THE EFFECT OF ETHNICITY AND BODY SIZE ON THE ATHLETE'S HEART AND THEIR IMPACT ON CARDIOVASCULAR PRE-PARTICIPATION SCREENING

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ABSTRACT

In response to the augmented haemodynamic load placed upon the heart by intense and prolonged exercise, various forms of physiological remodelling are elicited. The resultant cardiac structural, functional and electrical adaptations are coined the athlete's heart. Due to the nature of the remodelling, in some cases these adaptations may however overlap with the diagnostic criteria for varying pathological conditions, often related to sudden cardiac death. Several variables are associated with the athlete's heart including age, sex, sport, body size, and ethnicity. Ethnicity is of particular importance as athletes of an African/Afro-Caribbean ethnicity demonstrate a greater prevalence of abnormal changes suggestive of pathology. There is however paucity in the literature of the athlete's heart among other ethnicities. For this reason Study 1 investigated the impact of Arabic ethnicity upon the structure, function and electrophysiology of the heart in male athletes. Study 1 identified that while Arabic athletes had larger hearts than Arabic controls, they had significantly smaller hearts than their Black and Caucasian athletic counterparts. While Black athletes had a significantly greater prevalence of training unrelated/abnormal ECG findings, Arabic and Caucasian both had similar levels of training unrelated/abnormal findings, suggesting the European Society of Cardiology guidelines for ECG interpretation in athletes are applicable for the ethnicity.

Study 2 investigated another important facet of the athlete's heart, which is body size. Study 2 identified that while there was a progressive relationship between body size and cardiac dimensions, the previously identified upper limits of cardiac structural remodelling were applicable even among those with a body surface area (BSA) over $2.3m^2$. Among the cohort of athletes with a BSA $>2.3m^2$, Black athletes demonstrated significantly greater wall thickness' than Caucasian and Arabic athletes.

The second aspect to the thesis highlighted how the findings of Study 1 and 2 impact upon pre-participation screening. While debate still exists around the most effective methodology to screen for pathological cardiac conditions, several organisations mandate the use of the echocardiography alongside the resting 12-Lead ECG. Study 3 established that should echocardiography be limited to use as a follow up investigation, significant cost benefits could be elicited (47% reduction). The premise of this significant cost reduction was that no pathological case was identified by echocardiography in isolation. While still found to be useful in confirming pathology, significantly, in our study the investigation failed to identify two cases of hypertrophic cardiomyopathy.

Study 4 investigated the implications of adopting modified ECG interpretation guidelines in light of the criticism that ECG screening should be avoided due to a high false positive rate. Utilising an ethnically diverse cohort, Study 4 demonstrated that using the 'Refined' criteria reduced the false positive rate from 22% when using the 2010 ESC guidelines to 5%. Importantly both criteria achieved 100% sensitivity, highlighting the importance of the ECG in cardiovascular screening.

CHAPTER ONE

1.0 INTRODUCTION

The benefits of exercise are profound and well established. These encompass a multitude of factors including a reduction in resting blood pressure, a reduction in low density lipoprotein cholesterol and increased insulin sensitivity (Myers, 2003); ultimately leading to the demonstration of an inverse relationship between physical activity and mortality risk (Singer, 2008). The significance of this relationship has contributed to the emphasis placed upon encouraging the implementation of physical activity in daily living (Pate et al., 1995).

In order to meet the physical demands regular intense exercise places on the body, numerous physiological adaptations are elicited. From a cardiological perspective these adaptations comprise of structural remodelling leading to functional and electrical changes resulting in an enhanced exercise capacity. First researched in the late 1800's, Henschen (Henschen, 1899) demonstrated larger hearts in Nordic skiers than in their sedentary counterparts using auscultation, concluding that the observed enlargement represented a beneficial adaptation to exercise which was of no clinical concern. This assumption was supported by Darling in 1889 among Harvard University rowers (Darling, 1899). While auscultation is still clinically relevant, it was the technological advancement in subsequent years which allowed for a more detailed investigation of the heart. Aside from chest radiography, the introduction of the electrocardiogram (ECG) provided a more comprehensive study of the electrical activity of the heart (Winsor and Beckner, 1955, Beckner and Winsor, 1954, Smith et al., 1964, Lichtman et al., 1973). From a structural and functional perspective the development of 2D, M-mode and

Doppler echocardiography and, more latterly, cardiac magnetic resonance imaging (CMR) further extended understanding and constitute the latest progression in cardiac investigations.

These new technological advancements have led to a greater understanding of the 'athlete's heart' paradigm. While the adaptive response is not uniform among all athletes, the hallmark of the 'athlete's heart' is left ventricular enlargement. Pluim *et al.* (Pluim et al., 2000b) conducted a meta-analysis of 59 studies examining 1451 athletes demonstrating that although different remodelling patterns exist between sports, when taken collectively there was a 27% greater maximal ventricular wall thickness compared with age- and gender-matched sedentary individuals. In addition to changes in left ventricular (LV) wall thickness (LVWT), Pelliccia *et al* (Pelliccia et al., 1999) in their seminal paper reported an increased left ventricular end-diastolic diameter (LVID) in athletes, with values of up to 70mm with 45% of athletes having an LVID greater than 55mm. In accordance with the upper limits of normality set by Pelliccia *et al.* (Pelliccia et al., 1991b), and supported among more recent studies (Whyte et al., 2004a, Scharhag et al., 2002, Utomi et al., 2013, Chevalier et al., 2013) such morphological adaptations are considered physiological. These upper limits of physiological adaptation were, however, collated from an athletic population consisting of predominantly Caucasian athletes with similar anthropometric characteristics. It is widely recognised that body size impacts upon cardiac dimensions (Batterham et al., 1999a, George et al., 2009), however little attention has been devoted to understanding the relationship between anthropometry and cardiac structure. Consequently, it is unknown if the upper limits of cardiac structure are applicable in athletes with extreme body surface areas (>2.3m^2).

Athletes commonly demonstrate physiologically derived changes on the ECG including: sinus bradycardia, sinus arrhythmia, first degree atrioventricular block and incomplete right bundle branch block, with 60% of athletes demonstrate such modifications (Pelliccia et al., 2007). It is important to differentiate these physiological anomalies from pathological conditions associated with sudden cardiac death (SCD) in young athletes. This is pertinent when one considers the increased relative risk of a cardiac event in an athlete with an underlying condition to SCD during exercise (RR=2.8) (Corrado et al., 2003).

SCD is defined as a natural, unexpected death within one hour of the onset of symptoms. Among athletes, the prevalence is reported to be between *c*.0.6-2.6% in 100,000 (van der Werf et al., 2010, Van Camp et al., 1995, Steinvil et al., 2011). The main causes for SCD among young athletes are: (1) heart muscle disease including: hypertrophic cardiomyopathy (HCM); and arrhythmogenic right ventricular cardiomyopathy (ARVC); (2) electrical abnormalities including: long QT, short QT and Brugada syndrome; and (3) congenital abnormalities including: coronary artery anomalies (CAA)(Maron, 2003, Maron et al., 2009, Link and Mark Estes, 2008). In some cases distinguishing between the physiologic and pathologic changes can be challenging and represent a diagnostic dilemma, collectively termed the 'grey zone'(Maron, 2003).

Pre-participation screening has been increasingly adopted among various organisations in an attempt to identify young athletes who might be at risk of SCD due to an undiagnosed cardiac condition. Both the American Heart Association (AHA) and the European society of Cardiology (ESC) advocate the need for screening based on legal, ethical and medical grounds.

Nevertheless the two cardiology bodies differ in the recommended screening methodology, with the ESC including a 12-Lead ECG alongside a questionnaire and physical examination, while the AHA excludes the ECG relying simply on the a questionnaire and physical examination. The AHA opposition to the inclusion of ECG is based upon the cost-effectiveness of screening, and the purported excessive false positive rate associated with the ESC guidelines for ECG interpretation (Corrado et al., 2010).

A major limitation to the ESC guidelines is the almost exclusive use of Caucasian athletes. It has become apparent that an important determinant of morphological remodelling for athletes is ethnicity. Basavarajaiah *et al* (Basavarajaiah et al., 2008a) and Papadakis *et al* (Papadakis et al., 2011c) both reported that while revealing similar LVIDd's, LVWT was significantly greater in Black athletes vs. Caucasian athletes. Moreover, the prevalence of LVWT above the normal upper limit (≥12mm) in Black athletes was greater than that of their Caucasian athletic counterparts (18% vs. 4%). Black athletes also exhibit a higher incidence of repolarization changes on the ECG compared with Caucasian athletes. Furthermore, 22.8% of Black athletes demonstrated T-wave inversion, primarily confined to the contiguous anterior leads of V1-4 (12.7%), compared to only 3.7% of Caucasian athletes (Papadakis et al., 2011c). This is important as T-wave inversions are reported in >90% of individuals with HCM. Overall, 30% of Black athletes demonstrate at least one abnormal ECG alteration, in comparison to only 13% in Caucasians (Magalski et al., 2008); leading to the suggestion that Black ethnicity is an independent predictor of uncommon ECG traits (Wilson et al., 2012b). Whilst Maron *et al* (Maron et al., 2003a) report that 55% of all SCD cases that were attributed to HCM were in Black African athletes.

When investigating the impact of ethnicity, those of African/Afro Caribbean descent have received much of the attention, possibly due to the volume of athletes participating in European and American sport. However, data from other ethnic groups is currently lacking. Of note, studies examining athletes of Arabic descent are limited in the literature. Athletes of Arabic descent are an emerging presence in the international sporting arena, with 243 Arabic athletes competing at the London 2012 Olympics. Wilson *et al* (Wilson et al., 2011c) identified that athletes from West-Asia had a greater prevalence of cardiovascular disease related markers; a notion potentially attributable to the rapid economic growth and widespread urbanization. However, only one study exists examining ECG variants in Arabic athletes compared with their Caucasian or Afro-Caribbean counterparts (Wilson et al., 2012b). They conclude that the electrocardiographic characteristics of the Arabic athletes are comparable to those of Caucasian athletes, and with a similar prevalence of abnormal findings (7.9 vs.5.8%). Athletes of Arabic descent also demonstrate a 50% lower prevalence of inherited cardiac pathology than Black athletes (0.5 vs. 1%). However, no data exists examining the cardiac structure and function of the Arabic athletes heart, thus it is unknown if established screening guidelines derived for Caucasian athletes are applicable in Arabic athletes.

Recently, new ECG interpretation guidelines have recently been published(Drezner et al., 2013b) with the aim of improving specificity, yet the true clinical implications of these enhanced guidelines have yet to be elucidated. Furthermore, certain sporting organisations such as Fédération Internationale de Football Association (FIFA) mandate the inclusion of a resting echocardiogram in the screening work up of athletes prior to FIFA sanctioned events. This

decision is based upon consensus rather than scientific fact, with the clinical and financial value yet to be elucidated.

1.1 Aims

The aims of this thesis were:

- To examine the cardiac structure and function of high-level Arabic athletes when presenting for pre-participation cardiovascular screening, using ECG and echocardiography.

- To investigate the cardiac structure and function in professional male athletes with extreme anthropometry (≥2.3 m^2), to confirm if the established upper limits of physiological cardiac adaptation to intensive and sustained physical activity are applicable for this unique population.

- To examine the efficacy of systemic echocardiography alongside the ECG, personal/family history questionnaires, and physical examination, as collective tools to identify diseases with the potential to cause SCD within a population of athletes; and to provide a cost-analysis of a government-funded pre-participation screening programme.

- To assess the performance of a new 'Refined Criteria' for mass pre-participation cardiovascular screening versus the 2010 ESC recommendations for ECG interpretation and the 2013 'Seattle Criteria' in a large cohort of Arabic, Black and Caucasian athletes.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Physiological mechanisms of cardiac adaptation to training

Research investigating the athletes heart has been on-going for over 100 years since Henschen (Henschen, 1899) documented larger hearts among Nordic skiers compared with their sedentary counterparts using simple percussion. Whilst it has led to the demonstration of cardiac adaptation through sporting participation and its related ability to improve athletic performance through guiding the development of training regimes; importantly, research has led to the differentiation between normal physiological variants of adaptation and those of inherited or congenital cardiac pathology (Prior and La Gerche, 2012).

Numerous areas of the cardiovascular system are modified by sustained and intensive physical activity. These manifestations include structural, functional and electromechanical adaptations, that are collectedly referred to as the 'athlete's heart'. The manifestations of the athlete's heart can however vary, depending on numerous factors; with 75% of the variability in LV cavity size determined by non-genetic factors (Pelliccia et al., 1999). Influencing factors which have been shown to alter cardiac remodelling include: sex, age, body surface area (BSA), type of sport, drug use and ethnicity. The key factors from this list, pertaining to the nature of the thesis will be discussed in the following sections, with critical appraisal of how they influence the development of the athlete's heart.

