THE “ATHLETIC HEART”: INSIGHTS FROM MODERN IMAGING TOOLS IN CAUCASIAN AND WEST AFRICAN ATHLETES.

Victor Segun Utomi

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Director of Studies

Professor Keith George PhD, FACSM, FECSS, FBASES

Associate Dean for Scholarship, Research and Knowledge Transfer Faculty of Sciences Tom Reilly Building Liverpool John Moores University

Second Supervisor

Professor Greg Whyte

Professor of Applied Sport & Exercise Sciences

Research Institute for Sport & Exercise Sciences

Liverpool John Moores University

Third Supervisor

Professor John Somauroo

Honorary Research Fellow, Liverpool John Moores University

& Consultant Cardiologist, Countess of Chester Hospital, Chester.

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ABSTRACT

A seminal study by Morganroth et al (1975) demonstrated a differential pattern of cardiac adaptation with prolonged exercise training; of eccentric pattern of left ventricular hypertrophy (LVH) in endurance trained athletes (ET) and concentric LVH in resistance trained athletes (RT). Specific inconsistencies related to the nature of any adaptation to RT; the value of new imaging technologies; the relative importance of scaling of cardiac data for differences in body size; the impact of training on the right ventricle (RV) and the fit of differential pattern of adaptation in athletes with Black ethnicity have driven the rationale for the studies included in this thesis.

Study one employed meta-analysis techniques to critically evaluate the evidence base supporting or refuting that MH exists in elite male Caucasian ET & RT. Modern echocardiographic techniques were used to test whether a dichotomous LV and RV structural as well as global and regional functional adaptation was apparent in elite Caucasian ET & RT in studies 2 & 3. The final study (exploratory) was to characterize the athletic heart phenotype in a homogenous population of elite RT of West African origin (WRT) to provide new insight in relation to cardiac adaptation and ECG characteristics in non-Caucasian athlete groups. Allometric scaling approach was deployed to index LV and RV data for individual body variance in body size.

The novel findings of this thesis; larger LV data in ET (LVMg: ET 232 (200 to 260), RT 220 (205 to 234), CT 166 (145 to 186) but no concentric hypertrophy in RT within the meta-analysis, predominance of normal geometry in male athletes (65% of ET and 95% of RT) and the lack of concentric pattern of hypertrophy in RT in a cross-sectional study; no RV adaptation in RT athletes (RVD1mm: ET 45 ± 5 (39 to 57), RT 40 ± 5 (32 to 51) CT 39 ± 4 (31 to 45); no LV or RV adaptation in WRT athletes; the importance of appropriate scaling of cardiac parameters; provide a useful re-evaluation of concepts and models in the athletic heart literature. The findings have important implications for cardiovascular screening of athletes.

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GLOSSARY OF TERMS AND ABBREVIATIONS

A = Peak late diastolic velocity

AH = Athlete's heart

ARVC = Arrhythmogenic right ventricular cardiomyopathy

ASE = American Society of Echocardiography

BSA = Body surface area

CT = Control subjects

CCT = Caucasian control subjects

CMR = cardiac magnetic resonance imaging

CRT = caucasian resistance trained athletes

ε = Strain

E = Peal early diastolic velocity

EF = Ejection fraction

ET = Endurance trained athlete

FAC = Fractional area change

HR = Heart rate

ICC = Intraclass correlation coefficient

IVCT = Isovolumic contraction time

IVRT = isovolumic relaxation time

IVSWTd = diastolic inter-ventricular septal wall thickness

IVSs = systolic inter-ventricular septal wall thickness

LA = Left atrium

LAD = Left atrial dimension

LV = Left ventricle

LVEDV = Left ventricular end diastlic volume

LVIDd = Left ventricular internal diameter at end diastole

LVIDs = Left ventricular internal diameter at end systole

LVEF = left ventricular ejection fraction

LVM = left ventricular mass

LV = Left ventricular

MH = Morganroth's Hypothesis

MST = Myocardial speckle tracking

PLAX = Parasternal long axis

PSAX = Parasternal short axis

PASP = Pulmonary artery systolic pressure

PLAX = Parasternal long axis

PSAX = Parasternal short axis

PW = Pulse wave

PWTd = Posterior wall thickness at end diastole

PWTs = Posterior wall thickness at end systole

ROI = Region of interest

RT = Resistance trained athlete

RV = Right ventricle

RVEDD = RV end-diastolic diameter

RVEDV = RV end-diastolic volume

RVD area = Right ventricular end-diastolic area

RVD1 = Right ventricular basal inflow

RVL = Right ventricular length

RVOT = Right ventricular outflow tract

RVWT = RV wall thickness

RWT = Relative wall thickness

S’ = Peak systolic velocity

SD = Standard deviation

SR = Strain rate

SRA’ = Strain rate during late ventricular diastole

SRE’ = Strain rate during early ventricular diastole

SRS’ = Strain rate during ventricular systole

STE = Speckle tracking echocardiography

SV = Stroke volume

TAPSE = Tricuspid annular plane systolic excursion

TDI = Tissue Doppler imaging

WA = West African

WCT = West African control subjects

WRT = West African resistance trained athletes

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CHAPTER 1

GENERAL INTRODUCTION

Athletes' (derived from the Romanization of the Greek word - ἀθλητὴς, *athlētēs)* are individuals who participate in a sporting contest. Elite athletes are those operating at the highest levels of their sport who strive to achieve optimum performance. Various adaptations may be observed in organ systems of athletes, in particular with the heart (Henschen, 1899, Shapiro, 1984, Morganroth et al., 1975, Maron and Pelliccia, 2006) that allows training and performance progression.

The term 'Athlete's Heart' (AH) is commonly used by the public, sporting community, physicians and research scientists to describe the physiological effects of long term athletic training on the heart. Clinical awareness of the AH came to light over a century ago (Bergmann, 1884, Henschen, 1899). Exercise training was found to be accompanied by hypertrophy of the heart, both in man (Henschen, 1899) and in experimental animals (Bergmann, 1884). Until the development of non-invasive imaging technologies, cardiac adaptation to exercise was identified by physical examination (Shapiro, 1987).

The AH as initially described, included sinus bradycardia with often a soft systolic murmur of mitral regurgitation and audible 3^{rd} and 4^{th} heart sounds (Henschen, 1899). Consequent to on-going technical developments it is currently believed that the AH represents a complex range of structural, functional and electrical adaptations to prolonged periods of training (Morganroth et al., 1975, Pelliccia et al., 1991, George et al., 1991, Naylor et al., 2008). The AH appears to be largely benign, but there have been specific concerns throughout the past 150 years about over exertion and negative effects in the heart (Whyte et al., 2004b, George et al., 2012).

A landmark sports medicine study involving echocardiographic assessment of the left ventricle (LV) was undertaken by Morganroth et al (1975) in a small sample of highly trained endurance (15 swimmers and 15 long-distance runners), resistance-trained athletes (12 wrestlers and 4 shot putters) and sedentary controls (15). Morganroth and colleagues used M-mode echocardiography, which was at its infancy in the mid 70's, to describe two different morphological forms of the AH, often referred to as a dichotomous pattern of LV hypertrophy/geometry (Morganroth et al., 1975, Morganroth and Maron, 1977).

Morganroth et al (1975) postulated that endurance or aerobic training (swimming, running) was associated with prolonged periods of high cardiac output and increased LV volume (preload) at end-diastole. The chronic adaptation to these repeated exercise bouts (isotonic) was an increase in LV volume at rest with minor but proportional changes in LV wall thickness. This has been termed eccentric hypertrophy (balanced increase in chamber and wall dimensions).

Conversely, with repeated periods of high afterload (pressure overload) in resistance training (isometric - wrestlers, shot putters, and weight lifters), Morganroth and colleagues postulated that LV wall hypertrophied, with little or no change in LV dimension/volume. This was termed concentric hypertrophy i.e. a disproportionate increase in wall thickness (Morganroth and Maron, 1977, George et al., 1991, Naylor et al., 2008). Morganroth's cross-sectional observations were thus easily mapped differential haemodynamic loading during acute training (Grossman et al., 1975).

This differential adaptation of the AH has been referred to as the 'Morganroth's hypotheses' (MH) and has been widely adopted in textbooks, scientific papers and professional guidelines (Lang et al., 2005, Rudski et al., 2010, Naylor et al., 2008), including the 26th Bethesda Conference: Recommendation for determining eligibility for competition in athletes with cardiovascular abnormalities (Mitchell et al., 1994).

Despite the pervasive nature of the MH, continuous evaluation of both our understanding and application of the AH phenotype is clinically important (George et al., 1991, Fagard, 1996, Pluim et al., 2000, Whyte et al., 2004a, Naylor et al., 2008). There have been specific concerns related to the nature of any adaptation to resistance training as work subsequent to Morganroth et al. (1975) has been inconsistent (Haykowsky et al., 2001, Naylor et al., 2008). Other issues pertinent to the MH are noteworthy. Specifically, the impact of training on the right ventricle (RV) and left atria (LA) is less clear although a recent studies from Italy and around the world have reignited the debate about how the RV responds to training (Oxborough et al., 2012b, D'Andrea et al., 2013).

Part of the reason that the MH did not include the RV and LA is related to the technical difficulties associated with echocardiography in the 1970's. 'Ice-pick' M-mode echocardiography used by Morganroth was in its infancy in the mid-1970s (Henry et al., 1980). Most now recognize the technical limitations of M-mode echocardiography. Aside from the limited B-mode spatial resolution (1-2 mm) and M-mode axial resolution of approximately 0.5 mm (Henry et al., 1980, George et al., 1991, Lang et al., 2005, Mor-Avi et al., 2011), geometric assumptions for volume calculations were applied in estimating LV mass which can lead to significant prediction error (Lang et al., 2005, Naylor et al., 2008, Spence et al., 2011).

Recent developments in echocardiography have improved spatial resolution due to transducer technology and processing capabilities, and new studies continue to shed light on this field, especially in relation to elite resistance training. Also, new modes of imaging e.g. Tissue Doppler Imaging (TDI) and Speckle Tracking Echocardiography (STE) have developed our understanding of global and regional function in the AH. The MH made no references to LV function and despite more recent studies assessing global and regional systolic and diastolic function in small groups of athletes, contradictory data still exist (Maron et al., 1993, Pelliccia et al., 1993, Scharhag et al., 2002, George et al., 2010, Spence et al., 2011). The emergence of tissue Doppler Imaging (TDI) and myocardial speckle tracking (to quantify strain, strain rates, rotation, rotation rates and twist) promise to grossly enrich scientific knowledge about the AH (Jenkins et al., 2006, Marwick, 2006, Mor-Avi et al., 2011).

Of emerging interest, as technology spreads globally, is the application of basic and advanced cardiovascular research tools (physical examination, history, ECG and ultrasound echocardiography) to describe the cardiac phenotype in athletes of different ethnicity (Lewis et al., 1989, Ekelund et al., 1990, Basavarajaiah et al., 2008, Rawlins et al., 2010, Sheikh et al., 2013). Current data suggests that the AH phenotype, as observed by ECG and echocardiogram, may be different in Black versus Caucasian athletes (Basavarajaiah et al., 2008, Magalski et al., 2011, Rawlins et al., 2010, Papadakis et al., 2012, Sheikh et al., 2013).

The development of an appropriate AH phenotype for use in cardiac screening, to diagnose the presence of diseases that promote the risk of sudden cardiac death, has been poorly observed and characterized in resident West African groups (Chandra et al., 2012). This would be helped by fully describing the AH phenotype in these athletes. The rationale is that the incidence of sudden cardiac death in Black athletes has been reported to be higher than in Caucasian athletes (Maron and Pelliccia, 2006 , Chandra et al., 2012).

Intuitively, the lack of normative values of upper limits of quantitative ECG and echocardiographic data in West African athletes, coupled with the lack of established pre-participation screening guidelines specific to this athlete group, indicates the specific rationale for detailed study of the AH in West African athletes. Finally, to date there is no clear knowledge of how different training stimuli would alter the AH phenotype in West African (WA) athletes and as such it is clear we need to develop knowledge in relation to the presentation of the AH phenotype in WA athletes.

Finally, an another important concern in the interpretation of AH research is the association between body size and cardiac morphology (George et al., 2001). Most studies now recognise that potential differences in body size between athletes and sedentary subjects could alter cardiac data interpretation (Batterham et al., 1999) but the impact of body size and composition on the AH remains contentious. The use of simple ratio scaling is popular in the published literature despite the fact that a large number of cardiovascular variables relate to body size in a nonlinear fashion (Batterham et al., 1999, Dewey et al., 2008, George et al., 2001). Appropriate scaling in a re-evaluation of the MH will be unique.

In summary, concerns and controversies in previous / contemporary works related to the AH drives the rationale for the following studies included in this thesis; a) A systematic review and meta-analysis of training mode, imaging modality and body size influences on the male AH, b) A comprehensive technical assessment of the left and right ventricles to determine AH phenotype, c) An assessment of the impact of resistance training on a homogenous group of West African athletes. In order to develop our knowledge of the AH, this thesis will attempt to achieve the following aims and specifically test the stated hypothesis. We have linked these aims and hypothesis to four empirical studies included within this thesis.

1.1 Aims

The aims of this thesis are to;

1) Critically evaluate the evidence base, supporting or refuting that Morganroth's hypothesis exists in elite male Caucasian resistance and endurance trained athletes.

2) Determine the structural, global and regional function of the LV in Caucasian resistance and endurance trained athletes using a cross sectional design with standard 2D, Doppler, tissue-Doppler and speckle tracking echocardiography.

3) Describe the structural, global and regional function of the RV in Caucasian resistance and endurance trained athletes using the above mentioned state-of-the-art echocardiographic assessment tools.

4) Assess the impact of resistance training on cardiac structure, function and electrical conduction in male elite WA and Caucasian athletes.

1.2 Hypotheses

1) I hypothesize that training mode, imaging modality and body size influence the morphology and function of the male AH in chapter 2.
2) I hypothesize that LV structure and function will follow a dichotomous training specific adaptation in chapter 3.
3) I hypothesize that global RV adaptation to exercise is mediated by training type and that scaling of RV data will alter specific direction and data interpretation in chapter4.
4) I hypothesize that elite male West African resistance trained athletes will not present with a concentric AH pattern in chapter 5.

CHAPTER 2

LITERATURE REVIEW

2.1 Background context: Historical perspectives of the Athlete's Heart

The heart, as a muscle, has the ability to respond to chronic training and the elevated demand for blood flow to the body during training and competition. In physiological terms, the structural response of the heart is largely a change in the size of the chambers and heart walls due to signalling events in the cardiac myocyte that lead to protein synthesis. The exact mechanisms and signalling pathways are still debated but the outcome is that the heart has the potential to increase its size and efficiency when adapting to the increased load on the heart that occurs with exercise (George et al., 2011).

Exercise remains one of the most popular and best studied models of physiologic cardiac adaptation. The study of cardiac adaptation to exercise really came to the fore over a century ago when Bergmann (1884) noted that wild animals had bigger hearts in proportion to their body size in comparison to their domestic counterparts. Similar observations have been made in exercised dogs versus untrained dogs, and migratory birds were also found to have bigger hearts (Pedoe, 2003).

The ability of the human heart to adapt to endurance exercise was first documented in the nineteenth century by Henschen (1899). During a physical examination Henschen found, by percussion, "dullness" of the anterior chest wall in well-trained cross-country skiers suggesting a cardiac hypertrophy. It was also noted that cross country skiers with bigger hearts did better in endurance events (Henschen, 1899). In association with suspected cardiac hypertrophy Henschen also observed reduced resting heart rates and presence of a 3rd and 4th heart sound on auscultation of the heart in the cross-country skiers. Consequently, the heart of an athlete became associated with functional, structural and electrical differences compared to the normal or untrained heart. In the scientific literature, these observations have been popularised under the general term of the ‘athletic heart syndrome’ (Gott et al., 1968 , Morganroth and Maron, 1977, George et al., 1991).

With the discovery of X-rays in 1895 by Wilhelm Conrad Roentgen the field of radiology was born and the first “imaging” studies of the athlete’s heart were produced (Blake and Larrabee, 1903, Bardeen, 1918, Gott et al., 1968). Cardiac hypertrophy can be demonstrated by X-ray but a major limitation remained in that only a silhouette of the heart is produced and this reduces effective interpretation of physiological and pathological adaptation.

Numerous studies have shown that even when there were no differences between the athletic group and untrained subjects in physical findings, a relative increase in heart size on X-rays was more apparent in athletes (Gott et al., 1968, Ikäheimo et al., 1979, Assmus, 1995, Howell and Harden, 1996). Ikaheimo et al (1979) reported that 75% of endurance athletes and 20% of sprinters studied demonstrated a higher relative cardiac size on chest x-ray ($p<0.02$). It is important to note that results of x-ray are quite often challenging, difficult to interpret and cannot discriminate between specific/finite cardiac structures (Roeske et al., 1976, Peronnet et al., 1980, Rost, 1982).

In tandem with evolving scientific understanding of the athlete’s heart was the observation that physiological adaptations of the heart to prolonged, intense physical training produced electrocardiographic (ECG) changes considered abnormal in untrained persons. Increased vagal tone, anatomical and / or chemical changes in the heart (Beswick and Jordan, 1961, Gott et al., 1968 , Ikaheimo et al., 1979) and recently, ethnicity

(Basavarajaiah et al., 2008, Magalski et al., 2008, Maron et al., 2009) were thought to cause a spectrum of ECG changes characteristic of the AH in professional athletes.

The ECG changes associated with intense training are of interest because they are similar, and often difficult to differentiate from pathological ECG changes in certain disease states that can result in the sudden death of an athlete (Lichtman et al., 1973, Ferst and Chaitman, 1984, Cuspidi et al., 1996, Pelliccia et al., 2002, Corrado et al., 2003).

Historically, it could be argued that the advent of ultrasound imaging was the greatest single radiological advance in the 20th century (Coleman et al., 1966, Haber, 1980). Though sonar technology has been around since 18th century (Donald, 1980, Haber, 1980), it was not until 1950 that Ian Donald, an Obstetrician in Glasgow, began to experiment with the use adapted industrial sonar equipment to examine the pregnant uterus (Donald, 1980, Haber, 1980, Oakley, 1986). The importance of ultrasound lay in the fact that it made possible the examination of organs which had previously been completely inaccessible, or which had only been imperfectly visualised using complex invasive procedures (Feigenbaum, 2001). Edler and Hertx (1954) were the first to publish the use of ultrasound for cardiac investigations i.e. echocardiography (Feigenbaum et al., 1968, Edler and Lindström, 2004).

Cardiac ultrasound began with a single-crystal transducer display of the amplitude (A-mode) of reflected ultrasound waves versus depth on the oscilloscope screen (Troy et al., 1972, Luisada et al., 1975). Repeated pulse transmission and receive cycles allow rapid updating of the amplitude versus depth information so that rapidly moving structures such as aortic valve or mitral valve can be identified by their characteristic timing and pattern of motion (Teichholz et al., 1976, Henry et al., 1980).

Whilst A-mode displays are limited to amplitude of reflected ultrasound waves at different depths, M–mode (motion) extended this by the inclusion of a temporal factor of time dimension explicitly on the horizontal axis. Each amplitude signal along the length of the ultrasound beam is converted to a corresponding grey scale level to produce a motion display on the oscilloscope. Because only a single ultrasound beam is included in an A-mode / M-mode display, both techniques share an advantage of high sampling rate (1800 s^{-1}) which is valuable for accurate evaluation of rapid normal intra-cardiac motion (Sahn et al., 1974, Luisada et al., 1975).

Morganroth and colleagues employed the "ice-pick" M-mode technique using an Aerotech gamma transducer (Aerotech laboratories, Division of Branson Instrument Co., Lewiston, Pennsylvania) available in the mid 70's. The transducer was attached to a modified Ekoline 20A ultrasonic unit (Smith Kline Instrument Co., Philadelphia, Pennsylvania) with a signal component custom built video amplifier – Honeywell 1856 Viscorder (Honeywell Co., Denver, Colarado). This study literally "opened the flood gates" for AH research with thousands of athlete's research to date. These investigations enabled a detailed description of cardiac structure and function (George et al., 2011; 2012). Since then there has been significant technological advancements with improved spatial resolution of cardiac images as well as the development of new imaging modalities which will be described later.

2.2 The Morganroth Hypothesis (MH)

Echocardiographic evidence of the cardiac adaptation to exercise has been reported since the mid-1970s. A landmark assessment of the left ventricle (LV) was undertaken by Morganroth and colleagues (Morganroth et al., 1975) in a small sample of highly-trained endurance (15 swimmers and 15 long distance runners), resistance-trained athletes (12 wrestlers and 4 shot putters) and sedentary controls (15). Mean LV end-diastolic diameter (LVIDd) (figure 2.1) and mass (figure 2.2) were increased in endurance athletes; swimmers 56.6 ± 0.8 mm, 308g ± 9.3; runners 54.1 ± 0.9 mm, 302 g ± 9.0, compared to controls, 46.4 ± 0.7 mm, 211g ± 7.7, wall thickness was normal (≤ 12mm) (figure 2.3).

The Figure 2.1: Echocardiographically measured LV internal dimensions at end diastole in college athletes originally presented here cannot be made freely available via LJMU Digital Collections because of copyright reasons. The image was sourced at Morganroth et al 1975, page 52, http://annals.org/article.aspx?articleid=689311).

The Figure 2.2: Echocardiographically measured LV mass in college athletes, numbers represent mean values ± SEM. Data of swimmers and runners are statistically different from wrestlers and normal subjects ($p < 0.001$), originally presented here cannot be made freely available via LJMU Digital Collections because of copyright reasons. The image was sourced at Morganroth et al 1975, page 53, http://annals.org/article.aspx?articleid=689311).

The Figure 2.3: Echocardiographically measured LV free wall thickness (upper panel) and septal wall thickness (mm) in college athletes, numbers represent mean values ± SEM. Data of swimmers and runners are statistically different from wrestlers and normal subjects ($p < 0.001$), originally presented here cannot be made freely available via LJMU Digital Collections because of copyright reasons. The image was sourced at Morganroth et al 1975, page 53, http://annals.org/article.aspx?articleid=689311).

Resistance trained athletes (college wrestlers, world class short-putters) had normal mean LVEDV (110ml, 122ml), but increased wall thickness (13 mm, 14mm) and mass (330g, 348g). Thus endurance trained athletes demonstrated an increased left ventricular mass with cardiac geometry similar to chronic overload states e.g. mitral regurgitation. The resistance trained athletes had increased LV mass with cardiac geometry similar to those in pressure overload e.g. aortic stenosis. Despite limited details related to training-related haemodynamic loading on the LV, a dichotomous morphology was observed with an eccentric hypertrophy - (balanced increase in chamber and wall dimensions) in endurance athletes versus a concentric hypertrophy (disproportionate increase in wall thickness) in resistance athletes. It was hypothesised that these adaptations reflect differential haemodynamic loading during acute training (Grossman et al., 1975).

This differential adaptation of the athlete's heart (AH) has been referred to as the "Morganroth Hypothesis" (Morganroth et al., 1975, George et al., 1991, George et al., 1995) and has been widely adopted in textbooks, scientific papers and professional guidelines (Rudski et al., 2010) including the 26th Bethesda Conference: Recommendation for cardiovascular screening among athletes (Maron et al., 1994a).

The reason for the broad adoption of the MH is that it made teleological sense. In endurance sports the AH, including chamber enlargement, allow an increased maximal stroke volume (SV) and cardiac output (CO) and thus blood flow, and oxygen delivery, to the skeletal muscles which is vital to maintain exercise. This adaptation also underpins the increase in maximal oxygen delivery to meet the expanded metabolic needs of the trained state since no training effect is evident at maximal heart rate (HR_{max}) (Blomqvist and Saltin, 1983, Whyte et al., 2008).

Endurance sports is characterised by rhythmic contraction and shortening of large muscle group i.e. dynamic exercise activity (isotonic) which subjects the LV to repetitive increase in cardiac preload (Schaible and Scheuer, 1985) e.g. running. In endurance athletes, the myocardium remodels proportionately in cavity dimension and wall thickness to normalise end-diastolic wall stress.

In contrast, resistance exercise has been categorised as predominantly involving static muscle contraction at high force/power levels with very limited joint and muscle group movements (isometric) e.g. wrestling and weight lifting (Mitchell and Wildenthal, 1974). It is thought that the repetitive increase in skeletal muscle tension results in increased peripheral vascular resistance that results in a potentially vast increase in systemic arterial blood pressure and afterload on the LV (MacDougall et al., 1985). This results in cell signalling and adaptation that manifests as a disproportionate increase in LV wall thickness with little or no effect on cavity dimension. This increase in wall thickness serves to normalise the increase in end-systolic wall stress associated with the rise in arterial pressure and LV afterload (Mitchell and Wildenthal, 1974, Morganroth and Maron, 1977, MacDougall et al., 1985, Lentini et al., 1993).

In the context of the Law of La Place, the Morganroth schema is logical. An increase in preload or afterload can be normalised by chamber and/or wall adaptation (Sandler and Dodge, 1963, Moriarty, 1980). Empirical studies have demonstrated a strong correlation between sub maximal exercise systolic blood pressure (BP) and LV mass (LVM) in humans [$r=0.88$, $p < 0.05$] (Douglas et al., 1986) and in animals [$r = 0.71$, $P < 0.02$] (Muntz et al., 1981). This suggests a tight coupling of exercise haemodynamics, cardiac adaptation signalling and a hypertrophic response. Specific concerns with study design and the methodology employed by the seminal study of Morganroth will be evaluated in the following sections.

Despite the pervasive nature of the MH there are pertinent methodological concerns with conduct of this seminal study that are worthy of contiuing (re)evaluation. Firstly, the study subjects were not completely homogenous (97% Caucasians) although homoegeneity in age [18 to 24 years] limits the impact of accumulated years of training on the AH and may not reflect the reality of range of age in real life sports competitions.

Secondly, though no subject was known to be on any pharmacological agent, there is anecdotal evidence of unregulated use of metabolic supplements and anabolic drugs for muscle building to improve performance in mostly resistance trained athletes in the 70's (Salva, 1987, Sjöqvist et al., 2008). In a CMR (Cardiac Magnetic Resonance) study of 156 male subjects (52 resistance athletes, 52 endurance athletes and 52 controls), Lujikx et al (2013) reported that RT who used anabolic steroids demonstrated significantly different cardiac dimensions, biventricular systolic dysfunction and impaired ventricular inflow as compared to non-athletes and non-anabolic steroid using athletes (Luijkx et al., 2013).

The use of anabolic agents also raises another relevant issue; that of disparate or variation in body size. In the work of Luijkx et al (2013) there was a severe disparity in BSA of world class runners (1.82 ± 0.4) vs shot putters (2.52 ± 0.03 m^2). Interestingly, the authors did not observe a statistically significant difference in cardiac parameters between the results of any set of data corrected to BSA; hence all data were presented as absolute values.

Given that body organs do not relate to size and weight in a log linear fashion, the complexity of the influence of body size and composition on cardiac dimension has been demonstrated in a number of empirical studies (De Simone et al., 1992, George et al., 1998, Oxborough et al., 2012b) and has been highlighted in review articles (Batterham et al., 2008, Dewey et al., 2008). More so, appropriate scaling is known to alter data interpretation in a small number of previous studies (George et al., 1999, Oxborough et al., 2012b). The deployment of appropriate scaling model to re-evaluate the MH in on-going research is vital.

Finally, Morganroth et al (1975) obtained echocardiograms with Aerotech gamma transducers (Aerotech Laboratories, Division of Branson Instrument Co., Lewistown, Pennsylvania) and a modified Ekoline 20A ultrasonic unit. 'Ice pick' T-scan technique was used to visualise the interventricular septum (IVS) and the posterior basal LV wall (Henry et al., 1973). LVEDV was estimated at end diastole using the method of Feigenbaum et al (1972). LV mass was calculated from the echocardiographic measurement methods of Troy, Pombo and Rackey (1972).

Aside from the limited resolution of M-mode echocardiography in the mid 70's, it is interesting to note Troy et al's method of calculation of LV mass was derived from a cross-sectional study that validated echocardiogram against angiography in 24 patients with valvular and/or myocardial disease. An arbitrary correction factor of 1.047 and 1.05 were added to the formulae for LVEDV and LV mass (Feigenbaum et al., 1968, Troy et al., 1972) and current professional guidance has largely superceded the work and analysis processes adopted by Morganroth and colleagues.

