3	28
Apical SRE'	2.5 ± 0.5	2.2 ± 1.7	27
Apical SRA'	0.7 ± 0.3	0.6 ± 0.3	30

Chapter 4: A Meta-Analysis for the Echocardiographic Assessment of Right Ventricular Structure and Function in ARVC

This study has been published :

Qasem, M., Utomi, V., George, K., Somauroo, J., Zaidi, A., Forsythe, L., Bhattacharrya, S., Lloyd, G., Rana, B., Ring, L., Robinson, S., Senior, R., Sheikh N., Sitali, M., Sandoval, J., Steeds, R., Stout, M., Willis J. and Oxborough, D. (2016). A meta-analysis for the echocardiographic assessment of right ventricular structure and function in ARVC. *Echo research and practice*, *3*(3), 95-104. It is available at the following address : (https://www.ncbi.nlm.nih.gov/pubmed/27686556)

Chapter 5: Influence of Different Dynamic Sporting Disciplines on Right Ventricular Structure and Function in Elite Male Athletes

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Chapter 6: Right Ventricular Function in Elite Male Athletes Meeting the Structural Echocardiographic Task Force Criteria for Arrhythmogenic Right Ventricular Cardiomyopathy

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Chapter 7: Electrocardiographic findings in Elite Male Athletes who meet the Structural Echocardiographic Task Force Criteria for Arrhythmogenic Right Ventricular Cardiomyopathy

This chapter compares ECG data for MTFC group and NMTFC and sought to establish if there are any differences and correlations between RV dimensions and the 12-lead ECG parameters.

7.1 Introduction

ARVC is one of the leading causes of sudden SCD in young athletes (Finocchiaro et al., 2016). Recent guidelines (Mont et al., 2017) for pre-participation cardiac screening highlight the importance of the role for the ECG in the diagnosis of this condition with specific criteria identified as meeting the TFC (Marcus et al., 2010) (see Table 2.1).

The development of the ARVC phenotype is progressive, often with early electrical maladaptation occurring prior to any structural changes (Gaido et al., 2017) . In turn, maladaptions may then result in life threatening arrhythmias. The 12-lead ECG can detect these changes as either: a prolonged S-wave duration of 55 ms in V1-3; localised QRS widening of 110 ms in V1-3; the presence of an epsilon wave (observed in 30% of ARVC patients) or the presence of TWI in the anterior leads (observed in 85% of

patients) (Perez Diez & Brugada, 2008; Corrado et al., 2009; Marcus et al., 2010; Biernacka et al., 2017). (see Figure 7.2)

Figure 7. 1: Epsilon wave (adapted from Corrado et al., 2009)

Figure 7. 2: Prolonged S-wave upstroke and localized QRS widening in V2 (adapted from Corrado et al., 2009)

Figure 7. 3: T-wave inversion in the anterior leads (adapted from Corrado et al., 2009)

As demonstrated in Chapter 5 and a number of previous studies (Oxborough et al., 2012b; D'Andrea et al., 2013; Oxborough et al., 2016), physiological RV enlargement is a common manifestation of the AH, occurring at both the inflow and outflow portions. This adaptation has been documented to meet the structural criteria for ARVC and even exceed it in a high proportion of athletes (Maron & Pelliccia, 2006; D'Andrea et al., 2010; Utomi et al., 2013; D'Ascenzi et al., 2017a, 2017b). It is well known that alongside the structural adaptation of both the right and left sides of the heart, elite athletes demonstrate a range of ECG changes (Zaidi et al., 2013a; McClean et al., 2017; Drezner et al., 2017). These ECG changes have been described in a range of different athlete groups (Drezner et al., 2017; McClean et al., 2017) and consequently, these observations have informed the development of International ECG criteria. Furthermore, these support diagnostic decision-making in cardiac pre-participation screening (Drezner et al., 2017; Sharma et al., 2017).

The association between physiological adaptation of the structural and electrical components of the RV in the AH are not fully understood. As it is clear that structural adaptation of the RV in athletes may "mimic" the ARVC phenotype, it is important to ascertain in such athletes what type and degree of ECG adaptation (or abnormality) they present with and whether this may also mimic ARVC. It is, therefore, the aim of this chapter, to document the ECG patterns in those athletes with augmented RVOT dimensions that meet the structural TFC for ARVC compared to those athletes NMTFC.

This study hypothesizes that those athletes that meet structural TFC will present a greater degree of training related ECG changes.

7.2 Methods

7.2.1 Participants

One hundred and thirty-nine male competitive athletes at national level (mean ± SD: 24 ± 1 years) allocated to one of two groups: 1) those MTFC; indexed RVOT (from the parasternal long axis view) (RVOT-PLAX ≥ 19 mm/m^2) and indexed RVOT (from the parasternal short axis view) (RVOT-PSAX ≥ 21 mm/m^2] and 2) those athletes that those NMTFC.

7.2.2 Study Design and Procedures

A retrospective cross-sectional study design was undertaken. Twenty-eight athletes met RV structural TFC with 111 athletes not meeting TFC and were grouped accordingly. Both groups were from mixed ethnicity [MTFC: white=93% and other=7%; NMTFC: White=79%, Mixed=6%, Asian=3%, Black=5% and other=7%] and sporting disciplines [low dynamic sporting disciplines = 18% and 7%, moderate dynamic sporting

disciplines = 7% and 22% and high dynamic sporting disciplines = 75% and 71% for MTFC and NMTFC respectively] (Mitchell et al., 2005; Levine et al., 2015). All the assessments and procedures were acquired and analysed as described in Chapter 3.

7.2.2.1 12-Lead Electrocardiogram

A standard resting 12-lead ECG (CardioExpress SL6, Spacelabs Healthcare, Washington US) was undertaken in accordance with the American Heart Association (AHA) (Mason et al., 2007). Measurements were obtained for the following measurements: heart rate (HR), PR interval, QT interval, corrected QT interval calculated by the Bazzet formula, QRS duration, R wave axis, P wave axis and T wave axis. Isolated QRS voltage criteria for LV hypertrophy (LVH) and RV hypertrophy (RVH) were determined manually by using Sokolow-Lyon criteria (LV>35 mV and RV>10.5mV). In addition, all ECGs were interpreted using the International Consensus Standards for electrocardiographic interpretation in athletes (Drezner et al., 2017; Sharma et al., 2017) and described as either a normal or abnormal ECG for an elite athlete (see Figure 2.13).

7.2.3 Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) (version 23.0, Chicago IL, USA). Normal distribution was tested using a Kolmogorov-Smirnov test. Analysis between both groups was undertaken using independent t-tests, where normal distribution was presented, and Mann-Whitney U tests when the distribution was not normal. Two-tailed $P<0.05$ were set as a significant. All continuous ECG parameters were presented as mean ± SD whilst prevalence of training and non-training related ECG changes were presented as %. Supplementary

analysis included Pearson's correlation analysis of the association between ECG indices and RV structural measures. A standard linear correlation was undertaken to determine the relative contribution of each independent parameters (i.e. absolute RVOT-PLAX) on the dependent variable (i.e. QRS axis and isolated QRS voltage criteria for RVH).

7.3 Results

Participants baseline demographic data were presented in Table 7.1. As per group selection, RV structural parameters for the RVOT were significant higher in MTFC ($P<0.05$) compared to NMTFC group.

Table 7. 1:ECG participant demographics comparing between athletes meeting structural task criteria (MTFC) for ARVC and those athletes not meeting task force criteria (NMTFC) (Mean ± SD)

	NMTFC (n=111)	**MTFC (n=28)**	**P Value**
Age (years)	23 ± 6	26 ± 6	0.169
BSA	1.9 ± 0.1	1.8 ± 0.2	0.116
Systolic blood pressure (mmHg)	123 ± 5	118 ± 11	0.052
Diastolic blood pressure (mmHg)	69 ± 8	69 ± 8	0.853
Heart Rate (beats.min^{-1})	51 ± 7	53 ± 9	0.308
Training (years)	13 ± 5	14 ± 7	0.688
Training (days per week)	6 ± 1	6 ± 1	0.079
Training (hours per week)	18 ± 9	20 ± 12	0.291

There were no significant differences between MTFC compared to NMTFC (P>0.01) for any of the ECG parameters except for P duration, QRS voltage criteria for LVH and QRS duration (see table 7.2).

Table 7. 2: ECG parameters comparing between athletes meeting structural task criteria (MTFC) for ARVC and those athletes not meeting task force criteria (NMTFC) (Mean ± SD)

	NMTFC (n=111)	**MTFC (n=28)**	**P Value**
P Duration (ms)	106 ± 21	96 ± 16	0.033
PR Interval (ms)	173 ± 31	169 ± 29	0.539
QRS Duration (ms)	93 ± 9	99 ± 16	0.018
QT Interval (ms)	418 ± 24	419 ± 36	0.848
QT Corrected (Bazett)	384 ± 23	390 ± 22	0.189
P Axis	39 ± 28	44 ± 27	0.449
QRS Axis	66 ± 26	53 ± 52	0.072
T Axis	37 ± 16	42 ± 14	0.117
R wave in V1 + S wave in V5	7 ± 4	7 ± 4	0.727
S wave in V1 + R wave in V5	31 ± 10	37 ± 13	0.012

85% of MTFC and 83% of NMTFC had normal training related ECG findings (see Figure 7.4). 8% of MTFC and 4% NMTFC of athletes was present in a single athlete from both groups had abnormal ECG criteria. Anterior TWI in 4% of both MTFC (a single athlete) and NMTFC athletes as well as inferior T-wave inversion in a single

MTFC athlete (4%). No athletes from both groups presented with any borderline ECG finding.

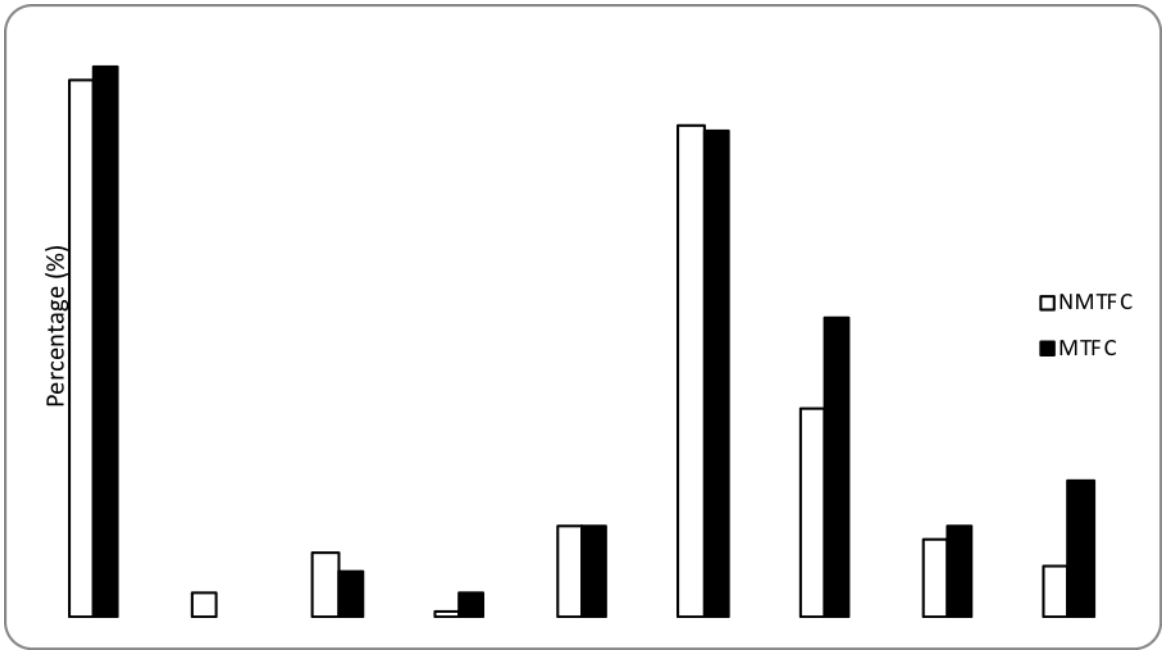

Figure 7. 4: Normal Training Related ECG Finding (%): sinus bradycardia (SB); ectopic atrial rhythm (EAR); right bundle branch block (RBBB); early repolarisation (ER); isolated QRS voltage criteria for LVH without LAD (ECG LVH); isolated QRS voltage criteria for RVH without RAD (ECG RVH); sinus arrhythmia (SA)

There was no significant correlations between ECG criteria for RV enlargement (i.e. QRS voltage criteria for RVH and RBBB) and absolute RV size structure (P>0.01). There was however a significant correlation between QRS axis correlated with absolute RVOT-PLAX (r= -0.311 and p= 0.001) accounted for 10% (see Figure 7.5)

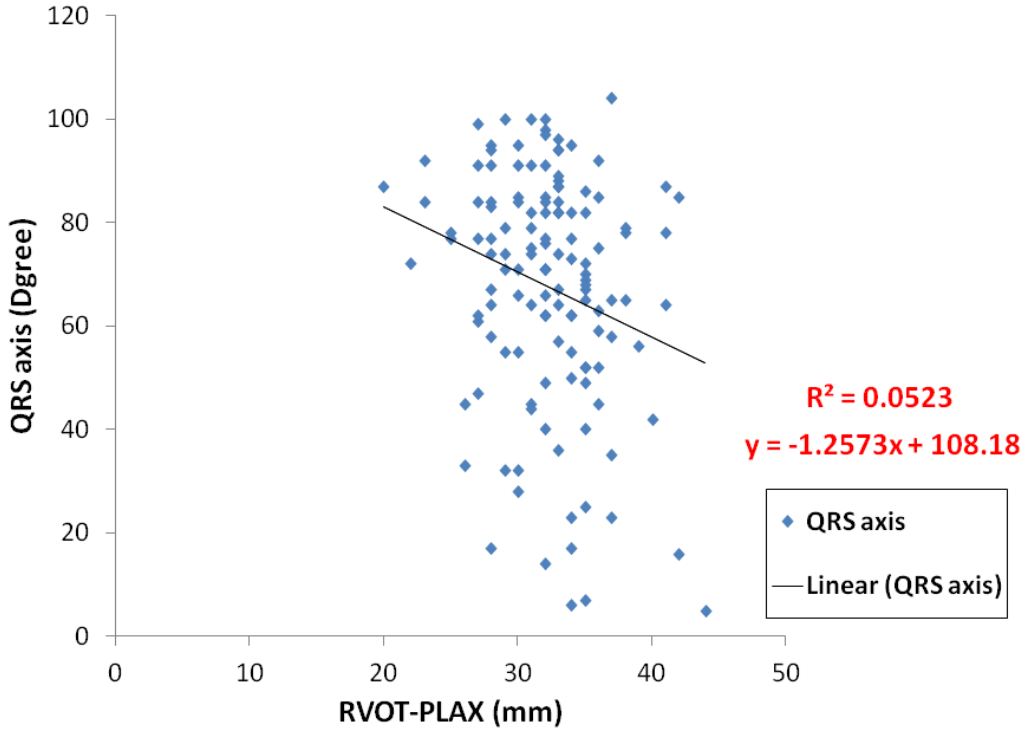

Figure 7. 5: Scatter Plot of a crroleting between absolute RV outflow tract diameter at the parasternal long-axis view (RVOT-PLAX) and ECG QRS

The single athlete presented with abnormal ECG finding i.e. TWI in the inferior leads and met the full structural TFC for ARVC, had RVFAC= 42%, TDI RVS'= 16 cm/s and RV ε= -25%. The other single health athletes from the same group i.e. MTFC presented with TWI in the anterior leads had RVFAC= 44%, TDI RVS'= 12 cm/s and RV ε= -19%. That aside, the NMTFC has 4 healthy athletes presented with TWI in the anterior leads had RVFAC= 59,33,40 and 40%, TDI RVS'= 13, 14,14 and 15 cm/s and RV ε= -26, -28, -26 and -21%, respectively.