2.2 Structural and function indices of the athlete's heart

2.2.1 Effects of body size on cardiac adaptation to training

A large body surface area (>2.0m^2), has been associated with an increase in the likelihood of left ventricular hypertrophy (LVH) (Pluim et al., 2000b), with the identification of a linear relationship between cardiac dimensions and an athlete's body size. Whilst increases in cardiac morphology amongst the largest athletes are typical of a normal anthropometric adaptation, certain cardiomyopathic processes may go undetected among smaller athletes. This physiological/pathological differentiation is crucial; especially when one considers that a misdiagnosis has the potential to jeopardize an athlete's life. Alternatively however, a false diagnosis also carries considerable risk, with the disqualification from sporting activity, in addition to further social and psychological distress (Rawlins et al., 2009b). In order to avoid such events, 'scaling' is a mathematical process commonly used to remove the influences of body size. The process is commonplace in paediatric medicine, however has been poorly adopted among the sports cardiology fraternity.

Traditionally scaling has been accomplished using the per-ratio standard approach, by dividing the physiological variable (y) by the body size variable (x). However (y/x) assumes a constant linear and proportional relationship between the two. This process has not only been criticised on theoretical and empirical grounds (Tanner, 1949) but also contradicting the theory of geometric similarity which indicates that the relative geometries govern to some extent the relationship between the two variables. To address such concerns, the application of a general allometric equation has been suggested as a more viable model to adopt (Batterham et al., 1999a).

The allometric model takes the form of y/x^b, where '*b*' is a scalar exponent, and thus allows relationships between the cardiovascular and body size variable with different relative geometries, in addition to also being purportedly size independent, assuming a non-linear relationship (Dewey et al., 2008a). Having determined the scaling method the selection of an appropriate body size variable is of equal importance; a fundamental factor often neglected among scaling studies (Jungers and German, 1981). General body size has frequently been accounted for using height or body mass; the simplicity of measuring these being the most logical reason favouring their adoption among clinical practice. Despite their practicality, they also constitute measures that are uniform and without error; an important factor when using least-square regression models.

Application of an appropriate scaling method allowing for individual variations in body size is important, permitting valid individual patient assessment, inter- and intra-group cross sectional comparisons, and allows for the establishment of upper normal limits in respect to an athlete's anthropometry (Batterham et al., 1999a, George et al., 2009). However, very few papers in the literature have considered adult anthropometry in relation to the upper limits of cardiac structure and function. This is particularly relevant in athletes with extreme body size, such as rugby players, basketball players, handball players and American football players.

2.2 Effects of sporting discipline on cardiac adaptation to training

The mode of physical activity impacts the size of cardiac remodelling. Morganroth *et al* (1975) were the first to propose such a hypothesis, indicating that the morphological adaptations to exercise can be partitioned into two separate categories (Morganroth et al., 1975). Athletes

incorporating a high dynamic component such as endurance training were suggested to present with eccentric LVH characterized by an increased LV chamber size with a proportional increase in WT. Those athletes involved in strength based events were proposed to develop concentric hypertrophy, attributable to a pronounced increase in afterload exerted on the LV, yet only small increases in cardiac output (Prior and La Gerche, 2012).

2.2.1 LV cardiac adaptations among endurance trained athletes

Due to the high dynamic load placed upon the heart during endurance training, cardiac output may increase from 5 l/min at rest to up to 40 l/min during maximal exercise (Ekblom and Hermansen, 1968). The result of this volume overload is the adaptive generation of new sarcomeres, allowing for an increase in LV dilation. While this adaptation has been supported in research with low numbers of endurance athletes (Scharhag et al., 2002, Whalley et al., 2004, Fagard et al., 1984, Urhausen et al., 1996), a study with a large cohort of athletes (n=947) reported that LVIDd was increased in 38% of athletes; with the breakdown by sport demonstrating a predominance towards endurance sports, with endurance cycling, cross-country skiing and swimming being the 3 sports with the largest LVIDd's(Pelliccia et al., 1991b). While the cavity dilatation, with a modest parallel increase in septal and posterior wall thickness has been consistently demonstrated (King et al., 2008), importantly, Pelliccia et al (Pelliccia et al., 2010) demonstrated there were no adverse effects of such intense endurance training. Indeed they identified that after up to 17 years of intense uninterrupted training, no deleterious effects with regards to LV morphology, function or the occurrence of symptoms or adverse events among 114 Olympic athletes.

2.2.2 LV cardiac adaptation among strength trained athletes

Athletes participating in strength trained sports must overcome blood pressure responses in the magnitude of 320/250mmHg (MacDougall et al., 1985). To overcome this increase in afterload, it was hypothesised by Morganroth that in accordance with the Law of LaPlace, an increased WT would result as a compensatory mechanism. A meta-analysis by Fagard (2003) partially refutes this theory, demonstrating that in 178 strength trained athletes, a significant difference in maximal WT was observed compared to controls (10.3 vs. 8.9 mm, $p<0.05$); however absolute values fail to demonstrate marked hypertrophy (Fagard, 2003). Further work by Pelliccia *et al* (1993) in 100 highly conditioned strength athletes, demonstrates that maximal WT and LVM index were significantly greater than controls ($p<0.001$), with no difference in LVID (Pelliccia et al., 1993). However, with a mean WT of 9.6 ± 0.8 mm (maximal thickness of 12 mm) it demonstrated that strength training does not necessarily represent a strong stimulus for distinct LV hypertrophy. One reason for this could be the short period of time the athletes spend in periods of high static strain. Accordingly, the myocardium is not 'stressed' adequately with only short periods of excessive afterload failing to stimulate extensive hypertrophy.

2.2.3 LV cardiac adaptation among sports combining both strength and endurance

Most athletic disciplines fail to be categorised as either entirely endurance of strength and may display markers of both eccentric and concentric hypertrophy. A meta-analysis by Pluim *et al.* (Pluim et al., 2000b) deduced that athletes engaged in sport with both strength and endurance elements present with the greatest increases in LV internal diameters and a significant increase in relative wall thickness, placing them at a higher risk of penetrating the 'grey zone'; attributable to the sustained volume overload coupled with extreme pressure load. Despite this, contrasting

findings were presented by Whyte *et al* (2004) where athletes with a wall thickness of >13mm were from a range of sporting disciplines and despite their inclusion were not found in athletes competing in rowing and canoeing (Whyte et al., 2004a). Cyclists and triathletes did present with large WT, with three athletes recording a maximal WT of 13 mm and a fourth with 14 mm.

A maximal wall thickness of ≥13 mm as demonstrated in the aforesaid study has been defined as the basis for mild pathological hypertrophy due to its association with HCM (Williams et al., 2009). As a result, athletes presenting with maximal LVWT ≥13 mm may represent a diagnostic challenge for physicians. Pelliccia *et al* (Pelliccia et al., 1991b) screened 947 elite male athletes from 25 sports, reporting that an LV wall thickness ≥13 mm was unusual (16 of the 947 athletes; 1.7 %); participating in rowing and canoeing (n = 15), and cycling (n = 1). All athletes with LV walls ≥13 mm thick also had enlarged LV end-diastolic cavities (55 to 63 mm); ultimately proposing guidelines for the upper limits of physiological development of 16 mm and 66 mm for maximal wall thickness and LV cavity dimension respectively. Whyte *et al* (2004) were more cautious concluding that the upper normal limits should be 15 mm and 65 mm respectively, after screening 442 elite British athletes.

2.3 The impact of exercise upon Systolic and Diastolic Function

2.3.1 The impact of exercise upon systolic function

Endurance athletes in particular have been shown to demonstrate lower resting systolic function (ejection fraction; EF) than the general population, with values as low as 41%, placing them in the range of suspected heart failure. This was supported among findings from Abergel *et al* (Abergel et al., 2004) where among a cohort of 286 world class professional cyclists 11% had an

LVEF <52%. Despite these low values, this was mechanistically explained by the presence of a dilated LVIDd (>60 mm), the authors noting that this dilatation among most of these cyclists suggests a diminished need for vigorous contraction to maintain stroke volume at rest. Supporting this notion is the methodological considerations and concerns for adoption of LVEF as a valid measure of systolic function among such populations. This is with respect to the difficulty of EF to account for the geometric changes in the presence of significant changes in chamber architecture (Baggish et al., 2008b).

Classically, most research has been conducted using the traditional measures of EF and area change; however as described both indices have been suggested that due to a lack of sensitivity they fail to account for the impact of myocardial mechanics, i.e. longitudinal, radial and circumferential function, and consequently only offer a representation of chamber mechanics (Baggish et al., 2008b, Pluim et al., 2000b). Indeed when utilising the direct, more sensitive techniques of strain imaging and tissue Doppler echocardiography, enhanced resting systolic myocardial function has been reported among athletes (La Gerche et al., 2009, Mantziari et al., 2010, Baggish et al., 2008b).

2.3.2 The impact of exercise upon diastolic function

Diastolic function comprises of two mechanisms that allow the refilling of the ventricles prior to the next ejection period: 1) lusitropy (active relaxation); and 2) compliance. Ventricular relaxation refers to the process by which the ventricular pressure drops to below that of the atria to facilitate passive filling due the elevated pressure gradient. While often described as a

separate entity, compliance refers to the pressure-volume relationship as the ventricle is filled (Rosenberg and Manning, 2012). Diastolic function is known to be highly adaptive to the stress placed upon the heart.

Among athletes, regular training elicits a 10-30% improvement in maximal cardiac output which, due to the limited capacity for change in heart rate, is attributable to an increase in stroke volume (Ekblom and Hermansen, 1968, Whyte et al., 2008, Vella and Robergs, 2005). Although several contributing factors have been proposed to explain this, the improvements in LV relaxation and compliance have been indicated to play a prominent role. The implication of one of these factors - LV torsion deformation - is a greater lengthening of the myocytes, ultimately allowing for lower LV pressures. A resultant factor of this is the greater suction of the ventricle when exercising. Mechanistically, apical rotation and back-rotation, decreases wall stress, eliciting a faster decline in LV pressure creating an intra-ventricular pressure gradient between the base and apex and thus allowing for the filling to be conducted at lower atrial pressures (Rovner et al., 2005, Notomi et al., 2006, Nikolic et al., 1995), with the end result being a greater filling capacity.

The predominant method used to assess diastology has been cross-sectional mitral filling velocities using Doppler echocardiography to measure early peak filling velocity (peak E) and late (A) filling velocities together with E to A ratio (E:A). Although some studies have reported increases in the peak E between athletes and controls (Karjalainen et al., 1997), most studies have failed to establish any differences in the peak E between athletes and controls (Douglas, 1989, Caso et al., 2000, Baldi et al., 2003, Triposkiadis et al., 2002, Obert et al., 1998, Baggish et

al., 2010b, George et al., 1999). However, given that an 8-fold increase in cardiac output is demonstrated during exercise and coupled with a significant decrease in diastolic filling time from around 0.55 s to 0.12 s, the maintenance of end diastolic volume is a prominent physiological response among healthy individuals. The development of more sophisticated echocardiographic techniques has allowed the investigation of strain and tissue Doppler imaging, reportedly independent of haemodynamic load. Despite this, studies are limited and those that have been conducted vary in their findings (Teske et al., 2009, Teske et al., 2010, Nottin et al., 2004, Moro et al., 2013, Baggish et al., 2008a).

2.4 Right ventricular (RV) structure and function in athletes

The haemodynamic overload induced by long-term training elicits not only profound remodelling of the LV but also the RV. Together with increased trabeculae, the complex and asymmetric shape of the RV results in the difficulty in delineating structure and function (D'Andrea et al., 2011). Moreover, its anatomical position beneath the sternum further influences RV shape (Haddad et al., 2008).

This disparity between the LV and RV physiology leads to different structural and functional changes. La Gerche *et al* (La Gerche et al., 2011) found that RV end systolic wall stress was increased in athletes when compared to non-athletes, with a greater percentage increase than the equivalent LV end systolic wall stress. Such evidence is suggestive of hemodynamic stressors during exercise eliciting the chronic structural changes of RV chamber enlargement and wall thickening. Whilst limited research has been conducted, some authors assessing the chronic RV structural remodelling in athletes have demonstrated proportional increases in volume and mass (Scharf et al., 2010, Scharhag et al., 2002). Acute changes in RV structure and function were

established as more prevalent and profound than that of the LV following intense prolonged exercise (La Gerche et al., 2008, Mousavi et al., 2009, Trivax et al., 2010, Douglas et al., 1990).