2.3 Contemporary evaluation of Morganroth's Hypothesis

Whilst the conceptual framework of cardiac adaptation to exercise based on MH has been dominant for many decades, contradictory evidence exists (Fagard, 1996, George et al., 1991, Haykowsky et al., 2001, Pluim et al., 2000, Whyte et al., 2004a) and often relates to the methodological issues raised above. Numerous, usually small studies have undertaken echocardiographic examinations in athletes and compared the results with those of sedentary control subjects who are non-athletes. A PubMed MESH search of 'athlete's heart' post 1975 gave over 3000 hits. Consequently, a plethora of original AH research papers, supplemented by numerous reviews (George et al., 1991, Naylor et al., 2008) and meta-analysis (Fagard, 1996, Pluim et al., 2000, Whyte et al., 2004a) provide analysis demonstrating no, partial or total support of the MH.

Specifically, Fagard et al (1996) tested the hypothesis of divergent cardiac adaptation to different sports by applying meta-analytical techniques to published echocardiographic data on competitive male long distance runners, cyclists, and resistance athletes (135 athletes, 173 controls). Athletes had lower heart rate, larger LV internal diameter (LVID) and wall thickness. The calculated LV mass was larger in athletes by 67g or 48% ($p < 0.001$). Relative wall thickness (RWT), i.e. the ratio between wall thickness and LV internal diameter (LVID), was slightly but significantly higher in runners than in controls ($p < 0.05$) (Fagard, 1996). Contrary to the MH, the increase in wall thickness was pronounced in the runners who have generally been considered to demonstrate pure eccentric LV hypertrophy (LVH). Secondly, the value of LV septal wall thickness of the runners fell within normal limits.

The resistance component of Fagard et al's study included 178 athletes (42 weight or power lifters, 40 body builders, 50 wrestlers, 25 throwers, and 21 bobsledders) and 105 age, size and sex matched controls. LVID, wall thickness and LV mass were all larger in the resistance athletes group (RWT > 12%; $p < 0.05$). Despite this there was no convincing evidence of an isolated increase in septal or posterior wall ratio in resistance athletes, but rather a relative pattern of LV hypertrophy (Fagard, 1996). These results contribute to the controversy over the MH.

A few years later, and in an attempt to shed more light on the interpretation of the AH with a larger sample size, Pluim et al (2000) incorporated 59 echocardiographic studies involving 1451 male athletes. The study participants were endurance trained (413 runners), combined endurance 494 (cycling and rowing), resistance trained 544 (weight lifting, power lifting, body building, throwing and wrestling), and 813 control subjects aged between 18-40 years (Pluim et al., 2000). The authors reported that overall mean relative wall thickness (RWT) of control subjects (0.36) was significantly smaller than that of ET (0.39, $p = 0.001$), combined endurance + resistance trained athletes (0.40, $p = 0.001$) or resistance trained athletes (0.44, $p = 0.001$). LVIDd, inter ventricular septal wall thickness (IVSWT) and posterior wall thickness (PWT) were higher in athletes than controls. The results of Pluim et al's meta-analysis provide some support for the MH, with an intermediate form of LV hypertrophy in those sports with combined components (Pluim et al., 2000).

Previous studies and meta-analysis have focused mostly on investigating the AH in male athletes and with conflicting outcomes related to the MH (Fagard, 1996, Pluim et al., 2000). Whyte et al (2004a) applied meta-analytical techniques to 13 published echocardiographic studies between 1987 – 2000 examining cardiac structure and function in female athlete (Whyte et al., 2004a). Their study group included 890 athletes and 333 control subjects of which 227 were strength and sprint athletes, 442 were endurance athletes and 168 team game players. The authors reported that significant ($p < 0.05$) differences existed between sporting groups for LVID and LV mass only, with ET and team games demonstrating the larger effect size when compared to strength athletes. No significant effect of training was observed for LV function with exception of stroke volume (SV) – athletes > controls ($p < 0.05$) with no observed difference between sporting groups (Whyte et al., 2004a). The results of this meta-analysis offered little support for MH of a differential cardiac remodelling relating to sporting discipline.

The variance in individual studies and meta-analysis is worthy of some reflection and assessment of technical issues. Given that different researchers employ different measurement techniques (Figure 2.4) and formulae for the calculation of cardiac parameters, it is not unlikely that the lack of clear standardised guidelines for much of the last 40 years may partially contribute to inconsistencies in echocardiographic measurements and lack of consensus in previous work.

The Figure 2.4: Methods for echocardiographic measurement of inter-ventricular septal thickness (IVSWT), LV internal dimension (LVID) and posterior wall thickness (PWT). Panel A) The standard measurement convention includes the thickness of the right and left septal endocardial echoes in IVSWT and includes the posterior wall endocardial echoes in PWT. Panel B) The Penn Convention excludes right and left septal endocardial echo thickness from IVSWT and excludes the posterior wall endocardial echoes from PWT. Left septal endocardial echo thickness and posterior wall endocardial thickness are thus included in the LVID by this method originally presented here cannot be made freely available via LJMU Digital Collections because of copyright reasons. The image was sourced at Devereux et al 1977, page 614 http://circ.ahajournals.org/content/55/4/613.full.pdf+html.

For instance, some researchers may include (Paterson et al 2006) or exclude (Esch et al 2010) the papillary muscles in their methods of cardiac assessments. LV mass can be derived from multiple equations and measurements of IVSWT, PWT and LVID with different geometric assumptions using various methods: ***Troy et al (1972) method*** - Morganroth et al (1975), Cahill et al (1979), Hauser et al (1985,) Vos et al (1985); or ***Schiller and Bird (1983) method*** - Gregorie et al (1989); or ***Devereaux and Reichek (1986) method*** – George et al (1999), D' Andrea et al (2003); or ***Teichloz method*** – Indermule et al (2009); or ***Feigenbaum***

method – Brown et al (1987); or ***Benneth and Evans (1994) method*** – Nishimura et al (1981); or ***Cubed function method*** – Bekaert et al (1981); or ***cross sectional area method*** – Selpulveda et al (1989); or ***Wyatt method*** – Giada et al (1998); or ***Simpsons biplane method*** – Caselli et al (2008); ***Area length method by Helak and Reichek (1981)*** – Pelliccia et al (2000); ***Reichek method*** – Pluim et al (1997); ***ASE method*** – Oxborough et al (2012), La Gerche et al (2012). There are significant differences in results obtained by different measurements techniques and mathematical assumptions in deriving formulae and algorithms for the calculation of cardiac parameters. These differences should be taken into account to limit heterogeneity in any propsective study or meta-analysis.

A smaller number of recent works have used cardiac magnetic resonance imaging (CMR; De Castro et al 2006, Prakken et al 20011) or a combination of echocardiography and CMR (Petersen et al 2005, Scharhag et al 2010, La Gerche et al 2011, Armstrong et al 2012) with significant difference being noted between the two imaging modalities (Bellenger et al., 2003, Prakken et al., 2011b, Armstrong et al., 2012). Whilst CMR has now become the gold standard for cardiac structural measurement it is still expensive and has made only a limited penetration into the AH field. Despite this some reflection on CMR data is warranted in any new meta-analysis.

Because of the contentious nature of data related to LV morphology and function in small case series reports in the published literature, the American Society of Echocardiography (ASE), working together with the European Association of Echocardiography, a branch of the European Society of Cardiology, has critically reviewed the literature and updated the recommendations for quantifying cardiac chambers using echocardiography (Lang et al., 2005). Forteen years of new data with new technical guidelines, inconsistencies in previous studies and meta-analysis, the developing role of CMR and a growing knowledge base related to scaling of data (none of the previous meta analyses have analysed scaled data) suggest that it is important to re-visit the AH data base to ascertain the veracity of MH in a modern meta-analysis.

Whilst a number of meta-analyses have been produced targetted at understanding the AH, original research studies continue to be produced and often provoke new technical issues or specific hypotheses. Recent investigations in clearly distinct athlete groups with similar accumulated years of training stimuli have reported AH data partially in support (Maron and Pelliccia, 2006, Pelliccia et al., 2010, D'Andrea et al., 2013, Baggish et al., 2008) or refuting (Haykowsky et al., 2002, George et al., 2011, Oxborough et al., 2012b, Spence et al., 2011) the MH. Of specific interest are the large database studies from Italy. Previous reports by Pelliccia et al (1993) in 100 resistance trained athletes demonstrated that no athlete showed a maximal absolute LV wall thickness that exceeded the generally accepted upper limits of normal [i.e., 12 mm; (Pelliccia et al., 1993)]. However, when compared with 26 normal sedentary control subjects, there was partial support for a concentric LVH in that LVID and LV mass was similar in both groups but maximal septal thickness was mildly but significantly greater in athletes (9.6 ± 0.6 vs 9.0 ± 0.5 mm; $p < 0.001$), as was the calculated LV mass index (96 ± 12 vs 61 ± 6 g/m; $p < 0.001$). Also, LVID was similar in athletes and controls (55 ± 4 and 54 ± 3, respectively; $p > 0.05$) (Pelliccia et al., 1993).

Of recent interest has been a small number of longitudianal studies which do not suffer from the same extent of selection bias and unknown factors (i.e. genetics) influencing cardiac structure and function. Not surprisingly the two most cited training studies have presented differential outcomes. Baggish et al (2008) performed a 90 days longitudinal study of 40 endurance and 24 resistance-trained athletes, and reported that LV mass increased by 11% in the endurance (116 ± 18 vs. 130 ± 19 g/m^2; P < 0.001) and by 12% in resistance athlete (115 ± 14 vs. 132 ± 11 g/m2; P < 0.001). The endurance trained experienced LVID dilation (66.6 ± 10.0 vs. 74.7 ± 9.8 ml/m^2, P < 0.001) while resistance trained athletes presented with greater PWT 4.5 ± 0.5 vs. 5.2 ± 0.5 mm/m^2 (p < 0.001) after training. The authors concluded that the endurance athletes demonstrated an eccentric LVH adaptation whereas the resistance trained athletes demonstrated an isolated concentric LVH adaptation (Baggish et al., 2008) that mirrored and outcome predicted by the MH.

A recent CMR study by Spence et al (2011) contradicted both Baggish et al (2008) and the MH. Spence et al (2011) completed a longitudinal CMR study in young (27.4 ± 1.1 years) untrained male subjects who were randomly assigned to supervised, intensive, endurance (*n* = 10) or resistance (*n* = 13) exercise. CMR scans, 2D standard echocardiography and myocardial speckle tracking echocardiography were performed at baseline, after 6 months of training and after a subsequent 6 weeks of detraining.

The authors reported that CMR derived left ventricular (LV) mass increased significantly following endurance training (112.5 ± 7.3 to 121.8 ± 6.6 g, P < 0.01) but not with resistance training, whilst training increased LV end-diastolic volume (LVEDV) to a greater extent with endurance training: + 9.0 ± 5.0 *vs.* resistance training + 3.1 ± 3.6 ml, P = 0.05). IVSWT significantly increased with endurance-training (1.06 ± 0.0 to 1.14 ± 0.06, P < 0.05) but not with resistance-training. Longitudinal strain and strain rates did not change following either form of exercise training (Spence et al., 2011).

In the scientific literature, there is a comparatively small number of echocardiographic research on the right ventricle (RV) in athletes (Vos et al., 1985, Schattke et al., 2012). A MESH search of PubMed with key words ‘right ventricle’ and ‘athlete’s heart’ yielded less than 500 hits. This is partially because earlier investigators found assessment of the morphology and functional properties of the RV to be problematic (Ho and Nihoyannopoulos, 2006) due to its crescent shape wrapped around the LV, a lack of uniformity, excess trabeculation, and a separate infundibulum (Levine et al., 1984, Foale et al., 1986).

It is not surprising, therefore, that the seminal work of Morganroth et al (1975) did not assess the RV. Consequently, whether the RV demonstrates a training dependent AH phenotype has received less attention. Technological advancements of modern imaging techniques, with greater access to structural and functional data from the RV and left atrium (LA) (Mor-Avi et al., 2008, Rudski et al., 2010, Prakken et al., 2010) have resulted in the establishment of standardised assessment protocols for the RV (Lang et al., 2005, Rudski et al., 2010).

A limited number of studies have demonstrated greater RV structural parameters in endurance athletes compared to controls (Baggish et al., 2008, Teske et al., 2009b, D'Andrea et al., 2013). In a cross sectional study, Teske et al (2009) evaluated RV dimension and echocardiographic tissue deformation imaging parameters in 61 non-athletes, 58 non-elite athletes and 63 elite athletes and reported that RV dimensions were significantly increased ($P < 0.001$) in both groups of athletes compared with controls.

Similar to work by D’ Andrea et al (2003) RV systolic velocities and displacement were not different between the groups (D'Andrea et al., 2003, Teske et al., 2009b). D’ Andrea et al (2003) was one of the few studies to look at athletes with divergent training emphasis when assessing 32 endurance (long distance swimmers) and 26 sprint athletes (short distance swimmers) and reported that though LV mass index did not differ between the 2 groups. RV end-diastolic diameter was significantly larger in the endurance focussed swimmers ($p < 0.001$) and TDI parameters (LV and RV) were higher values in the endurance group (D'Andrea et al., 2003). This hardly fits the true divergent training background observed in the Morganroth study and there is surprisingly little RV data reported in elite resistance-trained athletes.

In summary of this section there are some specific directives for the content of this thesis. It is important to conduct a new inclusive (echocardiography and CMR datasets) systematic review and meta-analysis of published AH studies from 1975 to date to re-visit the MH and most importantly to gain new insight in our understanding of the AH phenotype. The impact of body size scaling must be addressed in any meta-analysis. There is still the requirement for more prospective studies of athletes vs. controls, especially when one consider previous contradictory data, the newly developed echocardiogrpahic tools now available and, again, the issue of scaling should be integrated appropriately. These prospective studies should move beyond the LV and the caucasian athlete.

2.4 Contemporary technical developments in Echocardiogrpahy

As detailed earlier, echocardiography utilises ultrasound to image the heart and great vessels. Early developments of echocardiography provided amplitude-mode (A-mode more latterly referred to as M-mode) technique as was used in the seminal study of Morganroth et al (1975). Over time, and due to significant advances in technology and scientific evidence, echocardiography has gained a wide acceptance in the assessment of cardiac patients (Cheitlin et al., 2003) as well as in the world of sports cardiology and the assessment of the AH. "Traditional" echocardiographic tools for the assessment of LV and RV are detailed in appendix – 9.1, 9.2, 9.3. Because of the contentious nature of data related to LV morphology and function in small case series reports in the published literature, new echocardiographic measurement guidelines from expert consensus panels are currently available (Lang et al., 2005, Mor-Avi et al., 2011, Rudski et al., 2010).

Additionally, a number of new technologies have emerged to address image quality, accurate quantitative / qualitative assessments and inter observer variability in measurements and interpretations of cardiac data. Two such technologies have dominated the research arena of echocardiography a) Doppler based tissue velocity measurements, and b) speckle tracking echocardiography (STE) on the basis of displacements (Mor-Avi et al., 2011). Guided by these expert consensus guidelines, upper limits of physiological cardiac adaptations have been assessed in highly trained athletes (Naylor et al., 2008, George et al., 2011, Oxborough et al., 2012b, Spence et al., 2011).

2.5 Tissue-Doppler Velocity Imaging

Tissue-Doppler echocardiography is based on the interrogation of high amplitude and low velocity reflected ultrasound signals from the myocardium Doppler signals from an echocardiographic region of interest (ROI). Tissue-Doppler velocity imaging applies different threshold algorithms using high/low pass filters to display myocardial velocities (Sutherland et al., 1999) and consequently can record both systolic and diastolic velocities within the myocardium (Figure 2.5) (Naguehet al., 1997, D'Andre et al., 2010). The velocity data can be obtained during pulsed- (Isaaz et al., 1989) and colour-Doppler techniques (McDicken et al., 1992). Miyatake et al (1995) and Sutherland et al (1994) confirmed the clinical feasibility of TDI by demonstrating the potential for quantifying regional myocardial function (Sutherland et al., 1994, Miyatake et al., 1995).

For instance, the assessment of myocardial function in the longitudinal plane has been documented to be more sensitive to discrete pathological changes (Price et al., 2000) primarily because longitudinal functional impairment precedes circumferential dysfunction (Vinereanu et al., 2001, Mädler et al., 2003). Numerous studies have reported that longitudinal plane excursion is directly related to global LV and RV function and important in assessing pathology (Kaul et al., 1984, Simonson and Schiller, 1989, Hammarström et al., 1991, Mädler et al., 2003, Yu et al., 2007).

The image of Figure 2.5: Echocardiographic evaluation of athlete's heart in an endurance trained athletes. (A) Standard echocardiography, apical four-chamber view: LV. (B) Trans-mitral flow pattern: high early diastolic wave - E. (C) Pulsed tissue Doppler pattern: increased early diastolic myocardial velocity - E'. (D) Two-dimensional strain: normal myocardial longitudinal deformation originally presented here cannot be made freely available via LJMU Digital Collections because of copyright reasons. The image was sourced at D' Andrea et al 2010, page 496 - http://www.ncbi.nlm.nih.gov/pubmed/20551250.

One attraction of tissue Doppler velocity imaging (TDI) is that it can scan information obtained from echoes generated by a rapid succession of transmitted pulses in a single direction. With ease of alignment of longitudinal shortening with the ultrasound beam, TDI is less reliant on 2D image quality and has a good reproducibility (Fleming et al., 1994, Ommen et al., 2000). Because TDI is dependent on angle of isonation, there is a limitation to discrete regions of the inter-ventricular septum (IVS) and posterior wall of the ventricles as well as the detrimental effects of translation, rotation and tethering of adjacent myocardial segments which can affect the accuracy of data (D'hooge et al., 2000, Sutherland et al., 2004).

TDI has been reported to be more load dependent (Sohn et al., 1997, Frommelt, 1999) than originally proposed (Dumesnil et al., 2002, Andersen et al., 2004, Hart et al., 2007). A surrogate of the ratio of early diastolic tissue velocity (E’) and late diastolic myocardial tissue velocity (A’) defined as E’/A’ was reported to be load–independent (Pelà et al., 2004) but this has been questioned during volume shifts associated with haemodialysis (Oğuzhan et al., 2005). Based on the principle that E’ is a more sensitive measure of LV relaxation and less influenced by left atrial (LA) pressure, Nagueh et al (1997) proposed E/E’ was as a surrogate of left atrial (LA) pressure which correlated with invasive measure of pulmonary wedge pressure in patients with diastolic dysfunction (Nagueh et al., 1997).

Numerous AH studies (Fagard et al., 1989, Caso et al., 2000, D'Andrea et al., 2002, Koc et al., 2007, Vinereanu et al., 2002, Florescu et al., 2010), and previous meta-analysis (Fagard, 1996) have reported that LV long-axis diastolic function is augmented in the hearts of endurance-trained compared with strength-trained athletes. Controversy exists in that some other studies (Pluim et al., 1999, Schannwell et al., 2002) and meta-analysis (Pluim et al., 2000) found LV diastolic function to be similar in athletes and controls, whilst the most recent meta-analysis by Whyte et al (2004) reported enhanced stroke volume in athletes (Whyte et al., 2004a).

Emperical studies have demonstrated the clinical utility of Tissue Doppler indices as a non-invasive techniques for evaluating LV relaxation and estimation of filling pressures (Ha et al., 2004, Klein et al., 1994, Nagueh et al., 1997, Nagueh et al., 2009, Ruan et al., 2006). Disparate findings of normal LV relaxation (Firstenberg et al., 2000, González-Vilchez et al., 2002) and decompensated heart failure patients (Mullens et al., 2009) warrants further research in select athlete groups to investigate whether training stimuli influences TDI derived functional parameters.

2.6 Tissue-Doppler Strain Imaging

Derived from colour Doppler technique, colour Doppler myocardial imaging is a relatively new technique that can resolve all mean velocities along its image lines (Sutherland et al., 1994). One important attraction is the provision of a raw dataset for offline analysis, allowing samples to be placed on a region of interest (ROI) on the myocardium. By vector principles, a better description of regional myocardial function can be given by determining local deformation characteristics i.e. thickening and thinning or contraction and lengthening. The optimal regional myocardial function dataset defines deformation characteristics (Figure 2.6). Whereas grey scale M-mode provide unidirectional data for a limited ROI, tissue-Doppler strain imaging deformation characteristics of myocardial strain (ε) and strain rate (SR) are three-dimensional (3D) (D'hooge et al., 2000).

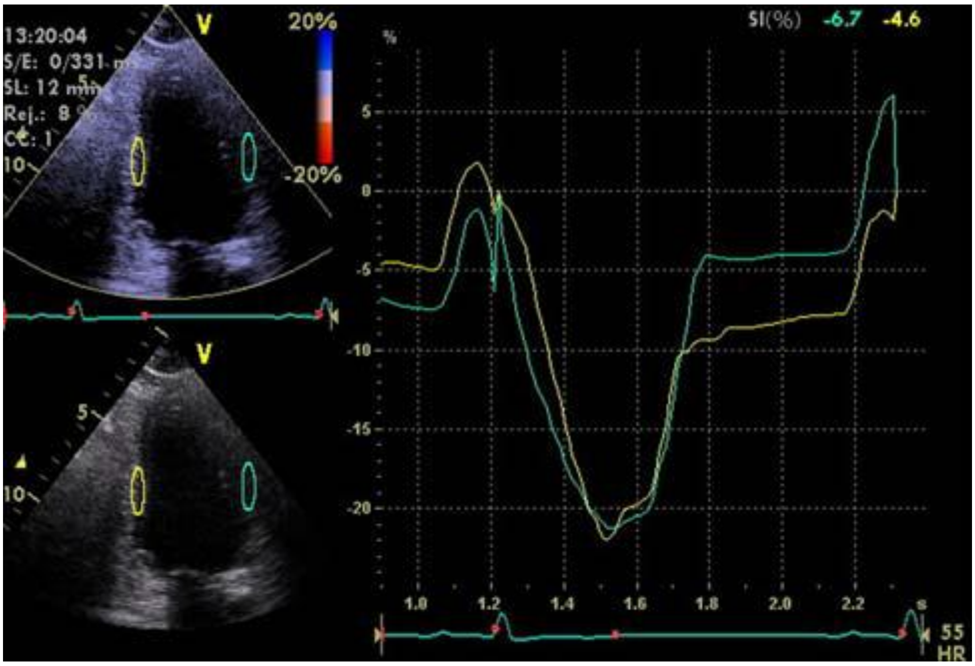


Figure 2.6: An examplar scan from a colour tissue-Doppler assessment of regional wall strain and strain rate in the apical four-chamber view (note the apical LV view and longitudinal tissue strain traces measured in the septal and free wall at the mid-wall level).

Myocardial ε is a dimensionless quantity that defines the % change in deformation i.e. myocardial lengthening or shortening rather than movement as depicted by velocity data (Heimdal et al., 1998, Sutherland et al., 2004). Taken together, the rate of deformation per second, defined as SR, and ε have been reported to be an objective estimate of myocardial contractility and relaxation (Fleming et al., 1994, Yip et al., 2003). SR appears to correlate with rate of change in pressure (dP/dT) whereas ε correlates with regional EF (Marwick, 2006). Following a combination of in vitro – phantoms (Heimdal et al., 1998) and in vivo ultrasonic crystal (Urheim et al., 2000) validity studies, a good correlation between TDI and CMR derived ε has been reported (Edvardsen et al., 2002, Amundsen et al., 2006).

Unlike tissue-Doppler velocities, ε is independent of motion artefacts from translation and tethering, however the quality of ε data is dependent on the underlining tissue velocity and therefore sensitive to noise and angle of isonation. Importantly, ε Values are less related to preload and after load (Andersen et al., 2004, Marwick, 2006, Yu et al., 2007). Regional systolic RV function could be estimated using TDI and has been used to demonstrate functional differences in athletes as compared with control subjects. Teske et al (2009) examined 180 individuals (61 healthy controls; 58 athletes and 63 elite endurance athletes) and demonstrated that LV and RV dimensions were significantly increased ($p < 0.001$) in both group of athletes compared with controls, however RV systolic velocities were not different between groups (Teske et al., 2009b).

Similary, Pagourelias et al (2013) obsereved that different training modes induced different morphologic patterns, leading to greater RV dilatation in ET, with no significant diffences concerning TDI functional parameters between athlete groups and controls. Poulsen et al (2007) found comparable and normal longitudinal LV systolic function in a cross sectional study of 17 male ET, 15 male resistance athletes and 12 male controls (Poulsen et al., 2007). However, other studies have reported that regional systolic RV function estimated using TDI could be used to demonstrate functional differences in athletes as compared with control subjects (D'Andrea et al., 2003, Prakken et al., 2010). Baggish et al (2008) documented the relationship between competition level and RV parameters in a population of 40 athletes and found a significant enhancement of both RV systolic and diastolic function by TDI (Baggish et al., 2008). The physiological mechanism that underpins these various outcomes remains an area of considerable debate and warrants further investigations.

2.7 Myocardial Speckle Tracking Echocardiography: The Left Ventricle

Speckle tracking is an echocardiographic method based on the tracking of characteristic speckle patterns created by constructive and destructive interference of ultrasound back scattered by structures smaller than the wavelength of the ultrasound beam in the myocardium (Amundsen et al., 2006, Mor-Avi et al., 2011). STE is an offline technique that is applied to previously acquired 2 D image files. The technique involves the use of speckle tracking algorithm that tracks the uniform motion of a speckle generating object (kernels). STE is angle independent and can assess radial, circumferential and longitudinal deformation (Andersen et al., 2004).

The provision of a very good spatial resolution of 1 to 2 mm, provided potential application in measurement of myocardial ε and SR (D'hooge et al., 2000). STE derived measurements has been validated against sonomicrometry (Korinek et al., 2005, Sivesgaard et al., 2009) and CMR (Langeland et al., 2005, Amundsen et al., 2006) showing good reproducibility of longitudinal and circumferential ε, however it has been reported that at lower deformation magnitudes weakens the agreement by an over estimation of absolute values with STE (Korinek et al., 2005).

Because MSTE allows for the measurement of temporal information throughout the cardiac cycle (Figure 2.7), the assessment of LV rotation and twist can establish rates of untwisting (Helle-Valle et al., 2005, Burns et al., 2009) which is an important factor in generating early diastolic intra ventricular pressure gradient (Burns et al., 2009) and extends knowledge of LV mechanics in both physiology (Notomi et al., 2006, Nottin et al., 2009, Esch et al., 2010, Burns et al., 2009) and pathology (Amundsen et al., 2006, Borg et al., 2008, Galderisi et al., 2010, Leitman et al., 2010).

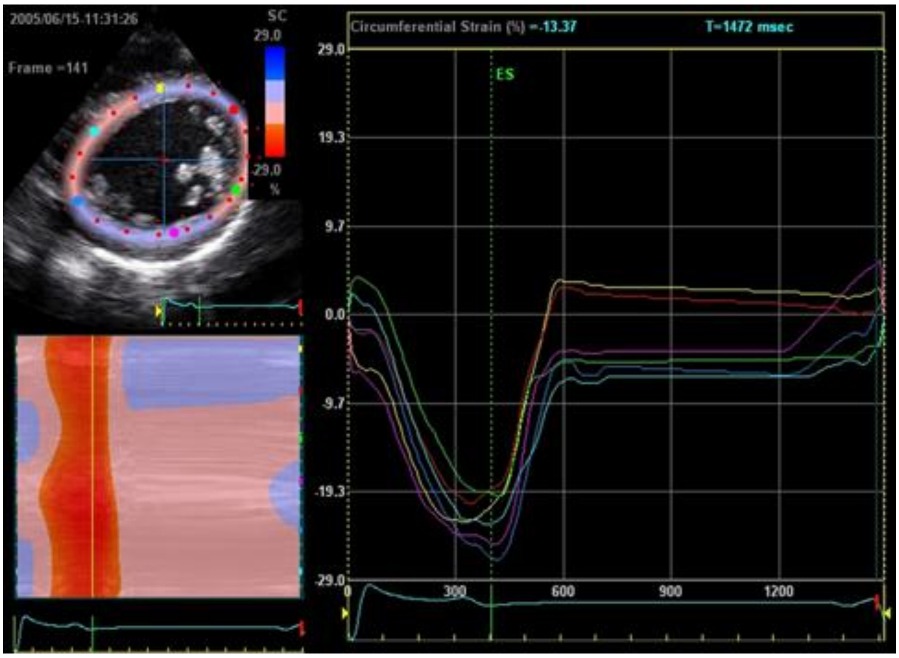


Figure 2.7: An examplar scan of myocardial speckle tracking assessment of regional wall strain and strain rate in the para-sternal short-axis view (note the short axis LV view at the level of the papillary muscle and the circumferential strain traces from six LV wall segments).