7.4 Discussion

The key findings from this study were: 1) that there were no differences in training and non-training ECG findings between MTFC and NMTFC healthy athletes including, having TWI in both groups and thus demonstrating a problem with TFC when applying it to populations of athletes and; 2) there was no relationship between RV size and those ECG indices that are of indicative RV enlargement.

The current study presents normal ECG findings related to exercise training in the MTFC athlete's group and hence there are no significant difference in most of ECG parameters when compared to the NMTFC athletes group. Both groups also exhibit an approximately similar percentage of normal training related ECG criteria. Chronic exercise training is associated with changes in electrical parameters that reflects the global effects of training on chamber size as demonstrate by QRS voltage criteria for RVH and incomplete RBBB (Drezner et al., 2017). Additionally, this study presents no difference in isolated QRS voltage criteria for RVH as well as a lack of any correlation with ECG parameter between both groups and thus, supports the findings from previous studies (Kim et al., 2011; Zaidi et al., 2013b). In isolation it these changes are considered to be normal physiological adaptation of exercise training (Uberoi et al., 2011; Zaidi et al., 2013b; Drezner et al., 2013). Previous studies (Kim et al., 2011; Zaidi et al., 2013b; Drezner et al., 2013) have demonstrated that the presence of incomplete RBBB in athletes is considered normal, caused by RV adaptation coupled with increased in the RV dimension.

On the other hand, many previous studies (Brosnan et al., 2014; Wasfy et al., 2014; Malhotra et al., 2016) have reported TWI in healthy athletes in anterior leads , as well as

the inferior leads (Brosnan et al. 2014). A single healthy athlete from MTFC presented with TWI in the inferior leads and another with anterior t-wave inversion without systolic dysfunction. These findings in isolation do not suggest ARVC (Drezner et al., 2017). In addition to these 2 athletes, 4 athletes in the NMTFC group also presented with TWI in the anterior leads highlighting no predominance between groups. Along with this, it has been reported TWI in the anterior leads can be a normal finding (Brosnan et al., 2014; Wasfy et al., 2014; Malhotra et al., 2016) and is reflective of the degree of RV adaptation to exercise (Wasfy et al., 2014; Malhotra et al., 2016). In view of this, in contrast to the previous statement that electrical presentation often precedes any structural adaptation (Gaido et al., 2017), this study demonstrates that electrical changes do not necessarily precede changes in physiological cardiac morphology or function and thus is an important issue to be considered during pre-participation screening.

7.4.1 Clinical Implication/Perspective

In pre-participation cardiac screening programs, the differentiation of RV physiological adaptation from pathological changes altered by ARVC is of the utmost importance, in order to prevent false-positive or false negative screening outcomes. This is crucial for preventing SCD or, the unnecessary early retirement from professional sports. Consequently, this study provides valuable information on the electrical conduction system in athletes meeting structural TFC for ARVC, which may aid in specific screening programs. The findings advocate the combination of both ECG with an echocardiogram in order to detect the physiological structural RV adaptation.

7.4.2 Limitation

The limitations of this study include the small sample size in the MTFC group, larger samples would have improved the power and generalisability of the data. The addition of a sedentary control group and ARVC group would also provide some insight. Furthermore, this study only investigated RV remodelling among male athletes but, it is apparent that further studies in female athletes and/or different ethnicities would be valuable.

Additionally, it is well known that highly trained athletes exhibit cardiac adaptation including LV hypertrophy (Utomi et al., 2013) and this physiological adaption will contribute to changes that occur to the RV through the principle of ventricular interdependency (Duncan, 2012). As per design, this study focused only on the RV and therefore future studies are needed to assess both ventricular structure and functions as determined by echocardiography and 12-lead ECG.

7.5 Conclusion

Athletes meeting structural TFC for ARVC did not show significant differences on the 12-lead ECG compared to those athletes NMTFC. These data suggest that training related and raining non related and RV ECG indices are independent of physiological structural adaptation. In view of this it is apparent that electrical changes do not precede changes in RV structure and function in athletes meeting TFC.

Chapter 8: General Discussion

The results of this thesis provide an understanding into the nature of RV structure and function pertaining to the AH. In addition, these data will provide information to enhance ECG and echocardiography criteria in PPCS for elite male athlete that present with extreme phenotypical expression of the AH and meeting TFC for ARVC disease.

8.1 Summary of Findings

Chapter 4 described the extent and magnitude of conventional echocardiographic and STE measures of RV function in patients with ARVC. This evidenced lower cut-off values for both RVOT1 and RVDA than the normative cut-off value proposed by ASE, and lower than ARVC TFC for RVOT1; thus indicating the potential for a false negative result when using the existing criteria in PPCS. In addition, the RVFAC cut-off value is higher in this study, than ARVC TFC, which raises another question, of what is considered normal. This study demonstrates that additional measures reflect the complex geometry and functioning in ARVC, clearly differentiated between ARVC and healthy controls. Thus, the finding may provide additional diagnostic and management values, especially for PPCS.

Chapter 5 aimed to determine the nature of the impact of the RV phenotype of sporting discipline, and its dynamic component, on RV structure and function, as determined by conventional echocardiography and STE, in a large sample of elite male athletes. The absolute structural measures were reported to be greater in athletes engaged in the Moderate dynamic group and High Dynamic training compared to the Low Dynamic training group. However, when these absolute measures scaled to the HD training group

had the greatest values, when compared to MD and then LD, and even for the RV inflow tract (i.e. RVD1). There was no difference in conventional and STE function between the three groups. Athletes in the MD training groups, demonstrated smaller base to apex ε gradient in both septal and lateral walls, largely due to reduced apical ε and this appears to be partly related to absolute RV chamber size.

Chapter 6 and 7 provided additional insight into the AH on those athletes with extreme phenotypical presentation of RV dimensions that met for ARVC compared to those not meeting TFC. Chapter 6 assessed RV structure and function via echocardiography. By design, this study demonstrated greater absolute and scaled RV structural values at outflow tract; however, there is a lack of proportional enlargement of the inflow and RVDA with an increased RVOT/RVD1 ratio. In addition, functional parameters in this study found no differences between both groups for RV FAC and TAPSE with absolute RV FAC that met TFC in a small proportion of the athletes. Athletes in the MTFC group had lower global RV ε, SRS' and SRA' compared to the NMTFC athletes, which may be explained by the larger RVOT dimension. In chapter 7, data was compared between both groups via 12-ECG. Results evidenced general normality in the ECG findings, and that electrical changes do not necessary precede changes in cardiac morphology or function; thus this is an important consideration in PPCS.

8.2 Overarching Issues and Implications for Pre-Participation Screening

8.2.1 Athletes heart adaptation

In study 2 within this thesis, findings confirmed the importance of the dynamic component as a primary factor for cardiac adaptation in a variable population of elite

athletes, and its association with. This supporting the concept that chronic dynamic training contributes to a 'bi-ventricle' hypertrophy of the myocardium (Utomi et al., 2013). Ventricular enlargement is likely related to the sustained elevation in preload experienced during dynamic training that causes a repetitive volume challenge (McClean et a., 2014; Oxborough et al., 2016). This enlargement permits an increased capacity to meet the high intensity workload through an amplified atrial ejection volume to the simultaneously dilating ventricle (Maron et al., 2006). Enlargement may further be compounded by increased expression levels of the b-myosin heavy chain isoform (fundamental to chamber enlargement) as evidenced from chronic dynamic training within animal studies (Hoit et al., 1995). In contrast, structural remodelling was not observed in LD athletes. This could be explained by the limited elevation in preload during static training, due to its intermittent nature of repetitions with sets and work-to-rest ratios. Additionally, a Valsalva manoeuvre may be integrated into a static exercise, which would have the impact of increasing intra-thoracic pressures and thereby concomitantly reducing atrial preload (Haykowsky et al., 2003). Our data suggest that, for an athlete to undergo physiological structural remodelling of the ventricle, a chronic sustained elevation of preload must be present. Also along with cardiac adaptation, exercise in high dynamic training was found to elicit higher inflow and outflow tract values, unlike findings reported in an earlier meta-analysis study that reported no differences in outflow tract values between different sport disciplines (D'Ascenzi et al., 2017b). As a result, it is more challenging to differentiate between physiological adaptation and RV pathology, such as ARVC in those athletes participating in high dynamic exercise training. Importantly, clinical decision-making based on absolute cardiac dimension is challenging due to anthropometric differences (Brown et al., 2017), particularly in bigger athletes as was noted in the MD group. Thus, this study

confirms that allometrical scaling to BSA is essential for more effective and accurate data interpretation in PCSS.

Furthermore, despite the structural differences in RV structure between different dynamic components, there are no general differences in functional parameters; conventional, TDI and peak longitudinal RV ε and SR, to support prior studies' findings (D'Andrea et al., 2013; Oxborough et al., 2016). This suggests that long term cardiac adaptation occurs primarily at a structural level, providing the same stroke volume under different dynamic loads. That aside, Chapter 7 reported general normal ECG findings in MTFC with no correlation between RV dimension and ECG, findings that are related to RV size (i.e. QRS voltage criteria for RVH and incomplete RBBB). This demonstrates that electrical changes do not precede changes in RV structure and function in athletes meeting TFC and that echocardiography should be undertaken alongside the 12-lead ECG. Also, it is important to state that all participants in the three studies in this thesis are healthy athletes therefore more studies are needed to include ARVC patients in their data in order to confirm and translate this information into clinic.

8.2.2 ARVC and the task force criteria

ARVC patients tend to have no general RV structural overlap with healthy people as demonstrated in Chapter 4. Importantly, there was a lower cut-off value in RVDA compared to the ASE recommendations, and lower RVOT1 than ARVC TFC. Thus is identifying the potential of raising the false-negative result when using existing criteria, especially for those athletes who are involved in high dynamic exercise training. Further to this, as has been previously mentioned when exercising, the HD group would

increase the RV cavity; inflow and outflow tract, increasing the challenge of diagnosing ARVC among athletes. Chapter 6 in this thesis evidenced that even in healthy athletes that met structural TFC for ARVC, RV inflow tract and RV end-diastolic area were not necessarily greater and that increase the possibility of false-negative and false-positive results. Therefore, it is important to understand the local focus on the RVOT may not necessarily reflect the overall RV dimension. That aside, RVFAC is considered to be an important element and one of the major functional criteria in the TFC for diagnosing ARVC. However in Chapter 4, RVFAC reported a higher cut-off value of 42%, compared with 33% in the TFC (i.e. 11% difference) and this uncertainty around RVFAC continued to arise in athletes in Chapter 5 where healthy athletes in the MTFC group exhibited lower RVFAC than proposed by the TFC for RVFAC. Therefore, it is suggested that athletes can show a slightly lower RV function at rest as a result of a physiological consequences of the extreme RV remodelling, which is induced by exercise. Therefore, relying on RVFAC for elite male athletes is not appropriate. Future studies are needed therefore, to investigate the effect of chronic exercise on RV function via RV FAC and its practicality in cardiac pre-participation screening among elite athletes.

The meta-analysis in this thesis reports that additional parameters besides the two RV structural and functional parameters recommended by the TFC for ARVC may improve the diagnostic ability in PPCS. This is due to the findings of significant differences in longitudinal RV ε between ARVC patients and the healthy control group. Further to this, chapter 5 presented no significant differences for longitudinal RV ε between healthy athletes in different sporting disciplines in different dynamic components. Initially, this may present a clinical implication for longitudinal RV ε in diagnosing RV

pathology. However, study 3 reported lower longitudinal RV ε in healthy athletes in the MTFC groups when compared to NMTFC. Although, this reduction is considered small, it is significant in terms of its potential usefulness in differentiating between healthy athletes with healthy extreme phenotypical presentations of RV dimensions that meet TFC for ARVC and athletes with RV pathology ,however further study needed to compare these results to ARVC patients. Along with this, the European Association of Cardiovascular Imaging (Pelliccia et al., 2017) recommended the use of the regional RV ε as being able to objectively quantify regional RV dysfunction. Despite the regional RV ε between MTFC and NMTFC showing no significant difference in the 2nd study showing significant difference between MD group compared to both HD and LD groups that correlate partly to the BSA. This raise the uncertainty regarding the valuably of regional RV ε in PPSC.