While some studies suggest that the RV myocardium is intrinsically different to that of the LV, the characteristics of RV contraction are primarily dependent on loading (Redington, 2009). At rest the workload of the RV is minimal due to the very low RV afterload (La Gerche and Heidbuchel, 2013). In this regard, the myocardial energy cost of RV cardiac output is approximately $1/5^{th}$ of the LV; again attributable to the unique characteristics of the RV pressure-volume relationship and the notable low pressure pulmonary system. Yet due to the lower impedance and greater distensibility of the pulmonary artery bed, it still manages to maintain a similar output. The work requirements do, however, significantly increase during exercise, with pulmonary artery pressure more pronounced as the intensity of exercise increases (Stanek et al., 1975, Kovacs et al., 2009, Bevegård et al., 1963). While no plateau has been documented, it has been observed that the greater the cardiac output, the greater the pulmonary artery pressure (PAP) and RV load. Ultimately this translates into an increase in wall stress, coronary perfusion and oxygen extraction (Zong et al., 2005, La Gerche et al., 2011).

Elite athletes demonstrate greater RV size (volumes and wall thicknesses) than non-elite athletes. Furthermore, endurance athletes have greater RV size compared with strength trained athletes (Baggish et al., 2010b, Oxborough et al., 2012, D'Andrea et al., 2011). As with the LV, it is important for clinicians to establish the upper limits for physiological adaptation in the RV due to the cross over between athlete's heart and DCM. In 2005, the American Society of Echocardiography published normal ranges for RV dimensions (Lang et al., 2006), with an

updated version in 2010 (Rudski et al., 2010). While representing progress in the quantification of RV morphology, the guideline was based upon sedentary individuals and thus inappropriate to translate over to the athletic population. Oxborough *et al* (Oxborough et al., 2012) demonstrated that 40% of athletes had a RV outflow tract greater than the ASE guidelines, with 57% presenting an abnormal RV inflow dimension and 67% having an RV length greater than normal limits. Consequently, it is evident that the generation of upper limits for RV physiological remodelling are necessary for athletes.

2.5 Electrocardiographic modifications of the athlete's heart

The structural and functional changes seen as an adaptive response to exercise training are concomitant to changes on the electrocardiogram. These differing electrocardiographic patterns are commonly indicative of the benign remodelling associated with the athlete's heart. The typical alterations seen in athletes include sinus bradycardia, sinus arrhythmia, first degree atrioventricular (AV) block, incomplete right bundle branch block (IRBBB), isolated Sokolow voltage criteria for LVH and early repolarization. With the possibility of making an erroneous diagnosis of cardiac pathology, it is imperative the ECG findings commonly observed in athletes are taken in context with the physiological adaptation of athletic training.

2.5.1 Vagotonia

An increase in vagal tone encompasses the most prominent alteration among athletes and is often interpreted as an independent marker of physical fitness. A resting heart rate of less than 60 beats.min^{-1} is the accepted definition of bradycardia and itself is the most common index of vagatonia. Bradycardia is common in the athletic population, with heart rates as low as 30

beats.min^{-1} falling within the premise of accepted physiological variation (Drezner et al., 2013d). A complex interrelation of different systems determine the autonomic tone at the sinoatrial node, however it is acknowledged that through the adoption of endurance exercise training, an increase in parasympathetic activity and a concomitant decrease in sympathetic activity are elicited (Dixon et al., 1992, Goldsmith et al., 2000, Amano et al., 2001).

Additional indices of exercise induced increases in vagal tone include AV conduction disturbances. A PR interval of greater than 200 ms indicative of first degree AV block among athletes has a documented prevalence of between 28-40%, while second degree type 1 has a prevalence of 15-22% (Palatini et al., 1985, Talan et al., 1982, Viitasalo et al., 1982). Importantly these bradyarrhythmias are characteristically reverted among athletes upon the initiation of exercise, hyperventilation, the infusion of atropine, or detraining. Conversely, second degree AV block Mobitz type II is illustrated by an abrupt loss of P-wave conduction without prior P-wave prolongation, and may be indicative of underlying structural heart disease. Whilst third degree AV block or complete heart block is a further variation of conductance abnormality and is not an expression of the athlete's heart and should be considered an abnormal finding (Drezner et al., 2013c).

2.5.2 Incomplete Right Bundle Branch Block (RBBB)

Incomplete RBBB (IRBBB) is defined by a QRS duration of less than 120 ms with the characteristic pattern of a terminal R wave in lead V1 (rsR) and wide terminal S wave in leads V1 and V6 (Drezner et al., 2013d). In highly trained athletes, up to 40% demonstrate IRBBB patterns compared to less than 10% of the general population. The benign nature of the complex

was highlighted in research as early as 1944 (Stewart and Manning, 1944). Moore *et al* (Moore et al., 1971) suggested that IRBBB is suggestive of a development in RV wall thickness, as opposed to an abnormality of the RV conduction system. Nevertheless, IRBBB is seen in patients with ARVC, however; it is often associated with other abnormalities such as anterior T-wave inversion in this condition. As such IRBBB must not be immediately disregarded as benign without first checking for other ECG anomalies.

2.5.3 Voltage criteria for left ventricular hypertrophy (LVH)

LVH has commonly been associated with athletic training, and as a physiological response to the increased hemodynamic load placed upon the heart. Its manifestation on the ECG is illustrated by meeting fixed voltage criteria of the QRS waveform. Several criteria for electrocardiographically determined LVH have been proposed including: Sokolow (Sokolow and Lyon, 1949), Romhilt-Estes (Romhilt and Estes, 1968) and Cornell voltage criterion. The adopted criteria are however often subject to extra-cardiac factors such as gender, age, weight, LV volume and chest wall configuration (Devereux et al., 1983). Typically, the specificity of these criteria are high (>90%) (Casale et al., 1985, Levy et al., 1990) but the sensitivity is much lower, ranging from 7-34% (Reichek and Devereux, 1981, Devereux et al., 1984, Casale et al., 1985, Hameed et al., 2005, Rodrigues et al., 2008, Levy et al., 1990).

Ultimately, a voltage criterion for isolated LVH raises little concern among athletes. Voltage criterion for LVH has been shown to be met in up to 45% of male and 10% of female athletes (Sharma et al., 1999, Rawlins et al., 2010a). However, should LVH be seen in the presence of

left axis deviation, ST segment depression, T-wave inversions or pathological Q waves, a pathological basis for the LVH should be considered warranting further investigation.

2.5.4 Early Repolarization (ER)

The electrophysiological expression of ER, affecting 1-5% of the general population, is considered a benign manifestation, with 35-91% of athletes also demonstrating this electrocardiographic morphology (Papadakis et al., 2011c, Di Paolo et al., 2012b, Leo et al., 2011, Uberoi et al., 2011a). However, ER does have a pertinent clinical value considering it may mimic the ECG of myocardial infarction, pericarditis, ventricular aneurysm, hyperkalemia, hypothermia (Klatsky et al., 2003) or Takotsubo syndrome (Zorzi et al., 2012). Traditionally characterized as ST segment elevation of >1 mV in two or more contiguous leads, there has subsequently been an inclusion of J waves, and terminal QRS slurring (Drezner et al., 2013d).

The presence of these morphologically distinct patterns may however represent those of differing subsets of individuals. Tikkanen *et al* (Tikkanen et al., 2009) large scale, longitudinal study involving a community based population of 10,864 middle aged subjects; found that an ER pattern in the inferior leads is associated with a greater risk of cardiac related mortality (adjusted relative risk, 1.28, 95% CI, 1.04-1.59, p=0.03) and from arrhythmia (adjusted relative risk 1.43, 95% CI, 1.06-1.94, p=0.03). Although these findings do challenge the previously accepted view of the ER syndrome being benign, it does support previous work (Rosso et al., 2008, Nam et al., 2008, Haïssaguerre et al., 2008, Sinner et al., 2010).

Tikkanen *et al* (Tikkanen et al., 2011) continued to identify the risk of life-threatening arrhythmia among specific variants of ER. They identified that the upsloping or rapidly ascending ST segment was associated with no increase in relative risk for arrhythmic death; however the alternate pattern of horizontal or descending ST segment subsequent to ER led to individuals having an increased hazard ratio (relative risk 1.43). Despite this, in athletes the pattern remains classified as an innocuous demonstration of the athletes heart (Pelliccia et al., 2000a).

2.6 Impact of ethnicity upon the 'grey zone' conundrum

The typical remodelling seen as a result of athletic training may sometimes mimic mild phenotypical expression of pathological conditions such as HCM or ARVC. When the term 'grey zone' was coined by Maron *et al* (Maron, 2003), literature detailing the athlete's heart was predominantly confined to Caucasian athletes. Since then it has become apparent that an important determinant of morphological remodelling for athletes is ethnicity; a factor subsequently found to exaggerate the grey zone responses, particularly within Black athletes. The increased prevalence of exaggerated structural remodelling is however coupled with documented increases incidences of SCD from HCM and ARVC in Black athletes (Maron et al., 2003a).

2.6.1 Impact of Black African/Afro-Caribbean ethnicity

The notion of ethnicity influencing cardiac remodelling in response to exercise is not a new concept and unique to athletic participation. A large body of literature has long investigated and resultantly established a significant relationship between African/Afro-Caribbean ethnicity and

LVH. Investigations conducted as early as 1992 found there to be racial differences in LV structure in healthy young adults (Hinderliter et al., 1992b). The authors focused upon the established link between black ethnicity and hypertensive heart disease and determined that independent of these haemodynamic incompetencies, LV size was greater among black individuals. Even among young adults free from hypertension and other cardiovascular disease, the 'Coronary Artery Disease Risk Development in Young Adults' (CARDIA) study demonstrated that there was a propensity towards LVH among participants of an African American heritage compared to Caucasians (Kamath et al., 2006). During baseline measures, both male and female African Americans had greater LVM. At 5 years follow up, the prevalence of LVH was 5-times greater in African American males than Caucasian males and 3-fold among African American females than Caucasian females. However, the absolute prevalence of LVH was still low; at 5% African American males.

Exacerbated LVH remodelling among Black patients with hypertension has further driven the hypothesis that exercise, and the associated alterations in preload and afterload may elicit a greater stimulus, acting as a catalyst for LV remodelling among Black athletes. Basavarajaiah *et al* (Basavarajaiah et al., 2008a) and Papadakis *et al* (Papadakis et al., 2011c) both demonstrate that Black athletes demonstrate a greater prevalence of LVH than their Caucasian counterparts. Basavarajaiah et al (2008) compared the structure and function of 300 asymptomatic Black athletes against 300 age and BSA matched Caucasian athletes, in addition to 150 Black and 150 Caucasian controls. While it was to be expected that Caucasian athletes had larger hearts than Caucasian control participants, they also demonstrated bigger hearts than Black controls (mean LVWT: +1.5mm; mean LVIDd: +4.6mm). When comparing the two athletic groups, while

Caucasian and Black athletes demonstrated similar LVIDd's (Black: 53.0 ± 4.4mm vs. Caucasian: 53.6 ± 4.1mm) there was a significant disparity when assessing maximal LVWT. The finding that Black athletes had a mean LVWT of 11.3 ±1.6mm, compared to the mean finding of 10.0 ± 1.5mm among Caucasian athletes not only signifies that Black athletes have a greater cardiac adaptation to exercise but that this ventricular adaptation relates to a uniquely global concentric pattern. Interestingly their findings also split the African athletes further by ancestral origin, and demonstrated that there was a significant disparity between West and East African. While 20% of West African athletes showed characteristic LVH, those from East Africa only had a prevalence of 7%; this certainly denotes that care must be taken when generalising ethnic origins so broadly and highlights the need for further research. Importantly the previously established upper limits of physiological adaptation were exceeded in 18% of Black athletes. It was therefore suggested that among this population of athletes, an abnormal finding for LVH should only be considered when this value exceeds 15mm.

Over a 14 year period Papadakis et al. (Papadakis et al., 2011c) performed cardiovascular screening in 904 Black athletes, compared to 1819 Caucasian athletes, 119 Black controls and 52 Black HCM patients. It was observed that Black and Caucasian athletes had similar cavity dimensions (Black: 52.6 ± 4.4mm vs. Caucasian: 52.6 ± 4.3mm), yet Black athletes presented a significantly greater mean maximal LVWT than Caucasian athletes. In absolute terms the prevalence of LVH (>12mm) was almost 8 times greater in the Black athletes in comparison to Caucasian athletes.