Nottin et al (2008) evaluated LV regional strain in 16 male elite cyclist and 23 controls. They reported that Apical radial strain (42.7±10.5% *vs.* 52.2±14.3%, $P < 0.05$) and LV torsion (6.0 ± 1.8 degrees *vs* 9.2±3.2 degrees, $P < 0.01$) were lower in cyclists than in controls, respectively (Nottin et al., 2008). Quite recently, Monte et al (2014) studied 26 resistance trained, 40 endurance athletes and 40 sedentary subjects and documented that LV mass indexed for BSA, IVSWT and PWT mean values were significantly increased in athletes ($p < 0.001$, $p < 0.01$ and $p < 0.001$, respectively). Despite a preserved mean value of LV ejection fraction

(LV EF) in all the groups, resistance trained athletes showed a significant reduction of strain in the longitudinal, radial and circumferential directions ($p < 0.05$ for all variables) (Monte et al., 2014).

In contrast, Simsek et al (2013) demonstrated increased global longitudinal strain velocities in both resistance and endurance athletes greater than controls ($p < 0.001$) (Simsek et al., 2013). Although the potential for STE in discriminating disease states and the association between LV function independent of LVH has been highlighted (Amundsen et al., 2006, Borg et al., 2008, Galderisi et al., 2010, Bellini et al., 2011), there are limited reports on the relationship between exercise training stimuli. This builds the rationale for further studies included in this thesis.

2.8 Myocardial Speckle Tracking Echocardiography: The Right Ventricle

The RV appears to have completely different cardiac mechanics in comparison to the LV. In contrast to the homogenously distributed deformation properties in the LV, the ε and SR values in the RV are less homogenously distributed (Weidemann et al., 2002) and show a reverse base to apex gradient reaching the highest values in the apical segments and outflow tract (Teske et al., 2009a) (Mor-Avi et al., 2011). This reverse gradient is attributed to the complex geometry and the thin walled crescent shape of the RV as well as the above mentioned less homogenously distribution of regional wall stress (Rudski et al., 2010, Mor-Avi et al., 2011).

Due to predominance of longitudinal fibres in a thinner RV wall, a simple quantitative approach to estimate RV function is Tricuspid Annular Plane Systolic Excursion (TAPSE)

(Kukulski et al., 2000). Longitudinal shortening is a major contributor to RV function with an equal contribution from the free wall and inter-ventricular septum (IVS). Similarly, longitudinal deformation is known to contribute significantly to RV SV (Pellerin et al., 2003, Rudski et al., 2010). The thinner RV chamber is associated with low pressure in the pulmonary circulation, which facilitates quick adaptation to changes in preload.

Therefore, ε and SR abnormalities of the RV can be an early indicator of RV pathologies e.g. pulmonary hypertension (Borges et al., 2006), arhythmogenic RV cardiomyopathy (ARVC) (Teske et al., 2009a, Marcus et al., 2010, Meris et al., 2010) and hypertrophied cardiomyopathy (Mörner et al., 2008) with a potential to differentiate from physiologic RV remodelling to exercise. Teske et al (2009) demonstrated that strain and strain rate of the RV free wall were reduced in 63 highly trained athletes relative to controls ($p < 0.001$), particularly in the basal segments of athletes with RV dilatation. The authors proposed that this reflected normal physiological adaptation consequent upon a base to apex gradient in RV deformation (Teske et al., 2009b). These findings were extended to the clinical population by D' Andrea et al (2010) who demonstrated that RV global and regional 2D STE measurements were largely impaired in HCM compared to athletes. The authors also reported significant differences between athletes and control subjects. However, other studies have reported no between group difference in RV STE functional indices between athlete groups and control subjects (Prakken et al., 2010, Oxborough et al., 2012b, Pagourelias et al., 2013).

These new techniques were not available more than a decade ago when the last meta-analysis of the AH was conducted. Therefore, the studies included in this thesis are designed to apply these new techniques in a re-visit of the Morganroth's hypothesis using a robust carefully crossmatched and rigourously selected cross section of elite athletes where the exercise training stimulus (ET vs RT) simulates the participants of Morganroths seminal study.

2.9 Body size influence on the athlete's heart

There is extensive evidence that cardiovascular structural and functional variables, along with other biological properties that span the range of organism size, scale with body size (Batterham et al., 1999, George et al., 2001, Dewey et al., 2008, Oxborough et al., 2009). Although technological advancements in cardiac imaging technology has greatly improved measurement accuracy, clinical decision based on these measurements are difficult when overlap is present between normal and abnormal ranges of cardiovascular variables (figure 2.8) (Whyte et al., 2004b).

Such areas of diagnostic uncertainty are common in pre-participation screening of athletes to differentiate the AH from cardiomyopathies. Similarly, the interpretation of AH phenotypes in athletes with different body habitus is complex and controversial. These concepts of individual descision making and data interpretation in people of divergent body size underscores the necessity for appropriate scaling procedures (George et al., 2001).

The image of Figure 2.8. Diferential diagnosis of structural adaptations that occur with athletic conditioning, originally presented here cannot be made freely available via LJMU Digital Collections because of copyright reasons. The image was sourced at Dewey et al., 2008, page 2280 http://circ.ahajournals.org/content/117/17/2279.short.

Despite this, the practise of scaling cardiovascular measurements is poorly applied in the scientific literature. Scaling approaches, exclussively using ratiometric or linear relationships are popular in the AH literature. LV mass and LV cavity dimensions and volumes are often scaled via simple division by BSA i.e. adopting the per ratio standards (*y/x*) method of scaling (Morganroth et al., 1975, Maron et al., 1995, Pluim et al., 2000). Empirical evidence in the normalization of cardiac data suggests that a curvilinear, allometric scaling model ($y = ax^b$) is the most appropriate scaling procedure for cardiac data (Tanner, 1949, De Simone et al., 1992, Gutgesell and Rembold, 1990, Batterham et al., 1999, George et al., 2001, Dewey et al., 2008).

In the first large sample (n = 464) analysis of the relationship between cardiac dimension and body size variables in male and female athletes, George et al 1991 demonstrated that the calculated *b* exponent (y/x^b) generally tend to be dimensionally consistent and agree with previous clinical data. However, the relationship between RV internal diameter was not geometrically consistent as was with the use of height (cm) as a body size scaling variable (George et al., 2001).

Gutgesell and Rembold (1990) evaluated the relationship between cardiac dimension and BSA in 7 theoretical "subjects" spanning human age ranges whose cardiac and body dimensions were modelled by values obtained from several large studies of healthy individuals. The authors reported that linear cardiac dimension (LV, aortic and pulmonary artery diameter) were proportional to BSA raised to the power of 0.5 and that the relationship between BSA and LV volume was better modelled by allometric scaling in a dimensionally consistent manner than by ratiometric scaling (Gutgesell and Rembold, 1990).

Similarly, Oxborough et al (2012) observed, in 102 endurance athletes, that RV size is allometrically related to BSA, therefore scaling for population specific *b* exponents is encouraged. Considering that Morganroth et al (1975), and subsequent meta-analysis larglely adopted absolute or ratiometric scaling of data, in deriving the hypothesis of a divergent cardiac adaptation to exercise training, a repeat of the MH, using new technologies and deploying appropriate scaling in the studies included in this thesis will be unique.

2.10 Ethnicity and the athlete's heart

To date the study of the AH and the definition of normal limits for cardiac structure and function included in clinical algorithms for cardiac screening have been largely based on data from Caucasian athletes. The increasing globalisation of sports has led to the development of elite athletes from a wide range of different nationalities and ethnicity. Recent data from studies examining the AH phenotype in Black athletes (Africans and Afro-Caribbean descent) has demonstrated that black athletes (BA) develop more striking repolarization changes on the ECG and exhibit a greater magnitude of left ventricular hypertrophy (LVH) than white male athletes of similar age and size participating in identical sports (Basavarajaiah et al., 2008, Magalski et al., 2008, Rawlins et al., 2009, Sheikh et al., 2013).

In a male AH study, Basavarajaiah et al (2008) investigated 300 nationally ranked black athletes (mean age 20.5 years); 300 white athletes; 150 black and white subjects and reported that black athletes had greater LV wall thickness and LV mass compared with whites (11.3 ± 1.6 mm vs. 10 ± 1.5 mm, $p < 0.001$); (286 ± 78 vs. 250 ± 62 g, $p < 0.001$) amounting to a 12% and 13% difference respectively. The authors demonstrated that in absolute terns, 54 black athletes (18%) had LV wall thickness > 12 mm compared to white athletes (4%) and 3% black athletes exhibited LV wall thickness ≥ 15 mm compared with none of the white athletes (Basavarajaiah et al., 2008). However, black athletes with LVH displayed an enlarged LV cavity and normal diastolic function. In comparison with white athletes, Black athletes with LVH exhibited a higher prevalence of voltage criteria for LVH (37 [68%] vs. 5 [40%]); displayed a higher prevalence of repolarisation changes specifically

ST – segment elevation (46 [85&] vs. 7 [62%], $p < 0.001$) and deep T – wave inversion (7 [12%] vs. none [0%] $p < 0.001$).

Similar to the study by Basavarajaiah et al (2008), Rawlins et al (2010) investigated 240 nationally ranked black female athletes and compared their ECG (Electrocardiogram) and echocardiographic indices with 200 matched female athletes, the authors report that Black athletes demonstrate greater LV wall thickness and LV mass (9.2 ± 1.2 vs 8.6 ± 1.2 mm, $p < 0.001$) and (187.2 ± 42 vs. 172.3 ± 42 g, $p = 0.008$) than white athletes (Rawlins et al., 2010). Although all athletes revealed normal indices of systolic and diastolic function, black athletes ECG data revealed higher prevalence of T – wave inversion (14% vs 25, $p < 0.001$) and ST segment elevation (11% vs 1%, $p < 0.001$) respectively.

Although in Rawlins et al's (2010) study, black ethicity was determined by self report questionnaire and included terms such as black African, Afro-caribbean, black British and black French, the research confirmed that black ethnicity was the strongest independent predictor of maximal LV wall thickness ($\beta = 0.263$, CI 0.29 to 0.855, $p < 0.006$) but contrary to the MH, did not observe any relationship between sporting discipline and LVH (Rawlins et al., 2010).

Ethnicity has emerged to be an important determinant of the electrical (Magalski et al., 2008) and structural manifestation of the AH (Basavarajaiah et al., 2008, Sheikh et al., 2013, Rawlins et al., 2010). Importantly, in the development of cardiac screening procedures, it has emerged that BA are more susceptible to sudden cardiac death (SCD), with a 2-fold higher incidence compared to Caucasian athletes (Maron and Pelliccia, 2006 , Maron et al., 2009, Harmon et al., 2011). The issue of ethnicity and its impact on the AH phenotype is complex not least because of ethnic and genetic dispersal and mixing.

Previous cross-sectional studies on BA have included Afro-Caribbean's, African Americans, Black French, Black British (Basavarajaiah et al., 2008, Magalski et al., 2008, Rawlins et al., 2010, Magalski et al., 2011). Intra ethnic differences to cardiac adaptation based on ancestral origin exists within blacks. Basavarajaiah et al (2008) documented that 50 (20%) of the 246 athletes of West African ancestry (including caribbeans) exhibited LVH vs. 4 (7%) of 54 athletes of East African origin ($p < 0.01$). It is important to partition these athletes to ascertain whether these participants were first or second generation blacks because there is a potential for genetic mix in these populations over time which could have a significant influence of the AH phenotype (Dunn et al., 1983, Mayet et al., 1994, Bhopal, 2004, Agyemang et al., 2005, Basavarajaiah et al., 2008).

Previous studies have not specifically examined the training stimulus particularly with the impact of resistance training activity on the AH and how it relates to a homogenous group of West African athletes. Consequently, understanding the impact of resistance training and ethnicity on the AH phenotype requires substantially more work.

As detailed earlier, technological advancements in echocardiography technology has enabled researchers to gain new insights of the AH. The few previous studies describing the AH in BA were limited to standard or 'traditional' echocardiography measurement techniques (Basavarajaiah et al., 2008, Rawlins et al., 2010, Magalski et al., 2011).

Newer imaging modes such as tissue-Doppler imaging (TDI) and speckle tracking echocardiography (STE) estimation of strain and (ε) and strain rate (SR) can provide detailed information related to global and regional function to partition any signficant influence of resistance training and black ethnicity on the AH phenotype. With these rationales in mind, an AH research on a homogenous group of West African RT athletes using novel echocardiographic techniques will provide valuable data with important implications for cardiovascular screening programmes routinely incorporating ECG and Echocardiography.

2.11 Summary

This review has defined, described and critically appraised the concept of both the AH and the MH, in light of developing databases, evolving techniques and awareness of key issues such as scaling and ethnicity. In the 4 decades since Morganroth's initial study, the progressive evolution echocardiography, driven by researchers and ultrasound equipment manufacturers, has led to new insights and potential for further study of the AH. These overarching issues provide the broad rationale for studies in this thesis.

Consequently, the studies in subsequent chapters will provide further evidence to support or refute different AH phenotypes, the importance of taking into account individual variability in body size as well as the value provided by new echocardiographic techniques describing regional cardiac function. Finally, the impact of ethnicity on the AH will be studied in a pilot trial of West African elite male resistance athletes.

CHAPTER 3

MORPHOLOGY AND FUNCTION OF THE ATHLETE'S HEART: META-ANALYSIS EVALUATION OF THE IMPACT OF TRAINING MODE, IMAGING MODALITY AND BODY SIZE.

This work has been presented as *'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'* at the 18th Annual Congress of the European College of Sport Science, Baarcellona, Spain. *www.sport-science.org/index.php?option=com_content&view.* Balagué, N., Torrents, C., Vilanova, A., Cadefau, J et al (2013): BOOK OF ABSTRACTS, 18th annual Congress of the EUROPEAN COLLEGE OF SPORT SCIENCE 26th - 29th June 2013, Barcelona – Spain, Page 325.

This work has been published as '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, 2013;99, 1727-1733.doi:10.1136/heartjnl-2012-303465. http://heart.bmj.com/content/99/23/1727.full.pdf+html?sid=6f368e01-ae3a-4592-9aed-31c6d8ed5c07

3.1 Introduction

The Athlete's heart (AH) has been extensively described in male athletes (George et al., 2011). A cornerstone of this phenomenon has been the concept that cardiac structural adaptation follows a dichotomous course of eccentric hypertrophy (balanced increase in chamber and wall dimensions) with endurance training versus concentric hypertrophy (disproportionate increase in wall thickness) (Bardo et al., 2008), with resistance training,((Morganroth et al., 1975, Pelliccia et al., 1991, Pluim et al., 2000). It is hypothesised that these adaptations reflect differential hemodynamic loading during acute training (George et al., 1991). The 26th Bethesda Conference adopted training-specific changes in cardiac morphology as a base for its recommendations for cardiovascular screening (Maron et al., 1994b) and this "hypothesis" has been broadly reported in textbooks and teaching.

Despite this pervasive "knowledge", contradictory evidence exists (Baggish et al., 2008, Spence et al., 2011) mainly reflecting a lack of concentric hypertrophy in resistance trained athletes (Haykowsky et al., 2000). Haykowksy et al (2001) suggested that the stimulus for concentric remodelling, a hemodynamic pressure overload on the LV, may not actually occur during heavy resistance training due to a simultaneous Valsalva (Haykowsky et al., 2001). Allied to this on-going controversy, two specific technical issues warrant evaluation.

Firstly, only echocardiographic AH studies were included in a previous meta-analysis (Pluim et al., 2000) Cardiac magnetic resonance imaging (CMR) has now become the gold standard tool for cardiac structural assessment. Clinically significant differences between echocardiography and CMR have been reported (Bellenger et al., 2003). Whilst eccentric hypertrophy has been reported when CMR is used in endurance trained participants (LaGerche et al., 2011), no concentric adaptation has been noted in resistance-trained athletes (Scharhag et al., 2002). Developments in CMR and echocardiography have also resulted in novel regional functional indices (*i.e.* tissue-Doppler analysis) as well as greater access to morphological and functional data from the right ventricle (RV) and left atrium (LA).

A second issue of concern relates to the impact of body size on cardiac structure. Pluim et al.,(2000) reported absolute cardiac dimensions in their between-group comparisons (Pluim et al., 2000). Whilst informative, this does not account for potential differences in both body size and composition that occur between athlete and sedentary controls which could alter the interpretation of AH studies (George et al., 1998, Batterham et al., 1999, Dewey et al., 2008, Oxborough et al., 2012b).

Consequently the aim of this systematic review and meta-analysis was to provide new insight in relation to: 1) cardiac adaptation to divergent training patterns in male athletes, 2) a developing research database using CMR in athletes; 3) functional data derived from tissue-Doppler analysis as well as RV and LA measurements in athletes; and 4) an awareness of the impact of body size on cardiac dimensions. This study applied a quality-criteria guided approach to study selection, common in current meta-analyses, but not overtly applied in previous AH meta-analyses (Pluim et al., 2000, Whyte et al., 2004a).

3.2 Methods

3.2.1 *Search criteria and processes*

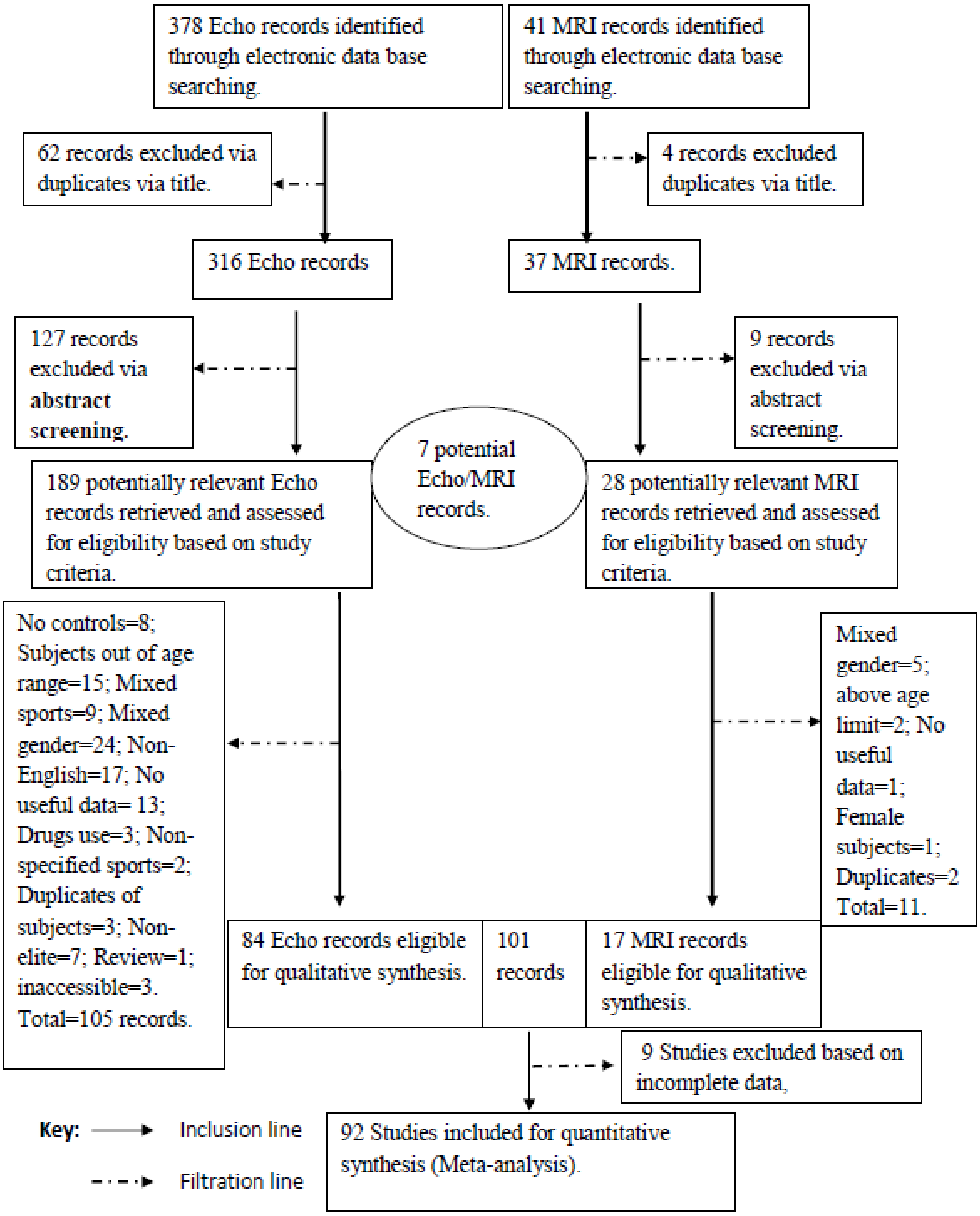
Our initial aim was to identify all echocardiographic and CMR studies examining the AH in male populations published between 1975 and 2012 using a number of electronic search engines (e.g. Pub Med, Medline, Scopus and ISI Web of knowledge scholarly data base). Relevant MeSH subject terms and keywords pertaining to the structure and function of the AH and Boolean operators were used in 2 separate searches for echocardiographic and CMR studies. The following search strings were employed:

- "Cardi$ OR Ventric$ OR Atria$ AND Athlet$ AND Echocardio$"
- "Cardi$ OR Ventric$ OR Atria$ AND Athlet$ AND Magnetic resonance imag$"
- "Cardi$ OR Ventric$ OR Atria$ AND Athlet$ AND MRI$"

As well as date limits we concentrated the search to human studies and those with an English language abstract. Finally this initial search was extended by a thorough cross-reference to reference lists from previous reviews and meta-analyses to find studies not cited in electronic databases. The search process identified 377 echocardiography and 41 MRI records for potential inclusion. The filtration process from this point is detailed in Figure 3.1.

The first stage of the filtration process reviewed titles and then abstracts. This process was completed independently by two authors (VU, KG) who compared decision making and discussed disagreements. Inclusion criteria were: 1) male subjects, 2) aged 18 – 45 years, 3) elite athletes at international or national level of participation for at least 2 years, 4) clear ability to define athletes as endurance or resistance focused, 4) healthy with no history of cardiovascular disease, and 5) age-matched sedentary control group with low documented levels of physical activity. We excluded review papers as well as trials on children, veteran athletes, female athletes, mixed-sex athlete groups, patient groups, steroid users and sporting groups with a cross-training focus (e.g. boxing).

Figure 3.1: Flow diagram of the Literature filtration process



Sixty-six records were excluded at the **title level** largely due to a non-athlete focus to the studies. Examination of the echocardiography records at the **abstract filtration level** identified and excluded 128 studies out of which 101 papers had no control group. A further

9 studies were rejected as athletes were not deemed to be elite. Twelve CMR studies were excluded due to: lack of control group (n=4); non-elite athletes (n=2); veteran athletes (n=2); no cardiac data (n=2) as well as case studies and reviews (n=2).

All remaining records were obtained for the **full record appraisal level.** At this stage 115 records were excluded on assessment of the full paper against the stated inclusion and exclusion criteria: female athletes (n=8); mixed-sex athlete data (n=23); non-English language (n=19); duplicate data sets (n=3); no absolute cardiac data (n=8). The remaining 101 studies were then scored by a single researcher (VU) using a quality criteria checklist specifically compiled for this systematic review, (Appendix 9.4).

This was adapted from the STROBE statement (von Elm et al., 2008) to improve the systematic appraisal of quality of observational studies. Nine records were excluded due to low quality scores, largely based on missing data related to training or athlete status and/or a lack of reference to professional guidelines for assessment and measurement (Moher et al., 2009). Consequently, 92 records (Appendix 9.5) were eligible for quantitative analysis including 185 echocardiographic and 41 MRI data sets.

3.2.2 *Data retrieval and meta-analysis*

All relevant cardiac and BSA data were extracted directly from individual trials into a spreadsheet (Excel 2010, Microsoft Corp). Athlete groups and imaging modalities were coded discretely for each study. Continuous data for BSA as well as LV, RV and LA morphology and functional data were recorded as group mean ± SD for each study. For the LV we recorded LV mass, inter ventricular septal wall thickness (IVSWT), posterior wall thickness (PWT), LV end-diastolic diameter (LVEDD), LV end-diastolic volume (LVEDV), stroke volume (LV SV), ejection fraction (LV EF), the ratio of peak early to atrial trans-mitral Doppler flow velocities (LV E/A), peak septal longitudinal tissue velocity in early diastole (LV E'), late diastole (LV A') and systolic phase (LV S'). In the RV we recorded RV mass, RV end-diastolic diameter (RVEDD), RV end-diastolic volume (RVEDV) and RV stroke volume (RVSV). Finally for the LA we recorded left atrial dimension (LAD). Other parameters were considered at initial screening but too few papers recorded these data (e.g. lateral LV wall tissue velocities).

To explore the impact of training group on structural and function parameters of the AH, we applied a mixed effect random meta-analysis model (DerSimonian, 1986). To quantify study-to-study heterogeneity a Q statistic at $p<0.05$ and I-square statistic >50% was deemed significant (Higgins et al., 2003). In further sub-group analyses we explored the impact of imaging modality upon AH data, again, using a mixed effect random meta-analysis model. Finally, we used a multiple meta-analysis regression model (Kendall's non-parametric statistic) to explore the impact of the covariate, BSA, on LV mass, RV mass and LAD. All statistical analysis was carried out with Comprehensive Meta-analysis software version 2.0 (Biostat, Englewood, NJ, USA) and Stata version 12 (Stata corp, college station, Texas, USA). Statistical significance was set at $p \leq 0.05$.

3.3 Results

Across all studies the mean age of all male athletes and controls ranged from 18-38 years. The results of the impact of different training stimuli on various indices of LV structure and function are summarised in Table 3.1. There were more data sets for endurance athletes and limited data prevented a mean pooled estimate for peak septal early diastolic tissue velocity in resistance athletes. All LV structural parameters were increased in athletes compared to sedentary controls. Differences between athlete groups were only noted for LVEDD and LVEDV, which were larger in endurance compared to resistance athletes. There were no differences between athlete groups for IVSWT or PWT. The larger LV chamber accounted for a greater SV in endurance athletes compared to resistance athletes and controls but LV EF was not different between all groups. Both LV E/A and LV E' were larger in endurance athletes than controls.

Table 3.1: Left ventricular structural and functional data in male endurance-trained, resistance-trained and sedentary control subjects. Data are mean (95% confidence intervals), [number of studies; number of participants].

Parameter	Endurance-Trained (ET)	Resistance-Trained (RT)	Sedentary Controls (CT)	P-value (All groups)	Post-hoc Significant Differences	Heterogeneity test		
						Hetero-geneity	I squared (%)	P value
LV mass (g)	232 (200 to 260) [n=64; 1099]	220 (205 to 234) [n=25; 510]	166 (145 to 186) [n=59; 1239]	P<0.001	ET, RT>CT	21	99.8%	<0.001
IVSWT (mm)	11.0 (10.8 to 11.3) [n=68; 1802]	11.0 (10.3 to 11.8) [n=19; 408]	9.2 (8.9 to 9.5) [n=63; 1352]	P<0.001	ET, RT>CT	98	99.2%	<0.001
PWT (mm)	10.6 (10.3 to 10.9) [n=57; 1928]	10.4 (9.8 to 10.9) [n=14; 370]	8.8 (8.6 to 9.1) [n=53; 1433]	P<0.001	ET,RT>CT	87	99.2%	<0.001
LVEDD (mm)	54.8 (54.1 to 55.6) [n=61; 1548]	52.4 (51.2 to 53.6) [n=17; 384]	50.1 (49.5 to 50.7) [n=56; 1174]	P<0.001	ET>RT, CT RT>CT	95	99.1%	<0.001
LVEDV (ml)	171 (157 to 185) [n=34; 493]	131 (120 to 142) [n=14; 189]	135 (125 to 145) [n=34; 539]	P<0.001	ET>RT, CT	23	99.2%	<0.001
LV SV (ml)	106 (97 to 116) [n=28; 479]	86 (77 to 95) [n=9; 125]	83 (77 to 90) [n=27; 590]	P<0.001	ET>RT, CT	16	98.7%	<0.001
LV EF (%)	63 (61 to 64) [n=42; 1330]	66 (62 to 70) [n=7; 85]	64 (62 to 65) [n=37; 878]	P=0.365	NS	2.0	97.7%	<0.001
LV E/A	2.0 (1.9 to 2.1) [n=34; 844]	1.9 (1.7 to 2.0) [n=8; 214]	1.8 (1.7 to 1.9) [n=34; 868]	P=0.014	NS	8.5	98.8%	<0.001
LV E'	13.6 (12.3 to 14.9) [n=7; 204]	*	11.0 (9.4 to 12.6) [n=4; 183]	P=0.014	NS	18	98.6%	<0.001

LV-left ventricle, IVSWT-inter ventricular septal wall thickness, PWT-posterior wall thickness, EDD-end-diastolic dimension, EDV-end-diastolic volume, SV-stroke volume, EF-ejection fraction, E/A-peak early to atrial Doppler trans-mitral flow velocities, E' peak septal early diastole longitudinal tissue velocity. One-way ANOVA analysis, P-value are significant at <0.05.