In view of this, longitudinal and regional RV ε seems to be influenced by different factors, when assessing athletes and consequently, longitudinal and regional ε might not appropriate measure for RV in elite athletes in order to differentiate physiological adaptation from RV pathology.

8.3 Future Research

Changes in RV ε may occur in different seasonal variation, and thus, this raises the importance of investigating the alteration of RV function in different seasons in PCCS. The evidenced strong relationship between training amount (i.e. intensity and duration), fitness and cardiac dimension, with the extent of cardiac changes that are physiologically appropriate or not, raises questions as to the appropriateness of utilising Mitchell Classification without verifying athletes fitness level (Beaudry et al., 2016)

that plays important role in determining the time course and pattern of ventricular remodelling that related to underlying training load (intensity and duration) and prior training exposure (Haykowsky et al., 2018). Moreover, this classification does not consider the emotional stress that an athlete experiences during a competitive event, the effects of environmental factors, electrolyte abnormalities, or the specific training regimen used by the athlete (Mitchell et al., 2005).

Furthermore, few studies from meta-analysis study have examined the LV side in ARVC (Prakasa et al, 2007; Bauce et al 2008; Tops et al 2009; Teske et al 2009a; Lacoviello et al 2011; Aneq et al 2012). However those available did not offer sufficient data to justify inclusion in this study's data analysis. Notably, researchers have reported no difference in LVEF % between ARVC patient and healthy control (Prakasa et al, 2007; Bauce et al 2008; Tops et al 2009; Lacoviello et al 2011), but this can be explained by that the TFC when it established and it was focusing on the RV and including only patients without or with mild LV involvement (Marcus et al., 2010). Thus it is difficult when using TFC to diagnose ARVC among athletes with LV hypertrophy and it is notable that the third study reported significant differences in RV: LV ration between MTFC and NMTFC groups, supporting the need for a modified TFC for athletes. Future studies should examine also the LV, particularly in athletes with hypertrophy.

The studies included in this thesis were cross sectional design as well as meta-analysis of male athletes. These methodological designs cannot directly support a 'cause effect' relationship between exercise, mode and physiological cardiac remodelling. Further work should expand the participant base and dataset; to increase the sample size and therefore

adequate statistical power, include female subjects as well as a development of a prospective cohort design. Another important limitation in our clinical trials is that ECG and echocardiography acquisition and post-processing, though performed by experienced research scientists, were not blinded to participant identity, therefore the potential for bias exists.

8.4 Conclusion

The nature and extent of the RV adaptation influenced by different dynamic exercise training reflects the RV complexity as a result of adaptation to different workloads and to provide same stroke volume in different conditions. The normative RV echocardiographic structural and functional parameters in ARVC that have been presented in this thesis are expected to enhance the efficacy of echocardiography in diagnosing ARVC. RVFAC is shown to possess the possibility to go below the range that was proposed by the TFC for ARVC in healthy athletes and this demonstrates uncertainty when utilised in PPCS. The use of the novel echocardiographic technique is evidenced to demonstrate key issues when utilised on athletes in PPCS that needs for further investigation before utilising it in PPCS, in differentiating between physiological adaptations and ARVC.

References

Abraham, P., Dimaano, L. and Liang, Y. (2007) Role of tissue Doppler and strain echocardiography in current clinical practice. *Circulation*.,116(22), 2597–609.

Amundsen, H., Helle-Valle, T., Edvardsen, T., Torp, H., Crosby, J., Lyseggen, E., Stoylen, A., Ihlen, H., Lima, C., Smiseth, A. and Slordahl, A. (2006) Noninvasive Myocardial Strain Measurement by Speckle Tracking Echocardiography: Validation Against Sonomicrometry and Tagged Magnetic Resonance Imaging. *Journal of the American College of Cardiology*, 47(4), 789–793.

Anavekar, S., Gerson, D., Skali, H., Kwong, Y., Kent Yucel, E. and Solomon, D. (2007) Two-Dimensional Assessment of Right Ventricular Function: An Echocardiographic-MRI Correlative Study. *Echocardiography*, 24(5), 452–456.

Aneq, M. (2011) Arrhythmogenic right ventricular cardiomyopathy: Is it right? Linköping University Medical dissertation no. 1257.

Aneq, M., Engvall, J., Brudin, L. and Nylander, E. (2012) Evaluation of right and left ventricular function using speckle tracking echocardiography in patients with arrhythmogenic right ventricular cardiomyopathy and their first degree relatives. *Cardiovascular Ultrasound*, 10(1), 37.

Aneq, M., Lindström, L., Fluur, C. and Nylander, E. (2008) Long-term follow-up in arrhythmogenic right ventricular cardiomyopathy using Tissue Doppler Imaging. *Scandinavian Cardiovascular Journal*, 42(6), 368–374.

Andersen, H., Terkelsen, J., Sloth, E. and Poulsen, H. (2004) Influence of preload alterations on parameters of systolic left ventricular long-axis function: a Doppler tissue study.*Journal of the American Society of Echocardiography*, 17(9) , 941–947.

Arbab-Zadeh, A., Perhonen, M., Howden, E., Peshock, M., Zhang, R., Adams-Huet, B., Haykowsky, J. and Levine, D. (2014) Cardiac remodeling in response to 1 year of intensive endurance training. *Circulation.*, 130(24), 2152–2161

Artis, J., Oxborough, L., Williams, G., Pepper, B. and Tan, B. (2008) Two-dimensional strain imaging: A new echocardiographic advance with research and clinical applications. *International Journal of Cardiology*, 123(3), 240–248.

Baggish, L., Wang, F., Weiner, B., Elinoff, M., Tournoux, F., Boland, A., Picard, H., Hutter, M., Wood, J., Al, B., Wang, F., Rb, W., Jm, E., Tournoux, F., Boland, A., Mh, P., Jr, M. and Training-, J. (2008) Training-specific changes in cardiac structure and function : a prospective and longitudinal assessment of competitive athletes. *Journal of Applying Physiology*, 104, 1121–1128.

Baker, D. W. (1970) Pulsed ultrasonic Doppler blood flow sensing. *IEEE Transactions on Sonics and Ultrasonics*,17(3).

Bansal, M. and Kasliwal, R. (2013) How do i do it? Speckle-tracking echocardiography. *Indian Heart Journal*. Cardiological Society of India, 65(1) , 117–123.

Basso, C., Corrado, D., Marcus, I., Nava, A. and Thiene, G. (2009) Arrhythmogenic right ventricular cardiomyopathy. *Lancet*, 373(9671),1289–300.

Basso, C., Thiene, G., Corrado, D., Angelini, A., Nava, A. and Valente, M. (1996) Arrhythmogenic right ventricular cardiomyopathy Dysplasia, dystrophy, or myocarditis? *Circulation*. Am Heart Assoc, 94(5), 983–991.

Batterham, M., George, P., Whyte, G., Sharma, S. and McKenna, W. (1999) Scaling cardiac structural data by body dimensions: a review of theory, practice, and

problems. *International journal of sports medicine*. University, 20(8), 495–502.

Bauce, B., Frigo, G., Benini, G., Michieli, P., Basso, C., Folino, F., Rigato, I., Mazzotti, E., Daliento, L., Thiene, G. and Nava, A. (2010) Differences and similarities between arrhythmogenic right ventricular cardiomyopathy and athlete's heart adaptations. *British journal of sports medicine*, 44(2),148–154.

Berge, M., Isern, B. & Berge, E. (2014) Blood pressure in elite athletes: a systematic review. *British Journal of Sports Medicine*, 48(7), 567-567.

Biernacka, K., Platonov, G. and Fronczak, A. (2017) Should epsilon wave be considered as a major diagnostic criterion in arrhythmogenic right ventricular cardiomyopathy? *Polish Heart Journal*, 75(3),191–195.

Bleeker, B., Steendijk, P., Holman, R., Yu, M., Breithardt, A., Kaandorp, M., Schalij, J., Van der Wall, E., Nihoyannopoulos, P. and Bax, J. (2006) Assessing right ventricular function: the role of echocardiography and complementary technologies. Heart, 92,i19–i26.

Bom, N., Lancee, C., Van Zwieten, G., Kloster, F. and Roelandt, R. (1973) Multiscan Echocardiography: I. Technical Description. *Circulation*, 48(5),1066–1074.

Borges, C., Knebel, F., Eddicks, S., Panda, A., Schattke, S., Witt, C. and Baumann, G. (2006) Right Ventricular Function Assessed by Two-Dimensional Strain and Tissue Doppler Echocardiography in Patients With Pulmonary Arterial Hypertension and Effect of Vasodilator Therapy.*The American Journal of Cardiology*, 98(4), 530–534.

Brosnan, M., La Gerche, A., Kalman, J., Lo, W., Fallon, K., MacIsaac, A. and Prior, L. (2014) Comparison of Frequency of Significant Electrocardiographic

Abnormalities in Endurance Versus Nonendurance Athletes. *American Journal of Cardiology*, 113(9), 1567–1573.

Brown, B., Somauroo, J., Green, J., Wilson, M., Drezner, J., George, K. and Oxborough, D. (2017) The Complex Phenotype of the Athlete ' s Heart : Implications for Preparticipation Screening. Exercise and Sport Sciences Reviews, 45(2), 96–104.

Brown, B., Raina, A., Katz, D., Szerlip, M., Wiegers, E. and Forfia, R. (2011) Longitudinal shortening accounts for the majority of right ventricular contraction and improves after pulmonary vasodilator therapy in normal subjects and patients with pulmonary arterial hypertension. *Chest*, 140(1), 27–33.

Buckberg, G. and Hoffman, E. (2014) Evolving Technology/Basic Science Right Ventricular Architecture Responsible for Mechanical Performance : Unifying Role of Ventricular Septum. *The Journal of Thoracic and Cardiovascular Surgery*, 148(6), 3166–3171.

Burns, T., La Gerche, A., Prior, L. and MacIsaac, I. (2010) Left Ventricular Torsion Parameters are Affected by Acute Changes in Load. *Echocardiography*. Blackwell Publishing Inc, 27(4), 407–414.

Caso, P., Galderisi, M., Andrea, D., Maggio, Di, Simone, De, Martiniello, R., Mininni, N. and Calabro, R. (2002) Analysis by Pulsed Doppler Tissue Imaging of Venticular Interaction in Long-Distance Competitive Swimmers, 9149(02), 193–197.

Chandra, N., Bastiaenen, R., Papadakis, M. and Sharma, S. (2013) Sudden Cardiac Death in Young Athletes: Practical Challenges and Diagnostic Dilemmas. *Journal of the American College of Cardiology*, 61(10), 1027–1040.

Cho, J., Jiamsripong, P., Calleja, M., Alharthi, S., McMahon, M., Khandheria, K.

and Belohlavek, M. (2009) Right ventricular free wall circumferential strain reflects graded elevation in acute right ventricular afterload. *American journal of physiology. Heart and circulatory physiology*, 296 (2), 413-20.

Coats, J., Quarta, G., Flett, S., Pantazis, A., McKenna, J. and Moon, C. (2009) Arrhythmogenic left ventricular cardiomyopathy. *Circulation*, 120(25), 2613–2614.

Conti, G., Cipolletta, L., Marino, V., Zucchetti, M., Russo, E., Pizzamiglio, F., Al-mohani, G., Pala, S., Catto, V., Biase, D., Natale, A., Tondo, C. and Carbucicchio, C. (2015) Right Ventricular Outflow Tract Arrhythmias : Benign Or Early Stage Arrhythmogenic Right Ventricular Cardiomyopathy / Dysplasia ? Journal of Atrial Fibrillation, 7(4).

Corrado, D., Basso, C., Rizzoli, G., Schiavon, M. and Thiene, G. (2003) Does sports activity enhance the risk of sudden death in adolescents and young adults? *Journal of the American College of Cardiology*, 42(11), 1959–1963.

Corrado, D., Basso, C. and Thiene, G. (2009) Arrhythmogenic right ventricular cardiomyopathy: an update.' *Heart*, 95(9), 766–773.

Corrado, D., Basso, C., Thiene, G., McKenna, J., Davies, J., Fontaliran, F., Nava, A., Silvestri, F., Blomstrom-Lundqvist, C. and Wlodarska, K. (1997) Spectrum of clinicopathologic manifestations of arrhythmogenic right ventricular cardiomyopathy/dysplasia: a multicenter study. *Journal of the American College of Cardiology*, 30(6), 1512–1520.

Corrado, D., Pelliccia, A., Bjørnstad, H., Vanhees, L., Biffi, A., Borjesson, M., Panhuyzen-Goedkoop, N., Deligiannis, A., Solberg, E. and Dugmore, D. (2005) Cardiovascular pre-participation screening of young competitive athletes for prevention

of sudden death: proposal for a common European protocol: consensus statement of the Study Group of Sport Cardiology of the Working Group of Cardiac Rehabilitation and. *European heart journal*, 26(5), 516–524.

Corrado, D., Schmied, C., Basso, C., Borjesson, M., Schiavon, M., Pelliccia, A., Vanhees, L. and Thiene, G. (2011) Risk of sports: do we need a pre-participation screening for competitive and leisure athletes? *European heart journal*, 32(8), 934–944.

Corrado, D. and Thiene, G. (2006) Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia: Clinical Impact of Molecular Genetic Studies. *Circulation*, 113(13), 1634–1637.

Dalen, H., Thorstensen, A., Aase, A., Ingul, B., Torp, H., Vatten, J. and Stoylen, A. (2010) Segmental and global longitudinal strain and strain rate based on echocardiography of 1266 healthy individuals: the HUNT study in Norway. *European journal of echocardiography*, 11(2), 176–83.

Dambrauskaite, V., Delcroix, M., Claus, P., Herbots, L., D'Hooge, J., Bijnens, B. and Al, E. (2007) Regional Right Ventricular Dysfunction in Chronic Pulmonary Hypertension. *Journal of the American Society of Echocardiography*, 20, 1172–1180.

D'Andrea, D., Bossone, E., Radmilovic, J., Caso, P., Calabrò, R., Russo, G. and Galderisi, M. (2015) The role of new echocardiographic techniques in athlete ' s heart. *F1000Research*, 289, 1–11.