In contrast to the exaggerated LV remodelling process of Black athletes Zaidi *et al* (Zaidi et al., 2013a) found that Black athletes exhibit smaller RV dimensions than Caucasian athletes. Following the analysis of 675 athletes including 300 black African athletes, the authors revealed that the right ventricular measures of proximal outflow tract (POT) and; longitudinal dimension were reduced in athletes of Black African ethnicity, when compared to Caucasian athletes (POT: 30.9 vs. 32.8 mm; longitudinal dimension: 86.6 vs. 89.8 mm respectively). Whilst the study also found similar LV parameters among ethnicities, both LV and RV results may be a product of the greater proportion of white athletes from a sporting discipline which was both of a high dynamic and high static component.

The impact of ethnicity on cardiovascular remodelling is also apparent upon electrocardiographic investigation. As early as the 1940s, doctors had identified that there was a persistence of the juvenile ECG pattern among healthy Black individuals (Littmann, 1946). Following ECG investigation among 500 healthy individuals (300 Black, 200 Caucasian subjects), 14 (4.7%) Black individuals demonstrated either diphasic or inverted T waves, compared to only one Caucasian (0.5%) with the same ECG pattern. Even in these early investigative years, it was still concluded that this pattern found among those of African/Afro-Caribbean origin was a benign phenomenon and not a manifestation of organic heart disease. This finding has since been echoed in several studies among the general population (Gottschalk and Craige, 1956, Wasserburger, 1955, Grusin, 1954, Thomas et al., 1960).

When focusing on the athletic population, those of a Black ethnicity also exhibit a higher incidence of repolarization changes on the ECG. Papadakis *et al* (Papadakis et al., 2011c)

reported that 22.8% of Black athletes demonstrate T-wave inversion, compared to only 3.7% of Caucasian athletes; yet the majority were confined to the contiguous anterior leads V1-4 (12.7%). T-wave inversions are a characteristic indicator of HCM and though their occurrence in the lateral leads may be indicative of underlying pathology, their presence in these anterior leads has recently been described as a physiological variant unique to Black athletes only.

The ethnicity influence upon ECG alterations is not limited to T-wave inversion. The overall number of abnormal ECG patterns is consistently higher in Black athletes, with 30% of Blacks recording at least one abnormal alteration, in comparison to only 13% in Caucasians (Magalski et al., 2008); leading to the concept that black ethnicity is an independent predictor of uncommon ECG findings (Wilson et al., 2012b). These characteristics are also evident among young black athletes, with suggested decreases in ECG alterations as Black athlete matures throughout adolescence. This is in line with data from Di Paolo *et al* (Di Paolo et al., 2012b) where the cross sectional analysis of 154 black adolescent football players (<17 years) identified significantly greater prevalence of LVH (89 vs. 42%), ST-elevation (91 vs. 56%), and deeply inverted or diffusely flat/biphasic T waves (14 vs. 3%) than in age matched Italian Caucasian football players.

Ultimately the clinical implications of these findings cloud the cardiological interpretation of the investigations conducted in Black athletes. In this regard the previously established upper limits of physiological adaptation among Caucasian athletes are evidently not necessarily applicable to those of an African/Afro-Caribbean descent. The consequences of failing to acknowledge these ethnic differences will likely increase false positive rates, and the potential for unnecessary

testing with resulting psychological implications. Evidently given the aforementioned increase in prevalence of ECG abnormalities and borderline cases of pathology in this ethnicity, coupled with the poor infrastructure and knowledge base in home countries, such screening is widely considered unfeasible in certain developing African countries (Schmied et al., 2013)

2.6.2 Impact of East Asian ethnicity

Athletes of African/Afro-Caribbean descent have received much of the scientific attention, possibly due to the volume of athletes competing in European and America. Data regarding the cardiovascular characteristics of East and South Asian athletes is limited.

The largest screening study to be conducted among those from East Asia examined 18,476 young male individuals from the armed forces. While not athletes *per se*, they represent a trained group of people involved in regimented daily exercise. In total, 1285 (7%) demonstrated an abnormal ECG; however 70% of these were attributed to increased lead voltages, a parameter of abnormality which has been discarded as abnormal since the reclassification of ECG interpretation in 2010. However, T-wave inversions were identified among 4.3% and ST depression in 1.1%.

Examing athletes, Kervio *et al* (Kervio et al., 2012) reported a similar amount of training related ECG changes in East Asians compared to Black and Caucasian athletes. Importantly, despite the small cohort, no Japanese athlete presented with T-wave inversions, in comparison to 6% of Black athletes. One striking observation was the increased prevalence of eccentric LV enlargement among Japanese football players (LVIDd - 55.2 vs. 52.2 and 53.9 mm respectively).

When investigating the impact of screening in East Asian athletes, Ma et al. (2007) ultimately failed to identify any athlete with pathology. With regards to the structural modifications, 11% were found to have an LVIDd beyond 60mm, with an upper limit identified at 65.5mm. While the study in question failed to incorporate athletes of other ethnicities and thus no direct comparison could be drawn, the results corroborate with those typically found among Caucasian athletes (Ma et al., 2007). Nevertheless, a study using 291 Japanese 100km Ultra-marathon competitors reported greater LV dimensions than those previously observed; with a mean LVIDd of 61.8 mm (max: 75 mm), in addition to LVWT's of 10.2 mm (max: 19 mm). Care is warranted however in the interpretation of this study, as no study has ever replicated this data in athletes, suggesting methodological and/or experimenter error (Nagashima et al., 2003).

Further data has been published among 331 extremely overweight Japanese professional sumo wrestlers (Kinoshita et al., 2003). Akin to previous data, similarly enlarged left ventricular internal diameters were documented among this ethnicity. LVIDd was greater than 60mm in 41% of athletes, with all presenting normal cardiac function. However, no control group was provided and thus investigator bias cannot be discounted. Given the anthropometric measures of the sumo athletes (mean height: 179±5cm; weight: 118±22kg; BSA: 2.34±0.2m^2) the significant correlation with LVIDd and these body size measures suggests that should scaling have been adopted, meaning than cardiac dimensions would fall in line with normality. Ultimately, it is clear that more research is needed among this ethnic group in order to build on the established knowledge base pertaining to the impact of ethnicity upon the east Asians athlete's heart.

2.6.3 Impact of Arabic (West-Asian) ethnicity

Data on the general Arabic population remains scarce, with limited knowledge regarding all aspects of cardiovascular health. Of the research conducted in this geographical area, researchers from Qatar did profile the incidence of congenital heart disease among Qatari children (Robida et al., 1997). The established rate of such conditions was elevated with regard to previous studies (12.23/1000), with ventricular septal defects (41%) accounting for the majority of these abnormalities. In the gulf region, parental consanguinity is common, which Robida et al., (1997) suggest may be a contributing factor in the greater number of congenital heart conditions than typically seen in other populations.

Athletes of Arabic descent are having an ever emerging presence in the international sporting stage, with 13 Arabic nations competing at the London 2012 Olympics. Wilson *et al* (Wilson et al., 2011c) identified that athletes from West-Asia had a greater prevalence of cardiovascular disease related markers; a notion potentially attributable to the rapid economic growth and widespread urbanization the area is going through. This coupled with a divergent demographic profile means it is inappropriate to blindly apply already established guidelines for physiological morphological remodelling for this ethnicity. With regard to the clinical interpretation of the athletes heart, Wilson *et al* (Wilson et al., 2012b) profiling of the ECG characteristics of Arabic athletes has been the only article to demonstrate any comparison between other ethnicities. The group found that in line with recognized ECG characteristics among other ethnicities, Arabic athletes demonstrated significantly more training related ECG changes than in the Arabic control group (90.4 vs. 77.8%) and uncommon changes apparently unrelated to training (7.9% vs. 0%). The electrocardiographic findings of the West Asian athletes were, however, comparable to those

of Caucasian descent. Moreover the 0.5% prevalence of SCD related conditions among the West-Asian athlete group was also consistent with that found among the Caucasian athletes. However, while aiding the clinical interpretation of the ECG, no further work has been conducted in this ethnicity.

2.7 Exercise related sudden cardiac death (SCD)

Having established the physiological determinants of the athlete's heart, it is essential to establish the mechanisms of sudden cardiac death (SCD) in young athletes, to allow for the differentiation of physiologic and pathologic changes and provide normative values among athletes of different sports and ethnicities.

The participation in sport is of benefit for both the young and general population. These benefits include reducing the risk of type two diabetes mellitus, cancers, depression and augmenting cognitive function and quality of life (Farrell et al., 2007, Helmrich et al., 1991, Lautenschlager et al., 2008, Blair and Morris, 2009, Camacho et al., 1991, Friedenreich and Orenstein, 2002). While offering protection, exercise can simultaneously act as a substrate for SCD among those with an underlying cardiovascular condition, increasing the risk of death 2.3 fold (Basso et al., 2013).

Sudden death in young athletes (<35 years) is predominantly cardiovascular in nature, with cerebral and respiratory causes rare (Thiene et al., 2012). Often deemed to be in the upper echelons of physical fitness, SCD is not a term immediately associated with high performing athletes. It is therefore a tragic and often highly publicized event should an athlete fall victim.

The precise prevalence of SCD varies widely, with numerous variables affecting interpretation, effectively leading to varying estimations among the different research groups. In an Italian prospective study the incidence among young athletes aged between 12-35 years was 2.3/100,000 (Corrado et al., 2003); with similar values recorded by others: Harmon *et* al, 2.3/100,000 (Harmon et al., 2011b); Steinvil *et al,* 2.6/100,000 (Steinvil et al., 2011). The incidence, in the USA, has been recorded to be much lower, with Van Camp reporting a prevalence of <1/100,000 among high school and college athletes. Following the documentation of SCD over 27 year period, an even lower prevalence was found (0.6/100,000) by Maron et al (Maron et al., 2009).

2.7.1 Issues with SCD data interpretation

The concern regarding a retrospective approach is that the true to risk of SCD via sporting participation is unknown. Typically, this is calculated by dividing the number of deaths per year (numerator) by the number of people playing sport per year (denominator). The first aspect to consider when calculating the numerator is the definition of SCD. SCD is generally classified as natural, unexpected death within one hour of the onset of symptoms (van der Werf et al., 2010). A pathologist's interpretation is also of importance because many sudden deaths are silent, as found in around 18% of cases (van der Werf et al., 2010), and unless a cardiac cause can be ascertained, the death will be categorized as sudden unexplained death. This can also lead to a misrepresentation due to missing certain ion channel disorders at autopsy (Sheppard, 2012a).

There are further problems with respect to the retrospective approach of data collection and are highlighted in the study conducted by Steinvil *et al* (Steinvil et al., 2011). Their methodology of

case identification consisted of the retrospective analysis of just two newspapers, asserting that because of the devastating nature of the incident and due to the two newspapers reaching 90% of the readership, then all cases would be covered. Such approach lacks any scientific rigour and thus their conclusion suggesting a prevalence of 2.6/100,000 cannot be deemed reliable. Drezner et al (2011) highlighted this issue, commenting on the lack of central registries providing an area of ambiguity (Drezner et al., 2011a), leading to the inappropriate method of searching media reports, with only 56% of SCD cases from an NCAA death registry being available in media reports (Harmon et al., 2011b). Further data from this group using the NCAA database found that only 89% of cases were reported, with only 20% confirmed via insurance forms. While this numerator has been shown to lack scientific validity, the same may be said for the denominator (Pedoe, 2004).

Understanding the denominator starts with the actual definition of a young athlete**.** Typically a young athlete is identified as someone under the age of 35 years, however what constitutes an athlete asks the question whether it be the number of hours spent training per week, the intensity training, and/or the type of sport. Once this has been established the number of athletes participating in sport must be determined, which can be somewhat difficult in practice. For example, Steinvil *et al* (Steinvil et al., 2011) ultimately failed to reliably quantify the number of athletes engaging in sport. They estimated the population at risk thanks to data from 2009 provided by the Israeli sports authority; however they then extrapolated these figures to the growth of the general population.

2.7.2 Mechanisms of Sudden Cardiac Death in Athletes

The majority of sudden deaths are attributable to cardiac causes, with 69% being identified as structural cardiac disease, yet in approximately 18% (van der Werf et al., 2010), no structural disease is identifiable upon autopsy; the result is a diagnosis of sudden unexplained death.

SCD is associated with a number of aetiologies that are age-dependent. Above the age of 35 years, even in trained athletes, the predominant cause of sudden cardiac death is that of atherosclerotic coronary artery disease (Zipes and Wellens, 1998). Below the age of 35 years, a number of inherited and congenital cardiac disorders predominantly the cardiomyopathies and ion chanelopathies are more likely to be the pathological substrate for SCD. The predominant causes are HCM, ARVC, anomalous coronary arteries and myocarditis and among athletes are commonly linked to physical exertion. Other less common conditions include dilated cardiomyopathy, aortic aneurysm, Long QT, WPW and idiopathic left ventricular hypertrophy(Maron, 2003).