Table 3.2: Right ventricular structural and functional data as well as left atrial diameter in male endurance-trained, resistance-trained and sedentary control subjects, Data are mean (95% confidence intervals), [number of studies, number of participants].

Parameter	Endurance-Trained (ET)	Resistance-Trained (RT)	Sedentary Controls (CT)	P-value (All groups)	Post hoc Significant Differences	Heterogeneity test		
						Heterogeneity	I squared (%)	P value
RV mass (g)	91 (63 to 119) [5; 116]	*	37 (24 to 50) [4; 102]	P<0.01	ET>CT	3.5	99.3%	0.174
RVEDD (mm)	33.5 (21.0 to 46.0) [4; 140]	*	26.1 (16.1 to 36.1) [4; 95]	P=0.347	NS	0.81	99.7%	0.367
RVEDV (ml)	222 (216 to 227) [6; 136]	*	156 (153 to 159) [6; 150]	P=0.627	NS	2.8	99%	0.248
RV SV (ml)	114 (11 to 122) [5; 66]	*	94 (92 to 98) [4; 66]	P=0.415	NS	0.84	99.8%	0.657
LAD (mm)	39.2 (35.9 to 42.5) [10; 206]	31.9 (29.7 to 34.1) [2; 58]	34.9 (31.9 to 37.9) [11; 243]	P<0.001	ET>RT	13.2	98.1%	<0.001

RV-right ventricle, RVEDD-RV end diastolic diameter, RVEDV- RV end diastolic volume, RVSV- RV stroke volume, LAD-left atrial diameter, One-way ANOVA analysis, P-value are significant at <0.05.

Table 3.2 contains between group comparisons for indices of RV structure and function as well as LAD. Noticeably, fewer studies have reported these data in cross-sectional athlete-controls comparisons and we could not generate pooled mean estimates for resistance-trained athletes in respect to RV data. Mean RV mass, RVEDV and RV SV were greater in endurance athletes than controls. Data for LAD were greater in endurance than resistance-trained athletes but not controls.

For many LV and RV variables there was significant evidence of study-to-study heterogeneity (see Table 3.1 and 3.2). This provided support for our *a-priori* rationale to assess subsidiary factors. Substantial differences between imaging mode were noted (Table 3.3). Pooled mean estimates for LV mass, LV EF and LAD were higher when using echocardiography. Conversely, pooled mean estimates for LVEDV and LV E/A were higher when using CMR. No imaging mode comparison was possible for the RV because of limited data using echocardiography.

Table 3.3: Left ventricular structural and functional data as well as left atrial diameter in male athletes measured using echocardiography and CMR, Data are mean (95% confidence intervals), [number of studies, number of participants].

Parameter	Echocardiography	CMR	P-value	Post hoc Significant Differences
LV mass (g)	212 (195 to 229) [118; 2403]	173 (156 to 190) [30; 445]	P<0.001	Echo>CMR
LVEDV (ml)	135 (128 to 142) [54; 791]	178 (162 to 194) [28; 430]	P<0.001	CMR>Echo
LV EF (%)	64 (63 to 66) [42; 1915]	61 (59 to 62) [26; 378]	P<0.001	Echo>CMR
LV E/A	1.8 (1.7 to 1.9) [69; 1806]	2.3 (2.0 to 2.6) [7; 120]	P<0.001	CMR>Echo
LAD (mm)	36.9 (34.6 to 39.2) [21; 436]	32.7 (29.8 to 35.6) [2; 71]	P=0.026	NS

LV mass, Left ventricular mass; LVEDV, LV end-diastolic volume, LV EF, LV ejection fraction, LV E/A, Ratio of LV early diastolic and late diastolic velocity, LAD, Left atrial diameter. One-way ANOVA P-value are significant at <0.05.

Across all studies the mean BSA ranged from 1.69 to 2.52. Multiple meta-analysis regression analysis resulted in significant and positive relationships between BSA and LV mass (b= 0.010; Tauˆ2 p>/z/ 0.01; CI 0.001-0.010), LAD (b= 0.001; Tauˆ2 p>/z/ 0.001; CI 0.008-0.012) and RVM (b= 0.001; Tauˆ2 p>/z/ 0.001; CI 0.008-0.012) at p<0.05. This suggests that as BSA increases across studies cardiac dimensions also increase.

3.4 Discussion

The key findings from this systematic review and meta-analysis of the AH in male athletes are: 1) both endurance and resistance trained athletes demonstrate larger LV structures than sedentary controls with the greater dimensions in endurance athletes suggestive of an eccentric hypertrophy. Similar LV wall thickness in the two athlete groups provides minimal support for a concentric hypertrophy in resistance athletes; 2) imaging mode has a significant, but inconsistent, effect on a range of LV indices and LAD; 3) Differences between endurance athletes and controls were noted for LV function, RV structure and LAD whilst limited resistance athlete data was available; and 4) BSA has a significant positive relationship with LV mass, RV mass and LAD. These data should inform current knowledge of the AH and prompt on-going research.

3.4.1 *The impact of training group*

Both athlete groups had larger LV wall, chamber dimensions and mass than the control group, which supports the existence of a morphological AH (Pluim et al., 2000). The endurance-trained athletes had marginally larger LV mass and significantly greater LVEDD and LVEDV than resistance athletes, supporting the contention that endurance athletes tend to present with the largest LV dimensions (Naylor et al., 2008). Furthermore, the pattern of LV morphology in the endurance-trained athletes, a bigger LV chamber and proportionately larger LV walls, is commensurate with an eccentric LV hypertrophy first proposed by Morganroth and co-workers (Morganroth et al., 1975). The mechanism(s) underpinning training-induced changes in LV morphology in endurance athletes are poorly understood but a hemodynamic volume overload is widely quoted (George et al., 1991).

Endurance athletes had a larger LV SV than controls and resistance-trained athletes. This adaptation makes some teleological sense as an augmented LV SV is likely a key contributor to an enhanced endurance capacity (George et al., 2011). The lack of difference in LV EF at rest between all groups confirms data from Pluim et al (2000), and suggests no between group differences in contractility at rest (Pluim et al., 2000). Both the LV E/A and LV E' were significantly greater in endurance athletes than controls.

Although controversial, individual studies have reported an improved diastolic filling at rest in athletes (Pluim et al., 2000, D'Andrea et al., 2002) yet this has often been dependent upon the specific parameter assessed (George et al., 2010). The potential importance of enhanced diastolic function in the development of maximal SV (Gledhill et al., 1994) as well as putative mechanisms (preload or intrinsic relaxation properties), requires further evaluation. Finally it is interesting to note that the endurance-training related changes in LV morphology and function are quite closely mirrored in RV and LA data. This supports a balanced cardiac hypertrophy that is assumed to be wholly physiological in nature.

Whilst there are noticeable fewer resistance-training studies in the extant literature, the current data confirm the observation by Pluim et al (2000) that resistance athletes display some morphological characteristics of the AH (Pluim et al., 2000).

Both IVSWT and PWT were bigger in resistance-trained athlete's controls and were similar to endurance athletes. Cavity dimension, but not volume, data were greater in resistance athletes than controls but were smaller than endurance athletes.

Pluim et al, (2000) noted some support for concentric hypertrophy in resistance athletes due to an increased wall to chamber ratio (relative wall thickness). Use of mean data from all groups in the current meta-analysis results in a relative wall thickness of 0.40 for endurance athletes compared to 0.41 in resistance athletes (Pluim et al., 2000). These data are within normal ranges (Lang et al., 2005) and not meaningfully different. As opposed to dichotomous cardiac structural responses to endurance and resistance-training, it could be argued that both athlete groups present with a similar qualitative cardiac adaptation on a continuum, with greater cardiac dimensions in endurance athletes reflecting a greater overall training volume.

The lack of concentric-type hypertrophy in resistance athletes could be due to; (a) a limited exposure time to an elevated hemodynamic afterload as an increase in blood pressure only occurs sporadically during resistance training because of the intermittent nature of repetitions, sets and work-to-rest ratios (Naylor et al., 2008). The exposure to an elevated hemodynamic load during exercise is likely much more consistent and substantial during endurance training; (b) the absence of any real afterload stimulus when resistance training is performed with a valsalva manoeuvre (Haykowsky et al., 2002). The resistance-trained athletes demonstrated no increase in resting LV SV or either index of diastolic function, compared to controls. Given that an enhanced SV is an unlikely contributor to resistance sports performance the lack of difference between the controls and athletes is not surprising. Data for RV and LA morphology and function are extremely limited in resistance-trained athletes and this requires further study.

3.4.2 *The impact of imaging mode*

There was strong evidence of study-to-study heterogeneity within the meta-analysis, suggesting that sub-factor analysis may be relevant in this area. CMR is the gold standard tool for morphological assessment of cardiac chambers and mass due to its greater spatial resolution and 3-D data provision. Recent, direct comparisons between echocardiography and MRI-derived measures of left ventricular (LV) mass and volume in athletes suggest that large absolute differences exist between these measurement modalities (DeCastro et al., 2006, Prakken et al., 2011a, Wernstedt et al., 2002).

Measurement variability is also substantially greater with echocardiography (Bellenger et al., 2003). In this study the use of CMR resulted in a higher LVEDV than echocardiography and this agrees with previous comparative studies (LaGerche et al., 2011, Petersen et al., 2005, Caselli et al., 2011, Scharhag et al., 2010). The difference is likely due to the biplane Simpson's technique that uses estimation and geometric modelling allied to poorer lateral resolution that makes clear delineation of the endocardium difficult.

Conversely, LV mass, was greater in echocardiography in comparison to MRI which supports previous work by Prakken et al.,(2011) but contradicts other work

(DeCastro et al., 2006). Because CMR provides a more accurate and precise measurement of LV mass (Armstrong et al., 2012) we can assume that echocardiography over-estimates, again likely due to the limitations of geometric assumptions (Missouris et al., 1996) possibly compounded by the nature of any eccentric LV enlargement in endurance athletes.

These results, allied to the modality-related differences in LAD and LV function, highlight that imaging modalities should not be used interchangeably (Bottini et al., 1995). For training studies or other within subject testing at multiple epochs, a single modality should be used. Given the higher variability in echocardiographic estimates of LV dimensions, compared to CMR, some caution is warranted in the interpretation of small-sample echocardiographic AH studies. Further CMR studies in resistance athletes, or focusing on the RV and LA, are required.

3.4.3 *The impact of BSA*

Finally, we sought to explore the effect of between-study differences in BSA on LV mass, RV mass and LAD. Multiple meta-regression data clearly demonstrated that as BSA increased so did measures of cardiac structure. Consequently, it is likely that some portion of the between-group difference in LV mass, RV mass and LAD are explained by those with larger cardiac dimensions having larger body dimensions. Whether this reflects a higher total body mass or more specifically a higher lean body mass in the athlete groups is impossible to determine from the use of BSA alone.

The importance of body size on cardiac dimensions has been demonstrated in a number of empirical studies (De Simone et al., 1992, George et al., 1998, Oxborough et al., 2012b) and has been highlighted in review articles (Batterham et al., 1999, Dewey et al., 2008). The current data provide further support that between individual or group comparisons of cardiac dimensions must take account of individual variability in body size otherwise data interpretation and conclusions could be flawed.

The current study does not determine the best body size scaling index (mass, BSA, lean mass) or the most appropriate approach to scaling (ratio standards, allometry). These issues have been debated before (Batterham et al., 1999, Dewey et al., 2008) and further empirical work is required. It is of critical importance that future AH studies report anthropometrics and/or scaled data.

3.5 Implications, limitations and future research

Strong evidence supports an "eccentric-type" hypertrophy of the LV, RV and LA in endurance athletes. Resistance-trained athletes do not present with concentric LV hypertrophy. This data prompts a re-evaluation of the long held belief that different exercise training produces divergent cardiac adaptation (Morganroth et al., 1975). A caveat is important here; we report substantial numbers of endurance athlete groups but fewer resistance athlete groups. This issue is magnified for studies of RV and LA structure and function in athletes. It is clear from this met-analysis data set that further cross-sectional athlete-control studies are required to develop the database for resistance-trained athletes generally and with new imaging technologies specifically. It would also be pertinent to extend a similar endurance-resistance study specifically to investigate “old” and “new” imaging tools with respect to the RV and atria.

The current findings also provide relevant information for those interested in the nature of the upper limits of human cardiac, physiological adaptation to training. It is likely that the upper limits for chamber dimensions will be observed in endurance athletes. This knowledge will inform cardiac screening and the differential diagnosis of AH from pathological adaptation. Further, it is unlikely that the upper limits of LV wall dimensions will be exclusively observed in resistance athletes. It is also important to highlight that absolute wall thicknesses and the LV end diastolic dimension, although increased when compared to sedentary controls, do not fall within the pathological range seen in hypertrophic or dilated cardiomyopathy in either resistance or endurance trained athletes. This knowledge will further aid the diagnostic challenges associated with pre-participation screening of the competitive athlete.

In this meta-analysis, we examined the influence of BSA on sample differences in cardiac dimensions via a multiple meta-regression approach. Whilst this analysis goes some way in partitioning out the influence of BSA on the cardiac dimension estimates, ideally proper allometric scaling approaches should be applied at the individual study level. Unfortunately, this analysis approach is rare at present. It would be pertinent to include this as a secondary focus in further studies in this thesis addressing athlete group comparisons for various LV and RV structural data.

The current study has some limitations. As already noted, data for resistance athletes is relatively scarce. Functional measures in high quality case-control series studies are largely limited to global echocardiographic parameters *i.e.* LV EF, SV and E/A. The current study excluded older athletes and all female athlete studies. These limitations prompt on-going evaluation in this area.

3.6 Conclusions

This large scale systematic review and meta-analysis in male athletes provides strong evidence of LV, RV and LA hypertrophy with athletic training that is not dichotomous in form, but quantitatively greater with endurance training. Significant evidence of study-to-study heterogeneity was noted that could be due to the use of different imaging modalities as well as the approach to scaling (or indexing) cardiac structural data for individual differences in body size. Consequently, this meta-analysis provides a useful re-evaluation of concepts and models in the AH literature.

CHAPTER 4

A COMPREHENSIVE TECHNICAL ASSESSMENT OF THE ATHLETE'S HEART: THE "MORGANROTH HYPOTHESIS" RE-VISITED

This work has been presented as *'a comprehensive technical assessment of the athlete's heart: the "morganroth hypothesis" re-visited'* at the 19th Annual Congress of the European College of Sport Science, Amsterdam, The Netherlands.

De Haan, A., De Ruiter, C. J., Tsolakidis, E et al 2014: BOOK OF ABSTRACTS, 19th annual Congress of the EUROPEAN COLLEGE OF SPORT SCIENCE, 2nd - 5th July 2014, Amsterdam – The Netherlands, Page 173.

This work has been published as 'Predominance of normal left ventricular geometry in the male athlete's heart'. Heart 2014;0:1–8.doi:10.1136/heartjnl-2014-305904. *http://heart.bmj.com/content/100/16/1264.full*

4.1 Introduction

A landmark assessment of the left ventricle (LV) was undertaken by Morganroth and colleagues (Morganroth et al., 1975) in a small sample of highly-trained endurance (15 swimmers and 15 long distance runners) and resistance-trained athletes (12 wrestlers and 4 shot putters). Despite limited details related to training-related haemodynamic loading on the LV a dichotomous morphology was observed with an eccentric hypertrophy (balanced increase in chamber and wall dimensions) in endurance athletes versus a concentric hypertrophy (disproportionate increase in wall thickness) in resistance athletes.

It is hypothesised that these adaptations reflect differential haemodynamic loading during acute training (Grossman et al., 1975). This differential adaptation of the athlete's heart (AH) has been referred to as the "Morganroth Hypothesis" (MH) and has been widely adopted in textbooks, scientific papers and professional guidelines (Rudski et al., 2010) including the 26th Bethesda Conference: Recommendation for cardiovascular screening among athletes (Mitchell et al., 1994). Despite the pervasive nature of the MH, continuous evaluation of the AH phenotype is clinically important (George et al., 1991).

A plethora of original AH research papers, supplemented by numerous reviews and meta-analyses have raised specific questions related to the nature of cardiac adaptation to resistance training (Haykowsky et al., 2001). The meta-analysis conducted in the previous chapter confirmed only an eccentric-type cardiac phenotype in endurance athletes with limited adaptation in resistance trained athletes, with significant caveats about limited data sets and the requirement for further study.

Inconsistency in AH research may be related to multiple factors including; 1) on-going developments in non-invasive imaging, and 2) the importance of appropriate scaling for between subject differences in body size. Morganroth et al (1975) employed “ice pick” M-mode echocardiography and since then technological advancements have included improved spatial resolution as well as two- and three-dimensional imaging that provide more accurate estimates of cardiac structure and function (Mor-Avi et al., 2011).

Newer imaging modes such as tissue-Doppler imaging (TDI) and speckle tracking echocardiography (STE) estimation of strain (ε) and strain rate (SR), can provide detailed information related to global and regional function in the AH. Although used in a small number of cross-sectional athlete-control studies (La Gerche et al., 2011) they have not specifically evaluated the MH with very limited data available in resistance trained athletes (Utomi et al., 2013).

The association between body size and cardiac morphology is well known (Batterham et al., 1999, Dewey et al., 2008) but inconsistently applied. The use of simple linear ratio-standard scaling of cardiac structures is popular in the published literature despite the fact that a large number of cardiovascular variables relate to body size in a non-linear fashion (George et al., 2001). Appropriate scaling in a re-evaluation of the MH would be unique.

The following hypotheses were tested: A) Dichotomous LV structural adaption is not apparent in elite male endurance and resistance-trained athletes, B) modern imaging technologies will determine training-specific adaptation in global and regional LV function, and C) indexing LV data for individual variance in body size will have a significant impact on the interpretation of the AH.

4.2 Methods

4.2.1 *Study design and procedures*

A prospective cross-sectional study design was employed with data acquired in a resting state at a single testing session. All subjects were advised to abstain from caffeine, exercise training and alcohol consumption at least 3 hours prior to the investigation. Height and body mass were assessed using a stadiometer and digital weighing machine (SECA 764, Birmingham, UK) and body surface area (BSA) was calculated. After 5 minutes of supine rest, brachial artery blood pressure was assessed with an automated sphygmomanometer (DINAMAP 300, GE Medical Systems, Milwaukee, Wisconsin).

4.2.2 *Echocardiographic assessment*

A standard echocardiographic investigation was performed using a Vivid Q ultrasound machine (GE Medical System, Horten, Norway) with a 2.5-5 MHz transducer. All acquisitions were made with the subject lying in the left lateral decubitus position by the same experienced echocardiographer using a standard echocardiography-protocol in accordance with American Society of Echocardiography (ASE) guidelines (Lang et al., 2005). Offline analysis was performed using commercially available software (EchoPAC Version 7.0; GE Vingmed Ultrasound, Horten, Norway).

4.2.3 *Conventional 2D and Doppler / Tissue-Doppler*

Inter-ventricular septal wall thickness (IVSW), LV internal diameter (LVID) and LV posterior wall thickness (PWT) were measured at end-diastole (IVSWd, LVIDd and PWTd), using 2D imaging and LV mass was calculated. In order to establish LV geometry, relative wall thickness (RWT) was calculated using the general formula (RWT = (IVSWd + PWTd) / LVIDd) and participants were classified as eccentric hypertrophy, concentric hypertrophy, concentric remodelling or normal geometry (Lang et al., 2005). LV volumes, stroke volume (SV) and ejection fraction (EF) were calculated using Simpson's biplane method (Otto and Pearlman, 2004).

Doppler assessment of trans-mitral flow allowed the measurement of peak early diastolic (E), late diastolic (A) flow velocities, E deceleration time (Edecel) and isovolumic relaxation time (IVRT). Pulsed-wave TDI was undertaken with assessments of the basal septum and lateral wall where peak early diastolic (E'), late diastolic (A') and systolic (S') myocardial velocities were obtained. The ratio E/E' was calculated as a surrogate measure of LA pressure.

All LV structural variables were scaled to individual differences in BSA. This was achieved by the linear ratiometric method by simple division of the structural variable by BSA. Scaling was also performed allometrically according to the laws of geometric similarity (i.e. linear dimensions were scaled to $BSA^{0.5}$, volume and mass measurements were scaled to $BSA^{1.5}$ and area measurements to $BSA^{1.0}$) as well as LV mass being scaled to $height^{2.7}$. TDI data were also scaled linearly to LV length as previously demonstrated (George et al., 2001).

4.2.4 ***Speckle tracking echocardiography (STE)***

The apical 4-chamber view was used for the assessment of longitudinal LV ε and SR. For the assessment of LV basal circumferential ε, SR and rotation a parasternal short axis views was acquired at the tips of the mitral valve. The parasternal short axis at the apex defined as the level just above the point of systolic cavity obliteration was acquired to allow the assessment of apical rotation.

For offline analysis and assessment of longitudinal function, the region of interest (ROI) was placed around the LV basal septum through to basal lateral wall encompassing the mid and apical wall segments. Peak global LV ε and SR were obtained as the average of the base, mid and apical wall segments. The SR curves provided peak measures of systolic SR (SRS), early diastolic SR (SRE) and late diastolic SR (SRA). Peak global LV circumferential ε, SR and rotation were averaged from six myocardial segments with the ROI placed around the circumference of the LV at basal and apical levels. Left ventricular twist was calculated as the net difference between apical and basal rotation.

Intra class coefficient for LV ε for our laboratory are good to very good (0.714-0.807) with coefficient of variation for LV peak circumferential and longitudinal ε (7% and 6%), basal rotation (21%) and twist (10%) (Oxborough et al., 2012a).

4.2.5 *Statistical analysis*

Statistical analyses were performed using SPSS, version 20.0, for Windows (SPSS, Chicago, IL, USA) and the critical alpha was set at $p < 0.05$. Data are presented as mean ± SD [Range], and were analysed between groups using one-way ANOVA and Bonferoni correction for the post hoc test for multiple comparison to estimate differences between groups. A priori, a sample size of 15 from each target population (CT, ET and RT) was prospectively determined to achieve 80% statistical power, accommodate data variability in the study population and detect the minimum difference of 3 mm in LV chamber dimension between groups (Minitab 16, Minitab ltd, Coventry, United kingdom).

4.3 Results

4.3.1 *Study population*

A total of 54 males provided written informed consent to participate in the study. We recruited elite athletes (competitive at a national or international level) of which 18 were endurance (ET) athletes recruited from an international field at the 100-mile Western States Endurance Run (California, USA), and 19 were resistance trained (RT) athletes recruited from national Weightlifting and Aikido squads. The ET and RT were matched for accumulated mean training years, training hours per week and training days per week of (11 yrs., 12 hours/wk. and 6 days/wk.) and (12 yrs., 11 hours/wk. and 6 days/wk.), respectively. In addition, 17 sedentary controls (CT) were recruited from a university staff/student population in a similar age range. The CT were healthy individuals who were not engaged in systematic sport-related training and engaged in less than 3 hours recreational activity per week. All participants self-reported being healthy and free from any known cardiovascular disease, and were not currently taking any form of prescribed medication (Appendix 9.6 – participant information ship; 9.7 - Consent form and 9.8 - Health questionnaire). The study conformed to the 'STROBE STATEMENT: Guidelines for reporting observational studies' (Appendix 9.9) (von Elm et al., 2008) and to the standards set by the Declaration of Helsinki and ethical approval was granted by the Ethics Committee of Liverpool John Moores University (Appendix 9.10). The demographic characteristics of all participants are presented in Table 4.1.

Table 4.1: Demographic and resting cardiovascular data of male endurance-trained (ET), resistance-trained (RT) and sedentary control (CT) subjects, Data are mean ± SD (Range).

Parameter	ET	RT	CT
Sample Size (n)	18	19	17
Age (yrs)	34±5 (23 to 41)†	29 ± 8 (18 to 44)	27 ± 8 (20 to 43)
Body Mass (kg)	74 ± 9 (59 to 87)	83 ± 14 (61 to 111)	76 ± 10 (61 to 91)
Height (m)	1.8 ± 0.1 (1.5 to 1.9)	1.8 ± 0.1 (1.7 to 1.9)	1.8 ± 0.1 (1.6:1.9)
BSA (kg/m^2)	2.1 ± 0.2 (1.7 to 2.4)	2.3 ± 0.3 (1.8 to 2.9)	2.1 ± 0.2 (1.7 to 2.5)
Heart rate (beats.min^{-1})	56 ± 11 (40 to 80)	70 ± 11 (56 to 98) ‡	63 ± 10 (53 to 84)
Systolic BP (mmHg)	132 ± 10 (110 to 142)	134 ± 9 (110 to 145)	128 ± 12 (104 to 140)
Diastolic BP (mmHg)	78 ± 11 (58 to 90)	76 ± 7 (59 to 89)	75 ± 8 (59 to 89)

SA – Body surface area; BP – Blood pressure; † P<0.05 vs CT and ‡ P<0.05 vs. ET (Post hoc statistical significance at P<0.05).

Body mass, height, BSA and resting blood pressure were similar between groups. ET had a lower heart rate than the RT (P<0.05) but not the CT group (Table 1). Mean age was slightly higher in ET and greater than CT (P<0.05).

4.3.2 *2D- Echocardiography*

LV structural data are contained in Figure 4.1. and Table 4.2. Higher LVIDd, LVEDV and LV mass were observed in the ET, compared to both RT and CT, irrespective of scaling approach.

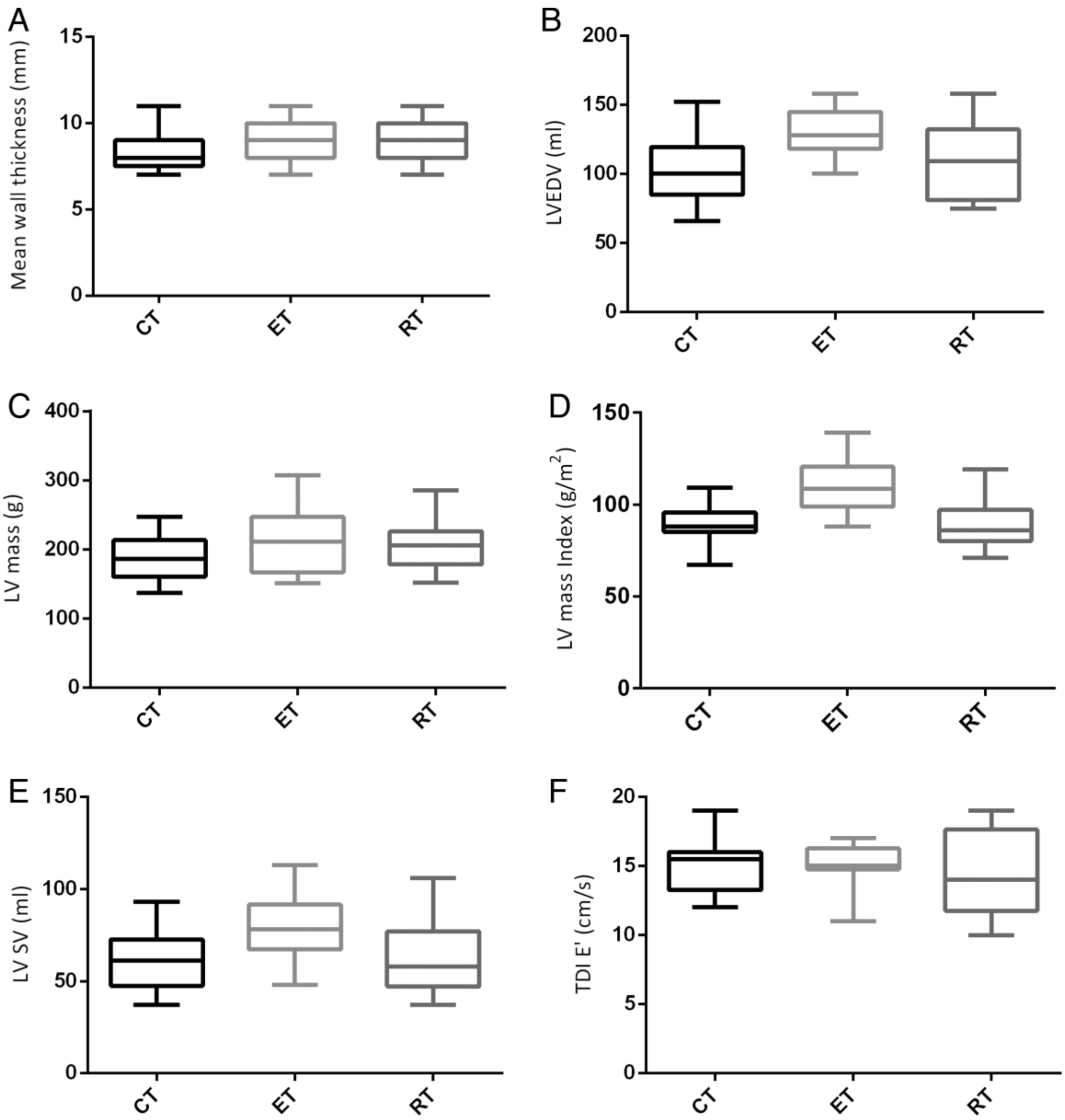


Figure 4.1: Box and whisker plots for selected LV structural parameters. The whiskers represent the minimum and maximum data value, the box represents the 1st and 3rd percentile while the Band within the box represents the median statistic (a) mean wall thickness, (b) LV end diastolic volume (LVEDV), (c) absolute LV mass, (d) LV mass index, and functional data (e) stroke volume (SV), and (f) early diastolic tissue velocity (TDI E').