D'Andrea, A., Caso, P., Bossone, E., Scarafile, R., Riegler, L., Di Salvo, G., Gravino, R., Cocchia, R., Castaldo, F., Salerno, G., Golia, E., Limongelli, G., De Corato, G., Cuomo, S., Pacileo, G., Russo, G. and CalabrÃ, R. (2010) Right ventricular myocardial involvement in either physiological or pathological left ventricular

hypertrophy: an ultrasound speckle-tracking two-dimensional strain analysis. *European Journal of Echocardiography*, 11(6), 492–500.

D'Andrea, D., Caso, P., Sarubbi, B., Limongelli, G., Liccardo, B., Cice, G., Andrea, D., Scherillo, M., Cotrufo, M. and Calabr, R. (2003) Right Ventricular Myocardial Adaptation to Different Training Protocols in Top-Level Athletes, 20(4), 329–336.

D'Andrea, D., Caso, P., Scarafile, R., Salerno, G., Corato, De, Mita, Di, Allocca, F., Colonna, D., Caprile, M., Ascione, L., Cuomo, S. and Calabrò, R. (2007) Biventricular myocardial adaptation to different training protocols in competitive master athletes, 115, 342–349.

D'Andrea, A., De Corato, G., Scarafile, R., Romano, S., Reigler, L., Mita, C., Allocca, F., Limongelli, G., Gigantino, G., Liccardo, B., Cuomo, S., Tagliamonte, G., Caso, P. and Calbrò, R. (2008) Left atrial myocardial function in either physiological or pathological left ventricular hypertrophy: a two-dimensional speckle strain study. *British Journal of Sports Medicine*, 42(8), 696–702.

D'Andrea, A., Naeije, R., D'Alto, M., Argiento, P., Golia, E., Cocchia, R., Riegler, L., Scarafile, R., Limongelli, G., Di Salvo, G., Citro, R., Caso, P., Russo, G., Calabrò, R. and Bossone, E. (2011) Range in Pulmonary Artery Systolic Pressure Among Highly Trained Athletes.*Chest*, 139(4), 788–794.

D'Andrea, A., Riegler, L., Golia, E., Cocchia, R., Scara, R., Salerno, G., Pezzullo, E., Nunziata, L., Citro, R., Cuomo, S., Caso, P., Di, G., Cittadini, A., Giovanna, M., Calabrò, R. and Bossone, E. (2013) Range of right heart measurements in top-level athletes : The training impact. *International Journal of Cardiology*, 164, 48–57.

D'Ascenzi, F., Cameli, M., Padeletti, M., Lisi, M., Morelli, M., Maria, G., Cosetta, V., Marco, M., Causarano, A. and Mondillo, S. (2013) Characterization of right atrial function and dimension in top-level athletes : a speckle tracking study. *International Journal of Cardiovascuolar Imaging*, 29:87–94.

D'Ascenzi, F., Caselli, S., Solari, M., Pelliccia, A., Cameli, M., Focardi, M., Padeletti, M., Corrado, D., Bonifazi, M. and Mondillo, S. (2015) Novel echocardiographic techniques for the evaluation of athletes ' heart : A focus on speckle-tracking echocardiography. *European Journal of Preventive Cardiology,* 0(00), 1-10

D'Ascenzi, F., Pelliccia, A., Corrado, D., Cameli, M., Curci, V., Alvino, F., Natali, M., Focardi, M., Bonifazi, M. and Mondillo, S. (2015) Right ventricular remodelling induced by exercise training in competitive athletes. *European Heart Journal : Cardiovascular Imaging* , 17, 301–307.

D'Ascenzi, F., Pelliccia, A., Solari, M., Piu, P., Loiacono, F., Anselmi, F., Caselli, S., Focardi, M., Bonifazi, M. and Mondillo, S. (2017b) Normative Reference Values of Right Heart in Competitive Athletes: A Systematic Review and Meta-Analysis. *Journal of the American Society of Echocardiography*, 30(9), 845–858.

D'Ascenzi, F., Pisicchio, C., Caselli, S., Paolo, D., Spataro, A. and Pelliccia, A. (2017a) RV Remodeling in Olympic Athletes.' *Journal of American College of Cardiology :Cardiovascular Imaging,* 10(4), 385-393.

De Luca, A., Stefani, L. and Galanti, G. (2013) Right Ventricle Chamber of Young Trained Athletes: Morphology and Function. *Asian Journal of Sports Medicine,* 4 (4), 281-288.

Dewey, E., Rosenthal, D., Murphy, J., Froelicher, F. and Ashley, A. (2008)

Contemporary Reviews in Cardiovascular Medicine Does Size Matter？ Clinical Applications of Scaling Cardiac Size and Function for Body Size. *Circulation*, 117, 2279-2287.

Douglas, S., Garcia, J., Haines, E., Lai, W., Manning, J., Patel, R., Picard, H., Polk, M., Ragosta, M., Ward, P. and Weiner, B. (2011) ACCF/ASE/AHA/ASNC/ HFSA/HRS/SCAI/SCCM/SCCT/SCMR 2011 Appropriate Use Criteria for Echocardiography: A Report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Society of Echocardiography, American Heart Associat. *Journal of the American College of Cardiology*, 57(9), 1126–1166.

Douglas, S. and Toole, O. (1990) Different Effects of Prolonged Exercise on the Right and Left Ventricles.' *Journal of the American College of Cardiology*, 15(1), 64–69.

Drezner, J. (2012) Standardised criteria for ECG interpretation in athletes: a practical tool. *British Journal of Sport and Excercise Medicine*, 46, 335–340.

Drezner, J., Ackerman, M., Anderson, J., Ashley, E., Asplund, C., Baggish, L., Börjesson, M., Cannon, B. , Corrado, D. and DiFiori, J. (2013) Electrocardiographic interpretation in athletes: the "Seattle criteria." *British Journal of Sport and Excercise Medicine*, 47(3), 122–124.

Drezner, J., Sharma, S., Baggish, A., Papadakis, M., Wilson, M. G., Prutkin, J., Gerche, A., Ackerman, M. , Borjesson, M., Salerno, J., Asif, I., Owens, D., Chung, E., Emery, M., Froelicher, V., Heidbuchel, H., Adamuz, C., Asplund, C., Cohen, G., Harmon, K., Marek, J., Molossi, S., Niebauer, J., Pelto, H., Perez, M., Riding, N., Saarel, T., Schmied, C. , Shipon, D., Stein, R., Vetter, V., Pelliccia, A. and Corrado, D.

(2017) International criteria for electrocardiographic interpretation in athletes: Consensus statement. *British Journal of Sports Medicine*, 51(9), 704–731.

Duncan, R. (2012) *Non-Invasive Cardiac Imaging for the Quantification of Venticular Function Potential and Future Application*. University of Newcastle Tyne and Wear (United Kingdom) and Cardiovascular Research Centre, Royal Adelaide Hospital (Australia), Doctorate of Medicine Theis.

Durrer, D., Van Dam, R., Freud, E., Janse, J., Meijler, L., Arzbaecher, C. (1970). Total excitation of the isolated human heart. *Circulation,* 16, 899–912.

Edler, I. and Hertz, C. (1954) The use of Ultrasonic Reflectoscope for the Continuous Recording of the Movements of Heart Walls.'*Kungl.Fysiografiska Sallskapets I Lund Forhandlingar*, 24, 5.

Ekblom, B., Hermansen, I. (1969) Cardiac output in athletes. *Journal of Applied Physiology*, 27(3), 350-355

Ellinor, P., MacRae, C. and Thierfelder, L. (2010) Arrhythmogenic right ventricular cardiomyopathy. *Heart failure clinics*, 6(2), 161–77.

Elliott, A. and La Gerche, A. (2015) The right ventricle following prolonged endurance exercise : are we overlooking the more important side of the heart ? A meta-analysis. *British Journal of Sport Medicine*, 49, 724–729.

Elm, E., Altman, D., Egger, M., Pocock, S., Gøtzsche, P., Vandenbroucke, J. and Initiative, S. (2014) The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement : Guidelines for reporting observational studies. *International Journal of Surgery*, 12(12), 1495–1499.

Erol, M. and Karakelleoglu, S. (2002) Assessment of right heart function in the

athlete ’ s heart. *Heart Vessels*, 16, 175–180.

Chan-Dewer, F. (2012) The cardiac cycle. *Anaesthesia and Intensive Care Medicine*, 13(8), 391–396.

Ferreira, A., Garcia, S., Pasquale, M., Canoniero, M. and Peter, A. (2003) Arrhythmogenic right ventricular dysplasia in the elderly. *Heart disease*, 5(6), 393–396.

Finocchiaro, G., Papadakis, M., Robertus, J., Dhutia, H., Steriotis, A., Tome, M., Mellor, G., Merghani, A., Malhotra, A., Behr, E., Sharma, S. and Sheppard, M. N. (2016) Etiology of Sudden Death in Sports: Insights From a United Kingdom Regional Registry. *Journal of the American College of Cardiology*, 67(18), 2108-2115.

Fleming, A., McDicken, W., Sutherland, G. and Hoskins, P. (1994) Assessment of colour Doppler tissue imaging using test-phantoms. *Ultrasound in Medicine and Biology*, 20(9), 937–951.

Foale, R., Nihoyannopoulos, P., McKenna, W., Kleinebenne, A., Nadazdin, A., Rowland, E., Smith, G. and Klienebenne, A. (1986) Echocardiographic measurement of the normal adult right ventricle. *British Heart Journal*, 56(1), 33–44.

Focardi, M., Cameli, M., Carbone, S. , Massoni, A., De Vito, R., Lisi, M. and Mondillo, S. (2014) Traditional and innovative echocardiographic parameters for the analysis of right ventricular performance in comparison with cardiac magnetic resonance. *European Heart Journal: Cardiovascular Imaging*, 16(1), 47–52.

Fontaine, G., Guiraudon, G., Frank, R. (1978) Intramyocardial conduction defects in patients prone to ventricular tachycardia. I. The postexcitation syndrome in sinus rhythm. *II-A dynamic study of the post-excitation syndrome*, 39-55.

Gaido, L., Battaglia, A., Matta, M., Giustetto, C., Frea, S., Imazio, M., Richiardi,

E., Garberoglio, L. and Gaita, F. (2017) Phenotypic expression of ARVC: How 12 lead ECG can predict left or right ventricle involvement. A familiar case series and a review of literature. *International journal of cardiology*, 236, 328–334.

Galderisi, M., Cardim, N., Andrea, A. D., Bruder, O., Cosyns, B., Davin, L., Donal, E., Edvardsen, T., Freitas, A., Habib, G., Kitsiou, A., Plein, S. and Petersen, S. E. (2015) The multi-modality cardiac imaging approach to the Athlete ' s heart : an expert consensus of the European Association of Cardiovascular Imaging. European Heart Journal :Cardiovascular Imaging, 16, 353

Galiè, N., Humbert, M., Vachiery, J., Gibbs, S., Lang, I., Torbicki, A., Simonneau, G., Peacock, A., Vonk Noordegraaf, A., Beghetti, M., Ghofrani, A., Gomez Sanchez, M., Hansmann, G., Klepetko, W., Lancellotti, P., Matucci, M., McDonagh, T., Pierard, L., Trindade, P., Zompatori, M. and Hoeper, M. (2016) 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *European Heart Journal*, 37(1), 67–119.

Gemayel, C., Pelliccia, A. and Thompson, P. (2001) Arrhythmogenic Right Ventricular Cardiomyopathy. *Journal of the American College of Cardiology*, 38(7), 1773-1781.

George, K., Spence, A., Naylor, L., Whyte, G. and Green, D. (2011) Cardiac adaptation to acute and chronic participation in endurance sports. *Heart*, 97(24), 1999–2004.

Geyer, H., Caracciolo, G., Abe, H., Wilansky, S., Carerj, S., Gentile, F., Nesser, H., Khandheria, B., Narula, J. and Sengupta, P. (2010) Assessment of Myocardial Mechanics Using Speckle Tracking Echocardiography: Fundamentals and Clinical Applications. *Journal of the American Society of Echocardiography*, 23(4), 351–369.

Grabskaya, E., Spira, C., Hoffmann, R., Altiok, E., Ocklenburg, C. and Becker, M. (2010) Myocardial Rotation but Not Circumferential Strain Is Transducer Angle Dependent: A Speckle Tracking Echocardiography Study. *Echocardiography*, 27(7), 809–814.

Grazioli, G., Merino, B., Montserrat, S., Vidal, B., Azqueta, M., Pare, C., Sarquella-Brugada, G., Yangüas, X., Pi, R. and Til, L. (2014) Usefulness of echocardiography in preparticipation screening of competitive athletes. *Revista Española de Cardiología*, 67(9), 701–705.

Greiner, S., Heimisch, M., Aurich, M., He, J., Katus, H. and Mereles, D. (2014) Multiplane two-dimensional strain echocardiography for segmental analysis of right ventricular mechanics. *Clinical Research in Cardiology*, 103(10) , 817–824.

Griffith, J. and Henry, W. (1974) A Sector Scanner for Real Time Two-Dimensional Echocardiography. *Circulation*, 49(6), 1147–1152.

Haddad, F., Hunt, S., Rosenthal, D. and Murphy, D. (2008) Right ventricular function in cardiovascular disease, part I: Anatomy, physiology, aging, and functional assessment of the right ventricle. *Circulation*, 117(11), 1436–1448.

Hampton, J.(2013) *The ECG Made Easy*. Elsevier Health Sciences *E-Book*.

Harmon, K., Drezner, J., Maleszewski, J., Lopez-Anderson, M., Owens, D., Prutkin, J., Asif, I., Klossner, D. and Ackerman, M. (2014) Pathogeneses of sudden cardiac death in national collegiate athletic association athletes. *Circulation: Arrhythmia and Electrophysiology*, 7(2), 198–204.

Harper, R. and Mottram, P. (2009) Exercise-induced right ventricular dysplasia/cardiomyopathy—an emerging condition distinct from arrhythmogenic right

ventricular dysplasia/cardiomyopathy. *Heart, Lung and Circulation*, 18(3), 233–235.