Table 1. ECG features of cardiac diseases detectable at pre-participation screening in young competitive athletes. Corrado, D., Pelliccia, A., Bjørnstad, H. H., Vanhees, L., Biffi, A., Borjesson, M., Panhuyzen-Goedkoop, N., Deligiannis, A., Solberg, E. & Dugmore, D. Cardiovascular pre-participation screening of young competitive athletes for prevention of sudden death: proposal for a common European protocol Consensus Statement of the Study Group of Sport Cardiology of the Working Group of Cardiac Rehabilitation and Exercise Physiology and the Working Group of Myocardial and Pericardial Diseases of the European Society of Cardiology. *European heart journal,* 2005, 26**,** 516-524. With permission from Oxford University Press (Corrado et al., 2005b).

Disease	QTc Interval	P wave	PR Interval	QRS Complex	ST-interval	T wave	Arrhythmias
HCM	Normal	(Left atrial enlargement)	Normal	Increased voltages in mid-left precordial leads; abnormal Q waves in inferior and/or lateral leads; (LAD, LBBB); (delta wave)	Down-sloping (up-sloping)	Inverted in mid-left precordial leads; (giant and negative in the apical variant)	(Atrial fibrillation); (PVB); (VT)
ARVC	Normal	Normal	Normal	Prolonged >110ms in right precordial leads; epsilon wave in right precordial leads; reduced voltages ≤0.5mV in frontal leads (RBBB)	(Up-sloping in right precordial leads)	Inverted in right precordial leads	PVB with an LBBB pattern; (VT with an LBBB pattern)
Dilated Cardiomyopathy	Normal	(Left atrial enlargement)	(Prolonged ≥0.21s)	LBBB	Down-sloping (up-sloping)	Inverted in inferior and/or lateral leads	PVB; (VT)
Myocarditis	(Prolonged)	Normal	(Prolonged ≥0.21s)	(Abnormal 'q' waves)	Down- or up-sloping	Inverted in ≥2 leads	(Atrial arrhythmia); (PVB); (2^{nd} or 3^{rd} degree AV block); (VT)
Long QT syndrome	Prolonged >440ms in males >460ms in females	Normal	Normal	Normal	Normal	Bifid or biphasic in all leads	(PVB); (Torsades de pointes)
Brugada syndrome	Normal	Normal	(Prolonged ≥0.21s)	S1S2S3 pattern; (RBBB/LAD)	Up-sloping coved type in right precordial leads	Inverted in right precordial leads	(Polymorphic VT); (atrial fibrillation) (sinus bradycardia)
Lenegre disease	Normal	Normal	(Prolonged ≥0.21s)	RBBB; RBBB/LAD; LBBB	Normal	Secondary changes	(2^{nd} or 3^{rd} degree AV block)
Short QT syndrome	Shortened (<300ms)	Normal		Normal	Normal	Normal	Atrial fibrillation (polymorphic VT)
Pre-excitation syndrome (WPW)	Normal	Normal	(Shortened<0.12s)	Delta wave	Secondary changes	Secondary changes	Supraventricular tachycardia (atrial fibrillation)
Coronary artery diseases*	Prolonged	Normal	Normal	(Abnormal Q wave)	(Down-or up-sloping)	Inverted in >2 leads	PVB; (VT)

2.7.3 Hypertrophic cardiomyopathy (HCM)

HCM is a heterogeneous monogenic heart disease characterized by an unexplained non-dilated hypertrophied LV, in the absence of pressure overload or infiltrative disease (Maron et al., 2006). HCM has a prevalence of 1:500 in the general population (Maron et al., 1995b), and reported in over 50 countries (Zou et al., 2004, Hada et al., 1987, Maron et al., 2004b). Phenotypical expression varies widely among those with HCM, in terms of disease evolution, age of onset, the pattern and extent of LVH, degree of obstruction and of the risk for SCD (Ho, 2012); and while patients may present with symptoms (Alcalai et al., 2008), the vast majority are asymptomatic and the first expression of HCM is SCD. While age related penetrance for the disease has occasionally resulted in delayed appearance of LVH into the third decade (Maron et al., 2011a, Maron et al., 1999, Niimura et al., 1998), HCM typically has a high degree of penetrance (Clark et al., 1973, Maron et al., 1984a, Greaves et al., 1987), often manifesting itself phenotypically in adolescence.

HCM is inherited as an autosomal dominant trait and seen as a disease of the sarcomeral proteins (Seidman and Seidman, 2011), due to the mutation of genes encoding the contractile proteins (Maron et al., 2012). These factors stem from the histopathological remodelling which include the characteristic hallmark of myocyte disarray (present in up to 40% of cases) (Varnava et al., 2001); abnormalities of the intramyocardial small vessels (Maron et al., 1988), and myofibrillar disorganization and fibrosis (Sutton et al., 1980, Ferrans et al., 1972). In line with the heterogeneity of the disease, Sheppard (Sheppard, 2012a) noted that the degree of myocyte disarray may not be related to the degree of hypertrophy, and vice versa.

The precise mechanism by which sarcomere mutations lead to the aforementioned phenotypical expression is however not completely understood (Keren et al., 2008). The first genetic locus associated with HCM was the β-cardiac myosin heavy chain gene (MYH7) (Geisterfer-Lowrance et al., 1990). Together with myosin binding protein C (MYBPC3), they comprise the majority of mutations among the myofilament genes, accounting for around 80% of sarcomeric HCM (Ho, 2012), while mutations in genes encoding cardiac Troponin T, Troponin I, and a-Tropomyosin are less common accounting for between 1-5% of cases (Watkins et al., 1995, Thierfelder et al., 1994, Kimura et al., 1997, Landstrom et al., 2008). Since the early discovery of HCM mutations in MYH7 over 14000 mutations have been identified on at least 11 causative genes (Maron et al., 2012). Nevertheless it must be noted that a negative genetic analysis means that HCM cannot be conclusively ruled out (Marian, 2010, Bos et al., 2009).

This is particularly pertinent given that intrafamilial heterogeneity is common, suggesting that sarcomere mutations are not solely responsible for the HCM phenotype (Maron and Maron, 2013). This is exemplified in morphological features such as mitral-valve enlargement, microvascular abnormalities and segmental LVH not being fully determined by current disease causing mutations and thus could be indicative of a possible role for environmental factors and modifier genes (Maron and Maron, 2013, Maron et al., 2011b).

Consistently the greatest cause of sudden death in young people, HCM accounts for 1/3 of deaths (Van Camp et al., 1995, Maron, 1996, Maron et al., 2009). Responsible for a 2.6 fold increase in mortality risk, exercise has been shown to be a potent stimulator of associated tachyarrhythmias (Deo and Albert, 2012). Most cases of SCD attributed to HCM are seen among athletes

engaging in dynamic, intermittent sports such as basketball and football (Sheppard, 2012b). Rarely are deaths seen in endurance athletes, and it has been hypothesized that the combination of myocardial hypertrophy, impaired myocardial relaxation, myocardial ischemia and dynamic LV outflow tract obstruction impede augmentation of stroke volume for long periods, selecting out endurance sports to those with the condition (Chandra et al., 2013). Despite this, incidences have occurred among athletes competing in cross country (Roberts and Stovitz, 2013), marathons (Maron et al., 1984b) and ultra-marathons (Wilson et al., 2011a). In spite of no firm supportive clinical or experimental data (Pelliccia et al., 2008b), such findings have led to the two leading guidelines from both European and American criteria for sports eligibility recommending that athletes should be disqualified from all sports barring those of low static, low dynamic intensity (Maron et al., 2005, Pelliccia et al., 2005a).

2.7.4 Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

ARVC is a myocardial disease primarily affecting the RV characterized by a high incidence of arrhythmias and SCD (Basso et al., 2009a). The phenotypical presentation also extends to fibrofatty replacement of myocardial tissue and was first clinically described comprehensively in 1982 (Marcus et al., 1983), with additional electrocardiographic features being later recognized such as the epsilon wave (Fontaine et al., 1977).

The disease has a purported prevalence of 1 in 2000-5000, however it has been suggested that due to underreporting an incidence rate of 1 in 1000 may be more realistic (Sen-Chowdhry et al., 2010a, Corrado et al., 2006, Nava et al., 2000, Peters et al., 2004, Murray, 2012). Noted as originating from both an autosomal dominant and recessive patterns of inheritance (Paul et al.,

2012) It was not until 2000 that the first gene associated with the disease was discovered (plakoglobin) (McKoy et al., 2000) and since then, mutations in five genes (junction plakoglobin (JUP), desmoplakin (DSP), plakophilin-2 (PKP2), desmoglein-2 (DSG2) and desmocollin-2 (DSC2)) that encode key components of desmosomes have been identified as key protagonists in ARVC development. (Rampazzo et al., 2002), (Gerull et al., 2004), (Pilichou et al., 2006, Syrris et al., 2006), Previous studies have shown that although it is genetically determined, the disease is not present at birth, typically being diagnosed after maturation when the clinical signs are apparent, yet cardiac arrest may sometimes be the presenting manifestation

ARVC has been particularly noted for not being present at birth and thereafter having an unpredictable progression, spanning adolescence to adulthood. (Basso et al., 1996) (Basso et al., 2009b, Nava et al., 2000, Thiene et al., 1988, Bauce et al., 2011). In the latter stages of its progression, associated structural adaptations may lead to regional wall motion abnormalities, ventricular aneurysms and increased trabeculation (te Rijdt et al., 2013, Paul et al., 2012). At a cellular level, myocyte loss may be accompanied by inflammation, fibrosis, and adiposis (Sen-Chowdhry et al., 2010a, Corrado et al., 1997). In addition to the substantial fat replacement however, the presence of replacement type fibrosis and myocyte degenerative changes are vital for the determination of a clear cut diagnosis (Basso et al., 2009a).

Complicating the issue is the possible contribution of environmental factors include age, sex and strenuous exercise (Sen-Chowdhry et al., 2010b). Strenuous exercise and prolonged athletic training itself has been documented to cause an earlier onset and more rapid progression of the condition (Basso et al., 2007). Following a 20 year prospective study of young people among the

Veneto region of Italy, ARVC presented the second highest risk of sports related sudden death with a relative risk of 5.4 when compared to non-athletes; corresponding to 22% of SCD among athletes and 10% in non-athletes (Corrado et al., 2003). Exercise *per se* is not the cause of the enhanced mortality but triggers arrhythmogenicity that ensues as a potential substrate for SCD. The adverse effects of exercise on the phenotypic expression of ARVC were investigated among heterogeneous plakoglobin deficient mice by Kirchhof *et al* (Kirchhof et al., 2006), whereby the authors observed that endurance training caused premature ventricular dilation and dysfunction and more frequent and severe arrhythmias in the plakoglobin deficient mice. The mechanisms for this path of action has yet to be fully elucidated however the action of exercise acutely increasing RV afterload and cavity enlargement may be the source of ventricular arrhythmias by stretching the diseased myocardium (Douglas et al., 1990).

2.7.5 Coronary Artery Anomalies (CAA)

Non-atherosclerotic coronary disease has numerous forms including coronary artery dissection, vasculitis, spasm, idiopathic arterial calcification and fibromuscular dysplasia; however the most commonly identified abnormality is the anomalous coronary artery(ies), accounting for 48% of all such related cases of SCD. While HCM and ARVC have been most commonly identified as the leading cause of exercise related SCD, anomalies of the coronary artery origin also constitutes a significant proportion (3% to 33%) (Hill and Sheppard, 2010, Corrado et al., 1992, Burke et al., 1991, Maron et al., 1980, Maron, 2003, Topaz and Edwards, 1985, Chandra et al., 2013, De Noronha et al., 2009a, Suárez-Mier and Aguilera, 2002).

CAAs are characterized by deviation from the original location of one of the coronary arteries. Coronary artery anatomy is normally characterized by two ostia centrally placed in the right and left sinus of Valsalva; the left ostia hosts the origin for the location of the main left coronary artery (LCA), which branch into the left anterior descending and circumflex artery, and the right coronary artery arising from the right ostia (Hauser, 2005). Malformations in this anatomy, whereby the anomalous origin of a coronary artery stems from the opposite sinus are rarely suspected and often go undetected, even among cardiovascular pre-participation screening (Corrado et al., 1998, Maron et al., 1996c). This causes great concern considering that the malformations are more commonly identified among competitive athletes than in non-athletes (Corrado et al., 1998).