There was no between-group difference in absolute LV wall thickness; however after ratiometric and allometric scaling, LV wall thicknesses were higher in ET than RT and CT.

Parameter	ET	RT	CT
IVSWTd (mm)	10 ± 1 (9 to 13)	10 ± 1 (8 to 12)	9 ± 1 (8 to 12)
IVSWTd (mm/m^2)	4.8 ± 0.5 (4 to 5)	4.3 ± 0.6 (3 to 5)‡	4.5 ± 0.6 (3 to 5)
IVSWTd (mm/m$^{0.5}$)	6.3 ± 0.8 (5.1 to 7.1)	5.9 ± 0.7 (4.8 to 7.4)	5.9 ± 0.6 (5.0 to 7.1)
LVIDd (mm)	56 ± 2 (53 to 59)†	53 ± 2 (50 to 57)‡	51 ± 2 (48 to 55)
LVIDd (mm/m^2)	27 ± 3 (24 to 32)†	24 ± 3 (19 to 29)‡	25 ± 3 (21 to 29)
LVIDd (mm/m$^{0.33}$)	42.1 ± 2.4 (38 to 46)†	39.5 ± 3.2 (33 to 46)‡	38.8 ± 2.3 (34 to 42)
PWTd (mm)	9 ± 1 (8 to 12)	9 ± 1 (8 to 11)	9 ± 1 (7 to 11)
PWTd (mm/m^2)	4.9 ± 0.6 (3 to 5)	4.3 ± 0.7 (3 to 5)‡	4.6 ± 0.5 (3 to 5)
PWTd (mm/m$^{0.5}$)	6.4 ± 0.8 (5 to 8)	6.2 ± 0.6 (5 to 7)	6.3 ± 0.6 (5 to 8)
LV mass (g)	200 ± 34 (154 to 254)†	187 ± 31 (133 to 247)	165 ± 32 (131 to 247)
LV mass (g/ m^2)	98 ± 15 (70 to 124)†	78 ± 15 (53 to 107)‡	74 ± 11 (54 to 97)
LV mass (g/m$^{2.7}$)	29.8 ± 6.6 (17 to 41)	25.4 ± 8.7 (15 to 48)	25.9 ± 6.5 (13 to 38)
LVEDV (ml)	141 ± 12 (120 to 158)†	120 ± 17 (100 to 158)‡	116 ± 18 (92 to 152)
LVEDV (ml/m^2)	68 ± 7 (53 to 80)†	54 ± 8 (42 to 70)‡	55 ± 7 (44 to 69)
LVEDV (ml/m$^{1.5}$)	43.7 ± 6.8 (32 to 58)†	34.2 ± 7.4 (24 to 52)‡	32.5 ± 8.9 (18 to 47)
LV length (mm)	91 ± 7 (78 to 100)	87 ± 10 (76 to 110)	86 ± 7 (74 to 98)
LV length (mm/m^2)	44 ± 4 (36 to 50)	39 ± 6 (29 to 50)‡	41 ± 3 (33 to 46)
LV length (mm/m$^{0.5}$)	62.9 ± 3.8 (53 to 70)	57.5 ± 6.9 (47 to 71)‡	59.6 ± 3.1 (52 to 65)

Table 4.2: Left ventricular structural parameters measured using 2D echocardiography in male endurance-trained (ET), resistance-trained (RT) and sedentary control (CT) subjects. Data are mean ± SD (Range).

LV-left ventricle, IVSWT-inter ventricular septal wall thickness, d-at end-diastole, s-at end-systole, PWT-posterior wall thickness, LVIDd - LV internal diameter, LVEDV- LV end-diastolic volume. Post-hoc analysis from one-way ANOVA at † p<0.05 vs. CT; ‡ P<0.05 vs. ET; **P<0.05 vs. RT.

Normal geometry was present in most participants, with eccentric hypertrophy evident in only 30% of ET and no concentric hypertrophy in RT (Figure 4.2).

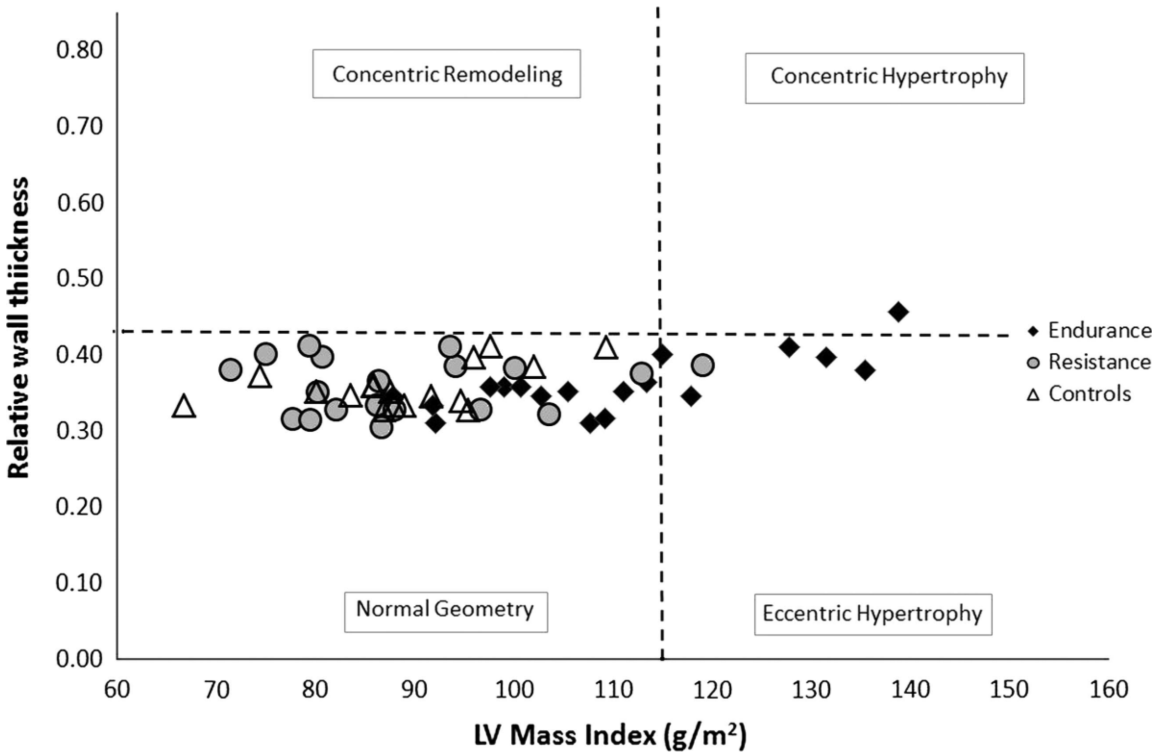


Figure 4.2 Comparison of the individual distribution of relative wall thickness (RWT) and LV mass index in all athletes. Normal geometry (LV mass ≤115 g/m2 with RWT ≤0.42), concentric remodelling (LV mass ≤115 g/m2 with RWT >0.42), concentric hypertrophy (LV mass >115 g/m2 with RWT >0.42) or eccentric hypertrophy (LV mass >115 g/m2 with RWT ≤0.42) as described by Lang et al (2005).

Global LV functional data are presented in Table 4.3a and 4.3b. SV was higher in ET compared to both RT and CT but there was no between-group difference in any other global measure of systolic or diastolic function. Likewise there were no between-group differences in regional TDI data.

Table 4.3a: Left ventricular systolic functional data in male endurance-trained (ET), resistance-trained (RT) and sedentary control (CT) subjects, data are mean ± SD (Range).

Parameter	ET	RT	CT
	Systolic function		
LVSV (ml)	80 ± 17(48 to 113)†	62 ± 20(37 to 106)‡	63 ± 17(37 to 93)
LVSV(ml/ m^2)	38 ± 8(26 to 56)†	28 ± 9(15 to 46)‡	30 ± 6 (20 to 40)
EF (%)	59 ± 3(54 to 66)	57 ± 4(50 to 65)	59 ± 2(54 to 63)
LV VTI (cm)	25 ± 3(19 to 29)†	20 ± 2(17 to 25)‡	22 ± 3(17 to 25)
Sep S'(cm/s)	10 ± 1(8 to 13)	10 ± 2(7 to 12)	10 ± 2(7 to 13)
Sep S'/LV	1.1 ± 0.2(1.1 to 1.4)	1.2 ± 0.2(0.9 to 1.6)	1.1 ± 0.2(0.9 to 1.5)
Lat S'(cm/s)	12 ± 2(9 to 16)	13 ± 4(8 to 21)	12 ± 2(7 to 15)
Lat S'/LV length	1.4 ± 0.2(1.1 to 1.9)	1.5 ± 0.4(0.8 to 2.1)	1.5 ± 0.3(1.1 to 2.1)

SV-stroke volume, EF-ejection fraction, E-early ventricular filling, A-late atrial contraction, Edecl-E deceleration time, IVRT-Isovolemic relaxation time, VTI-velocity time integral, AV max-aortic valve maximum velocity, TDI-tissue Doppler imaging, Sep-septal, Lat-lateral, S'-systolic tissue velocity, E'-early diastolic tissue velocity, A'-late atrial diastolic tissue velocity. Post-hoc analysis from one-way ANOVA, † P value <0.05 vs. CT; ‡ P value < 0.05 vs. ET.

Table 4.3b: Left ventricular diastolic functional data in male endurance-trained (ET), resistance-trained (RT) and sedentary control (CT) subjects, data are mean ± SD (Range).

Parameter	ET	RT	CT
	Diastolic function		
IVRT (ms)	71 ± 9(54 to 88)	76 ± 11(53 to 98)	77 ± 11(53 to 95)
E (m/s)	0.8 ± 0.2(0.6 to 1.2)	0.7 ± 0.2(0.5 to 1.0)	0.8 ± 0.2(0.5 to 1.0)
A (m/s)	0.5 ± 0.1(0.4 to 0.6)	0.5 ± 0.1(0.3 to 0.7)	0.5 ± 0.1(0.3 to 0.8]
E/A	1.7 ± 0.3(1.4 to 2.50	1.5 ± 0.5(0.9 to 2.7)	1.7 ± 0.4(1.2 to 2.5)
Edecl (ms)	140 ± 16([118 to 165]	141 ± 24 (102 to 178)	141 ± 49(99 to 190)
Sep E’(cm/s)	13 ± 2(10 to 15)	13 ± 3(6 to 18)	13 ± 2(9 to 17)
Sep A(cm/s)′	9 ± 2(6 to 11)	8 ± 2(4 to 13)	9 ± 1(6 to 11)
Lat E′(cm/s)	17 ± 4(8 to 23)	16 ± 4(8 to 24)	17 ± 3(13 to 23)
Lat A’(cm/s)	8 ± 1(6 to 10)	8 ± 2(4 to 13)	8 ± 2(6 to 14)
Sep E’/LV length	1.0 ± 0.2(0.6 to 1.3)	1.0 ± 0.3(0.4 to 1.7)	1.0 ± 0.2(0.7 to 1.3)
Sep A’/LV length	1.3 ± 0.2(0.9 to 1.8)	1.2 ± 0.5(0.9 to 1.9)	1.3 ± 0.3(0.9 to 1.8)
Lat E’/LV length	1.9 ± 0.5(0.9 to 2.7)	1.9 ± 0.5(1.0 to 2.7)	1.9 ± 0.3(1.5 to 2.5)
Lat A’/LV length	0.9 ± 0.2(0.6 to 1.2)	1.0 ± 0.3(0.5 to 1.4)	1.0 ± 0.2(0.7 to 1.5)
E/E′	5.5 ± 1(3.9 to 7.5)	4.9 ± 1.3(3.2 to 7.2)	5.3 ± 1.1(3.4 to 7.0)

SV-stroke volume, EF-ejection fraction, E-early ventricular filling, A-late atrial contraction, Edecl-E deceleration time, IVRT-Isovolemic relaxation time, VTI-velocity time integral, AV max-aortic valve maximum velocity, TDI-tissue Doppler imaging, Sep-septal, Lat-lateral, S’-systolic tissue velocity, E’-early diastolic tissue velocity, A’-late atrial diastolic tissue velocity. Post-hoc analysis from one-way ANOVA,† P value <0.05 vs. CT; ‡ P value < 0.05 vs. ET

4.3.3 *2D-STE*

Longitudinal and basal circumferential ε were not different between ET and CT but were significantly lower in RT compared to ET (Table 4.4). Likewise, basal circumferential SRS was significantly lower in RT than the ET (Figure 4.3). Longitudinal SRE and SRA were significantly lower in the RT group compared to the CT group. There was no significant between-group difference in basal and apical rotation and derived LV twist.

Table 4.4: Descriptive cohort data for two-dimensional STE derived LV strain (ε) and strain rate (SR S^{-1}), data are mean ± SD (range).

Parameter	ET	RT	CT
		Longitudinal	
Peak ε (%)	-18.6 ± 2.2 (-22.9 to -14.4)‡	-16.2 ± 1.7 (-20 to -12)	-17.7 ± 2.1 (-21.9 to -14.7)
Peak SRS (S^{-1})	-0.9 ± 0.1 (-1.2 to -0.8)	-0.9 ± 0.1 (-1.1 to -0.7)	-0.9 ± 0.1 (-1.2 to -0.7)
Peak SRE (S^{-1})	1.31 ± 0.21 (1.0 to 1.9)	1.14 ± 0.24 (0.8 to 1.6)	1.29 ± 0.19 (0.9 to 1.7)
Peak SRA (S^{-1})	0.7 ± 0.1 (0.5 to 0.9)	0.7 ± 0.2 (0.4 to 0.8)	0.7 ± 0.1 (0.5 to 0.8)
		Basal circumferential	
Peak ε (%)	-18.5 ± 3.4 (-22.5 to -12)‡	-13.5 ± 3.3 (-21.4 to -9.8)	-15.8 ± 2.9 (-20.8 to -11.6)
Peak SRS (S^{-1})	-1.15 ± 0.20 (-1.7 to -0.9)‡	-0.90 ± 0.19 (-1.3 to -0.7)	-1.1 ± 0.2 (-1.5 to -0.8)
Peak SRE (S^{-1})	1.7 ± 0.4 (1.2 to 2.3)	1.2 ± 0.4 (0.8 to 2.0)	1.3 ± 0.4 (0.9 to 2.1)
Peak SRA (S^{-1})	0.4 ± 0.1 (0.2 to 0.6)	0.5 ± 0.2 (0.2 to 0.7)	0.4 ± 0.1 (0.2 to 0.9)
		Rotation	
Peak apical rotation (^{o})	9.8 ± 3.1 (3.8 to 16.6)	8.2 ± 3.2 (3.8 to 14.5)	10.8 ± 3.5 (3.1 to 15.1)
Peak basal rotation (^{o})	-5.8 ± 2.3 (-10.4 to -2.8)	-4.7 ± 2.2 (-9.1 to -2.1)	-3.8 ± 2.1 (7.1 to -2.1)
Peak twist (^{o})	15.3 ± 4.4 (5.1 to 22.7)	12.5 ± 4.8 (5.9 to 22.1)	14.50 ± 3.9 (9.8 to 21.5)

Strain (ε), SRS-strain rate in systole, SRE-strain rate in early diastole, SRA-strain rate in late diastole. Post-hoc analysis from one-way ANOVA, ‡P<0.05 vs RT

4.4 Discussion

The key outcomes from this study were; 1) A normal geometry was predominant across all groups with only 30% of ET demonstrating an eccentric hypertrophy and no concentric hypertrophy in RT, 2) global LV function and TDI data were comparable between groups, but peak longitudinal and basal circumferential ε was lower in RT than ET, 3) indexing of LV structures for BSA uncovered increased wall thickness dimensions in ET compared to both RT and CT groups.

4.4.1 *The Morganroth Hypothesis*

The present study demonstrated that ET is associated with increased LV volume and mass but the geometry remained normal in the majority and eccentric hypertrophy in only 30% athletes. These finding partially conform to the MH as well as subsequent studies and reviews (Utomi et al., 2013, Pluim et al., 2000, Pelliccia et al., 1991, Baggish et al., 2008, Haykowsky et al., 2000) but suggests that the degree of hypertrophy is limited and varies between individuals. Endurance sporting activity entails a sustained high oxygen demand. An increased cardiovascular preload (La Gerche et al., 2011) and a haemodynamic volume overload is suggested as the primary stimulus for LV adaptation in ET (George et al., 1991).

Teleologically, an increase in LV volume and mass should contribute to a higher SV and cardiac output, thus underpinning an elevated performance capacity. Review of the 30% of ET with an eccentric hypertrophy revealed no systematic association with age, BSA, performance times and/or training history that could explain this adaptation.

There was no concentric hypertrophy in RT. This confirms previous cross-sectional data (George et al., 1999) and meta-analysis (Utomi et al., 2013) but conflicts with the MH. The lack of concentric adaptation in RT could be due to limited exposure to an increased haemodynamic afterload during resistance exercise training, or the potential lack of any afterload stimulus due to the fact that wall stress is not elevated during lifting when a brief phase 1 Valsalva manoeuvre is performed (Haykowsky et al., 2001).

A key take home message for clinicians is that normal cardiac geometry is predominant across all groups, and that the upper limits of LV wall thickness and cavity dimensions were within published normal limits (Lang et al., 2005) and recorded in ET athletes. These data, confirm current practice in relation to the cardiovascular pre-participation screening of athletes and the differential diagnosis of the AH from pathology.

4.4.2 *Left ventricular function*

A larger SV in ET has been reported in most athlete-control studies (Pelliccia et al., 1991) with no difference between RT and CT (Utomi et al., 2013). The current study confirms this pattern. The larger SV in ET is partially due to the larger LV dimensions at rest. Current data and previous studies (Utomi et al., 2013, Pelliccia et al., 1991, George et al., 1999) have demonstrated that LV EF is normal in athletes. This suggests that resting contractility in athletes is not augmented.

The assessment of diastolic flow yielded no significant between-group difference. Some individual studies have reported improved diastolic filling at rest in athletes (Florescu et al., 2010) but this observation is not consistent. It is possible that the important adaptation in LV diastolic filling in athletes is not apparent at rest but noticeable during exercise (Batterham et al., 2008).

4.4.3 *Novel techniques*

We did not observe any significant between group differences in systolic and/or diastolic LV TDI velocities. This supports some previous data (Baggish et al., 2008) but contradicts study by Florescu and colleagues, who observed significantly higher longitudinal velocities in ET in comparison to CT. One possible reason for the contradictory outcomes between studies in relation to TDI data could be the inconsistent approach to scaling tissue velocities (Florescu et al., 2010). Batterham et al documented that S′ and E′ were proportional to LV length, providing empirical support for the scaling procedures adapted by Pela et al and the current study (Batterham et al., 1999, Pela et al., 2004).

Despite the lack of between group differences in TDI data, we observed that highly trained RT had a lower peak longitudinal ε and peak SRS than ET, although neither RT or ET were significantly different from CT. Whilst there is limited data related to STE in athletes, the current ET data agrees with Stefani et al who reported no differences in LV STE measurements between 20 endurance athletes and 18 controls (Stefani et al., 2009). Similarly, Nottin et al documented that longitudinal ε, S’, E’ and A’ did not differ between endurance-trained cyclists (n=16) and controls (n=23) (Nottin et al., 2009). In contrast, Simsek et al reported higher ε values at rest in marathon runners compared to sedentary subjects (Simsek et al., 2013). These disparate findings warrants further evaluation as it calls the reliability of segmental ε to question.

Whilst there were no differences in STE data between ET and CT we noted lower ε data in RT. This data is at odds with a previous study by Simsek et al who documented higher systolic ε and SR in both runners and wrestlers compared to sedentary individuals (Simsek et al., 2013). The observation of lower ε in RT, compared to ET, requires further study and we cannot determine the mechanism(s) underpinning this data from the current cross-sectional study. It is, however, unlikely that this data represents an increased ε reserve in RT (Akagawa E et al., 2007) as this type of adaptation would serve no purpose to the RT sporting activity.

As well, it is unlikely to reflect a higher resting HR in RT as ε tends to increase with HR under inotropic stimulation (Gutgesell and Rembold, 1990). Whilst STE data in RT is limited, it is interesting to note that in a longitudinal training study, Baggish and colleagues documented a significant reduction in LV early and late diastolic tissue velocities in participants who undertook strength-training. Baggish et al speculated that training-related changes in LV afterload and increased peripheral vascular resistance could be implicated in these changes (Baggish et al., 2008). The current data prompt continuing research in this area.

4.4.4 *Impact of body composition on the athlete's heart phenotype*

Differences in absolute LV chamber size between the ET and both RT and CT were maintained with both ratio and allometric scaling for individual differences in BSA. Indexing of LV wall thickness for BSA did 'uncover' a higher LV wall thickness index in ET compared to RT. Scaling has been observed to alter data interpretation in a small number of previous studies (George et al., 1999) and the current data partially support this.

On the basis of the current data and previous theoretical (Gutgesell and Rembold, 1990) and empirical (George et al., 2001, De Simone et al., 1995) research we would argue that interpretation of absolute cardiac dimensions must take account of body size differences. Further, ratio scaling can be misleading and thus should always be empirically supported within the sample being studied, alongside an exploration of other potentially allometric approaches to determine which index is indeed size-independent (Batterham et al., 1999, George et al., 2001, Dewey et al., 2008).

4.5 Limitations and future research

This cross-sectional study, as well as the previous meta-analysis cannot directly support a "cause-effect" relationship between exercise mode and physiological cardiac remodelling. Significantly, our study is limited to the LV in adult male athletes. The assessment of RV and atrial structure and function in various athlete groups, with novel technologies, requires substantial development and is particularly relevant to interpretation of clinical data and should form the focus of the next study in this thesis.

4.6 Conclusions

Although ET express an AH phenotype with an increased LV chamber size, the overall LV geometry was normal in the majority of athletes. Highly-trained RT do not display concentric LV hypertrophy suggesting that the MH requires revision. Whilst global cardiac function and TDI data were largely similar between all groups there was some evidence of lower LV ε in RT. Finally, appropriate scaling of LV structural data for within subject differences in BSA can alter between group comparisons and should be adopted in future research.

CHAPTER 5

DOES TRAINING TYPE RESULT IN A DICHOTOMOUS RIGHT VENTRICULAR ATHLETIC HEART PHENOTYPE IN MALE ATHLETES

This chapter has been published as *'Does training type result in a dichotomous right ventricular athletic heart phenotype in male athletes'* in Eur J Appl Physiol DOI 10.1007/s00421-015-3147-3. http://link.springer.com/article/10.1007/s00421-015-3147-3.

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CHAPTER 6

THE ATHLETE'S HEART PHENOTYPE IN WEST AFRICAN RESISTANCE-TRAINED ATHLETES: AN EXPLORATORY STUDY

6.1 Introduction

The “athlete’s heart” (AH) reflects a complex range of structural, functional and electrical adaptations to prolonged periods of training (Morganroth et al., 1975). The AH has been the focus of substantial enquiry to determine; 1) how the heart adapts to training, 2) whether this adaptation is obligatory for enhanced athletic performance, and 3) how we can easily differentiate the athlete’s heart from hereditary disease states like hypertrophic cardiomyopathy (HCM) and arrythmogenic right ventricular cardiomyopathy (ARVC). These pathologies can present with phenotypes similar to the AH and place the athlete at risk of sudden cardiac death (SCD) (Maron and Pelliccia, 2006). As a consequence, the AH has been extensively described (George et al., 2011) in an attempt to develop rigorous clinical algorithms to identify at risk individuals.

Following from the systematic review and meta-analysis, and the 2 cross-sectional studies included in the earlier chapters of this thesis, the study of the AH and the definition of normal limits for cardiac structure and function included in clinical algorithms have been largely based on data from Caucasian athletes. The study of other ethnic groups is essential especially when one considers that Black athletes (BA) have a 2-fold higher incidence of SCD compared to Caucasian athletes (Maron and Pelliccia, 2006 , Magalski et al., 2011). Description of the AH in BA has developed recently, with evidence of greater LV wall thickness and elevated LV mass in generalised cross sectional groups of BA compared to Caucasian athletes (Basavarajaiah et al., 2008, Rawlins et al., 2010). These authors concluded that ethnicity was the strongest predictor of maximal LV wall thickness (LVWT). Other recent studies have described an increased prevalence of repolarisation abnormalities on ECG in BA (Corrado et al., 2009, Magalski et al., 2011, Drezner et al., 2013b) The updated

"Seattle ECG criteria for athlete screening" recognises these ethnic differences as normal ECG patterns in BA population (Appendix 9.11 & 9.12) (Drezner et al., 2013a).

Current ECG and echocardiographic studies in BA have largely ignored training type/mode as a specific issue of interest. This is despite recent data in Caucasian athletes that have questioned the existence of an AH phenotype in elite Caucasian resistance trained (RT) athletes (Haykowsky et al., 2001, Utomi et al., 2013, Utomi et al., 2014). Magalski et al (2011) reported that black ethnicity was a statistically significant predictor of distinctly abnormal ECGs (relative risk 1.82, 95% confidence interval, 1.22-2.73; $P<0.01$), however clinically important racial differences in cardiac structures were not apparent in their study on collegiate athletes(Magalski et al., 2011). Perhaps, there could be more insight on the AH phenotype if the data in their study was stratified into training groups. The effect of resistance training in BA has not been investigated comprehensively.

Finally, although informative the large-scale AH studies in BA by Basavarajaih et al (2008) and Rawlins et al (2010) were limited to standard or 'traditional' echocardiography measurement techniques (Basavarajaiah et al., 2008, Rawlins et al., 2010). Newer imaging modes such as tissue-Doppler imaging (TDI) and speckle tracking echocardiography (STE) estimation of strain and (ε) and strain rate (SR) can provide detailed information related to global and regional function in RT. TDI and STE have been used in a small number of cross-sectional athlete control studies in Caucasian athletes (CA) but never before in BA of West African origin.

Using ECG and novel echocardiographic technologies in a pilot study design, we proposed to define global and regional cardiac structure and function in elite West African resistance trained athletes (WRT). This data was compared to sedentary West African controls (WCT) as well as Caucasian RT athletes (CRT) and sedentary controls (CCT). Previous cross sectional studies on Black athletes were not homogenous. They included Afro Caribbean's, African Americans, Black French, Black British descents that were determined through self-report questionnaire (Basavarajaiah et al. 2008, Magalski et al. 2008, Rawlins et al. 2010, Magalski et al. 2011). Whether these participants were first or second generation blacks and the potential for genetic mix in these populations over time could be significant. Secondly, empirical studies have demonstrated that significant genetically mediated differences exist between, Black Asians, East Africans and West Africans (Dunn et al., 1983, Mayet et al., 1994, Bhopal, 2004, Agyemang et al., 2005).