Haykowsky, M., Eves, N., Warburton, D., Findlay, M. (2003) Resistance exercise, the Valsalva maneuver, and cerebrovascular transmural pressure. *Medical Science and Sports Exercise Journal*, 35(1) 65-68.

Haykowsky, J., Samuel, J., Nelson, D. & La Gerche, A. (2018) Athlete's Heart: Is the Morganroth Hypothesis Obsolete? *Heart, Lung and Circulation*.

Heidbuchel, H., Prior, D. and La Gerche, A. (2012) Ventricular arrhythmias associated with long-term endurance sports: what is the evidence? *British Journal of Sports Medicine*, 46, i44–i50.

Hein, I. and O Brien, W. (1993) Current Time-Domain Methods for Assessing Tissue Motion by Analysis from Reflected Ultrasound Echoes:A Review. *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control*, 40(2), 84–102.

Helbing, W., Bosch, H., Maliepaard, C., Rebergen, S., van der Geest, R., Hansen, B., Ottenkamp, J., Reiber, J. and de Roos, A. (1995) Comparison of echocardiographic methods with magnetic resonance imaging for assessment of right ventricular function in children. *The American Journal of Cardiology*, 76(8), 589–594.

Henry, W., DeMaria, A., Gramiak, R., King, D., Kisslo, J., Popp, R., Sahn, D., Schiller, N., Tajik, A., Teichholz, L. and Weyman, A. (1980) Report of the American Society of Echocardiography Committee on Nomenclature and Standards in Two-dimensional Echocardiography. *Circulation*, 62(2), 212–217.

Higgins, J. and Thompson, S. (2002) Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine*, 21(11) , 1539–1558.

Ho, S. and Nihoyannopoulos, P. (2006) Anatomy, echocardiography, and normal

right ventricular dimensions. *Heart*, 92, i2-13.

Hoffmann, R., Ficiketti, P., Flachskampf, F. and Hanrath, P. (1996) Analysis of Interinstitutional Observer Agreement in Interpretation Dobutamine Stress Echocardiograms, *Journal of American College of Cardiology*, 27(95), 330–336.

Hoit, B., Shao, Y., Gabel, M.,Walsh, R. (1995) Left atrial mechanical and biological adaptation to pacing induced heart failure. *Cardiovascular research*, 29 (4) 469-474

Hurst, J. (1998) Naming of the waves in the ECG, with a brief account of their genesis. *Circulation*, 98(18) , 1937–1942.

Iacoviello, M., Forleo, C., Puzzovivo, A., Nalin, I., Guida, P., Anaclerio, M., Marangelli, V., Sorrentino, S., Monitillo, F., Ciccone, M. and Favale, S. (2011) Altered two-dimensional strain measures of the right ventricle in patients with Brugada syndrome and arrhythmogenic right ventricular dysplasia/ cardiomyopathy. *European Journal of Echocardiography*, 12(10) , 773–781.

Ionescu, A. (2012) *The right heart*. British Society of Echocardiography (BSE). Available at https://www.bsecho.org/the-right-heart/. [Accessed 16th June, 2018]

Isaaz, K., Thompson, A., Ethevenot, G., Cloez, J., Brembilla, B. and Pernot, C. (1989) Doppler echocardiographic measurement of low velocity motion of the left ventricular posterior wall. *The American Journal of Cardiology*, 64(1), 66–75.

Jategaonkar, S., Scholtz, W., Butz, T., Bogunovic, N., Faber, L. and Horstkotte, D. (2009) Two-dimensional strain and strain rate imaging of the right ventricle in adult patients before and after percutaneous closure of atrial septal defects. *European Journal of Echocardiography*, 10(4), 499–502.

Jurcut, R., Giusca, S., La Gerche, A., Vasile, S., Ginghina, C. and Voigt, J. (2010) The echocardiographic assessment of the right ventricle: what to do in 2010? *European journal of echocardiography*, 11(2), 81–96.

Kim, H., Kim, Y., Chang, S., Kim, D., Sohn, D., Oh, B. and Park, Y. (2009) Impact of Cardiac Rhythm on Mitral Valve Area Calculated by the Pressure Half Time Method in Patients With Moderate or Severe Mitral Stenosis. *Journal of the American Society of Echocardiography*, 22(1), 42–47.

Kim, J., Noseworthy, P., McCarty, D., Yared, K., Weiner, R., Wang, F., Wood, M. , Hutter, A., Picard, M. and Baggish, A. (2011) Significance of electrocardiographic right bundle branch block in trained athletes. *American Journal of Cardiology*, 107(7), 1083–1089.

Kjaergaard, J., Snyder, E., Hassager, C., Oh, J. and Johnson, B. (2006) Impact of Preload and Afterload on Global and Regional Right Ventricular Function and Pressure: A Quantitative Echocardiography Study. *Journal of the American Society of Echocardiography*, 19, 515–521.

Koopman, L., Slorach, C., Hui, W., Manlhiot, C., McCrindle, B., Friedberg, M., Jaeggi, E. and Mertens, L. (2010) Comparison between different speckle tracking and color tissue Doppler techniques to measure global and regional myocardial deformation in children. *J Am Soc Echocardiogr*, 23(9), 919–928.

Korinek, J., Wang, J., Sengupta, P., Miyazaki, C., Kjaergaard, J., McMahon, E., Abraham, T. and Belohlavek, M. (2005) Two-dimensional strain--a Doppler-independent ultrasound method for quantitation of regional deformation: validation in vitro and in vivo. *Journal of the American Society of Echocardiography*, 18(12), 1247–1253.

Kothari, S. and Ramakrishnan, S. (2011) Tracking the Right Ventricle. *Journal of American College of Cardiology :Cardiovascular Imaging*, 4(2), 138–140.

Kukulski, T., Hübbert, L., Arnold, M., Wranne, B., Hatle, L. and Sutherland, G. (2000) Normal regional right ventricular function and its change with age: a Doppler myocardial imaging study.' *Journal of the American Society of Echocardiography*, 13(3) pp. 194–204.

Kumar, S., Kalman, J. and La Gerche, A. (2017) New International Guidelines for the Interpretation of the Electrocardiograph in Athletes: a "Traffic Light" Tool for Maximising Diagnostic Specificity. *Heart, Lung and Circulation*, 26(11) , 1119–1122.

La Gerche, A. and Claessen, G. (2015a) Is Exercise Good for the Right Ventricle ? Concepts for Health and Disease. *Canadian Journal of Cardiology*,31, 502–508.

La Gerche, A., Burns, A., D'hooge, J., Macisaac, A., Heidbuchel, H. and Prior, D. (2012a) Exercise Strain Rate Imaging Demonstrates Normal Right Ventricular Contractile Reserve and Clarifies Ambiguous Resting Measures in Endurance Athletes. *Journal of the American Society of Echocardiography*, 25, 253–262.

La Gerche, A., Burns, A., Mooney, D., Inder, W., Taylor, A., Bogaert, J., MacIsaac, A. , Heidbüchel, H. and Prior, D. (2012b) Exercise-induced right ventricular dysfunction and structural remodelling in endurance athletes. *European Heart Journal*, 33(8), 998–1006.

La Gerche, A., Heidbuchel, H., Burns, A., Mooney, D., Taylor, A. , fluger, H., Inder, W. , Macisaac, A. and Prior, D. (2011) Disproportionate Exercise Load and Remodeling of the Athlete's Right Ventricle. *Medicine and Science in Sports and*

Exercise, 43(6), 974–981.

La Gerche, A. and Roberts, T. (2015b) Straining the RV to Predict the Future. *Journal of American College of Cardiology :Cardiovascular Imaging, 8(2), 170-171*

Lai, W., Gauvreau, K., Rivera, E., Saleeb, S., Powell, A. and Geva, T. (2008) Accuracy of guideline recommendations for two-dimensional quantification of the right ventricle by echocardiography. *Internatinal Journal of Cardiovascular Imaging*, 24, 691–698.

Lang, R., Badano, L., Mor-avi, V., Afilalo, J., Armstrong, A., Ernande, L., Flachskampf, F., Foster, E., Goldstein, S., Kuznetsova, T., Lancellotti, P. and Muraru, D. (2015) Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults : An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Journal of the American Society of Echocardiography*, 28(1), 1–39.

Langeland, S., D'Hooge, J., Wouters, P., Leather, H., Claus, P., Bijnens, B. and Sutherland, G. (2005) Experimental validation of a new ultrasound method for the simultaneous assessment of radial and longitudinal myocardial deformation independent of insonation angle. *Circulation*, 112(14), 2157–2162.

Levine, B., Kovacs, R., Link, M. and Maron, M. (2015) Eligibility and Disqualification Recommendations for Competitive Athletes With Cardiovascular Abnormalities : Task Force 1 : Classification of Sports : Dynamic , Static , and Impact. *Journal of the American College of Cardiology*, 66(21), 2350–2355.

Levine, R., Gibson, T., Aretz, T., Gillam, L., Guyer, D., King, M. and Weyman, A. (1984) Echocardiographic measurement of right ventricular volume. *Circulation*,

69(3), 497–505.

Lindström, L., Wilkenshoff, U., Larsson, H. and Wranne, B. (2001) Echocardiographic assessment of arrhythmogenic right ventricular cardiomyopathy. *Heart*, 86(1), 31–38.

Lord, R., George, K., Somauroo, S. and Oxborough, D. (2014) Reproducibility and feasibility of right ventricular strain and strain rate (SR) as determined by myocardial speckle tracking during high-intensity upright exercise : a comparison with tissue Doppler-derived strain and SR in healthy human hearts, *Echo Research and Practice*,1, 31-41.

Lord, R., Somauroo, J., Stembridge, M., Jain, N., Hoffman, M. , George, K., Jones, H., Shave, R., Haddad, F., Ashley, E. and Oxborough, D. (2014) The right ventricle following ultra-endurance exercise: insights from novel echocardiography and 12-lead electrocardiography. *European journal of applied physiology*, 115, 71–80.

Malhotra, A., Dhutia, H., Gati, S., Yeo, T. , Dores, H., Bastiaenen, R., Merghani, R., Finocchiaro, G., Sheikh, N. and Steriotis, A. (2016) Prevalence and significance of anterior T wave inversion in young white athletes and non athletes. *Journal of the American College of Cardiology*, 69, 1–9.

Marcus, F. (2005) Prevalence of T-wave inversion beyond V1 in young normal individuals and usefulness for the diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia. *American Journal of Cardiology*, 95(9), 1070–1071.

Marcus, F., Fontaine, H., Guiraudon, G., Frank, R., Laurenceau, L., Malergue, C., Grosgogeat, Y. (1982) Right ventricular dysplasia: A report of 24 adult cases. *Circulation*, 65 (2), 384–398.

Marcus, F., McKenna, W., Sherrill, D., Basso, C., Bauce, B., Bluemke, D., Calkins, H., Corrado, D., Cox, M., Daubert, J., Fontaine, G., Gear, K., Hauer, R., Nava, A., Picard, M., Protonotarios, N., Saffitz, J., Sanborn, D., Steinberg, J., Tandri, H., Thiene, G., Towbin, J., Tsatsopoulou, A., Wichter, T. and Zareba, W. (2010) Diagnosis of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia. *Circulation*, 121(13), 1533–1541.

Marcus, F., Zareba, W., Calkins, H., Towbin, J., Basso, C., Bluemke, D., Estes, N., Picard, M., Sanborn, D. and Thiene, G. (2009) Arrhythmogenic right ventricular cardiomyopathy/dysplasia clinical presentation and diagnostic evaluation: results from the North American Multidisciplinary Study.' *Heart rhythm*, 6(7), 984–992.

Maron, B. and Pelliccia, A. (2006) The Heart of Trained Athletes Cardiac Remodeling and the Risks of Sports , Including Sudden Death. *Circulation*, 114, 1633–1644.

Mason, J., Hancock, E. and Gettes, L.(2007) Recommendations for the Standardization and Interpretation of the Electrocardiogram. *Journal of the American College of Cardiology*, 49(10), 1128–1135.

McClean, G., George, K., Lord, R., Utomi, V., Jones, N., Somauroo, J., Fletcher, S. and Oxborough, D. (2014) Chronic adaptation of atrial structure and function in elite male athletes, European Heart Journal :Cardiovascular Imaging, 16(4), 417-422.

McClean, G., Riding, N. R., Ardern, C. L., Farooq, A., Pieles, G. E., Watt, V., Adamuz, C., George, K. P., Oxborough, D. and Wilson, M. G. (2017) Electrical and structural adaptations of the paediatric athlete's heart: a systematic review with meta-analysis. *British journal of sports medicine*, 52(4), 230.

McKenna, W., Nava, A., Fontaliran, F., Blomstrom-Lundqvist, C., Fontaine, G. and Camerini, F. (1994) Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Task Force of the Working Group Myocardial and Pericardial Disease of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the International Society. *British heart journal*, 71(3), 215.

Meris, A., Faletra, F., Conca, C., Klersy, C., Regoli, F., Klimusina, J., Penco, M., Pasotti, E., Pedrazzini, G. B., Moccetti, T. and Auricchio, A. (2010) Timing and Magnitude of Regional Right Ventricular Function: A Speckle Tracking-Derived Strain Study of Normal Subjects and Patients with Right Ventricular Dysfunction. *Journal of the American Society of Echocardiography*, 23(8), 823–831.

Merner, N., Hodgkinson, K., Haywood, A., Connors, S., French, V., Drenckhahn, J., Kupprion, C., Ramadanova, K., Thierfelder, L. and McKenna, W. (2008) Arrhythmogenic right ventricular cardiomyopathy type 5 is a fully penetrant, lethal arrhythmic disorder caused by a missense mutation in the TMEM43 gene. *The American Journal of Human Genetics*, 82(4), 809–821.

Mirea, O., Duchenne, J. and Voigt, J. (2016) Recent advances in echocardiography : strain and strain rate imaging . *F1000Res*, 5(0), 1–10.

Mitchell, J., Haskell, W., Snell, P. and Van Camp, S. (2005) Task Force 8: classification of sports. *Journal of the American College of Cardiology*, 45(8), 1364–1367.