Myocardial ischemia is one of the consequences of aortic sinus coronary artery anomalies, resulting in patchy myocardial necrosis and fibrosis. This particular histology is due to infrequent bursts of ischemia, identified by the fact that trained athletes have often performed intense activity many times before a fatal event (Basso et al., 2000). Numerous mechanisms have been proposed to explain myocardial ischemia and SCD in these patients. These include the acute angle take off and kinking of the coronary artery as it arises from the aorta, and the flap like closure of the abnormal slit like coronary orifice and anomalous artery spasm (Taylor et al., 1992). Among athletes however, the mechanistic effect of intense exercise may cause compression of the coronary artery between the aorta and pulmonary trunk (Basso et al., 1995), or alternatively pull and thereby induce the occurrence of ostial-like ridges (Nakahara et al., 2012). Linked to this, is the fact an athlete with CAA is 79 times more likely to have a SCD than a non-athlete (Corrado et al., 2003).

2.7.6 Primary Cardiac Electrical Abnormalities

2.7.7 Congenital QT syndromes

Both long QT (LQTS) and short QT (SQTS) syndromes are genetically mediated conditions potentially provoking ventricular arrhythmias and associated SCD. LQTS has a prevalence of around 1:2000 in the general population (Schwartz et al., 2009), typically found alongside a structurally normal heart and is characterized by delayed repolarization of the myocardium and QT prolongation on the ECG. Ventricular repolarization is determined by cardiac ion channel proteins and how they regulate the movement of sodium, potassium and calcium ions across myocellular membranes. In this regard, the condition is mainly caused by mutations in the genes that encode for protein subunits of cardiac ion channels. Specifically, these genes encode for either macromolecular complex-forming ion channels or their regulatory peptides. The mechanistic action of these mutations prolongs the QT interval by either impairing repolarization currents or by increasing the depolarization currents (Napolitano et al., 2012). Despite this, it must be noted that in spite of its nomenclature, a long QT-interval in isolation is not the complete fulfilment of the diagnostic criteria (Schwartz et al., 1975).

In the early 1990's, a molecular genetic basis for LQTS was established and the concomitant disclosure of various attributable mutations (Wang et al., 1996, Wang et al., 1995). Since this early breakthrough, mutations in the first 3 genes identified (KCNQ1, KCNQ2 and SCN5A) comprise the majority of LQTS cases (80-90%) (Napolitano et al., 2012). There have nevertheless been 13 variants of LQTS identified, and while all are categorized as ion chanelopathies they each elicit varying degrees of disease severity, and the type and location of the mutation further determines the expression of the phenotype (Moss, 2003).

Of note, Scwartz *et al* (Schwartz et al., 2001) identified that in addition to individual ECG presentations, each genetic variant of the condition has its own distinguishing trigger for life-threatening arrhythmias. Among the predominant forms of the LQTS family, LQT3 patients become symptomatic at rest and during sleep, LQT2 patients have arrhythmias triggered by emotional events or auditory stimulation (Wilde et al., 1999), while those with LQT1 are more susceptible to death during physical exercise and in particular swimming (Ackerman et al., 1999).

Despite physical activity acting as a trigger among the common LQT1 syndrome, the condition is rare among athletes. reported a prevalence of 0.4-0.69% (Corrado et al., 2006, Basavarajaiah et al., 2007b). Moreover, the prevalence of LQTS may indeed be underestimated and alternatively classified as unexplained sudden death syndrome, due to its impossible detection at autopsy (Sheppard, 2012a). The low death rate in LQTS implies that the majority of causal mutations are either benign or the criteria used to identify LQTS is incorrect (Basavarajaiah et al., 2007b). The 2005 Bethesda guidelines and the European society of cardiology (ESC) guidelines recommend disqualification from all but class IA sports in athletes with genotype positive, phenotype positive LQTS (Zipes et al., 2005), while ESC further recommend disqualification in genotype positive phenotype negative athletes. In spite of these guidelines being issued, athletes still retain the ability to make informed choices regarding their future. Importantly, Johnson and Ackerman (Johnson and Ackerman, 2013) found that among 130 clinically diagnosed athletes with LQT and continued to play sport, none of the genotype

positive but phenotype negative athletes had an adverse effect, with only one ICD shock performed in a phenotype positive/ genotype positive athlete due to an adverse cardiac event.

2.7.8 Brugada Syndrome

Brugada syndrome is a somewhat newly established disease, identified in 1992 following the presentation of 8 individuals with recurrent episodes of aborted sudden death unexplained by know diseases (Brugada and Brugada, 1992). Based on clinical and electrocardiographic examination it differs from idiopathic ventricular fibrillation with the defining presentation noted as abnormal repolarization in the presence of RBBB, while posing a 30% risk of cardiac arrest (Brugada et al., 1998). The ECG pattern of Brugada syndrome may often be masked due to a dynamic ST segment elevation and thus may obscure the actual prevalence. Consequently, best estimates range of 4-12% of all sudden cardiac deaths (Antzelevitch et al., 2005).

It is an arrhythmogenic disease of an autosomal dominant inherited nature. Mutations in the gene that encodes for the α-subunit of the cardiac sodium channel gene, SCN5A account for 18-30% of Brugada cases, with over 300 mutations now linked to the syndrome (Chen et al., 1998, Balser, 2001, Antzelevitch, 2001, Kapplinger et al., 2010). The mutations are classically of a loss-of-function mechanism leading to the decrease in sodium current due to the expression of non-functional channels, decreased membrane channel expression or altered gating properties (Amin et al., 2010). In recent years, additional mutations in β-subunits have been related to Brugada syndrome and specifically that of SCN1B and SCN3B (Hu et al., 2009, Hu et al., 2012, Riuro et al., 2013). The three predominant types of Brugada syndrome are categorized based upon their ECG morphology, which is mechanistically determined by the varying degree of

transmural voltage gradient between the epicardium and endocardium; creating transient outward potassium current mediated notch in the ventricular epicardium but not endocardium (Antzelevitch, 2001).

The prognosis of patients with Brugada syndrome is still being debated. Among those with symptoms, there is universal acceptance that ICD implantation should be the primary treatment. Among those without symptoms however, the risk stratification is less clear. Priori *et al* (Priori et al., 2000) demonstrated that among their cohort of 30 asymptomatic patients no arrhythmic event was experienced over a 33 month period. Conversely, a meta-analysis of over 1500 patients showed that a history of syncope or SCD, male gender, and the spontaneous appearance of a type 1 ECG are all associated with an increased risk of arrhythmic event. Little work has been conducted in assessing the risk of athletic activity among those with Brugada syndrome; however as ventricular fibrillation and sudden death occurs more commonly during sleep SCD appears to be unrelated to exercise.

2.7.9 Wolff Parkinson White (WPW)

WPW is one member of the family of pre-excitation disorders. Normally the atria and ventricle are isolated chambers with electrical conductance only linked through passage to the AV node. In WPW however, the electrical conductance supplements this path by means of travelling through the bundle of Kent; doing so earlier than through the AV node, potentiating the ventricle to contract prematurely (Rao et al., 2013). This abnormality presents itself on the ECG as a shortened PR interval (<120ms) and widening of the QRS (>120ms) (Surawicz et al., 2009); in addition to the characteristic delta wave, seen as slurring of the initial QRS complex (Drezner et

al., 2013c). The substrate for SCD in those with the condition is through the short circuiting of this pathway, inducing tachycardia, atrial fibrillation and the potential consequential arrhythmia of ventricular fibrillation. It occurs in approximately 1:1000 of the athletic population (Pelliccia et al., 2007), and has been shown to account for 1% of SCD (Maron et al., 2009). All athletes with WPW should undergo electrophysiological study, and ultimately if the refractory period is increased, ablation is indicated. Fortunately for athletes, following this procedure, return to athletic participation is permitted following the completion of a 3 month period (Chandra et al., 2013).

2.8 Pre-participation screening

The majority of conditions implicated in SCD do not necessarily present with symptoms in the affected individual; often with SCD being the first presentation of any pathological condition. Together with the increased risk of SCD among athletes, pre-participation screening among this population is the most practical means of identifying young athletes at risk of these potentially fatal cases (Ghani and Sharma, 2012). The National Heart, Lung and Blood Institute stated that SCD in young athletes is a critical public health concern and that additional research and resources are needed to advance its prevention (Kaltman et al., 2011). Indeed both the American heart association (AHA) and the European society of cardiology (ESC) advocate the implementation of pre-participation screening for young athletes on the basis of ethical, legal, and medical grounds (Maron et al., 2007b, Corrado et al., 2005b). Despite this common appreciation of the need for screening, the methodology of best practice varies between these associations.

Cardiovascular pre-participation screening is by consensus understood to include a personal symptom and family history questionnaire, brachial artery blood pressure and physical examination; the disparity comes with regards to the inclusion of the resting ECG and whether this is a beneficial addition to the screening protocol.

2.8.1 The American Heart Association (AHA) approach

The American approach does not advocate the inclusion of the ECG, commonly citing the cost effectiveness and high false-positive rate as the basis for this viewpoint. In practice there are however evident limitations. For this, one must consider that the principle reasoning behind pre-participation screening must be to detect conditions which may predispose athletes to SCD. With this in mind the American method of screening offers a very low sensitivity and thus detection of the aforementioned conditions, a fact demonstrated by Maron *et al* (Maron et al., 1996b) who reported only 1 death out of 155 SCD's were identified using questionnaire and physical exam alone. Similar research carried out among various other groups from both Europe (Italy and the United Kingdom) and the U.S.A have echoed these findings (Pelliccia and Maron, 1995, Wilson et al., 2008b, Maron et al., 1982). After screening 1074 national and international athletes, Wilson et al (2008b) failed to identify pathology in any of the 9 athletes with a confirmed diagnosis of cardiac disease using personal symptom and family history questionnaires. Even ominous symptoms such as repeated syncope during exercise produced negative findings. The study highlights the unsuitability of using this approach in isolation; demonstrating the need for a validated questionnaire to be used and additionally ensuring the suitable interpretation of the questions by a trained physician.

In support of the AHA standpoint, a comparative study between the demographically similar Veneto region of Italy and Minnesota in the USA demonstrated similar levels of SCD, despite the differing screening approaches (Corrado et al., 2011). The similar magnitude of SCD in the most recent years (1993-2004), incidence was 0.87 vs. 0.93/100,000 respectively. Although the authors used SCD as a surrogate measure of screening performance, Baggish *et al* (Baggish et al., 2010a) demonstrated increased specificity of screening without ECG among a cohort of 510 collegiate athletes, where 5 out of 11 with underlying cardiovascular abnormalities were found. Sensitivity of the screening was 46% and abnormalities were only established through further testing with echocardiography. Ultimately, the authors do however concede that screening with ECG improves the overall sensitivity and may be necessary to detect those with pathology.

This lack of sensitivity of pre-participation screening without the use of ECG may be based around the reliability and validity of the questionnaire in use. Quantification of symptoms from questionnaires is difficult, with the definition of the subjective measures of chest pain and dizziness varying from patient to patient. Wilson *et* al (Wilson et al., 2008a) emphasized this point documenting that among 2720 young people who presented with adverse symptoms in a cohort of; all were entirely healthy. Other issues include difficulty or inaccuracy in the recollection of family history. Alternatively, a certain aspect of bias may present, whereby they refuse to reveal certain problems in case it means a failure to sign the often lucrative sporting contract. Furthermore, while many questionnaires have been proposed, there is still no data pertaining to their positive and negative predictive values. The family history questionnaire in the USA, in accordance with the AHA and the Pre-Participation Physical Evaluation Monograph suggest asking about a family history of heart problems or sudden death in relatives younger than

50 years of age. However, this higher age limit to screening enhances the potential for a greater number of false positives due to the common presence of coronary artery disease in individuals >35 years (Asif and Drezner, 2013).

One basis for not including the ECG as part of pre-participation screening is the cost effectiveness of screening. Based upon an athlete receiving a single ECG examination and any subsequent testing needed to exclude false positive results, the AHA estimated that, in the USA, the direct cost of preventing one SCD was about $3.4million (Maron et al., 2007a); while others highlight that should the cost of infrastructure and indirect costs be accounted then this value would be even further increased (Shephard, 2011).