Consequently, the purpose of this pilot study was to characterise the AH phenotype in a homogenous population of elite RT athletes of West African origin using state-of-the-art imaging technology. In a case control / cross sectional design, this study will provide new insight in relation to: 1) Cardiac adaptation to RT in elite WRT; 2) ECG characteristics in WRT in comparison with CRT; 3) functional data derived from tissue Doppler imaging (TDI) and speckle tracking echocardiography (STE).

6.2 Methods

6.2.1 *Study design and procedures*

A prospective cross-sectional study design was employed with data acquired in a resting state at a single testing session. All subjects were advised to abstain from caffeine ingestion and exercise training at least 3 hours prior to the investigation. Height and body mass were assessed using a stadiometer and digital weighing machine (SECA 764, Birmingham, UK) and body surface area (BSA) was calculated (Dubois and Dubois 1916). After 5 minutes of supine rest, brachial artery blood pressure was assessed with an automated sphygmomanometer (DINAMAP 300, GE Medical Systems, Milwaukee, Wisconsin).

6.2.2 *Echocardiographic assessment*

A standard echocardiographic investigation was performed using a Vivid Q ultrasound machine (GE Medical System, Horten, Norway) with a 2.5-5 MHz transducer. All acquisitions were made with the subject lying in the left lateral decubitus position by the same experienced echocardiographer using a standard echocardiography-protocol in accordance with American Society of Echocardiography (ASE) guidelines (Lang et al. 2005). Offline analysis was performed using commercially available software (EchoPAC Version 7.0; GE Vingmed Ultrasound, Horten, Norway).

6.2.2.1 *Conventional 2D and Doppler / Tissue Doppler: Left ventricule*

Inter-ventricular septal wall thickness (IVSW), LV internal diameter (LVID) and LV posterior wall thickness (PWT) were measured at end-diastole (IVSWd, LVIDd and PWTd), using 2D imaging and LV mass was calculated (Lang et al. 2005). LV volumes, stroke volume (SV) and ejection fraction (EF) were calculated using Simpson's biplane method (Lang et al. 2005).

Doppler assessment of trans-mitral flow allowed the measurement of peak early diastolic (E), late diastolic (A) flow velocities, E deceleration time (Edecel) and isovolumic relaxation time (IVRT). Pulsed-wave TDI was undertaken with assessments of the basal septum and lateral wall where peak early diastolic (E'), late diastolic (A') and systolic (S') myocardial velocities were obtained. The ratio E/E' was calculated as a surrogate measure of LA pressure (Nagueh et al. 1997, Burgess et al. 2006, George et al. 2010).

All LV structural variables were scaled to individual differences in BSA. This was achieved by allometrically according to the laws of geometric similarity (i.e. linear dimensions were scaled to $BSA^{0.5}$, LVIDd was scaled to $BSA^{0.33}$ and mass measurements were scaled to $BSA^{1.5}$ and area measurements to $BSA^{1.0}$) as well as LV mass being scaled to $height^{2.7}$ (Batterham et al. 1999, George et al. 2001). TDI data were also scaled linearly to LV length as previously demonstrated (Pela et al. 2004).

6.2.2.2 *Conventional 2D and Doppler / Tissue Doppler: Right ventricle*

In accordance with ASE guidelines, RV size was measured at end-diastole from the proximal RV out flow tract at the level of the aortic valve (PLAX RVOT and RVOT1), and at the pulmonary valve annulus (RVOT2) using a parasternal short-axis (PSAX) orientation. RV free wall was measures in diastole from the subcostal view and RV cavity dimensions at the basal RV inflow (RVD1), mid-level (RVD2) and RV length (RVD3) were measured from the modified apical 4-chamber orientation. RV diastolic and systolic areas were assessed by tracing around the endocardium from a modified apical 4-chamber orientation, and RV fractional area change (RV FAC %) was calculated (Rudski et al. 2010).

Tricuspid annular plane excursion (TAPSE) was obtained as a measure of RV longitudinal function. RV stroke volume (RVSV) was calculated using the general formula RVSV = π (RVOT/2)*2 x VTI, RV velocity time integral (VTI) was measured from the Doppler spectral envelop derived from a 4 mm sample volume placed at the RV outflow in the PSAX view (Rudski et al. 2010). All RV structural variables were allometrically scaled for individual differences in BSA according to laws of geometric similarity (Batterham et al. 1999). Pulsed wave TDI was used to assess RV myocardial velocities with a 4mm sample volume positioned in the lateral aspect of the tricuspid annulus of the RV lateral wall and peak velocities in systole (RVS'), early diastole (RVE') and late diastole (RVA') were measured. Tissue velocity data were scaled to RV length (Pela et al. 2004).

6.2.2.3 ***Speckle tracking echocardiography (STE): Left ventricle***

The apical 4-chamber view was used for the assessment of longitudinal LV ε and SR. For the assessment of LV circumferential, radial ε, SR and rotation, parasternal short axis views were acquired at the tips of the mitral valve (basal) and at the apex defined as the level just above the point of systolic cavity obliteration.

For offline analysis and assessment of longitudinal function, the region of interest (ROI) was placed around the LV basal septum through to basal lateral wall encompassing the mid and apical wall segments. Peak global LV ε and SR were obtained as the average of the base, mid and apical wall segments. A priori, each segment was visually inspected, and the ROI adjusted to track wall synchrony before approval. The SR curves provided peak measures of systolic SR (SRS), early diastolic SR (SRE) and late diastolic SR (SRA). Peak global LV circumferential, radial ε, SR and rotation were averaged from six myocardial segments with the ROI placed around the circumference of the LV at basal and apical levels. Left ventricular twist was calculated as the net difference between apical and basal rotation.

6.2.2.4 ***Speckle tracking echocardiography (STE): Right ventricle***

The modified apical 4-chamber orientation was used for the assessment of longitudinal RV ε and strain rate (SR). During off-line analysis, the region of interest (ROI) was placed around the RV lateral wall from the base to apex. A priori, each segment was visually inspected, and the ROI adjusted to track wall synchrony before approval. Regional peak values were obtained at the base, mid and apical RV wall and a base-to-apex gradient was calculated. Global peak values were calculated as an average of all 3 myocardial segments. Indices obtained included peak RV ε and SR during ventricular systole (SRS) and during early and late ventricular diastole (SRE and SRA).

Intra class coefficient for LV ε for our laboratory are good to very good (0.714-0.807) with coefficient of variation for LV peak circumferential and longitudinal ε (7% and 6%), basal rotation (21%) and twist (10%). For the RV, Intra-observer variation for structural and functional data demonstrated no systematic bias for peak *ε* or indices of SR ($P < 0.05$) with intra-class correlation coefficients of 0.834 and 0.610, respectively (Oxborough et al. 2012).

6.2.2.5 Electrocardiography (ECG)

A standard 12 lead Electrcardiogram (ECG) was performed after 5 minutes of rest in suppine position with an automated ECG machine (Cardioexpress SL3, Spacelabs Healthcare ltd. Hertford, United Kingdom). ECG tracings recorded the magnitude of electrical potentials through the cardiac cycle for P – wave (atrial depolarization). A tall or peaked P-wave indicates Right atrial hypertyrophy present in Tricuspid valve stenosis and also in pulmonary hypertension. A wide QRS complex (Ventricular depolarization) greater than normal values of 120s is suggestive of bundle branch block or extra-systole beat. The T-wave (ventricular repolarization) abnormality is be seen in ventricular hypertrophy, cardiac ischaemia and also in bundle branch block. The begining of the P-wave to begining of the QRS complex recorded the time interval of atrial contraction (PR-interva). Greater than normal value of PR interval 200ms suggests some degree of heart block. Whilst the begining of Q-wave to the end of T wave is the time interval for Ventricular replolarisation (QT interval) and corrected for variations in heart rate (QTc interval). Abnormalities in QTc interval is suggestive of repolarisation abnormalities and channelopathies like Bruggada's syndrome and long QT syndrome.

6.2.3 *Statistical analysis*

Statistical analyses were performed using SPSS, version 20.0, for Windows (SPSS, Chicago, IL, USA) and the critical alpha was set at $p < 0.05$. Data are presented as mean ± SD [Range], and were analysed between groups using two-way ANOVA and Bonferoni correction for the post hoc test for multiple comparison to estimate differences between groups. A priori, a sample size of 15 from each target population (CT, and RT) was prospectively determined to achieve 80% statistical power, accommodate data variability in the study population and detect the minimum difference of 3 mm in LV/RV chamber dimension between groups (Minitab 16, Minitab ltd, Coventry, United kingdom).

6.3 Results

6.3.1 *Study population*

A total of 66 males provided written informed consent to participate in the study. We recruited elite athletes (competitive at a national or international level) of which 19 were resistance trained Caucasian athletes (CRT) recruited from British national Weightlifting and Aikido squads, 6 were international West African black RT athletes (WRT) recruited from the - Nigerian track and field team at the London Olympics 2012. The CRT and WRT were matched for accumulated mean training years, training hours per week and training days per week of (12 yrs., 11 hours/wk. and 6 days/wk.), and (11 yrs., 11 hours/wk. and 6 days/wk.), respectively. In addition, 17 Caucasian sedentary controls (CCT) and 24 West African sedentary controls (WCT) were recruited from a university staff/student population in a similar age range.

The CT's were healthy individuals who were not engaged in systematic sport-related training and performing less than 3 hour's recreational activity per week. All participants self-reported being healthy and free from any known cardiovascular disease, and were not currently taking any form of prescribed medication (Appendix 9.6, 9.7, 9.8 and 9.9). The study conformed to the 'STROBE STATEMENT: Guidelines for reporting observational studies' (von Elm et al., 2008) and to the standards set by the Declaration of Helsinki. Ethical approval was granted by the Ethics Committee of Liverpool John Moores University (Appendix 9.10). The demographic characteristics of all participants are presented in Table 6.1.

6.3.2 *Demographic characteristics of the study population*

The four groups were comparable for body mass, height, BSA, heart rate and systolic blood pressure. WRT had a lower diastolic blood pressure than CRT ($P < 0.05$) but not significantly different from WCT and CCT groups (Table 6.1). Mean age were not significantly different between groups.

Table 6.1: Demographic and resting cardiovascular data of male resistance trained (RT) and sedentary control (CT) subjects. Data are mean ± SD (range).

Parameters	**West Africans (WA)**		**Caucasians (CA)**		**2 Way ANOVA**		
					Ethnicity (WA vs CA)	Sport (RT vs CT)	Interaction
Sample size (n)	WRT (6)	WCT (24)	CRT (19)	CCT (17)			
Age (years)	25 ± 4 (21 to 31)	25 ± 6 (18 to 40)	29 ± 8 (18 to 44)	27 ± 8 (20 to 43)	0.19	0.66	0.53
Heart rate (beats.min^{-1})	60 ± 9 (47 to 74)	65 ± 8 (48 to 84)	70 ± 11 (56 to 98)	63 ± 10 (53 to 84)	0.19	0.71	0.85
Systolic BP (mm Hg)	126 ± 8 (117 to 139)	127 ± 6 (116 to 136)	135 ± 9 (119 to 150)	129 ± 12 (107 to 150)	0.81	0.48	0.14
Diastolic BP (mm Hg)	67 ± 10 (51 to 82)	74 ± 8 (62 to 90)	76 ± 7 (59 to 89)	75 ± 8 (59 to 89)	0.03 WA < CA	0.12	0.09
Body Mass (kg)	81 ± 5 (75 to 89)	77 ± 14 (54 to 105)	83 ± 14 (61 to 111)	76 ± 11 (61 to 91)	0.87	0.12	0.64
Height (m)	1.8 ± 0.1 (1.7 to 1.9)	1.7 ± 0.1 (1.6 to 1.9)	1.8 ± 0.1 (1.7 to 1.9)	1.8 ± 0.1 (1.6 to 1.9)	0.88	0.17	0.16
BSA (Kg/m^2)	2.2 ± 0.1 (2.1 to 2.4)	2.1 ± 0.3 (1.6 to 2.7)	2.3 ± 0.3 (1.8 to 2.8)	2.1 ± 0.2 (1.7 to 2.5)	0.9	0.06	0.97

SA, body surface area; BP, blood pressure; WA, West Africans; WRT, West African resistance trained athletes; WCT, West African control subjects; CA, Caucasians; CRT, Caucasian resistance trained athletes; CCT, Caucasian control subjects. P values from 2-way ANOVA with main effects for ethnicity and sport.

6.3.3 *2D Echocardiography: Left ventricle*

LV structural data are contained in Table 6.2. Whereas absolute LV wall thickness (IVSWT and PWT) were similar between groups, allometric scaling uncovered an ethnicity effect (post-hocs p=0.01) of IVSWT. Although no significant differences were noted between athletes and controls. In contrast, scaling tended to decrease athlete-control differences in LV cavity (LVIDd), LV volume (LVEDV) and LV mass. Absolute LV length was similar across groups and was not altered by scaling. Global LV functional data are presented in Table 6.3. LVSV, EF (%) and other systolic functional parameters were similar across all groups (6.3a). IVRT, E/A, and other diastolic functional parameters derived by standard 2D echocardiographic assessment were not different between groups (Table 6.3b). TDI indices of diastolic function were not statistically different (post-hocs $p < 0.05$) within and between groups.

6.3.4 2D Echocardiography: Right ventricle

In Table 6.4 RV structural data (absolute and scaled) were mostly similar between groups with the exception of a training effect on absolute RV mid cavity dimension (RVD2) which was higher ($p = 0.01$) in both athlete groups (WRT and CRT). The observed difference was abolished with allometric scaling. We should also note that, absolute and scaled RV free wall thickness were higher in the athletes (post-hocs $p = 0.01$) than CT but there was no significant difference between both athlete groups. Table 6.5 presents results of RV global and regional functional indices. RVFAC (%), TAPSE and tissue Doppler parameters were not statistically different (post-hocs $p<0.05$) within and between study cohorts.

6.3.5 *Speckle tracking echocardiography (STE)*

LV longitudinal and circumferential ε and SR data were not statistically different between all groups (Table 6.6). Similarly, LV peak apical/basal rotation and peak twist parameters did not demonstrate between-group differences. Global RV ε, SRS as well as segmental ε did not differ between groups (Table 6.7). The base-to-apex gradient for ε was not statistically different (post-hocs $p < 0.05$) between groups.

6.3.6 *Electrocardiography (ECG)*

A statistically significant ethnicity was noted for PR interval ($p = 0.04$) with a greater PR interval in WRT/WCT (Table 6.8). WRT had the highest 156 (16.2%) QTc with a significant interaction ($p=0.05$).

Table 6.2: LV structural parameters measured using 2D echocardiography in male resistance trained (RT) and sedentary control (CT) subjects. Data are mean ± SD (range).

Parameter	West Africans (WA)		Caucasians (CA)		2 Way ANOVA		
Sample size (n)	WRT (6)	WCT (24)	CRT (19)	CCT (17)	Ethnicity (WA vs CA)	Sport (RT vs CT)	Interaction
IVSWT (mm)	10 ± 1 (8 to 110	9 ± 1 (7 to 11)	9 ± 1 (7 to 11)	8 ± 1 (7 to 10)	0.99	0.47	0.32
IVSWT (mm/m$^{0.5}$)	6.5 ± 0.7 (5.6 to 7.5)	6.2 ± 0.9 (4.6 to 7.7)	5.7 ± 0.7 (4.5 to 7.4)	5.6 ± 0.5 (4.7 to 6.5)	0.01 WA > CA	0.36	0.87
LVIDd (mm)	54 ± 3 (49 to 58)	51 ± 3 (44 to 56)	53 ± 2 (50 to 57)	51 ± 2 (48 to 55)	0.09	0.01 WRT & CRT > WCT & CCT	0.07
LVIDd (mm/m$^{0.33}$)	41 ± 2 (39 to 43)	40 ± 3 (33 to 43)	41 ± 3 (37 to 44)	40 ± 2 (36 to 42)	0.83	0.11	0.48
PWT (mm)	9 ± 1 (8 to 9)	9 ± 1 (7 to 11)	9 ± 1 (8 to 10)	9 ± 1 (7 to 11)	0.59	0.41	0.93
PWT (mm/m$^{0.5}$)	5.8 ± 0.3 (5.4 to 6.1)	6 ± 1 (4.3 to 8.3)	5.9 ± 0.6 (4.7 to 7.3)	5.9 ± 0.6 (5.0 to 7.1)	0.92	0.52	0.66
LV Mass (g)	190 ± 32 (158 to 254)	178 ± 27 (134 to 240)	186 ± 41 (152 to 252)	176 ± 31 (137 to 246)	0.07	0.03 WRT & CRT > WCT & CCT	0.15
LV Mass (g/m$^{2.7}$)	25 ± 2 (17 to 23)	24 ± 8 (11 to 32)	25 ± 9 (15 to 42)	26 ± 7 (13 to 38)	0.08	0.54	0.07
LVEDV (mL)	131 ± 14 (115 to 152)	115 ± 18 (91 to 151)	120 ± 17 (100 to 158)	116 ± 18 (92 to 152)	0.01 WRT > CRT	0.01 WRT & CRT > WCT & CCT	0.01
LVEDV (mL/m$^{1.5}$)	42 ± 5 (36 to 52)	39 ± 10 (23 to 62)	36 ± 7 (26 to 47)	38 ± 6 (30 to 52)	0.92	0.29	0.46
LV Length (mm)	84 ± 7 (75 to 96)	87 ± 7 (70 to 97)	86 ± 10 (76 to 104)	86 ± 9 (74 to 98)	0.69	0.69	0.55
LV Length (mm/m$^{0.5}$)	56 ± 5 (52 to 65)	60 ± 6 (50 to 73)	58 ± 7 (47 to 74)	59 ± 9 (52 to 65)	0.79	0.07	0.57

LV, left ventricle; IVSWT, interventricular septal wall thickness; LVIDd, LV internal diameter at end diastole; PWT, posterior wall thickness; LVEDV, LV end diastolic volume. Post-hoc 2 way ANOVA P < 0.05.

Table 6.3a: LV functional parameters measured using 2D echocardiography in male resistance trained (RT) and sedentary control (CT) subjects. Data are mean ± SD (range).

Parameter	West Africans (WA)		Caucasians (CA)		2 Way ANOVA		
Sample size (n)	WRT (6)	WCT (24)	CRT (19)	CCT (17)	Ethnicity (WA vs CA)	Sport (RT vs CT)	Interaction
Systolic function							
LVSV (mL)	66 ± 11 (54 to 94)	65 ± 16 (38 to 109)	64 ± 19 (37 to 106)	63 ± 17 (37 to 93)	0.96	0.89	0.65
LVSV (mL/m^2)	30 ± 6 (22 to 38)	31 ± 8 (20 to 40)	29 ± 8 (15 to 42)	30 ± 7 (20 to 41)	0.78	0.25	0.6
EF (%)	58 ± 3 (52 to 62)	57 ± 2 (51 to 62)	57 ± 4 (51 to 63)	58 ± 3 (54 to 63)	0.58	0.93	0.09
LV VTI (cm)	22 ± 2 (20 to 25)	20 ± 4 (11 to 26)	20 ± 2 (17 to 26)	21 ± 3 (17 to 25)	0.84	0.43	0.23
Sep S' (cm/s)	9 ± 1 (8 to 11)	10 ± 2 (7 to 12)	10 ± 2 (7 to 12)	10 ± 2 (7 to 13)	0.37	0.59	0.21
Sep S'/LV length	1.1 ± 0.2 (0.8 to 1.4)	1.1 ± 0.2 (0.8 to 1.4)	1.1 ± 0.2 (0.9 to 1.6)	1.1 ± 0.2 (0.9 to 1.5)	0.26	0.25	0.13
Lat S' (cm/s)	11 ± 1 (8 to 13)	11 ± 2 (7 to 14)	13 ± 2 (7 to 14)	12 ± 2 (7 to 14)	0.42	0.67	0.26
Lat S' cm/LV length	1.1 ± 0.2 (0.8 to 1.6)	1.1 ± 0.2 (0.8 to 1.7)	1.1 ± 0.2 (0.9 to 1.8)	1.1 ± 0.2 (0.9 to 1.7)	0.21	0.23	0.19

SV, stroke volume; EF, ejection fraction; LV, left ventricle; LV VTI, LV velocity time integral; Sep, septal; Lat, lateral; S’, systolic tissue velocity; IVRT, Isovolemic relaxation time; E, early ventricular filling; A, late atrial contraction; Edecl, E deceleration time; E’, early diastolic tissue velocity; A’, late atrial diastolic tissue velocity. P values from 2-way ANOVA with main effects for ethnicity and sport.

Table 6.3b: LV functional parameters measured using 2D echocardiography in male resistance trained (RT) and sedentary control (CT) subjects. Data are mean ± SD (range).

Parameter	West Africans (WA)		Caucasians (CA)		2 Way ANOVA		
Sample size (n)	WRT (6)	WCT (24)	CRT (19)	CCT (17)	Ethnicity (WA vs CA)	Sport (RT vs CT)	Interaction
Diastolic function							
IVRT (ms)	69 ± 11 (65 to 74)	76 ± 11 (58 to 99)	74 ± 10 (53 to 88)	77 ± 11 (53 to 95)	0.34	0.08	0.56
E (m/s)	0.9 ± 0.2 (0.6 to 1.2)	0.8 ± 0.1 (0.5 to 1.0)	0.7 ± 0.2 (0.5 to 1.1)	0.8 ± 0.2 (0.5 to 1.0)	0.14	0.45	0.08
A (m/s)	0.5 ± 0.2 (0.3 to 0.8)	0.5 ± 0.1 (0.3 to 0.7)	0.5 ± 0.1 (0.3 to 0.7)	0.5 ± 0.1 (0.3 to 0.8)	0.48	0.6	0.43
E/A	1.8 ± 0.5 (1.4 to 2.8)	1.6 ± 0.3 (1.1 to 2.3)	1.5 ± 0.1 (0.9 to 2.7)	1.7 ± 0.4 (1.2 to 2.5)	0.31	0.46	0.78
Edecl(ms)	141 ± 9 (128 to 156)	142 ± 14 (108 to 161)	141 ± 24 (102 to 170)	141 ± 21 (99 to 160)	0.86	0.92	0.94
Sep E' (cm/s)	12 ± 2 (9 to 15)	13 ± 2 (7 to 18)	12 ± 3 (6 to 16)	13 ± 2 (9 to 17)	0.55	0.36	0.65
Sep A' (cm/s)	8 ± 2 (6 to 11)	8 ± 1 (6 to 11)	9 ± 2 (4 to 12)	9 ± 2 (6 to 11)	0.33	0.59	0.78
Lat E' (cm/s)	18 ± 3 (15 to 23)	16 ± 3 (9 to 24)	16 ± 4 (8 to 24)	17 ± 3 (13 to 23)	0.52	0.41	0.16
Lat A' (cm/s)	8 ± 2 (5 to 11)	8 ± 2 (5 to 13)	8 ± 3 (4 to 13)	8 ± 2 (6 to 14)	0.65	0.58	0.72
Sep E'/LV length	1.4 ± 0.3 (1.0 to 1.9)	1.5 ± 0.3 (0.8 to 2.3)	1.3 ± 0.6 (0.1 to 2.1)	1.5 ± 0.3 (1.1 to 2.1)	0.64	0.53	0.88
Sep A'/LV length	1.0 ± 0.3 (0.6 to 1.3)	0.9 ± 0.2 (0.6 to 1.3)	1.0 ± 0.3 (0.4 to 1.7)	1.0 ± 0.2 (0.7 to 1.3)	0.37	0.84	0.74
Lat E'/LV length)	2.2 ± 0.4 (1.8 to 2.9)	1.8 ± 0.3 (1.1 to 2.6)	1.7 ± 0.8 (0.1 to 1.4)	2.0 ± 0.3 (1.5 to 2.5)	0.41	0.19	0.08
Lat A'/LV length)	0.9 ± 0.2 (0.6 to 1.3)	1.0 ± 0.2 (0.5 to 1.4)	0.9 ± 0.4 (0.1 to 1.4)	1.0 ± 0.2 (0.7 to 1.5)	0.59	0.69	0.57
E/E'	5.1 ± 1.1 (3.4 to 6.2)	5.4 ± 1.3 (3.4 to 7.8)	5.1 ± 1.2 (3.5 to 7.2)	5.3 ± 1.1 (3.4 to 7.0)	0.9	0.46	0.94

SV, stroke volume; EF, ejection fraction; LV, left ventricle; LV VTI, LV velocity time integral; Sep, septal; Lat, lateral; S', systolic tissue velocity; IVRT, Isovolemic relaxation time; E, early ventricular filling; A, late atrial contraction; Edecl, E deceleration time; E', early diastolic tissue velocity; A', late atrial diastolic tissue velocity. P values from 2-way ANOVA with main effects for ethnicity and sport.

Table 6.4: RV structural parameters measured using 2D echocardiography in male resistance trained (RT) and sedentary control (CT) subjects. Data are mean ± SD (range).

Parameter Sample size (n)	West Africans (WA)		Caucasians (CA)		2 Way ANOVA		
Parameter	WRT (6)	WCT (24)	CRT (19)	CCT (17)	Ethnicity (WA vs CA)	Sport (RT vs CT)	Interaction
PLAX RVOT (mm)	29 ± 4 (24 to 33)	30 ± 3 (24 to 35)	29 ± 4 (22 to 35)	30 ± 4 (23 to 38)	0.55	0.18	0.92
PLAX RVOT $(mm/[m^2]^{0.5})$	20 ± 3 (15 to 23)	21 ± 2 (16 to 24)	20 ± 3 (16 to 24)	21 ± 2 (17 to 25)	0.62	0.12	0.85
RVOT1 (mm)	31 ± 4 (27 to 38)	30 ± 4 (22 to 35)	31 ± 4 (22 to 42)	34 ± 4 (23 to 42)	0.07	0.59	0.10
RVOT 1 $(mm/[m^2]^{0.5})$	21 ± 3 (17 to 25)	21 ± 3 (15 to 25)	21 ± 3 (16 to 26)	23 ± 3 (17 to 27)	0.06	0.11	0.75
RVOT2 (mm)	27 ± 2 (25 to 30)	27 ± 3 (21 to 35)	26 ± 3 (20 to 32)	27 ± 4 (20 to 34)	0.44	0.12	0.19
RVOT2 $(mm/[m^2]^{0.5})$	18 ± 1 (17 to 20)	18 ± 2 (16 to 24)	18 ± 2 (13 to 20)	19 ± 2 (15 to 24)	0.43	0.10	0.18
RVD1 (mm)	43 ± 5 (34 to 49)	40 ± 5 (30 to 49)	39 ± 5 (32 to 49)	39 ± 4 (31 to 44)	0.08	0.35	0.29
RVD1 $(mm/[m^2]^{0.5})$	29 ± 3 24 to 32)	28 ± 3 (21 to 33)	27 ± 4 (24 to 38)	27 ± 3 (22 to 34)	0.10	0.91	0.34
RVD2 (mm)	32 ± 5 (25 to 37)	28 ± 4 (19 to 34)	30 ± 4 (24 to 38)	29 ± 3 (20 to 32)	0.41	0.01 RT > CT	0.19
RVD2 $(mm/[m^2]^{0.5})$	21 ± 3 (17 to 25)	19 ± 3 (13 to 25)	20 ± 3 (16 to 27)	20 ± 2 (15 to 23)	0.53	0.18	0.33

RVD3 (mm)	84 ± 8 (77 to 98)	82 ± 6 (73 to 98)	84 ± 9 (69 to 102)	81 ± 10 (64 to 98)	0.88	0.45	0.78
RVD3 (mm/[m^2]$^{0.5}$)	56 ± 5 (51 to 65)	57 ± 5 (48 to 67)	56 ± 6 (44 to 71)	56 ± 7 (46 to 69)	0.85	0.65	0.77
RV diastolic area (cm^2)	25 ± 6 (15 to 32)	23 ± 4 (17 to 33)	23 ± 5 (17 to 36)	22 ± 4 (15 to 29)	0.23	0.16	0.71
RV diastolic area (cm^2/m^2)	11 ± 2 (7 to 14)	11 ± 2 (8 to 15)	10 ± 3 (7 to 16)	10 ± 2 (7 to 14)	0.28	0.98	0.74
RV Systolic area (cm^2)	13 ± 3 (8 to 16)	13 ± 3 (9 to 20)	12 ± 3 (8 to 19)	11 ± 2 (7 to 18)	0.08	0.15	0.47
RV Systolic area (cm^2/m^2)	6 ± 1.1 (4 to 7)	6 ± 1.3 (4 to 9)	6 ± 2 (3 to 9)	5 ± 1.5 (3 to 9)	0.10	0.78	0.45
RV wall thickness (mm)	4 ± 0.5 (3 to 4)	3.5 ± 0.5 (3 to 5)	4 ± 0.5 (3 to 5)	3.1 ± 0.5 (2 to 4)	0.98	0.01 RT > CT	0.02 WRT > WCT & CCT WCT> CCT, WRT=CRT.
RV wall thickness (mm/[m^2]$^{0.5}$)	2.4 ± 0.3 (1.9 to 2.7)	2.4 ± 0.4 (1.8 to 3.1)	2.7 ± 0.3 (1.8 to 3.4)	2.2 ± 0.3 (1.5 to 2.9)	0.99	0.01 RT > CT	0.02 RT > CT, CRT > CCT, WRT = WCT.