Modesto, K., Cauduro, S., Dispenzieri, A., Khandheria, B., Belohlavek, M., Lysyansky, P., Friedman, Z., Gertz, M. and Abraham, T. (2006) Two-dimensional acoustic pattern derived strain parameters closely correlate with one-dimensional tissue Doppler derived strain measurements. *European Journal of Echocardiography*, 7(4),

315–321.

Moen, C., Salminen, P., Grong, K. and Matre, K. (2011) Left ventricular strain, rotation, and torsion as markers of acute myocardial ischemia.' *American journal of physiology.*, 300(6), H2142-54.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G. and Altman, G. (2009) Preferred reporting items for systematic reviews and meta-analyses : the PRISMA statement All use subject to JSTOR Terms and Conditions REPORTING items Preferred for systematic reviews reporting meta-analyses : the PRISMA statement, *British Medical Journal*, 339(7716) pp. 332–336.

Mont, L., Pelliccia, A., Sharma, S., Biffi, A., Borjesson, M., Terradellas, J., Carre, F., Guasch, E., Heidbuchel, H., La Gerche, A., Lampert, R., McKenna, W., Papadakis, M., Priori, S. G., Scanavacca, M., Thompson, P., Sticherling, C., Viskin, S., Wilson, M., Corrado, D., Gregory, L. Y. H., Gorenek, B., Lundqvist, C., Merkely, B., Hindricks, G., Hernandez-Madrid, A., Lane, D., Boriani, G., Narasimhan, C., Marquez, M., Haines, D., Mackall, J., Marques-Vidal, P., Corra, U., Halle, M., Tiberi, M., Niebauer, J. and Piepoli, M. (2016) Pre-participation cardiovascular evaluation for athletic participants to prevent sudden death: Position paper from the EHRA and the EACPR, branches of the ESC. Endorsed by APHRS, HRS, and SOLAECE. *Europace*, 19(1) , 139–163.

Mor-Avi, V., Lang, R., Badano, L., Belohlavek, M., Cardim, N., Derumeaux, G., Galderisi, M., Marwick, T., Nagueh, S., Sengupta, P., Sicari, R., Smiseth, O., Smulevitz, B., Takeuchi, M., Thomas, J., Vannan, M., Voigt, J. and Zamorano, J. (2011) Current and Evolving Echocardiographic Techniques for the Quantitative Evaluation of Cardiac Mechanics: ASE/EAE Consensus Statement on Methodology and Indications: Endorsed by the Japanese Society of Echocardiography. *Journal of the*

American Society of Echocardiography, 24(3), 277–313.

Mörner, S., Lindqvist, P., Waldenström, A. and Kazzam, E. (2008) Right ventricular dysfunction in hypertrophic cardiomyopathy as evidenced by the myocardial performance index. *International Journal of Cardiology*, 124(1), 57–63.

Moro, A., Okoshi, M., Padovani, C. and Okoshi, K. (2013) Doppler echocardiography in athletes from different sports. Medical Science Monitor, 19, 187–193.

Morris, D., Gailani, M., Vaz Pérez, A., Blaschke, F., Dietz, R., Haverkamp, W. and Özcelik, C. (2011) Left Atrial Systolic and Diastolic Dysfunction in Heart Failure with Normal Left Ventricular Ejection Fraction. *Journal of the American Society of Echocardiography*, 24(6), 651–662.

Mosteller, R. (1987) Simplified Calculation of Body Surface Area. *The New England Journal of Medicine*, 317(17), 1098 .

Nagueh, S., Middleton, K., Kopelen, H., Zoghbi, W. and Quiñones, M. (1997) Doppler Tissue Imaging: A Noninvasive Technique for Evaluation of Left Ventricular Relaxation and Estimation of Filling Pressures. *Journal of the American College of Cardiology*, 30(6), 1527–1533.

Nasir, K., Bomma, C., Tandri, H., Roguin, A., Dalal, D., Prakasa, K., Tichnell, C., James, C., Jspevak, P. and Marcus, F. (2004) Electrocardiographic features of arrhythmogenic right ventricular dysplasia/cardiomyopathy according to disease severity: a need to broaden diagnostic criteria. *Circulation*, 110(12), 1527–1534.

Nava, A., Bauce, B., Basso, C., Muriago, M., Rampazzo, A., Villanova, C., Daliento, L., Buja, G., Corrado, D. and Danieli, G. (2000) Clinical profile and long-term

follow-up of 37 families with arrhythmogenic right ventricular cardiomyopathy. *Journal of the American College of Cardiology*, 36(7), 2226–2233.

Nava, A., Thiene, G., Canciani, B., Scognamiglio, R., Daliento, L., Buja, G., Martini, B., Stritoni, P. and Fasoli, G. (1988) Familial occurrence of right ventricular dysplasia: a study involving nine families. *Journal of the American College of Cardiology*, 12(5) pp. 1222–1228.

O'Donnell, M., Skovoroda, A., Shapo, B. and Emelianov, S. (1994) Internal displacement and strain imaging using ultrasonic speckle tracking. *IEEE Trans Ultrason Ferroelectr Freq Control*, 41(3), 314–325.

Ommen, S., Nishimura, R., Appleton, C., Miller, F., Oh, J., Redfield, M. and Tajik, A. (2000) Clinical Utility of Doppler Echocardiography and Tissue Doppler Imaging in the Estimation of Left Ventricular Filling Pressures : A Comparative Simultaneous Doppler-Catheterization Study. *Circulation*, 102(15), 1788–1794.

Oxborough, D., Augustine, D., Gati, S., George, K., Harkness, A., Mathew, T., Papadakis, M., Ring, L., Robinson, S., Sandoval, J., Sarwar, R., Sharma, S., Sharma, V., Sheikh, N., Somauroo, J., Stout, M., Willis, J. and Zaidi, A. (2018) A guideline update for the practice of echocardiography in the cardiac screening of sports participants: a joint policy statement from the British Society of Echocardiography and Cardiac Risk in the Young. *Echo research and practice*, 5(1), G1–G10.

Oxborough, D., Birch, K., Shave, R. And George, K. (2010) Exercise-Induced Cardiac Fatigue-A Review of the Echocardiographic Literature. Echocardiography, 27(9), 1130-1140.

Oxborough, D., George, K. and Birch, K. (2012a) Intraobserver reliability of two-dimensional ultrasound derived strain imaging in the assessment of the left ventricle,

right ventricle, and left atrium of healthy human hearts. *Echocardiography*, 29(7), 793–802.

Oxborough, D., Heemels, A., Somauroo, J., Mcclean, G., Mistry, P., Lord, R., Utomi, V., Jones, N., Thijssen, D., Sharma, S., Osborne, R., Sculthorpe, N. and George, K. (2016) Left and right ventricular longitudinal strain-volume / area relationships in elite athletes. *The International Journal of Cardiovascular Imaging*,32, 1199–1211.

Oxborough, D., Sharma, S., Shave, R., Whyte, G., Birch, K., Artis, N., Batterham, A. M. and George, K. (2012) The right ventricle of the endurance athlete: the relationship between morphology and deformation. *Journal of the American Society of Echocardiography*, 25(3), 263–71.

Oxborough, D., Shave, R., Warburton, D., Williams, K., Oxborough, A., Charlesworth, S., Foulds, H., Hoffman, M., Birch, K. and George, K. (2011). Dilatation and dysfunction of the right ventricle immediately following ultra-endurance exercise: exploratory insights from conventional 2-dimensional and speckle tracking echocardiography. Circulation, 4,253-263

Pagourelias, V., Kouidi, E., Efthimiadis, G., Deligiannis, A., Geleris, P. and Vasilikos, V. (2013) Right atrial and ventricular adaptations to training in male Caucasian athletes: an echocardiographic study.' *Journal of the American Society of Echocardiography*, 26, 1344–52.

Pamuru, P., Dokuparthi, M., Remersu, S., Calambur, N. and Nallari, P. (2010) Comparison of Uhl's anomaly, right ventricular outflow tract ventricular tachycardia (RVOT VT) and arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) with an insight into genetics of ARVD/C. *Indian Journal of Medical Research*, 131(1), 35–45.

Pappano, A. and Wier, W. (2012) Cardiovascular Physiology E-Book. *Mosby Physiology Monograph Series*. Elsevier Health Sciences.

Pellerin, D., Sharma, R., Elliott, P. and Veyrat, C. (2003) Tissue Doppler, strain, and strain rate echocardiography for the assessment of left and right systolic ventricular function. *Heart*, 3, iii9-17.

Pelliccia, A., Caselli, S., Sharma, S., Basso, C., Bax, J., Corrado, D., Andrea, A., Ascenzi, F., Paolo, F., Edvardsen, T., Gati, S., Galderisi, M., Heidbuchel, H., Nchimi, A., Nieman, K., Papadakis, M., Pisicchio, C., Schmied, C., Popescu, B., Habib, G. and Grobbee, D. (2017) European Association of Preventive Cardiology (EAPC) and European Association of Cardiovascular Imaging (EACVI) joint position statement : recommendations for the indication and interpretation of cardiovascular imaging in the evaluation of the athlete. *European Heart Journal*, 0, 1–27.

Perez Diez, D. and Brugada, J. (2008) Diagnosis and Management of Arrhythmogenic Right Ventricular Dysplasia: An article from the E-Journal of the ESC Council for Cardiology Practice. *European Society of Cardiology*.

Peters, S., Trümmel, M., Koehler, B. and Westermann, K. (2007) The value of different electrocardiographic depolarization criteria in the diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Journal of electrocardiology*, 40(1), 34–37.

Piccini, J., Nasir, K., Bomma, C., Tandri, H., Dalal, D., Tichnell, C., James, C., Crosson, J. and Calkins, H. (2005) Electrocardiographic findings over time in arrhythmogenic right ventricular dysplasia/cardiomyopathy. *American Journal of Cardiology*, 96(1), 122–126.

Pinamonti, B. (2014) Arrhythmogenic right ventricular cardiomyopathy: From

genetics to diagnostic and therapeutic challenges. *World Journal of Cardiology*, 6(12), 1234.

Plana, J., Galderisi, M., Barac, A., Ewer, M., Ky, B., Scherrer-Crosbie, M., Ganame, J., Sebag, I., Agler, D., Badano, L., Banchs, J., Cardinale, D., Carver, J., Cerqueira, M., DeCara, J., Edvardsen, T., Flamm, S., Force, T., Griffin, B., Jerusalem, G., Liu, J., Magalhães, A., Marwick, T., Sanchez, L., Sicari, R., Villarraga, H. and Lancellotti, P. (2014) Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Journal of the American Society of Echocardiography*, 1063–1093.

Pluim, B., Zwinderman, A., Van Der Laarse, A. and Van Der Wall, E. (2000) The athlete's heart. A meta-analysis of cardiac structure and function. *Circulation*, 101(3), 336–344.

Prakasa, K., Wang, J., Tandri, H., Dalal, D., Bomma, C., Chojnowski, R., James, C., Tichnell, C., Russell, S., Judge, D., Corretti, M., Bluemke, D., Calkins, H. and Abraham, T. (2007) Utility of Tissue Doppler and Strain Echocardiography in Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy. *American Journal of Cardiology*, 100(3), 507–512.

Prakken, N., Velthuis, B., Teske, A., Mosterd, A., Mali, W. and Cramer, M. (2010) Cardiac MRI reference values for athletes and nonathletes corrected for body surface area, training hours/week and sex. *European journal of cardiovascular prevention and rehabilitation*, 17(2), 198–203.

Protonotarios, N., Anastasakis, A., Antoniades, L., Chlouverakis, G., Syrris, P., Basso, C., Asimaki, A., Theopistou, A., Stefanadis, C., Thiene, G., McKenna, W. and

Tsatsopoulou, A. (2011) Arrhythmogenic right ventricular cardiomyopathy/dysplasia on the basis of the revised diagnostic criteria in affected families with desmosomal mutations. *European Heart Journal*, 32(9), 1097–1104.

Rappaport, D., Adam, D., Lysyansky, P. and Riesner, S. (2006) Assessment of myocardial regional strain and strain rate by tissue tracking in B-mode echocardiograms. *Ultrasound in Medicine and Biology*, 32(8), 1181–1192.

Rawlins, J., Bhan, A. and Sharma, S. (2009) Left ventricular hypertrophy in athletes.' *European journal of echocardiography*, 10(3), 350–356.

Richand, V., Lafitte, S., Reant, P., Serri, K., Lafitte, M., Brette, S., Kerouani, A., Chalabi, H., Dos Santos, P., Douard, H. and Roudaut, R. (2007) An ultrasound speckle tracking (two-dimensional strain) analysis of myocardial deformation in professional soccer players compared with healthy subjects and hypertrophic cardiomyopathy. *The American journal of cardiology*, 100(1), 128–132.

Rojas, A. and Calkins, H. (2015) Present understanding of the relationship between exercise and arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Trends in Cardiovascular Medicine*, 25(3), 181–188.

Romero, J., Mejia-Lopez, E., Manrique, C. and Lucariello, R. (2013) Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC/D): A Systematic Literature Review. *Clinical Medicine Insights. Cardiology*, 7,. 97–114.

Rudski, L., Lai, W., Afilalo, J., Hua, L., Handschumacher, M., Chandrasekaran, K., Solomon, S., Louie, E. and Schiller, N. (2010) Guidelines for the Echocardiographic Assessment of the Right Heart in Adults: A Report from the American Society of Echocardiography: Endorsed by the European Association of Echocardiography.

Journal of the American Society of Echocardiography, 23(7), 685–713.

Sadeghpour, A. and Alizadehasl, A. (2015) The Right Ventricle : A Comprehensive Review From Anatomy , Physiology , and Mechanics to Hemodynamic , Functional , and Imaging Evaluation. *Archives of Cardiovascular Imaging*, 3(4), 1–14.