In spite of this evidently high cost, the majority of studies conclude that cardiac screening without ECG is the least cost effective of all options (Borjesson and Drezner, 2012). When adopted it has been suggested that ECG led screening comes below the ceiling ratio deemed acceptable for medical interventions, with cost effectiveness ratios of $42,900 and $44,000 per life year saved (Wheeler et al., 2010, Fuller, 2000). The nature of adopting the quality of life years saved (QUALY) in the field of sports cardiology has however come into question. In such studies the incidence of SCD among the athletic population has to be determined, these figures are often based upon vague methods. Drezner (Drezner et al., 2011a) highlighted this issue, commenting on the lack of central registries providing an area of ambiguity. This potentially leads to the inappropriate method of retrospectively searching media reports; a method shown to identify only 56% of SCD cases (Harmon et al., 2011b).

A further concern with the current implementation of QUALY is that without longitudinal data the aforementioned studies have estimated costs of procedures, based upon prices 6 years old. Wheeler et al. (Wheeler et al., 2010) calculated the SCD among the American population extrapolated from that calculated from an Italian institution, opening up an area for inaccuracy, with different rates of SCD between the two countries having been previously detailed. Ultimately, the main purpose of pre-participation screening is to detect silent conditions which may predispose the athlete to SCD. Whilst there are athletes who do present with symptoms, 80% of athletes diagnosed with a cardiac pathology are asymptomatic (De Noronha et al., 2009a), making the AHA recommendations limited in clinical utility.

2.8.2 The European Society of Cardiology approach

The approach typically associated with the European nations includes the utilization of the ECG, based upon its greater sensitivity in detecting underlying pathological conditions. While generically labelled as European, it is not restrictive to this geographical continent and indeed has been adopted among various sporting organizations, including FIFA and the International Olympic Committee.

Pre-participation screening with the inclusion of ECG has been mandated among young athletes in the Veneto region of Italy since 1982 (Pelliccia and Maron, 1995). Longitudinal trends of SCD death rates after the implementation of screening have seen an 89% reduction (Corrado et al., 2006); decreasing from an admittedly high 3.6/100,000 to 0.4 sudden cardiac deaths per 100,000. The authors state that the findings present a true reflection of the screening implementation and contest opposition stating there was coincidental timing between the

programmes initiation and the decline in SCD. Moreover, as the prevalence of SCD was declining in the region, there was a concomitant plateau in the rate among the unscreened age-matched general population (Figure 1). Nevertheless a notable limitation to the study was the retrospective data collection and with only two years of data preceding the legislation of mandatory screening, with the decreased SCD incidence potentially being attributable to other factors (Shephard, 2011). Furthermore, in addition to a high starting prevalence, the incidence at the time of publication was still higher than that experienced among some nations who do not mandate such screening including America and Denmark (Drezner et al., 2008, Holst et al., 2010).

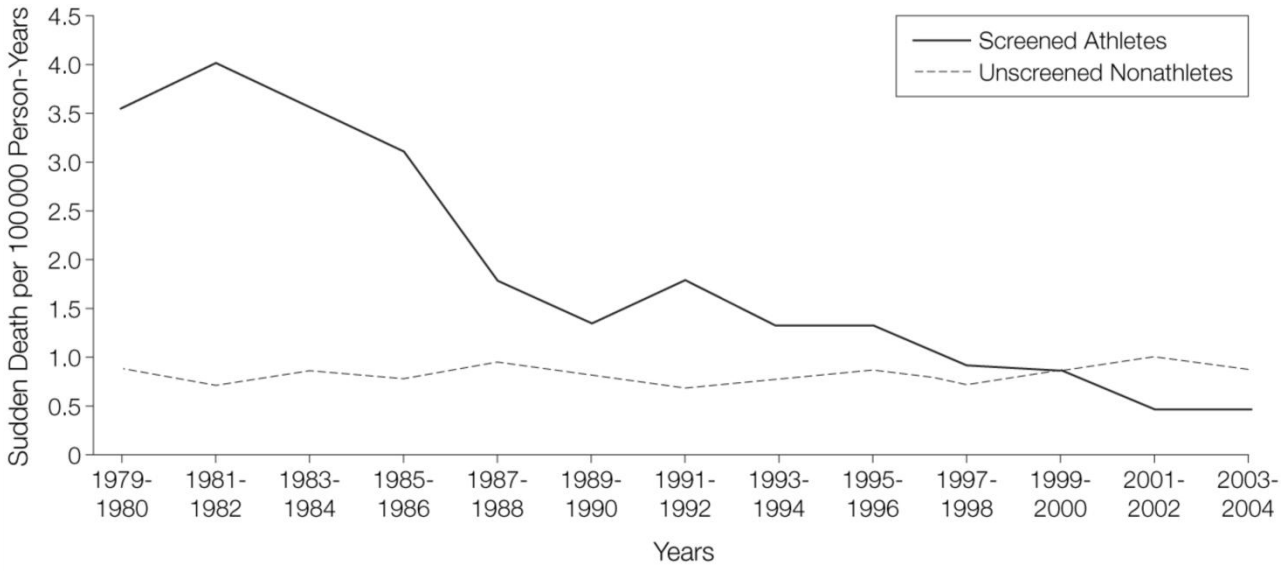


Figure 1. Annual incidence of sudden cardiac death in screened competitive athletes compared with unscreened non-athletes in Veneto region of Italy. (Reproduced from: Corrado D, Basso C, Pavei A, Michieli P, Schiavon M, Thiene G. Trends in sudden cardiovascular death in young competitive athletes after implementation of a preparticipation screening program. JAMA. 2006;296:1593–601. © American Medical Association, Chicago, USA. Reprint with kind permission (Corrado et al., 2006).

One major criticism of the ESC protocol is the failure to meet the WHO criteria for a successful screening programme, and although such criterion derives from 1968 the failure to meet these

points is evident (Wilson and Jungner, 1968), with antagonists implicating the low prevalence of SCD as a critical factor. Despite this, many years of an individual's life may be saved, and as such, any athlete death cannot be seen as acceptable (Papadakis and Sharma, 2009).

The associated concerns regarding ECG screening have been based around the high rate of false-positives, in the region of between 15 and 40% (Pelliccia et al., 2000a, Maron et al., 1987). Despite this, the developments in ECG criteria and understanding have progressed significantly since the early studies and represent a platform for lowering this value. In 2010, the ESC guidelines for ECG interpretation were revised, based upon large population studies in non-select groups of athletes. Of these updates one incorporated change of note was to accept that an isolated voltage criterion for LVH is a normal variant in young athletes. This alone was the factor among a study by Weiner *et al* for the decrease in false positives from 16% using the 2005 ESC guidelines to 10% with the updated 2010 version, and was achieved without compromising sensitivity (Weiner et al., 2011).

The continuing research in the area has led to further developments and in 2013 the 'Seattle Criteria'(Drezner et al., 2013b) has acknowledged the developing understanding of ethnicity as an impact upon electrocardiographic changes; in particular among African and Afro-Caribbean Black athletes. Following the evidence that 25% of Black athletes demonstrate T-wave inversions, and that those seen exclusively in V1-4 among this population are of a benign nature, the 'Seattle Criteria' suggests that this is a physiological finding and warrants no further testing; in turn allowing for a further decrease in the rate of false positives (Papadakis et al., 2011c). Work from Brosnan *et al* (Brosnan et al., 2013a) revealed the enhanced efficacy of the new

criteria, citing a decrease in the false positive rate from 17 to 4% among a cohort of 1197 elite athletes residing in Australia. This represents a significant improvement of the new criteria, and the authors mainly attribute this to the reclassification of 6.6% of athletes with equivocal QT findings and athletes with anterior T-wave inversions (3.9%). Ultimately these findings suggest that using the most contemporary guidelines significant cost savings will be made, whilst again not compromising the detection of underlying pathological conditions. Nevertheless, while a false positive rate of just 4% is within the realms of acceptability for a screening protocol, the cohort of athletes used was ethnically homogeneous. It therefore asks the question whether this false positive rate is replicable among other ethnicities, especially among athletes of Arabic and African descent. In this vein, more research is needed to assess this concern; after which the true suitability of the recent ECG interpretational guidelines can truly be elucidated.

In association with the false positive rate, the onus is on the successful ECG interpretation conducted by the affiliated cardiologist/physician. In this regard, Viskin *et al* (Viskin et al., 2005) presented findings questioning the reliability of this interpretation among those with LQTS. Twenty five world renowned LQTS experts, 106 arrhythmia specialists, 329 cardiologists and 442 non-cardiologists were presented four ECGs two of which had LQTS. The main findings highlight the disparity between the doctors field of expertise, and while 89% of arrhythmia experts correctly identified the QT interval, less than 50% of the cardiologists did so, with a large standard deviation between them of over 12%.

Whilst it is impractical to have experts in each particular area assessing all ECGs, it has been suggested that for this reason pre-participation screening should only be conducted by expert

cardiologists or other physicians with an interest in the cardiovascular adaptations to exercise (Papadakis and Sharma, 2009). A means to improve this has been targeted at developing the knowledge of sports physicians of what is normal or abnormal and distinguishing physiological adaptation to that of pathology. Drezner and colleagues tested this hypothesis by presenting 40 ECGs (28 normal, 12 abnormal) to 60 physicians and asked them to interpret them with and without published guidelines. They found that among physicians with varying expertise accuracy of the interpretation increased significantly from 77% to 92% and specificity and sensitivity both increasing from 70-91% and 89-94% respectively (Drezner et al., 2012). Regardless of the publication of guidelines, opinion implies that most sports medicine and cardiology training programmes lack a standard educational curriculum on ECG interpretation in athletes (Drezner et al., 2013a). In turn the publication of the 'Seattle Criteria' has been used by the authors to develop an online training module for physicians to acquire the fundamental knowledge and skills necessary to facilitate ECG interpretation in athletes (Drezner et al., 2013a). The primary aim of this is to enhance the efficacy of ECG led pre-participation screening and to decrease the number of false-positive cases.

As greater numbers of organizations adopt the European model, the greater number of athletes screened will facilitate the improvement in screening methodology, helping to minimise false positive and false negative results and stop unnecessary disqualifications. While ECG led programmes do display relatively high sensitivity in the recognition of most pathological states as 90% of patients with HCM and the majority of those with ARVC (Wilson et al., 2012a) present an abnormal ECG, there is the potential for false negatives from using ECG alone.

Furthermore, many anatomical abnormalities do not present ECG abnormalities such as CAA, bicuspid aortic valves or mitral valve prolapses.

The echocardiogram is generally accepted as the primary modality for further examination following the identification of an abnormal ECG, however it can also aid in the identification of such conditions as the bicuspid aortic valve and CAAs. Based upon this premise, Fédération Internationale de Football Association (FIFA) is a sporting organisation that recommends systematic echo to be included in the routine screening of their affiliated football players. The approach is however not based upon scientific evidence, believing that including echocardiography is a more robust CV screening protocol. More research should be undertaken to examine the clinical and ecnomic value of systematic echocardiography to establish if systematic echocardiography represents a cost- and clinically effective means to identifying cardiac pathology.

2.9 Literature Review Summary

It has been demonstrated that although the differentiation between physiological and pathological remodelling of the heart is not a new concept, it still generates a dilemma for the responsible physician; particularly exacerbated among high level athletes where the 'athlete's heart' is often seen as the rule as opposed to the exception. In particular there are several factors contribute to the manifestation of significant cardiac remodelling among athletes. Of these, in addition to the effects of extreme anthropometry, it is evident that ethnicity has a pivotal role within both the physiological development of the athlete's heart, and importantly the prevalence of pathological conditions linked to SCD. Considering the current dearth of research and the

emerging presence of not only African athletes, but Arabic athletes in the upper echelons of professional sport, it is of vital importance to establish whether such athletes of this ethnicity have divergent cardiac adaptation to the physical stressors of strenuous training and competitive sport.

The latter half of the literature review examines current concepts of pre-participation CV screening. In addition to establishing cost effectiveness, the implications of screening sensitivity and specificity are important, with both false positive and false negative rates having potentially life changing consequences on an athlete's career. Considering the noted debate surrounding pre-participation screening, efforts must be made to fully determine best practice. This relates not only to the inclusion of the ECG but also the echocardiogram. With these points in mind, the current thesis will expand upon this existing knowledge and explore the under-investigated concept of the Arabic athlete's heart. Given this unique subset, and substantial number of athletes we are presented with in Qatar we will not only be able to relate our findings of the Arabic athlete's heart with those of other ethnic origins, but aim to uncover the clinical significance of extreme anthropometry. Using our large scale cohort of ethnically diverse athletes we also aim to add a unique perspective to the debate regarding the adoption and best practice of cardiovascular pre-participation screening in athletes.