RV, Right ventricle; RVOT PLAX, RV outflow tract dimension parasternal long axis; RVOT1, basal parasternal short axis; RVOT2, distal parasternal short axis; RVD1, basal dimension; RVD2, mid cavity dimension and RVD3, longitudinal dimension. P values from 2-way ANOVA with main effects for ethnicity and sport. Post-hoc signficant was P < 0.05.

Table 6.5: RV functional parameters measured using 2D echocardiography in male resistance trained (RT) and sedentary control (CT) subjects. Data are mean ± SD (range).

Parameter	West Africans (WA)		Caucasians (CA)		2 Way ANOVA		
Sample size (n)	WRT (6)	WCT (24)	CRT (19)	CCT (17)	Ethnicity (WA vs CA)	Sport (RT vs CT)	Interaction
RVFAC (%)	47 ± 3 (42 to 50)	44 ± 6 (35 to 58)	46 ± 6 (37 to 56)	51 ± 8 (36 to 62)	0.16	0.38	0.64
TAPSE	23 ± 2 (21 to 26)	21 ± 3 (16 to 26)	21 ± 4 (14 to 27)	23 ± 3 (17 to 27)	0.99	0.77	0.08
RVOT VTI	18 ± 2 (16 to 22)	16 ± 3 (12 to 23)	18 ± 2 (13 to 23)	17 ± 3 (10 to 22	0.61	0.07	0.82
RVSV (mL)	101 ± 14 (86 to 119)	92 ± 21 (64 to 122)	84 ± 27 (48 to 132)	99 ± 33 (42 to 129)	0.65	0.85	0.08
RVSV (mL/[m2]1.5)	30 ± 6 (23 to 36)	31 ± 14 (20 to 68)	25 ± 7 (14 to 52)	32 ± 11 (16 to 55)	0.57	0.19	0.17
RVS' cm/s	12 ± 3 (6 to 14)	15 ± 2 (12 to 17)	14 ± 3 (10 to 19)	14 ± 2 (9 to 17)	0.08	0.08	0.07
RVS' ([cm/s]/cm)	0.4 ± 0.1 (0.2 to 0.6)	0.5 ± 0.2 (0.2 to 0.8)	0.8 ± 0.4 (0.3 to 1.1)	0.5 ± 0.2 (0.2 to 0.9)	0.12	0.99	0.06
RVE' (cm/s)	11 ± 3 (7 to 14)	12 ± 2 (8 to 16)	14 ± 4 (9 to 20)	13 ± 3 (8 to 18)	0.08	0.54	0.39
RVE' ([cm/s]/cm)	1.0 ± 0.6 (0.6 to 2.1)	0.8 ± 0.2 (0.6 to 1.1)	1.0 ± 0.3 (0.4 to 1.4)	1.0 ± 0.2 (0.6 to 1.3)	0.56	0.19	0.36
RVA' cm/s	12 ± 4 (8 to 18)	11 ± 3 (8 to 18)	11 ± 3 (7 to 18	11 ± 2 (6 to 14)	0.45	0.64	0.39
RVA' ([cm/s]/cm)	0.4 ± 0.2 (0.2 to 0.7)	0.4 ± 0.2 (0.1 to 1.0)	0.6 ± 0.3 (0.2 to 0.8)	0.4 ± 0.2 (0.1 to 0.8)	0.96	0.58	0.94

RV FAC, RV fractional area change; TAPSE, tricuspid annular plane systolic excursion; RVSV, RV stroke volume; RVS', RV lateral wall peak systolic tissue velocity; RVE', RV lateral wall peak early diastolic tissue velocity; RVA', RV lateral wall peak late diastolic tissue velocity, RVS', RV E' and RVA' were scaled to RV length. P values from 2-way ANOVA with main effects for ethnicity and sport.

Table 6.6: Descriptive cohort data for two-dimensional STE derived LV strain (ε) and SR parameters in male resistance trained (RT) and sedentary control (CT) subjects. Data are mean ± SD (range), 2-way ANOVA with Post-hoc analysis of main effects for ethnicity and sport significant at P < 0.05.

Parameter	West Africans (WA)		Caucasians (CA)		2 Way ANOVA		
Sample size (n)	WRT (6)	WCT (24)	CRT (19)	CCT (17)	Ethnicity (WA vs CA)	Sport (RT vs CT)	Interaction
Peak ε (%)	-17.6 ±1.2 (-20.0 to -16.7)	-17.2 ± 2.1 (-21.9 to -13.9)	-16.8 ± 1.7 (-20 to -12)	-17.7 ± 2.1 (-21.9 to -14.7)	0.24	0.36	0.15
Peak SRS (S^{-1})	- 1.0 ± 0.1 (-1.1 to -0.7)	-0.9 ± 0.2 (-0.2 to -0.7)	-0.9 ± 0.1 (-1.1 to -0.7)	-0.9 ± 0.1 (-1.2 to -0.7)	0.18	0.16	0.48
Peak SRE (S^{-1})	1.5 ± 0.2 (1.2 to 1.8)	1.4 ± 0.3 (0.9 to 1.9)	1.14 ± 0.24 (0.8: 1.6)	1.29 ± 0.19 (0.9 to 1.7)	0.46	0.32	0.18
Peak SRA (S^{-1})	0.7 ± 0.1 (0.5 to 1.0)	0.7 ± 0.1 (0.5 to 1.1)	0.7 ± 0.2 (0.4: 0.8)	0.7 ± 0.1 (0.5 to 0.8)	0.22	0.48	0.22
Peak ε (%)	-17.2 ± 3.1 (-23.2 to -15.1)	- 16.8 ± 2.8 (-23.2 to -13.7)	-15.5 ± 3.3 (-21.4 to -9.8)	-15.8 ± 2.9 (-20.8 to -11.6)	0.18	0.12	0.42
Peak SRS (S^{-1})	-1.2 ± 0.3 (-1.7 to -0.9)	-1.2 ± 0.3 (-1.7 to -0.9)	-0.90 ± 0.19 (-1.3 to -0.7)	-1.1 ± 0.2 (-1.5 to -0.8)	0.42	0.28	0.2
Peak SRE (S^{-1})	1.8 ± 0.5 (1.0 to 2.4)	1.5 ± 0.5 (0.8 to 2.6)	1.2 ± 0.4 (0.8 to 2.0)	1.3 ± 0.4 (0.9 to 2.1)	0.12	0.54	0.44
Peak SRA (S^{-1})	0.5 ± 0.1 (0.4 to 0.8)	0.6 ± 0.2 (0.3 to 1.0)	0.5 ± 0.2 (0.2 to 0.7)	0.4 ± 0.1 (0.2 to 0.9)	0.68	0.44	0.28
Peak apical rotation (o)	8.8 ± 2.1 (7.4 to 9.3)	10.0 ± 3.1 (4.3 to 14)	8.2 ± 3.2 (3.8 to 14.5)	10.8 ± 3.5 (3.1 to 15.1)	0.14	0.92	0.66
Peak basal rotation (^{o})	-3.8 1.3 (-6.2 to -1.5)	-5.3 1.9 (-7.6 to -2.0)	-4.7 ± 2.2 (-9.1 to -2.1)	-3.8 ± 2.1 (7.1 to -2.1)	0.08	0.48	0.14
Peak twist (^{o})	13.8 ± 2 (8.8 to 18.2)	14.2 ± 3.2 (8.9 to 21.4)	12.5 ± 4.8 (5.9 to 22.1)	14.50 ± 3.9 (9.8 to 21.5)	0.22	0.64	0.32

ε-strain, SRS -strain rates in systole, SRE- strain rate in early diastole, SRA- strain rate in late diastole.

Table 6.7: Descriptive cohort data for two-dimensional STE derived RV strain (ε) and SR parameters in male resistance trained (RT) and sedentary control (CT) subjects. Data are mean ± SD (range).

Parameter	West Africans (WA)		Caucasians (CA)		2 Way ANOVA		
Sample size (n)	WRT (6)	WCT (24)	CRT (19)	CCT (17)	Ethnicity (WA vs CA)	Sport (RT vs CT)	Interaction
Peak global ε (%)	-28.8 ±2.1 (-33.2 to -25.1)	-27.4 ± 3.2 (-33.8 to -22.4)	-27.4 ± 4.9 (-36.6 to -21.8)	-28.4 ± 2.7 (-37.0 to -25.0)	0.46	0.48	0.25
Peak basal ε (%)	-27.5 ± 1.7 (-30.6 to -24.8)	-25.7 ±3.2 (-32.7 to -20.6)	-26.5 ± 3.2 (-32.6 to -20.7)	-28.2 ± 3.0 (-34.8 to -24.5)	0.19	0.09	0.52
Peak mid wall ε (%)	-28.1 ±1.7 (-31.0 to -24.0)	-27.6 ± 3.8 (-35.4 to -23.3)	-27.5 ±2.5 (-33.6 to -23.6)	-28.4 ± 4.6 (-37.9 to -22.0)	0.56	0.29	0.22
Peak apical wall ε (%)	-31.3 ± 2 (-34.6 to -26.4)	-30.9 ±3.4 (-37.7 to -25.5)	-31.3 ± 3.3 (-36.6 to -26.2)	-32.6 ± 3.0 (-38.8 to -23.5)	0.09	0.51	0.64
Base to apex ε gradient (%)	-4.3 ±2.9 (-9 to - 2.4)	-5.3 ± 2.4 (-9.3 to -1.8)	-4.7 ± 2.5 [-8.3 to -1.0)	-4.4 ±2.9 (-9.1 to -1.9)	0.98	0.64	0.58
Peak global SRS (s^{-1})	-1.5 ±0.2 [-1.8 to -1.1)	-1.4 ± 0.2 (-1.7 to -1.0)	-1.5 ± 0.3 (-2.1 to -1.0)	-1.5 ± 0.2 (-2.0 to -1.2)	0.09	0.92	0.96
Peak global SRE (s^{-1})	1.6 ±0.4 (0.9 to 2.3)	1.6 ± 0.5 (0.2 to 2.3)	1.8 ± 0.5 (1.2 to 2.8)	1.9 ± 0.5 (1.2 to 2.8)	0.15	0.43	0.75
Peak global SRA (s^{-1})	0.9 ± 0.2 (0.7 to 1.4)	1.1 ± 0.2 (0.8 to 1.9)	1.1 ± 0.3 (0.5 to 1.6)	1.0 ± 0.3 (0.5 to 1.4)	0.82	0.84	0.44

WA, West African; WRT, WA resistance trained athletes; WCT, WA control subjects; CA, Caucasians; CRT, Caucasian resistance trained athletes; CCT, Caucasian control subjects; ε, strain; SRS, strain rates in systole; SRE, strain rate in early diastole and SRA, strain rate in late diastole. 2-way ANOVA with Post-hoc analysis of main effects for ethnicity and sport significant at P < 0.05.

Table 6.8: Descriptive cohort data for 12 lead ECG in male resistance trained (RT) and sedentary control (CT) subjects. Data are mean ± SD (range), 2 way ANOVA p-values < 0.05.

Parameter	West Africans (WA)		Caucasians (CA)		2 Way Anova		
Sample size (n)	WRT (6)	WCT (24)	CRT (19)	CCT (17)	Ethnicity (WA vs CA)	Sport (RT vs CT)	Interaction
HR	60 ± 9 (47 to 74)	63 ± 8 (48 to 84)	78 ± 20 (46 to 108)	63 ± 10 (9 to 84)	0.07	0.33	0.07
P-Wave	109 ± 4 (102 to 112)	110 ± 9 (90 to 126)	103 ± 22 (83 to 183)	103 ± 6 (4 to 114)	0.12	0.96	0.71
PR	168 ± 13 (150 to 184)	169 ± 23 (119 to 221)	157 ± 20 (112 to 205)	150 ± 17 (13 to 118)	0.04	0.32	0.26 (WRT/WCT) <(CRT/CCT)
QRS	93 ± 7 (82 to 102)	93 ± 9 (71 to 109)	93 ± 11 (69 to 113)	95 ± 9 (7 to 118)	0.55	0.72	0.71
QT	405 ± 28 (366 to 450)	363 ± 24 (326 to 404)	356 ± 36 (302 to 413)	373 ± 25 (28 to 415)	0.03	0.07	0.01 (WRT > WCT), (CRT < CCT), (WRT > CRT)
QTc	407 ± 13 (393 to 4224)	374 ± 17 (330 to 400)	399 ± 26 (359 to 467)	381 ± 10 (13 to 402)	0.43	0.01	0.05 (WRT > WCT), (CRT > CCT),(WRT = CRT)
P-axis	41 ± 26 (10 to 73)	50 ± 19 (-6 to 78)	54 ± 23 (-6 to 76)	51 ± 15 (10 to 76)	0.32	0.47	0.36
QRS-axis	51 ± 11 (35 to 63)	45 ± 30 (-35 to 83)	58 ± 22 (25 to 92)	58 ± 36 (-12 to 111)	0.14	0.41	0.78
T-axis	28 ± 22 (2 to 60)	36 ± 20 (2to 71)	33 ± 20 (-1 to 72)	39 ± 16 (2 ± 69)	0.41	0.21	0.83

HR-Heart rate, RT-Resistance trained athletes, CT-Sedentary control subjects, WRT-West African RT, WCT-West African CT, CRT-Caucasian RT, CCT-Caucasian CT, P wave – Atrial depolarization, QRS-Ventricular depolarization, T wave- Ventricular repolarization. 2-way ANOVA with main effects for ethnicity and sport, Post-hoc analysis significant at P < 0.05.

6.4 Discussion

The key outcomes of this exploratory study were; (1) there were few athlete vs. control or WA vs. Caucasian differences in LV structure, (2) some differences were mediated by the impact of body size; (3) RV structural parameters were largely similar across all groups, (3) Global LV and RV function, TDI data and longitudinal and segmental strain and strain rates were comparable within and between groups, and (4) athletes of WA ethnicity demonstrated longer PR and QT intervals than Caucasians but were well within normal Group 1 changes of the 'Seattle' ECG criteria.

6.4.1 *The impact of resistance training on athlete's heart phenotype: Left Ventricle*

Recent evidence from individual studies, meta-analysis and studies included in previous chapters supports the existence of an athletic heart phenotype in endurance trained athletes but casts doubt over the nature of any cardiac adaptation in RT (Pelliccia et al. 1991, Haykowsky et al. 2000, Utomi et al. 2013, Utomi et al. 2014a). The current study supports recent data in Caucasians and extends this to WA RT athletes, albeit in a small but very elite cohort of Olympians. Similar to reports by Basavarajaiah et al 2008, WRT/CRT demonstrated a slightly higher absolute LV mass (post-hoc $p = 0.03$) than WCT/CCT, however, this difference was removed after appropriate body size scaling of LV mass. There was no evidence of concentric LV hypertrophy in any RT athlete.

There is empirical evidence to suggest that the lack of concentric cardiac adaptation in RT could be due to limited exposure to an increased haemodynamic afterload during resistance exercise training (George et al. 2011) and the potential lack of any afterload stimulus due to the fact that wall stress is not elevated during lifting when a brief phase 1 Valsalva manoeuvre is performed (Haykowsky et al. 2000). This conceptual idea would also apply to WA RT athletes undergoing similar training regimes although it is unclear if there is any substantive ethnic difference in acute haemodynamic response to resistance exercise.

As was noted with the LV mass data scaling of LV structural data, in some cases, altered the interpretation of specific between group comparisons. Though absolute septal wall thickness was similar across all cohorts, scaling uncovered a higher IVSWT (post-hoc $p = 0.01$) in WRT. Conversely, higher cavity dimension ($p = 0.01$) and LV mass (post-hoc $p = 0.03$) were removed after scaling for differences in BSA. The importance of taking individual body size to account in quantitative cardiac assessment has been demonstrated in a number of empirical studies (George et al. 1999, Batterham et al. 1999), and the current data supports this.

6.4.2 ***The impact of resistance training on athlete's heart phenotype: Right ventricle***

Few studies have examined the impact of RT and ethnicity on RV structure (Pagourelias et al. 2013, Utomi et al. 2013). Similar to previous reports by Baggish et al (2008) and Pagourelias et al (2013), RVD2 was higher in athlete groups ($p = 0.01$), but other than that, few between group differences were apparent. RV wall thickness and cavity dimension did not demonstrate a consistent hypertrophic change in comparison to the control subjects (Baggish et al. 2008, Pagourelias et al. 2013).

It is likely that haemodynamic theories used to explain the lack of adaptation in the LV of RT athletes is a potential reason for the general lack of RV remodelling and again this can now be extended to WA RT athletes. The proposed theory of disproportionate haemodynamic overload on the RV during exercise (LaGerche et al. 2011) is not clear with respect to RT where there might not be any significant and sustained increase in pulmonary artery systolic pressure that could initiate structural adaptation to normalise wall stress (Grossman et al. 1975).

6.4.3 *The impact of resistance training on left and right ventricular function*

Both LV and RV function were largely similar between all groups. This supports data from the three previous studies in this thesis in Caucasian RT athletes and extends this to WA RT athletes. Given the absence of any regional wall motion abnormality as well as the fact that FAC was consistently > 40% in all subjects, none of the subjects met the revised ARVC criteria (Marcus et al. 2010). We did not observe any significant within and between group differences in systolic and/or diastolic TDI velocities, strain and strain rate values. This supports some previous data (Pagourelias et al. 2013) but contradicts studies by Baggish et al (2008) (Baggish et al.

2008). Whilst we observed a base to apex gradient in deformation, the trend was not different between all groups.

6.4.4 *The impact of ethnicity on the athelete's heart phenotype*

Previous studies have demonstrated that Black or African ethnicity is associated with greater prevalence of morphological and electrical cardiac alterations in response to exercise training than in white individuals (Mayet et al. 1994, Drazner et al. 2005, Basavarajaiah et al. 2008, Rawlins et al. 2010, Zaidi et al. 2013). This concept has rarely been specifically applied to RT athletes of different ethnicity. Whether RT exaggerates the degree of structural remodelling in WA similar to the exaggerated effects of hypertension in black patients (Mayet et al. 1994) is of key importance sports cardiology and CVS screening of BA to identify at risk individuals and ultimately to prevent sudden cardiac death (SCD).

In a study of 300 black and 300 white athletes, Basavarajaiah et al (2008) reported a greater mean wall thickness (11.3 ± 1.6mm vs 10.0 ± 1.5mm; $p<0.01$) and prevalence of LV hypertrophy ≥ 13mm (18% vs 4%; p 0.001) in the black athletes (Basavarajaiah et al. 2008). Similar outcomes have been demonstrated by others, although to a lesser extent (Rawlins et al. 2009, Papadakis et al. 2012, Sheikh et al. 2013). Our data does not support important role for WA ethnicity in mediating cardiac morphological adaptation in RT athletes.

Key differences in ECG have been reported in athletes of black ethnicity. T-wave changes on the ECG were reported in over 10% of blacks and recent studies have demonstrated a higher prevalence of marked repolarization changes and voltage criteria for left ventricular hypertrophy (LVH) when compared to Caucasian subjects (Xie et al. 1994, Papadakis et al. 2012, Chandra et al. 2012, Basavarajaiah et al. 2008). Magalski et al (2008) reported that ST elevation, consistent with early repolarization was 2.5 times more common in Blacks athletes than Caucasians athletes, and further identified black race as statistically significant predictor of distinctly abnormal ECGs [RR 1.82, 95% CI: 1.22 to 2.73, p = 0.01] (Magalski et al. 2008); [RR, 2.03, 95% CI: 1.56 to 2.64, p < 0.0001] (Magalski et al. 2011).

Further investigations (Holter monitoring and CMR) of abnormal ECG changes in BA subjects on a case-by-case basis have shown that these changes may be physiological adaptation to exercise rather than pathological, albeit more exaggerated in BA (Basavarajaiah et al. 2008, Chandra et al. 2012). The current study did not identify any significant T-wave inversion but this may reflect a small sample size. Fifty percent of BA, compared to less than 10% of Caucasian RT athletes, demonstrated early repolarization changes and isolated voltage criteria for LVH. Whilst it is thought that these are innocuous finding in BA, there is on-going controversies over the suggestion that racial predilection for BA to develop LVH in response to exercise is a combination of genetic (Barley et al. 1996, Mayet et al. 1994), endocrine and haemodynamic factors (Ekelund et al. 1990, Schmidt et al. 1993, Diet et al. 2001).

The definitive mechanisms remains unclear, and warrants further investigations. The current study did demonstrate higher PR interval (p = 0.04) and QT (p = 0.03) in BA and is similar to past work (Drezner et al. 2013c). A sports specific effect was also noted with higher QTc (p = 0.01) in both athlete groups. Similar to Wilson et al (2010), none of the subjects of this study demonstrated abnormal group 2 / uncommon ECG changes as defined in ESC and the Seattle Criteria (Drezner et al. 2013b).

6.5 Limitations and future research

This was an exploratory cross-sectional study in a very small but highly trained cohort of male WA and Caucasian RT athletes. Further work should expand the participant base; 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 is that ECG and Echocardiographic post processing, though performed by experienced research scientists, were not blinded to participant identity, therefore the potential for bias exists.

6.6 Implications

The results of this exploratory study provides relevant information on the ethnic differences in the upper limits of human cardiac adaptation to training and also provides foundations for the development of a pragmatic clinical algorithm for identifying the AH phenotype in BA. This knowledge will inform cardiac screening in the emerging population of BA to differentiate the electrical and morphological changes from cardiac pathologies like HCM, ARVC and Ion channelopathies.

6.7 Conclusions

This exploratory study observed no evidence of an exaggerated AH phenotype in WA RT athletes. LV and RV structural and functional parameters were largely similar across all groups including data derived from new echocardiographic techniques. Participants of Black ethnicity demonstrated longer PR and QTc intervals on ECG. These findings have important implications with regards to developing a wholly encompassing global screening algorithm to accommodate ethnic WA athletes.

CHAPTER 7

GENERAL DISCUSSION

7.1 Brief summary of findings

The following hypotheses were stated at the beginning of the thesis.

1) I hypothesize that training mode, imaging modality and body size influence the morphology and function of the male AH.
2) I hypothesize that LV structure and function will follow a dichotomous training specific adaptation.
3) I hypothesize that global RV adaptation to exercise will follow a dichotomous training specific adaptation.
4) I hypothesize that elite male West African resistance trained athletes will not present with a concentric AH pattern.

The following responses are made in reflection of the data collected.

1) This hypothesis was partially supported in that only endurance training had a significant impact upon cardiac structure and function in this meta-analysis. Resistance training did not result in a major impact upon cardiac structure and function. Imaging mode and body size significantly influence cardiac structural data in the large meta-analysis data set.
2) Within the cross-sectional study the impact of endurance training was more marked than that of resistance training which partially supported the hypothesis and confirmed the data trend reported from the meta-analysis. The addition of new imaging modalities provided extra descriptive insight

into the AH but were largely similar between all groups. Of note most individuals were still presenting with “normal” LV geometry questioning the broadly accepted view that endurance athletes develop an eccentric hypertrophy.

3) We partially accept the hypotheses as stated in that endurance training and body size did mediate RV structure and, to a lesser extent, function. Resistance training had no effect on RV structure and function.
4) We can largely accept the hypothesis as stated. In a small sample, pilot/exploratory study of West African resistance-trained athletes we did not observe any significant structural, functional or electrical features of the AH.

7.2 Overarching issues

Overall the results of this thesis provide a useful re-evaluation of concepts and models in the AH literature. The findings have expanded our understanding of the impact of training type, new imaging technologies and the influence of body size upon cardiac structures. These images have “resonated” across all the studies, validating the assertion that data interpretation should carefully consider all of these issues in scientific research and clinical decision making.

The novel findings of this thesis; the predominance of a normal geometry in male athletes; the lack of concentric pattern of LV hypertrophy in resistance athletes; the limited expression of the AH in the right ventricle; and the importance of appropriate scaling are all worthy of an overarching discussion as these outcomes have significant clinical implications for the sports cardiologist and should inform cardiac screening of athletes to identify those at risk of sudden cardiac death.

7.2.1 ***Lack of evidence of a distinctly divergent cardiac adaptation to different training stimuli***

Across the meta-analysis and first two cross-sectional studies we noted some morphological features of the male AH in both athlete groups and in both the LV and the RV. It is, however, important to state that a dichotomous training–specific pattern of cardiac adaptation did not fit with previous descriptions of the MH. Most notable was that concentric hypertrophy was not discerned in RT in any of the first data chapters in this thesis. The meta-analysis and cross-sectional findings when looked at together should, at the very least, prompt a re-evaluation of the long-held belief that different exercise training produces distinctly divergent cardiac adaptation as expounded in the MH.

The explanation for substantial difference in cardiac dimension between ET and RT is probably complex. The observed greater cardiac dimension in ET possibly reflects substantial hemodynamic burden (volume overload) engendered by a greater overall training volume (George et al., 2011). Conversely, the lack of a concentric pattern of hypertrophy in RT is likely related to the fact that RT may not acutely increase LV afterload and end systolic wall stress when resistance exercise is performed with a brief phase 1 Valsalva manoeuvre (Haykowsky et al., 2001).

The set-to-set repetitive pattern of resistance exercise activity also appears to negate any sustained increase in stroke volume that could remotely exert any substantial hemodynamic burden of volume overload to the LV (George et al., 2001). The lack of substantially increased LV wall thickness in male RT athletes actually can make cardiac screening somewhat easier. If concentric hypertrophy is seen in any athlete this may represent a "red flag" and prompt further evaluation of the athlete.

As a consequence of data in studies 1-3 in this thesis, the upper limits of chamber dimension and wall thickness are generally expressed in ET. Whilst we alluded to the lack of data on RT athletes in the meta-analysis, our cross-sectional studies clearly agree with the overall outcomes of the meta-analysis and consolidate our conclusions. Further care is required when utilising imaging tools to employ appropriately powered studies and choose validated novel techniques to fully describe the athletic heart phenotype.

An unexpected finding from the first cross-sectional study was the relative lack of eccentric hypertrophy in endurance-trained male athletes. The meta-analysis and the first cross-sectional study confirmed that endurance-trained athletes do present with larger LV chamber dimensions than controls and resistance-trained athletes that supports the MH and other previous work (Naylor et al., 2008, George et al., 2011). Despite this the degree of adaptation was, overall, quite small with the balance of wall and chamber adaptation still placing the majority of endurance-trained athletes in the "normal geometry" categorisation (Utomi et al., 2014). This would suggest that LV adaptation in endurance athletes is both highly individually variable and largely modest in nature. Again this has implications for screening programmes to the point where multiple athletes presenting outside the normal ranges in a small sample might be statistically rare.

It is important to note that the LV adaptation in ETT in the meta- analysis was not specifically mediated by age, performance times or training history. Based on the new findings of this study, it appears that the MH does not hold true for RT and only about a third of the time in ET. It might be that the MH does not manifest in the RV in the same way as just described in the LV. Whilst the RV of the ET presented with some structural characteristics of the AH this was limited to some, but not all, chamber dimensions. Again, the RT did not demonstrate any substantial RV adaptation and was not significantly different from control subjects. Again the potential explanation for this could easily be drawn from the hypothetical mechanisms that underpin LV adaptation and the lack of a meaningful haemodynamic stimulus on the RV during resistance exercise. In summary, the overarching opinion is that RT leads to very little cardiac adaptation in elite athletes and ET has an effect, largely on chamber dimensions, that is quite muted, compared to past literature and highly variable between individuals. These finding, individually and in combination, provide a substantial challenge to the MH in male athletes.