Sarvari, S., Haugaa, K., Anfinsen, O., Leren, T., Smiseth, O., Kongsgaard, E., Amlie, J. and Edvardsen, T. (2011) Right ventricular mechanical dispersion is related to malignant arrhythmias : a study of patients with arrhythmogenic right ventricular cardiomyopathy and subclinical right ventricular dysfunction. *European Heart Journal*, 32, 1089–1096 .

Sen-Chowdhry, S., Syrris, P., Prasad, S., Hughes, S., Merrifield, R., Ward, D., Pennell, D. and McKenna, W. (2008) Left-dominant arrhythmogenic cardiomyopathy: an under-recognized clinical entity. *Journal of the American College of Cardiology*, 52(25), 2175–2187.

Sengupta, P. and Narula, J. (2013) RV form and function: a piston pump, vortex impeller, or hydraulic ram? *American Journal of Cardiology*: Cardiovascular Imaging, 6 (5), 636-639.

Sharma, S., Drezner, J., Baggish, A., Papadakis, M., Borjesson, M., Salerno, J., Asif, I., Owens, D., Marek, J., Molossi, S., Niebauer, J., Pelto, H. and Perez, M. (2017) International Recommendations for Electrocardiographic Interpretation in Athletes. *Journal of the American College of Cardiology*, 69(8), 1057-1075.

Sheehan, F. and Redington, A. (2008) The right ventricle: anatomy, physiology and clinical imaging. *Heart*, 94(11), 1510-1515.

Sheppard, M. (2012) Aetiology of sudden cardiac death in sport: a histopathologist's perspective. *British Journal of Sports Medicine*, 46, i15–i21.

Sheikh, N., Papadakis, M., Ghani, S., Zaidi, A., Gati, S., Adami, P. E., Carré, F., Schnell, F., Wilson, M., Avila, P., Mckenna, W., Sharma, S. and Uk, F. (2014) Epidemiology and Prevention Comparison of Electrocardiographic Criteria for the Detection of Cardiac Abnormalities in Elite Black and White Athletes. Circulation, 1637–1650.

Sohaib, S., Payne, J., Shukla, R., World, M., Pennell, D. and Montgomery, H. (2009) Electrocardiographic (ECG) criteria for determining left ventricular mass in young healthy men; data from the LARGE Heart study. *Journal of Cardiovascular Magnetic Resonance*, 11(1), 2.

Sorrell, V., Kumar, S. and Kalra, N. (2009) Cardiac imaging in right ventricular cardiomyopathy/dysplasia--how does cardiac imaging assist in understanding the morphologic, functional, and electrical changes of the heart in this disease? *Journal of electrocardiology*, 42(2) 137.e1-137.e10.

Spence, A., Naylor, L., Carter, H., Buck, C., Dembo, L., Murray, C., Watson, P., Oxborough, D., George, K. and Green, D. (2011) A prospective randomised longitudinal MRI study of left ventricular adaptation to endurance and resistance exercise training in humans. *The Journal of Physiology*, 22, 5443–5452.

Spence, A., Naylor, L., Carter, H., Dembo, L., Murray, C., Driscoll, G., George, K. , Green, D. (2013) Does echocardiography accurately reflect CMR-determined changes in left ventricular parameters following exercise training ? A prospective longitudinal study. Journal of Aplied Physiology, 114(8), 1052–1057.

Stefani, L., Pedrizzetti, G., De Luca, A., Mercuri, R., Innocenti, G. and Galanti,

G. (2009) Real-time evaluation of longitudinal peak systolic strain (speckle tracking measurement) in left and right ventricles of athletes. *Cardiovascular Ultrasound*, 7(1), 17.

Stohr, E., Gonzalez-Alonso, J., Pearson, J., Low, D., Ali, L., Barker, H. and Shave, R. (2010) Effects of graded heat stress on global left ventricular function and twist mechanics at rest and during exercise in healthy humans. *Experament Physiologyl*, 96, 114–124.

Tabib, A., Loire, R., Chalabreysse, L., Meyronnet, D., Miras, A., Malicier, D., Thivolet, F., Chevalier, P. and Bouvagnet, P. (2003) Circumstances of death and gross and microscopic observations in a series of 200 cases of sudden death associated with arrhythmogenic right ventricular cardiomyopathy and/or dysplasia. *Circulation*., 108(24), 3000–3005.

Te Riele, A., James, C., Philips, B., Rastegar, N., Bhonsale, A., Groeneweg, J., Murray, B., Tichnell, C., Judge, D., van der Heijden, J., Cramer, M. , Velthuis, B., Bluemke, D., Zimmerman, S. , Kamel, I., Hauer, R., Calkins, H. and Tandri, H. (2013) Mutation Positive Arrhyhmogenic Right Ventricular Dysplasia/Cardiomyopathy: The Triangle of Dysplasia Displaced. *Journal of cardiovascular electrophysiology*, 24(12), 1311–1320.

Teske, A., Cox, M., De Boeck, B., Doevendans, P., Hauer, R. and Cramer, M. (2009a) Echocardiographic Tissue Deformation Imaging Quantifies Abnormal Regional Right Ventricular Function in Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy. *Journal of the American Society of Echocardiography*, 22(8), 920–927.

Teske, A., Cox, M. and Riele, A. (2012) Early Detection of Regional Functional

Abnormalities in Asymptomatic ARVD / C Gene Carriers. *Journal of the American Society of Echocardiography*, 25(9), 997–1006.

Teske, A., Prakken, N., De Boeck, B., Velthuis, B., Martens, E., Doevendans, P. and Cramer, M. (2009b) Echocardiographic tissue deformation imaging of right ventricular systolic function in endurance athletes. *European heart journal*, 30(8), 969–977.

Tops, L., Prakasa, K., Tandri, H., Dalal, D., Jain, R., Dimaano, V., Dombroski, D., James, C., Tichnell, C., Daly, A., Marcus, F., Schalij, M., Bax, J., Bluemke, D., Calkins, H. and Abraham, T. (2009) Prevalence and Pathophysiologic Attributes of Ventricular Dyssynchrony in Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy. *Journal of the American College of Cardiology*, 54(5), 445–451.

Uberoi, A., Jain, N., Perez, M., Weinkopff, A., Ashley, E., Hadley, D., Turakhia, M. and Froelicher, V. (2011) Early repolarization in an ambulatory clinical population.' *Circulation*, 111.

Utomi, V., Oxborough, D., Ashley, E., Lord, R., Fletcher, S., Stembridge, M., Shave, R., Hoffman, M., Whyte, G., Somauroo, J., Sharma, S. and George, K. (2014) Predominance of normal left ventricular geometry in the male "athlete's heart". *Heart*, 100(16), 1264–71.

Utomi, V., Oxborough, D., Whyte, G., Somauroo, J., Sharma, S., Shave, R., Atkinson, G. and George, K. (2013) Systematic review and meta-analysis of training mode, imaging modality and body size influences on the morphology and function of the male athlete's heart. *Heart*, 99(23),1727–33.

Van Brabandt, H., Desomer, A., Gerkens, S. (2016) Harms and benefits of screening young people to prevent sudden cardiac death. Beitish Medical Journal, 353:i1156.

Vitarelli, A., Cortes Morichetti, M., Capotosto, L., De Cicco, V., Ricci, S., Caranci, F. and Vitarelli, M. (2013) Utility of strain echocardiography at rest and after stress testing in arrhythmogenic right ventricular dysplasia. *American Journal of Cardiology*, 111(9), 1344–1350.

Voelkel, N., Quaife, R., Leinwand, L., Barst, R., McGoon, M., Meldrum, D., Dupuis, J., Long, C., Rubin, L., Smart, F., Suzuki, Y., Gladwin, M., Denholm, E. and Gail, D. (2006) Right Ventricular Function and Failure: Report of a National Heart, Lung, and Blood Institute Working Group on Cellular and Molecular Mechanisms of Right Heart Failure. *Circulation*, 114(17), 1883–1891.

Wang, J., Prakasa, K., Bomma, C., Tandri, H., Dalal, D., James, C., Tichnell, C., Corretti, M., Bluemke, D., Calkins, H. and Abraham, T.(2007) Comparison of novel echocardiographic parameters of right ventricular function with ejection fraction by cardiac magnetic resonance. *Journal of the American Society of Echocardiography*, 20(9),1058–1064.

Wang, S., Zhang, Z., Xu, Y., Jiang, Q., Li, H., Qian, M. and Li, Y. (2010) Diagnosis and treatment of arrhythmogenic right ventricular cardiomyopathy in children. *Chinese journal of contemporary pediatrics*, 12(3), 165–168.

Wasfy, M., DeLuca, J., Wang, F., Berkstresser, B., Ackerman, K. , Eisman, A., Lewis, G., Hutter, A., Weiner, R. and Baggish, A. (2014) ECG findings in competitive rowers: normative data and the prevalence of abnormalities using contemporary screening recommendations. *British Journal of Sports Medicine*

Weidemann, F., Eyskens, B., Jamal, F., Mertens, L., Kowalski, M., D'Hooge, J., Bijnens, B., Gewillig, M., Rademakers, F., Hatle, L. and Sutherland, G.(2002) Quantification of regional left and right ventricular radial and longitudinal function in healthy children using ultrasound-based Strain Rate and Strain Imaging. *Journal of the American Society of Echocardiography*, 15(1), 20–28.

Wharton, G., Steeds, R., Allen, J., Phillips, H., Jones, R., Kanagala, P., Lloyd, G., Masani, N., Mathew, T., Oxborough, D., Rana, B., Sandoval, J. and Wheeler, R. (2015) A minimum dataset for a standard adult transthoracic echocardiogram: a guideline protocol from the British Society of Echocardiography. *Echo Research and Practice*, 2(1) G9-G24.

Yip, G., Abraham, T., Belohlavek, M. and Khandheria, B. (2003) Clinical applications of strain rate imaging. *Journal of the American Society of Echocardiography*, 16(12), 1334–1342.

Yoerger, D., Marcus, F., Sherrill, D., Calkins, H., Towbin, J. a., Zareba, W. and Picard, M. (2005) Echocardiographic findings in patients meeting task force criteria for arrhythmogenic right ventricular dysplasia: New insights from the multidisciplinary study of right ventricular dysplasia. *Journal of the American College of Cardiology*, 45(6), 860–865.

Zaidi, A., Ghani, S., Sharma, R., Oxborough, D., Panoulas, V., Sheikh, N., Gati, S., Papadakis, M. and Sharma, S. (2013a) Physiological right ventricular adaptation in elite athletes of African and Afro-Caribbean origin. *Circulation*, 127(17), 1783–92.

Zaidi, A., Ghani, S., Sheikh, N., Gati, S., Bastiaenen, R., Madden, B., Papadakis, M., Raju, H., Reed, M. and Sharma, R. (2013b) Clinical significance of electrocardiographic right ventricular hypertrophy in athletes: comparison with

arrhythmogenic right ventricular cardiomyopathy and pulmonary hypertension. *European heart journal*, 34(47), 3649–3656.

Zaidi, A., Sheikh, N., Jongman, J., Gati, S., Panoulas, V., Carr-White, G., Papadakis, M., Sharma, R., Behr, E.. and Sharma, S. (2015) Clinical Differentiation Between Physiological Remodeling and Arrhythmogenic Right Ventricular Cardiomyopathy in Athletes With Marked Electrocardiographic Repolarization Anomalies. *Journal of the American College of Cardiology*, 65(25), 2702–2711.

Appendices

Appendix 1- Ethics Approval

From: McKeon, Jo
Sent: 25 January 2012 14:43
To: Utomi, Victor
Cc: George, Keith
Subject: Application for Ethical Approval No.: 11/SPS/045

Dear Victor,

Satisfaction of Provisos - Full Ethical Approval

With reference to your application for Ethical approval:

The "athletic heart": insights from modern imaging tools in Caucasian and West African Athletes

On behalf of Liverpool John Moores University Research Ethics Committee (REC) the Chair of the Committee has reviewed your response to the request for further information related to the above study. The Committee is now content to give a favourable ethical opinion and recruitment to the study can now commence.

Approval is given on the understanding that:

- any adverse reactions/events which take place during the course of the project will be reported to the Committee immediately;
- any unforeseen ethical issues arising during the course of the project will be reported to the Committee immediately;
- any substantive amendments to the protocol will be reported to the Committee immediately.
- the LJMU logo is used for all documentation relating to participant recruitment and participation eg poster, information sheets, consent forms, questionnaires. The JMU logo can be accessed at http://www.ljmu.ac.uk/corporatecommunications/60486.htm

For details on how to report adverse events or amendments please refer to the information provided at: http://www.ljmu.ac.uk/RGSO/RGSO_Docs/EC8Adverse.pdf

Please note that ethical approval is given for a period of five years from the date granted and therefore the expiry date for this project will be **25th January 2017.** An application for extension of approval must be submitted if the project continues after this date.

Yours sincerely

PP:

Professor Andrew Young
Chair of the LJMU REC
Tel: 0151 904 6463
E-mail: j.m.mckeon@ljmu.ac.uk

NHS
Health Research Authority

Mr Mohammad Qasem
Research Institute of Sport and Exercise Sciences
Tom Reilly Building ,Liverpool John Moores University
Byrom Street , Liverpool
L3 3AF

Email: hra.approval@nhs.net

Dr David Oxborough
Reader in Cardiovascular Physiology
Liverpool John Moores University
Tom Reilly Building
Liverpool
L3 3AF

23 January 2017

Dear Mr Qasem

Letter of HRA Approval

Study title:	**Differentiation of the Athlete's Heart from Cardiomyopathy using Novel Echocardiographic Techniques: An Aid to Pre-Participation Screening**
IRAS project ID:	**169429**
Protocol number:	**N/A**
REC reference:	**16/LO/2245**
Sponsor	**Liverpool Heart and Chest Hospital**

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit

NHS
Health Research Authority
London - West London & GTAC Research Ethics Committee
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

20 January 2017

Dr David Oxborough
Reader in Cardiovascular Physiology
Liverpool John Moores University
Tom Reilly Building
Liverpool
L3 3AF

Dear Dr Oxborough

Study title:	**Differentiation of the Athlete's Heart from Cardiomyopathy using Novel Echocardiographic Techniques: An Aid to Pre-Participation Screening**
REC reference:	**16/LO/2245**
Protocol number:	**N/A**
IRAS project ID:	**169429**

Thank you for your letter of 20th January 2017, responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved by the sub-committee.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact please contact hra.studyregistration@nhs.net outlining the reasons for your request.

Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Appendix 2- Participant Information Sheet

Athlete Information Sheet

Title of Research Study:
Differentiation of the Athlete's Heart from Cardiomyopathy (Heart Muscle Disease)

Principal Investigator: Dr David Oxborough, Liverpool John Moores University, Research Institute for Sport and Exercise Sciences.
Postgraduate PhD Student Researchers: Mr Mohammad Qasem and Ms Lynsey Forsythe, Liverpool John Moores University, Research Institute for Sport and Exercise Sciences.

Invitation

You are being invited to take part in a collaborative research study between Liverpool Heart and Chest Hospital (LHCH) and Liverpool John Moores University (LJMU). Before you decide to be a voluntary participant it is important that you understand why the research is being done and what it involves. Please take time to read the following information. Ask us if there is anything that is not clear or if you would like more information. Take time to decide if you want to take part or not.

1. What is the purpose of the study?

The aim of this study is to investigate the structure and function of the heart in athletes and in patients with a diagnosed cardiomyopathy in order to understand how best to differentiate between increased heart size due to exercise (athletic adaptation) and those due to disease (cardiomyopathy). The information obtained from this study may help reduce misdiagnosis of athletes during pre-participation cardiac screening. The results may contribute to future cardiac screening guidelines.

2. Why have I been chosen?

You have been invited to take part in this study because you are an elite athlete.

3. Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do, you will be asked to sign a consent form. You are free to withdraw at any time during and after the procedures and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care and the pre-screening examination you receive.

4. What will happen to me if I take part?

As a participant in this study, there are no additional costs to you. You will not be paid for participating in this study. The tests that are used in this study will be taken as part of your routine pre-participation cardiac screening. This will take place either at your sports club / venue or at Liverpool John Moores University.

Initially we will take a measurement of your height and your weight and blood pressure. Next you will have a tracing of your heart (a 12-lead electrocardiogram (ECG)). The ECG test involves you lying down quietly and it takes approximately 10 minutes. Small stickers (which we call electrodes) are placed at strategic points on your chest, arms and legs. Flexible leads that extend from the ECG machine are then attached to these stickers. The electrical rhythm of your heart is recorded and printed out.

Finally, you will lie down quietly to have an echocardiogram. An echocardiogram is very similar to the ultrasound scan that is used for a pregnant woman to check the health of her baby. In this study, an echocardiogram will be used to measure the dimensions of the heart and the flow of blood in and out of the heart. The echocardiogram will take up to 45 minutes. Finally, you will be required to fill in a health questionnaire which will take approximately 10 minutes.

The ECG and Echocardiogram are tests to check for problems with your heart. The ECG and Echocardiogram tests , and the health questionnaire, that are used in this study will be taken as part of your routine pre-participation cardiac screening. The experimental part of this work involves the researcher doing further analysis which are novel and essentially considered to be the extra element for our research. All investigations in this study will help in defining normal indices for athletes and to improve the ability to diagnose any conditions such as a cardiomyopathy. In view of this, there is a very small chance this test will pick up an unexpected finding. Should this occur our study cardiologist will contact you to arrange a suitable course of action.

5. Are there any benefits/risks involved?

The ECG and echocardiogram will be performed and interpreted by an experienced health care professional with expertise in the assessment of cardiac disease. These tests are considered standard and will be acquired as part of your cardiac screening regardless of whether you choose to participate in this study. In the very unlikely event that an unexpected cardiac abnormality is found you will be managed appropriately by the overseeing cardiologist.

Data collected may help to inform future pre-participation cardiac screening protocols for athletes it may help reduce misdiagnosis of athletes during cardiac screening.

There are no expected adverse effects or discomfort from the 12-lead ECG or echocardiogram.

6. Will my taking part in the study be kept confidential?

Any information which is collected from the cardiac assessment including the health questionnaire, the ECG and the Echocardiogram will be analysed and kept strictly confidential. Data collected for the purpose of this study will be fully anonymised using codes with no way of linking data to you. All data will be stored in a password protected computer file which only the clinical team (LHCH) and researchers (LJMU) will have access to.

7. What will happen to the results of the study?

After the tests are completed, your test results will be reported and a letter will be written by the consultant cardiologist to you and your doctor. This may be your club / sport doctor or your GP. If any further investigation should be necessary the consultant will make this clear in the letter.

We are asking you to consent to the use of data from the health questionnaire, ECG and echocardiogram for research purposes. Results may be reported at national or international conferences and/or in journal publications but your identity will be protected and you will not be identified.

8. What happens if something goes wrong on the day of my tests?

If you have a concern about any aspect of this study, you should speak with the study team. Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. Please raise your concerns in the first instance with the Principal investigator, Dr David Oxborough and the contact details can be found below.

9. Complaints procedure:

If you have any concerns regarding your involvement in this research, please discuss these with the researcher in the first instance. If you wish to make a complaint, please contact researchethics@ljmu.ac.uk and your communication will be re-directed to an independent person as appropriate.

10. What Insurance Provisions are in place?

In the unlikely event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against Liverpool John Moores University but you may have to pay your legal costs.

11. Who is organising the research?

This research is being organised by the principal investigator Dr David Oxborough, Research Institute for Sport and Exercise Sciences, Liverpool John Moores University in collaboration with Liverpool Heart and Chest Hospital. The data collected from this study will be used to support PhD projects for two postgraduate research students within the Research Institute for Sport and Exercise Sciences – Mr Mohammad Qasem and Ms Lynsey Forsythe. The study has gained ethical approval from Liverpool John Moores University and the NHS research ethics committee.

12. What happens now?

If you choose to participate, you will be asked to complete an informed consent form on the day of your screening. You will be asked to keep a copy of this information sheet and the signed consent forms.

Thanks for your time. If you have any further questions or want to participate in the study please contact Mohammad Qasem or Lynsey Forsythe

School of Sport and Exercise Sciences
Tom Reilly Building
Liverpool John Moores University
Byrom Street
Liverpool
L33AF
Email: M.E.Qasem@2014.ljmu.ac.uk or L.C.Forsythe@2014.ljmu.ac.uk

Contact Details of Principal Investigator /Academic Supervisor

Dr David Oxborough
School of Sport and Exercise Sciences
Tom Reilly Building
Liverpool John Moores University
Byrom Street
Liverpool
L33AF
Email: D.L.Oxborough@ljmu.ac.uk

Appendix 3- Consent Form

INFORMED CONSENT FORM (Athlete)

Title of Project: Differentiation of the Athlete's heart from Cardiomyopathy (Heart Muscle Disease)

Name of Principal Investigator: Dr David Oxborough, Liverpool John Moores University, School of Sport and Exercise Sciences

Centre Number:

Study Number:

Participant Identification Number:

Thank you for reading the information about this collaborative research project between Liverpool Heart and Chest Hospital (LHCH) and Liverpool John Moores University (LJMU). If you would like to take part, please read and sign this form.

Please initial all boxes

1. I confirm that I have read and understand the information sheet (Version 5, 20 January 2017) provided for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving a reason and that this will not affect my legal rights. ☐

3. I understand that any personal information collected during the study will be anonymised and remain confidential ☐

4. I agree to take part in the above study ☐

Name of Participant	Date	Signature
Name of Researcher	Date	Signature
Name of Person taking consent *(if different from researcher)*	Date	Signature

Note: When completed 1 copy for participant and 1 copy for researcher

Appendix 4- Health Questionnaire

Cardiac Screening Health Questionnaire

Participant Details

Participant ID:	Date of Screening:
Age:	Gender:

Which country were you born in?
…….Ethnicity *(please tick the appropriate box)*

White	Mixed	Black	Asian	Other
British ☐	White and Black Caribbean	Caribbean ☐	Indian ☐	Chinese ☐
Irish ☐	White and Black African ☐	East African	Pakistani ☐	Filipino ☐
European ☐	White and Asian ☐	West African	Bangladeshi	Vietnamese ☐
Turkish		North		Other ☐
Greek/Cypriot				
If other, please state your ethnic origin:				

Height …….cm Weight ……..Kg Blood Pressure ……./…….mmHg

1. Have you ever fainted?

During Exercise	Yes / No	How recently did this occur?	If yes, please describe the circumstances
Following Exercise	Yes / No	How recently did this occur?	
Unrelated to exercise	Yes / No	How recently did this occur?	

2. Do you experience dizzy turns?

During Exercise	Yes / No	How recently did this occur?	If yes, please describe the circumstances
Following Exercise	Yes / No	How recently did this occur?	
Unrelated to exercise	Yes / No	How recently did this occur?	

3. Do you experience palpitations? *(palpitations are a fluttering in your chest that you can notice whilst resting)*

Yes / No	If yes, how recently and please describe the circumstances

4. Do you experience chest pain, heaviness or tightness?

During Exercise	Yes / No	If yes, please describe the circumstances
Following Exercise	Yes / No	
Unrelated to exercise	Yes / No	

5. Do you feel that you are more breathless or more easily tired than your team mates?

Yes / No	If yes, please describe the circumstances

6. Is there a family history of (please tick):

High Blood Pressure ☐High Cholesterol ☐Diabetes ☐

7. Is there a family history of heart disease in anyone under the age of 50?

Yes / No	If yes, please state the age of onset

8. Has anyone died suddenly in your family under the age of 50?

Yes / No	If yes, please describe the circumstances and at what age did the death occur

9. Approximately, how many days per week are you physically active (playing sport)?
……

10. On average, how many hours per week are you physically active (playing sport)?
…….....

11. If you are competitive athlete what sports do you play and at what level?

e.g. International, National, County, Club, Other

A (main sport)…… Level:……

B.…… Level:……

C. ……. Level:……

12. How long (for how many years) have you been participated in sport?
…….

13. Do you agree for the results of your screening including investigations to be discussed with the Club doctor? Yes / No

14. Do you agree for your results to be kept on a database for research in the future? Your personal identity will never be disclosed to anyone if your data is used for research. Yes / No

Signature……. Date……

Appendix 6- Quality check list assessment (for study one)

	1	2	3	4	5	6	7	8	Total
Prakasa et al (2007)	+	+	+	+	+	+	+	-	7
Tops et al	+	+	+	+	-	-	+	-	5
Wang et al	+	+	+	+	-	-	+	-	5
Teske et al (2009)	+	+	+	+	+	+	+	+	8
Bauce et al	+	+	+	+	-	+	+	-	6
Iacoviello et al	+	+	+	+	-	-	+	-	5
Aneq et al	+	+	+	+	-	-	+	-	5
vitarelli et al	+	+	+	+	+	+	+	-	7
Lindstrom et al	+	+	+	+	+	+	+	-	7
Yoerger et al	+	+	+	+	-	-	+	-	5
	10	10	10	10	4	5	10	1	Total

+ Represents criteria achieved and one point is given.

− Represents criteria not achieved.

No. criteria:

1. Matched Control Group

2. Task Force Criteria

3. Participant Concent / Ethical approval

4. Echocardiography Protocol

5. Medication

6. Patient States

7. Eligibility criteria were specified

8. Genotype Detected

Appendix 7- Supplementary Table (for study two)

Regional RV Strain (ε) (%) and Strain Rate (SR) (l/s) including base to apex gradients (data are mean ± SD)

Base to apex ε gradient (%) and SR (l/s)	**LD**	**MD**	**HD**
lateral Wall:			
Basal ε	-26.4 ± 6.6	-26.4 ± 7.1	-25.9 ± 5.5
Basal SRS'	-2.1 ± 0.8^	-1.9 ± 0.6	-1.7 ± 0.5
Basal SRE'	2.5 ± 0.9	2.3 ± 0.8	2.2 ± 0.7
Basal SRA'	1.1 0.4	1.2 0.5	1.3 0.4
Mid ε	-27.3 ± 4.8	-27.3 ± 5.4	-27.8 ± 4.2
Mid SRS'	-1.4 ± 0.3	-1.6 ± 0.4	-1.4 ± 0.3
Mid SRE'	1.9 ± 0.5	1.8 ± 0.5	1.9 ± 0.4
Mid SRA'	0.9 ± 0.3	1 ± 0.4	0.9 ± 0.3
Apical ε	-30.9 ± 4.5	-28.7 ± 5	-31.4 ± 4.9¶
Apical SRS'	-2 ± 0.5	-1.8 ± 0.5	-1.9 ± 0.6
Apical SRE'	2.5 ± 0.6	2.1 ± 0.7	2.5 ± 0.6§
Apical SRA'	1.2 ± 0.5	1.3 ± 0.4	1.3 ± 0.4
Septal Wall:			
Basal ε	-17.6 ± 2.7	-18.6 ± 2.7	-18 ± 3.1
Basal SRS'	-1.2 ± 0.3	-1.2 ± 0.2	-1.2 ± 0.3
Basal SRE'	1.6 ± 0.4	1.5 ± 0.4	1.6 ± 0.4
Basal SRA'	0.8 ± 0.2	0.7 ± 0.3	0.7 ± 0.3
Mid ε	-18.3 ± 3.1	-17.8 ± 2.5	-17.6 ± 2.5

Mid SRS'	-1.1 ± 0.3	-1 ± 0.2	-0.9 ± 0.2
Mid SRE'	1.8 ± 0.4	1.5 ± 0.4	1.6 ± 0.4
Mid SRA'	0.7 ± 0.2	0.6 ± 0.2	0.6 ± 0.2
Apical ε	-22.9 ± 4.5*	-18.8 ± 4.8	-21.5 ± 4.7¶
Apical SRS'	-1.9 ± 0.7	-1.7 ± 0.7	-1.8 ± 0.9
Apical SRE'	2.3 ± 0.5	1.9 ± 0.6	2.1 ± 0.6
Apical SRA'	0.9 ± 0.4	0.8 ± 0.4	0.8 ± 0.3

*P <0.01: LD versus MD;§P <0.01: MD versus HD ; ¶ P <0.01: HD versus MD; ^ P <0.01: LD versus HD