7.2.2 *Scaling cardiac dimension to body size is crucial in the interprtation of cardiovascular measurements*

Scaling is an issue that permeates across all the studies in this thesis. As a backdrop we have observed (a) non-application of scaling models, (b) a rising popularity of linear scaling and (c) scant application of allometric scaling models in the AH literature over the 40 years' since Morganroth and colleagues seminal work (George et al., 1991, Naylor et al., 2008). Of note was the general lack of attention in previous meta-analyses (Fagard, 1996, Pluim et al., 2000, Whyte et al., 2004a).

The meta-analysis, explored the effect of between-study differences in BSA on LV mass, RV mass and LAD using a meta-regression approach that is different to any scaling application in original, cross-sectional studies (Batterham et al., 1999). Multiple meta-regression data clearly demonstrated that as BSA increased so did measures of cardiac structure. Consequently, it is likely that some portion of the between-group difference in LV mass, RV mass and LAD are explained by those with larger cardiac dimensions having larger body dimensions. Whether this reflects a higher total body mass or more specifically a higher lean body mass in the athlete groups is impossible to determine from the use of BSA alone in a meta-analysis.

The remaining studies in this thesis further support and re-enforce the assertion that appropriate scaling can alter data interpretation in LV and RV measurements, given that allometric scaling uncovered higher wall thickness index in ET compared to RT. In the final study we noted that allometric scaling of LV and RV structural data again, in some cases, altered the interpretation of within group comparisons. Though absolute LVSWT was similar across all cohorts, allometric scaling uncovered a higher IVSWT (post-hoc $p = 0.01$) in WRT. Conversely, higher cavity dimension (post-hoc $p = 0.01$) and LV mass (post-hoc $p = 0.03$) were removed after scaling for differences in BSA. This supports previous theoretical and empirical work form our laboratory (Batterham et al., 1999, George et al., 2011).

Clearly, it makes good sense to take account of body size differences in the interpretation of absolute cardiac dimension within athlete populations who via their training may see huge changes in body morphology. From our analysis, we argue that ratio scaling can be misleading and thus should always be supported within the sample being studied alongside an exploration of other potentially allometric approaches to determine which index is indeed size-independent.

7.2.3 *Black vs. white differences in the athlete's heart of resistance trained athletes: 'fact or fiction'*

A recent ethnicity study by Riding et al (2013) documented that Arabic athletes have significant, yet modest increases in cardiac dimensions compared with Arab controls; yet cardiac dimensions in all parameters were significantly smaller than Black African and Caucasian athletes (Riding et al., 2013). Although highly powered (n=600), the caveat here is that the participants of their study were not clearly partitioned into ET and RT, and as well, the black African athletes of their study were from nine African countries (Sudan, Somalia, Ghana, Nigeria, Chad, Ivory Coast, Senegal, Cameroon and Ethiopia). Clearly, there is a significant racial and demographic difference among people of African descent (Chandra et al., 2012). For instance, it may be erroneous to group the East Africans (Ethiopian, Somalia) with West Africans (Nigeria, Ivory coast, Ghana), considering the proven pedigree of endurance sporting excellence in the former.

Because of the key differences in ECG and the higher incidence of SCD in Black athletes when compared to Caucasian athletes (Xie et al., 1994), the rising presence of Black sportsmen in the international sporting arena has brought attention to the fairness of applying existing Cardiovascular (CVS) screening criteria on Black athletes. It is still contentious whether applying the existing CVS screening criteria (Weiner et al., 2011, Drezner et al., 2013a) is scientifically justifiable. Black athletes are known to exhibit a high prevalence of additional repolarization patterns that are usually categorised as abnormal in white athletes and often associated with cardiomyopathies and SCD (Corrado et al., 2010).

A great deal of evidence indicates that in the general population and in cohorts of patients with hypertension, Black individuals present with a greater magnitude of LVH compared to patients from other ethnic backgrounds (Chapman et al., 1999, Mayet et al., 1994). These observations advanced the probable hypothesis that exercise associated alterations in cardiac preload and afterload might exaggerate the degree and probably pattern of electrical and morphological adaptation in Black athletes (Drazner et al., 2005, Weiner et al., 2011, Harmon et al., 2011).

In a small sample pilot/exploratory study we observed some form of training mediated structural adaptation, given that the athlete groups had larger LV mass ($P = 0.03$) and RVD2 ($P = 0.01$) than control subjects. This observation was, however, quite limited across multiple LV and RV variables and was not distinct between ethnicities. Like previous studies in the thesis we did not observe higher values for cavity and wall dimensions in Black or Caucasian elite resistance-trained athletes. Drawing from our current understanding of hypothetical physiological mechanisms that underpin expression of a predominantly normal geometry in male athletes (Utomi et al., 2014) and the unexpected lack of concentric hypertrophy in healthy resistance trained athletes (Utomi et al., 2013) it would seem that resistance training in Black athletes presents no meaningful stimulus for cardiac adaptation.

ECG data from our study is also limited by sample size but data do follow previous athlete data patterns. For instance, 50% of BA in our study, compared to < 10% of Caucasian RT demonstrated early repolarization changes. These data are likely part of a normal "training-related" adaptation (Corrado et al., 2010). The Sports Cardiologist would normally align individual ECG indices to the recently revised recommendations on normal (Appendix 5) and abnormal (Appendix 6) 'Seattle' screening criteria (Drezner et al., 2013a).

Allied to this, there is a growing interest in the RV component of the AH, considering that the high prevalence of T-wave inversion in the right pre cordial lead (V1-V3) invariably raises suspicion of ARVC (Basso et al., 2009, Marcus et al., 2010, Drezner et al., 2013b). More studies are needed to investigate the 'facts and fictions' of the impact of Black ethnicity on the AH and shed more light on the prospects of applying the current diagnostic criteria derived from disparate cohorts to BA.

7.3 Technical considerations – Pros and Cons of new techniques

Although we are beginning to see the emergence of a substantive database using TDI in athletes, we report some rudimentary data in our meta-analysis, there are a number of important points with respect to the potential superiority of MST over TDI derived data and ε parameters in particular. Firstly, the accuracy of MST is dependent on image quality (Geyer et al., 2010) and depth (Sivesgaard et al., 2009). Secondly low fame rates creates an unstable speckle pattern and inaccurate peak ε values whereas high frame rates induce noise and reduce image resolution (Geyer et al., 2010).

Although MSTE is technically known to be angle independent, movement parallel to the ultrasound bean provides greater accuracy which explains the superior axial resolution (Grabskaya et al., 2010). This implies a more robust and reproducible dataset in the longitudinal plane, in comparison to radial and circumferential planes (Jenkins et al., 2006, Mor-Avi et al., 2011).

Because the dynamic LV moves longitudinally through a stationary ultrasound beam, as the base of the LV descends towards the apex in systole the ROI is at a slightly different level throughout the cardiac cycle. This can result in out of plane motion which is particularly important in radial and circumferential ε (Zhou et al., 2010, Mor-Avi et al., 2011). Another important limitation is its sensitivity to acoustic shadowing and reverberation which can result in underestimation of ε and SR.

7.4 Implications of the studies

Clinicians, athletes and patients are aware that the upper limits of human cardiac physiological adaptation to training is important for informing cardiac screening and the differential diagnosis of athlete’s heart from pathological adaptation. This thesis, from meta-analysis to prospective cross-sectional data, supports the contention that the upper limits of normal for chamber and wall dimensions (LV and RV) are generally expressed by ET.

It is also pertinent to note that these upper limits will be approached by very few elite athletes. Some evidence supports an “eccentric-type” hypertrophy of the LV and RV in ET but this occurred less frequently that hypothesised by the MH. RT’s whether Caucasians or West African Blacks did not present with concentric LV hypertrophy. It is also important to highlight that absolute wall thicknesses, LV end diastolic dimension and ECG changes although increased in athletes when compared to sedentary controls, do not fall within the pathological range seen in hypertrophic or dilated cardiomyopathy in either resistance or endurance trained athletes.

Although updated guidelines on the interpretation an athlete’s ECG make some broad allowance for African ethnicity (Wilson and Drezner, 2012, Drezner et al., 2013c), the criteria for further cardiac evaluation still rely on data from Caucasian athletes (Corrado et al., 2010). However, this is basically because data from homogenous cohorts of Black athletes are rare. To the best of our knowledge, this is the first attempt to gain new insight into the pattern of physiological cardiac adaptation in a homogenous group of Olympic grade West African resistance athletes.

Our data underscore the need for ethnicity specific criteria for differentiating normal cardiac adaptation to exercise from cardiac pathologies. This knowledge will further aid the diagnostic challenges associated with pre-participation screening of athletes against fatalities like sudden cardiac death.

7.5 Limitations and future research directions

A number of possible limitations apply to the present studies and where appropriate, specific future directions are directly related to the issues raised:

1) In study 1, data for RT is relatively scarce, further cross sectional studies are required to develop the data base for RT generally and with new imaging technology. It would also be pertinent to extend a similar ET / RT study specifically to investigate 'old' and 'new' imaging tools with respect to the RV and atria. Functional measures in high quality case-control series studies are largely limited to global echocardiographic parameters i.e. LV EF, SV and E/A. Future studies should use new technologies to investigate global and regional functional parameters.

2) 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 database to include females, older athletes as well as the development of a prospective cohort design. Significantly, our studies were limited to the LV and RV in adult male athletes. The assessment of the atrial compartments in various athlete groups requires substantial development and is particularly relevant to interpretation of clinical data.

3) The final study included in this thesis was an exploratory cross-sectional study in a very small but highly trained cohort of male RT athletes. It is very likely that increasing the sample size may have increased statistical power and ‘uncovered’ statistically significant changes in those variables that showed moderate alterations.

4) 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. Furthermore, although newer echocardiographic imaging tools are more useful and provide unique insight to the AH than traditional echocardiographic techniques, CMR is the gold standard with greater spatial resolution / sensitivity and has been applied to in various studies. Therefore, on-going studies in the field of AH where possible should utilise CMR to determine cardiac morphology. Where CMR is not available, newer echocardiographic technologies should be utilised in adequately powered cohorts.

A significant limitation of the current implementation of MSTE is inter vendor differences, driven by the fact that the analysis of MSTE derived ε and SR is performed offline on data stored on proprietary scan line format (Jenkins et al., 2006, Marwick, 2006, Mor-Avi et al., 2011). The lack of standardization and uniformity in respective vendor acquisition and measurement algorithms can result in conflicting strain reports, constituting a major constraint to establishing normative data (Marwick, 2010).

7.6 CONCLUSIONS

This thesis has provided new insight into the expression of the AH phenotype in male athletes. The conclusions with regard to the initial hypothesis, based upon the results of the four studies are as follows: 1) Only endurance training had a significant impact upon cardiac structure and function, 2) Resistance training did not result in a major impact upon cardiac structure and function, 3) Body size significantly influences cardiac structural data, 4) Of note most individuals were still presenting with "normal" LV geometry questioning the broadly accepted view that endurance athletes develop an eccentric hypertrophy. Finally, in a small sample, pilot/exploratory study of West African resistance-trained athletes we did not observe any significant structural, functional or electrical features of the AH. These findings have important implications in the cardiovascular screening of athletes to prevent sudden cardiac death.

CHAPTER 8

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REFERENCES

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CHAPTER 9

APPENDIX

APPENDIX 9.1 Traditional Echocardiographic development of the left ventricle

The early developments of echocardiography initially provided an A-mode technique, generating reflected signals of differing amplitude (depending on the degree of acoustic mismatch) from the region of interest on the hear (Otto and Pearlman, 2004). Further advancement converted the returning ultrasonic waves to dots of varying brightness relative to their amplitude which was aptly termed 'brightness-mode' (B-mode).

Development of Motion-mode (M-mode) echocardiography technique soon followed. M-mode demonstrates temporal movement of the cardiac structures by sweeping the B-dots of varying brightness across the screen (Sahn et al., 1978). A key strength of the M-mode technique is its temporal resolution of up to 0.2 ms and ability to operate at high pulse repetition rates such as 5000 s^{-1} with each pulse generating a scan line of echocardiographic information (Henry et al., 1980). But an M-mode (ice-pick) technique as a stand-alone is still limited due to lack 2D echocardiographic guidance. Therefore, with the M-mode cursor positioned through the base of the LV, M-mode technique allowed measurement of wall thickness and chamber dimension across the cardiac cycle (Sahn et al., 1974).

In 1977, Devereux and Reichek reported an anatomic validation of M-mode derived LV measurements by carrying out a systematic analysis of the relationship between the ante-mortem LV echogram and necropsy anatomic LV to calculate LV mass (g) (Devereux and Reichek, 1977). Further work led to the development of mathematical models utilizing single dimensions in diastole and systole to derive LV volumes based on geometric assumptions (Teichholz et al., 1976, Troy et al., 1972), but not without specific concerns on the assumptions (Lang et al., 2005). With the estimation of LV volume, it was possible to calculate ejection fraction (EF %) establishing a measure of global LV function. An expert consensus panel on standardisation of M-mode measurements recommended the 'leading edge to leading edge' method to ensure adequate reproducibility (Sahn et al., 1978).

Further developments utilised a number of beams to generate B-mode signals across an imaging sector. Typically, the B-mode technique has a temporal resolution of 20 ms. Depth and varying intensity of brightness were allocated which gave rise to the first 2D moving echocardiographic images and a build up to a systematic and synergistic approach to standard 2D and M-mode techniques (Henry et al., 1980). An added advantage of visualising the LV morphology was a more detailed and comprehensive assessment of LV structure and function from the acquisition of a 2D image using the bi-plane method of disc and the Simpson's rule (Wahr et al., 1983, Stork et al., 1991).

The accuracy of volumetric assessment over M-mode was demonstrated in vivo (Erbel et al., 1983) and in vitro (Helak and Reichek, 1981). At this point, standardization of echocardiography chamber quantification was a major concern due to emerging technology and study to study differences. Pragmatic recommendations (Sahn et al., 1978, Schiller et al., 1989) on how to measure such fundamental cardiac parameters became necessary to ensure consistency, clinical validity and reliability. In comparison with cardiac magnetic resonance (CMR), a systematic underestimation of absolute LV volume was demonstrated which was attributed to inferior spatial resolution and the bi-plane model (Gutiérrez-Chico et al., 2005, Mor-Avi et al., 2008b).

With continuous improvement in image quality as a result of the introduction of higher frequency transducers, harmonic imaging, fully digital machines, left sided contrast agents and other technologic advancements in the 80's, echo techniques improved dramatically. Echocardiography became the dominant cardiac imaging technique because of its portability, affordability and versatility (Gutiérrez-Chico et al., 2005, Lang et al., 2005). The American society of echocardiography (ASE), working together with the European Association of Echocardiography, a branch of the European Society of Cardiology (ESC), critically reviewed the literature and updated the recommendations for quantifying cardiac chambers using echocardiography (Lang et al., 2005).

Given the non-invasive, compact nature, comparative low cost, absence of any known side effects as well as the ability to allow dynamic imaging of the heart, echocardiogram imaging has received wide acceptance in the sports cardiology and exercise physiology communities to describe the AH. It is not surprising that the increasing prevalence of automated techniques for sophisticated analysis has been driven by researchers and manufacturers of ultrasound imaging equipment. A number of such technologies have emerged to address image quality, accurate quantitative / qualitative assessments and inter observer variability in measurements and interpretations of cardiac data. The following sections will focus on new echocardiographic technologies some of which have become part of clinical routine and have begun to be integrated into the AH research arena.

APPENDIX 9.2 Traditional Echocardiographic development of the right ventricle

Accurate assessment of the RV requires integration of multiple echocardiographic slices from different views, including parasternal short axis, short axis, RV inflow, apical 4-chamber and subcostal views (Lang et al., 2005). Earlier investigators proposed an approach of evaluating RV structure from an inflow and outflow dimension (Foale et al., 1986). Lai et al (2008) investigated the accuracy of the guidelines of the ASE for the two-dimensional (2D) quantitative assessment of right ventricular (RV) size and function against MRI-derived RV volumes in patients with congenital heart disease and RV volume overload and reported a weak correlation between 2D RV measurements by echocardiography and MRI-derived RV volumes (Group I: r = 0.15–0.54, Group II: r = 0.33–0.61, Group III: r = 0.32–0.85) in a normal RV group (Group I, n = 31), a repaired tetralogy of Fallot group (Group II, n = 33), and an unrepaired atrial septal defect and/or partially anomalous pulmonary venous connection group (Group III, n = 23) (Lai et al., 2008).

The ASE's guidelines and standard committee and the chamber quantification writing group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology proposed that qualitative and quantitative assessment of the RV can be accomplished from the apical 4 chamber view (4CH). However, care must be taken to obtain a true non-foreshortened 4CH view. For RV systolic assessment, the displacement of the tricuspid annulus should be observed. In systole, a tricuspid annular plane excursion (TAPSE) of 1.5 to 2.0 cm descent towards the apex was grouped as normal RV function (Alam et al., 2000, Samad et al., 2002).

Given the complex geometry of the RV, direct calculation of RV ejection fraction (EF %) and RV volumes remained a challenging feat. Nevertheless, RV fractional area change (FAC) measured in the apical 4CH view as an index of RV function and correlated with RV EF measured with CMR (r = 0.88). RV FAC is related to disease outcome (Maslow et al., 2002, Zornoff et al., 2002). Extending from the anterior superior aspect of the RV to the pulmonary artery and including the valvular system is the RV outflow tract (RVOT) (see figure x adapted from Lang et al., 2005). It is known that the most accurate pulmonary valve (Matsukubo et al., 1977) measurement of the RVOT is from the parasternal short axis view (PSAX), proximal to the pulmonary valve (Matsukubo et al., 1977, McKenna et al., 1988).

Furthermore, the examination of the inferior vena cava (IVC) from the subcostal view and with a long axis orientation of the transducer contributes to a comprehensive assessment of the RV. It allows an accurate assessment of the diameter of the IVC and the percent decrease in the diameter during expiration i.e. the collapsibility index which correlates with right atria (RA) pressure (Moreno et al., 1984). Additional assessment of RV function includes Tissue Doppler imaging (TDI) of tricuspid annular velocity (Nagueh et al., 1997, Sutherland et al., 1999). Despite these echocardiographic advancements, the assessment of the RV was not uniformly carried out and research output remained comparatively low partly due to a lack of familiarity with ultrasound techniques that can be used in imaging the RV, and a paucity of ultrasound studies providing normative data of right heart size and function (Lang et al., 2005, Rudski et al., 2010).

APPENDIX 9.3 Pulsed-Wave Doppler

The development of pulsed-wave Doppler (PWD) combined with 2D imaging allowed for evaluation of all 4 cardiac valves as well as cardiac shunts (Matsuo et al., 1977, Goldberg et al., 1982) and the ability to evaluate LV filling. Kitabatake and colleagues (1982) demonstrated early (E) and late (A) diastolic components and their ratio in healthy subjects, hypertension, hypertrophic cardiomyopathy (HCM) and old myocardial infarction patients, and reported that healthy individuals have higher early diastolic flow velocities when compared to cardiac pathologies (Kitabatake et al., 1982).

Subsequent guidelines highlighted specific patterns of LV diastolic dysfunction (Rakowski et al., 1996). Because PWD offers good inter and intra-observer variability with a high temporal resolution (Rakowski et al., 1996, Nagueh et al., 1997, Ruan et al., 2006), its usefulness as an indicator of global diastolic function is widely adopted (Nagueh et al., 2009). However, it is important to note that intrinsic properties of the LV – relaxation, compliance, and mitral valve (MV) function are encompassed within a global surrogate of LV filling defined by PWD, rather than specific elements of LV diastolic function (Nagueh et al., 2009, Mor-Avi et al., 2011). Fisman et al (1997), (2002) documented that athletes have significantly greater peak flow velocity when compared to controls whereas MacFarlane et al (1991) reported no defference between athletes and controls (MacFarlane et al., 1991, Fisman et al., 1997, Fisman et al., 1990, Ben-Ari et al., 1993).

Despite this PWD has been used widely in the athletic heart literature since the late 1980's to the point where it was included in the meta-analyses of Pluim et al (2000) and Whyte et al (2004). Further technological advancements to extend the assessment and segregation of global and regional myocardial properties, led to the development of Tissue Doppler Imaging (TDI).

Appendix 9.4 Table 9.1: Quality checklist for all studies [Adapted from STROBE Statement; (von Elm et al., 2008), PRISMA Statement; (Moher D et al., 2009)].

S/No.	Characteristic	No	Yes	Max score
1	Is a power calculation reported?		✓	1
2	Are the inclusion and exclusion criteria clearly stated?			1
	Test-Control			
3	Are activity levels for the control group reported?			1
4	Are the control group matched for age			1
5	If groups are unmatched, have statistical differences been controlled for?			1
	Test-athletes			
6	Are athletes of elite status (National & international athletes?			1
7	Are training details available (years, volume, duration/intensity)			1
	Image acquisition			
8	Is there detailed information to allow replication?			1
9	Are more than one observer used? If so is inter-observer variability stated?			1
10	Were investigators/assessors blinded to participant groups allocation			1
	Measurement technique			
11	Are professional guidelines observed/cited			1
	Reporting Data			
12	Is an explanation for missing data given?			1
13	Is data clearly and accurately presented?			1
14	Are absolute data values stated?			1
	Total Score			/14

Appendix 9.5 Strobe statement— Guideline for reporting of observational studies (Von Elm et al., 2008).

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	**YYes**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	**YYes**
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	**YYes**
Objectives	3	State specific objectives, including any prespecified hypotheses	**YYes**
Methods			
Study design	4	Present key elements of study design early in the paper	**YYes**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	**YYes**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	**YYes**
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	**YYes**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	**YYes**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **– Controls – Yes; Athlete groups – Yes**	**YYes**

Bias	9	Describe any efforts to address potential sources of bias	**YYes**
Study size	10	Explain how the study size was arrived at	**YYes**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	**YYes**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	**YYes**
		(*b*) Describe any methods used to examine subgroups and interactions	**YYes**
		(*c*) Explain how missing data were addressed **Not applicable**	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	**YYes**
		(*e*) Describe any sensitivity analyses	**YYes**

Appendix 9.6 References list of studies included in the systematic review and meta-analysis

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Appendix 9.7 Participant information sheet

LIVERPOOL JOHN MOORES UNIVERSITY

PARTICIPANT INFORMATION SHEET

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

Victor Utomi – Research Institute of Sport & Exercise Sciences

You are being invited to take part in a research study. Before you decide 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 me 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 purpose of this study is to characterise the structural and functional changes of the athlete's heart in a diverse groups of sportsmen and women using state state-of-the-art imaging technology. Initial research suggested that cardiac adaptation to exercise follows two types of outcomes as eccentric or concentric hypertrophy subsequent to endurance or strength exercise, respectively. Recently, expert commentary and the development of new highly-accurate imaging equipment have resulted in the need to re-evaluate the old hypothesis of cardiac adaptation to exercise training. New insights from novel imaging tools will provide in-depth data about cardiac structure and function in athletes with different training backgrounds as well as from different ethnic groups. Results from this research will provide useful information for clinical cardiovascular screening of athletes.

2. **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 given this information sheet and asked to sign a consent form. You are still free to withdraw at any time and without giving a reason. A decision to withdraw will not affect your rights or any future service you receive.

3. **What will happen to me if I take part?**

The study will involve visiting the sports science labs at LJMU or a field-based laboratory to carry out some tests on only one occasion. Prior to your arrival, you will need to fill in a personal and family history medical questionnaire and sign a consent form.

The testing session will initially involve measurement of your height and your weight. Next you will have an electrocardiogram (ECG), which is a simple, non invasive and painless test that examines the electrical activity within your heart. The ECG test involves lying down quietly and it takes 5-10 minutes only. Small stickers are placed at strategic points on your chest, arms and legs. Flexible leads (known as electrodes) that extend from the ECG machine are then attached to these stickers. The electrical rhythm of your heart is recorded and printed out. After this, your resting blood pressure (BP) will be measured from a cuff tied to your upper arm with a painless automated sphygmomanometer. 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 normally take 30 minutes.

4. **Does it hurt?**

Both the ECG and echocardiogram are painless, non-invasive procedures.

5. **Do I need to prepare anything prior to my appointment?**

You should rest for at least 30 minutes prior to your appointment. Please avoid caffeine intake or strenuous exercise for 3 hours prior to testing.

6. **Are there any risks / benefits involved?**

There are no known risks or hazards to electrocardiography and ultrasound at diagnostic frequency. You will gain valuable information on your current state of your own hearts structure, function and electrical activity. This is not a formal health screening examination but if the data collected suggests a medical problem we will provide information to your GP with your agreement.

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

All of the data collected will be anonymised so that your identity will not be revealed. All data will be stored on a password protected computer system and any paperwork stored in a locked cabinet for a specified time period.

Contact Details of Researcher

If you have any questions relating to any of the techniques used during the research study please feel free to contact me to discuss this further. Participation in this research study is voluntary and you are free to withdraw at any time without prior explanation.

Dr Victor S. Utomi (MBBCH, MSc, AFHEA)
PHD Candidate
School of Sport & Exercise Sciences
Liverpool John Moores University
Henry Cotton Campus
15-21 Webster Street
Liverpool L3 2ET
V.S.Utomi@2011.ljmu.ac.uk
+447427238373
+2347068110553

Appendix 9.8 Consent form

LIVERPOOL JOHN MOORES UNIVERSITY
CONSENT FORM

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

Victor Utomi – Research institute of Sport & Exercise Sciences

1. I confirm that I have read and understand the information 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 Date Signature
(If different from researcher)
Note: When completed 1 copy for participant and 1 copy for researcher

Appendix 9.9 SSES REC Health and training questionnaire

NON-VALIDATED QUESTIONNAIRE **Section One: Personal Information**

Full Name:		**Date of Testing:**
Home address:		**Doctors Name & Address:**
Post Code:		**Post code:**
Phone No:		**Phone No:**
E-mail:		
Date of Birth:	**Age:**	**Gender:**
Have you had Heart tests before?		**Do you have any illness:**
List illness:		**List medications if any:**

Which country were you born?

Ethnicity (please tick appropriate box)

White	**Mixed**	**Black**	**Asian**	**Other**
British	White & black Caribbean	Caribbean	Indian	Chinese
Irish	White & Black African	East African	Pakistani	Filipino
European	White & Asian	West African	Bangladeshi	Vietnamese
Turkish/Cypriot		North African		Other
Greek/Cypriot				
If other, please state your origin:				
Height……………….cm Weight……………. Blood Pressure………/………mmHg				

Section Two:

Medical History (adapted from PARQ/CRY) (Please circle answer)

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 please describe the circumstances

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

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?	

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 any one under the age of 50?

Yes/No	If yes please state 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 the 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 been participating in sport? ....

13. Please detail any further information you would like to tell us...
...

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

Participant signature____

Thank you for completing this questionnaire

Appendix 9.10 Ethics approval document

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

Appendix 9.11 Normal training related ECG findings – 'Seattle' criteria (Drezner et al., 2013).

ECG Change	Definition
Sinus Bradycardia	HR < 60bpm
First Degree AV Block	PR interval > 200ms
Incomplete RBBB	QRS <120ms
Early Repolarization	Max ST-J elev >=1mm and notching / slurring of terminal QRS complex
LVH on voltage criteria	RV5 + SV1 >35 mm - Sokolow Criteria

Appendix 9.12: Abnormal ECG - Seattle Criteria (Drezner et al., 2013).

Abnormal (group 2) ECG criteria	Definition
T-wave Inversion	> 1 mm deep in 2 or more leads V2-V6, II and aVF, or I and aVL
ST Segment Depression	≥ 0.5 mm deep, ≥ 2 adjacent leads
Pathological Q-waves	> 3mm deep and/or > 40 ms duration in ≥ leads except III and aVR
Left Atrial Enlargement	Negative portion of P wave ≥1mm in V1/2 and P duration >120 ms
Left-axis Deviation	-30˚ to 90˚
Right-axis Deviation	>110˚
Right Ventricular Hypertrophy	RV1 + SV5 > 10.5 mm AND RAD >120˚
Right Atrial Enlargement: P wave	>2.5 mm tall in II, III or aVF
Ventricular Pre-excitation	PR interval < 120ms with a delta wave in QRS
IVCD	Any QRS ≥140 ms including complete LBBB
Long QT Interval	QTc ≥ 470 (M) or ≥ 480 (F)
Short QT Interval	QTc < 320 ms
Brugada like ECG pattern	Brugada coved & ST amplitude J/J+80 >1 in V1 - V3
Profound Sinus Bradycardia	<30 bpm
Atrial tachyarrhythmias	SVT, atrial fibrillation/flutter
Ventricular Extra-systoles	Couplets, triplets, NSVT