CHAPTER THREE

3.0 General Methods

All data presented in this thesis was collected at Aspetar Sports Medicine Hospital in Qatar. In the state of Qatar, every athlete registered under the remit of the Qatar Olympic Committee must undergo full pre-participation screening. For completeness, this screening includes musculoskeletal, dental, haematological and cardiovascular screening; and is entirely government funded without financial reliance upon charitable or public health sector institutions.

We considered an athlete someone who was training regularly (>6 hours per week) and competing in structured competition with the aim of sporting excellence, and as previously stated must be registered with the Qatar Olympic Committee. When utilised, Arabic control participants were not sedentary, but exercised ≤ 2h/week. For the purpose of this thesis, any subsequent analysis for publication was restricted to male athletes and those between the ages of 12-35 years.

Athletes presenting for screening were not restricted to those from Qatar, and indeed consisted of athletes from 95 different countries. From this we categorised athletes into distinct categories with regards to their ethnicity; these being Arabic, Black or Caucasian. Any athletes outside of these brackets, was not included in any ethnicity specific analysis. The term "Arabic" denotes individuals of Gulf or Middle-Eastern descent, and "Black African" denotes individuals of African descent. Arabic athletes were recruited from 7 Gulf States (Qatar, Bahrain, Oman, UAE, Kuwait, Yemen and Saudi Arabia) and Middle-Eastern countries such as Egypt, Tunisia, Algeria, Jordan, Palestine and Iraq). Black African athletes were those from African countries such as

Sudan, Somalia, Ghana, Nigeria, Chad, Ivory Coast, Senegal, Cameroon and Ethiopia. The third group were those of Caucasian athletes, with these athletes descending from countries such as the U.S.A, Canada, Australia, Russia, Bosnia, Serbia and Croatia.

Strict exclusion criteria included individuals that had undergone previous cardiovascular screening with electrocardiography (ECG) and echocardiography. This was important as the population truly reflected those individuals who had not been excluded from competitive sport on the suspicion of harbouring an inherited cardiac pathology.

3.1 Systematic cardiovascular screening protocol

An all-encompassing systematic cardiovascular screening process was adopted, and therefore included a comprehensive anthropometric assessment, a full personal symptom and family history questionnaire, physical examination, 12-lead ECG and an echocardiogram. Should an abnormal finding be detected, further testing is available onsite to confirm or dismiss a pathological origin.

As a FIFA accredited F-MARC medical centre of excellence, football players were screened using FIFA's tailor made pre-competition medical assessment (PCMA). Modelled around the IOC pre-participation evaluation, and the IOC derived Lausanne recommendations the cardiovascular section of the FIFA PCMA is an extensive 55-step document excluding the ECG and echocardiogram sections; taking a 'tick box' approach with specific sections for symptoms experienced prior to or within the last 4 weeks. Non-football players undergo a very similar questionnaire but use the European Society of Cardiology guidelines. This is a more streamlined approach to that of the FIFA questionnaire, excluding questions such as whether the athlete has

asthma, a cough, or consumes alcohol, in addition to the omission of questions pertaining to the broader health of family members such as whether any have cancer or diabetes. Athletes completed the questionnaire regarding family history and personal symptoms in collaboration with an Arabic, French or English speaking cardiac nurse.

Anthropometric assessment included measurement of height (Seca, United Kingdom) and body mass (Detecto, U.S.A.), in addition to left brachial artery blood pressure (BP) which was measured digitally (GE DINAMAP PRO 400V2, New York U.S.A). A sports medicine physician conducted the assessment for any physical characteristics of Marfan's syndrome including precordial auscultation, which was done so in both supine and standing positions.

3.2 ECG

A standard 12-lead ECG was obtained using a GE Mac 5500 (New York U.S.A) following 5 minutes of rest in the supine position. All ECGs were independently reported by two experienced investigators; with a third opinion sought from two international cardiologists should there be a dubious case. The analysis of whether an ECG is normal or abnormal has been in conjunction with several interpretational criteria. Advancing knowledge led to two subsequent reclassifications since the initiation of this research process. Both take similar forms as the 2010 ESC guidelines in terms of classifying ECG patterns as either training related and physiologically derived (Type 1), or training unrelated abnormal findings potentially associated with pathology (Type 2), however make notable changes aimed at improving specificity. Chapters 4 and 5 include articles which have adopted the 2010 European Society of Cardiology guidelines (Corrado et al., 2010), with these being the most current and up-to-date at the time of

publication. The third article in this thesis, documented in chapter 6 used the 2013 Seattle criteria. The fourth article, found in chapter 7 was a direct comparison of these two ECG interpretational criteria, compared to the recently published 2014 'Refined' criteria (Sheikh et al., 2014a). Table 2-3 below demonstrates the continuing flux of ECG interpretation in athletes, with this being evident in terms of both the definition of patterns and the true benignity of said patterns.

Table 2. Common training related ECG changes among athletes, as defined by the ESC, Seattle and Refined interpretational guidelines.

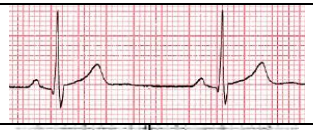
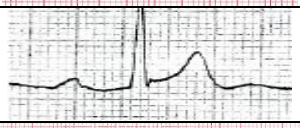
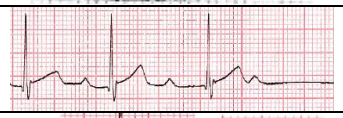
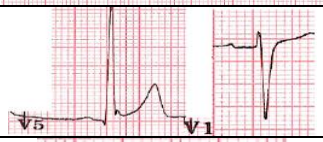
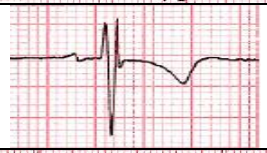
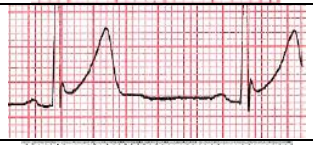
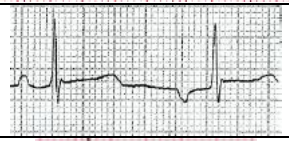
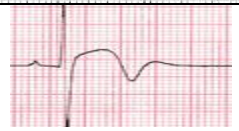
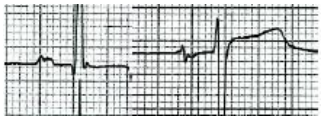
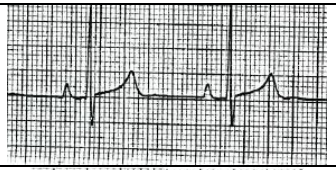
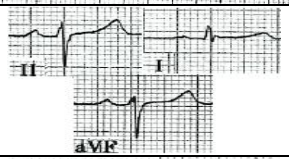
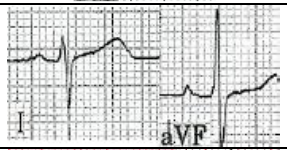
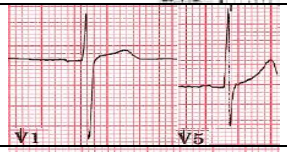
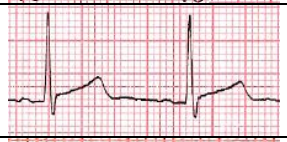
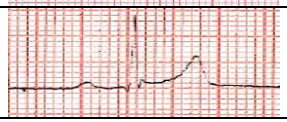
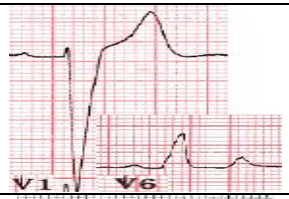
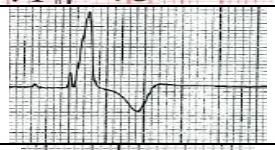
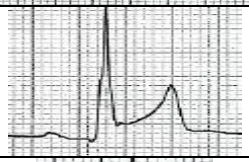
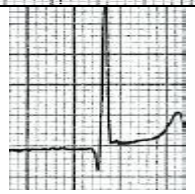
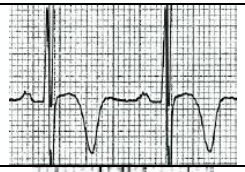
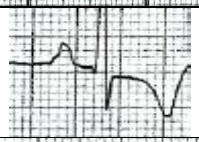
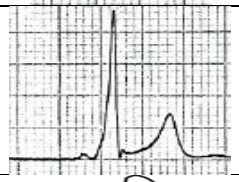
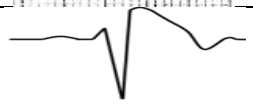
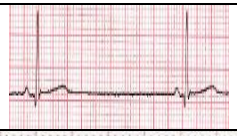
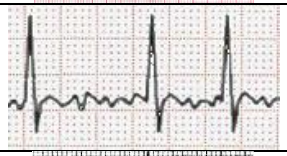
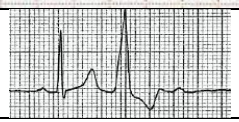
Common/training related	Description	ESC	Seattle	Refined
Bradycardia		<60bpm	As ESC	As ESC
First Degree AV Block		PR interval >200ms	As ESC	As ESC
Mobitz Type 1		A lengthening PR interval until a beat is dropped	As ESC	As ESC
Isolated LVH		Sole finding of an S wave from V1 and an R wave in either V5 or 6 ≥35mV	As ESC	As ESC
Incomplete RBBB		QRS <120ms with rsR pattern in V1	As ESC	As ESC
Early Repolarisation		QRS-ST junction, or J point of two contiguous leads was elevated ≥0.1mV from the isoelectric line, in addition to notching, or slurring of the terminal downslope of the QRS complex	As ESC	As ESC
Junctional escape rhythm		Flattening or inversion of the P wave	As ESC	As ESC
Convex ('domed') ST segment elevation combined with T-wave inversion		Abnormal Finding	In leads V1–V4 in Black/African athletes	As Seattle*

Table 3. Uncommon training unrelated ECG changes among athletes, as defined by the ESC, Seattle and Refined interpretational guidelines.

Uncommon/Training unrelated	Description	ESC	Seattle	Refined
Left atrial enlargement		Negative portion of the P wave in lead V1 ≥0.1mV in depth and ≥40msec in duration	Prolonged P wave duration of >120msec in leads I or II with negative portion of the P wave ≥1mm in depth and ≥40msec in duration in lead V1	As ESC*
Right atrial enlargement		P-wave amplitude ≥2.5mm in leads II, III or aVF	As ESC	As ESC*
Left –axis deviation		-30^{O} to -90^{O}	As ESC	As ESC*
Right –axis deviation		>115^{O}	Not applicable	As ESC*
Right ventricular hypertrophy		Sum of R wave in V1 and S wave in V5 or V6 ≥10.5mm	Sum of R wave in V1 and S wave in V5>10.5mm and right axis deviation >120^{O}	As ESC*
Long QT criteria		>440msec (males) and >460msec (females)	≥470msec (m) ≥480msec (f) ≥unequivocal LQT	As Seattle
Short QT criteria		<360ms	<320ms	As Seattle

Complete left bundle branch block		QRS ≥120msec predominantly negative QRS complex in lead V1 (QS or rS), and upright monophasic R wave in leads I & V6	As ESC	As ESC
Complete right bundle branch block		RSR' pattern in anterior precordial leads with QRS duration ≥120msec	Not applicable	As ESC
Intraventricular conduction delay		Any QRS duration >120msec including RBBB and LBBB	Any QRS duration ≥140msec or complete LBBB	As ESC
Pathological Q-wave		>4mm deep in any lead except III, aVR	>3mm deep and/or >40msec duration in ≥2 leads except III and aVR	≥40msec in duration or ≥25% of the height of the ensuing R-wave
Significant T-wave inversion		≥2mm in ≥2 adjacent leads (deep) or 'minor' in ≥2 leads	>1mm in depth in two or more leads V2−6, II and aVF or I and aVL (excludes III, aVR and V1)	As Seattle
ST-segment depression		≥0.5mm deep in ≥2 leads	As ESC	As ESC
Ventricular pre-excitation		PR interval <120msec with or without delta wave	PR interval <120msec with delta wave	As Seattle
Brugada like pattern		High take off, and down-sloping ST segment elevation V1-3	As ESC	As ESC

Pronounced bradycardia		Not applicable	<30bpm, or sinus pause ≥3 seconds	As ESC
Atrial tachyarrhythmia		Not applicable	Supraventricular tachycardia; atrioventricular nodal re-entrant tachycardia; atrial fibrillation/flutter	As ESC
Premature ventricular contractions		Not applicable	>2 per 10 second tracing	As ESC

*Denotes that should this parameter be found in isolation then it is to be considered a normal training related variant of athletic conditioning. If two or more of these are found in conjunction then it is to be classified as an abnormal/training unrelated finding and warrants further investigation (See Figure 2 below).

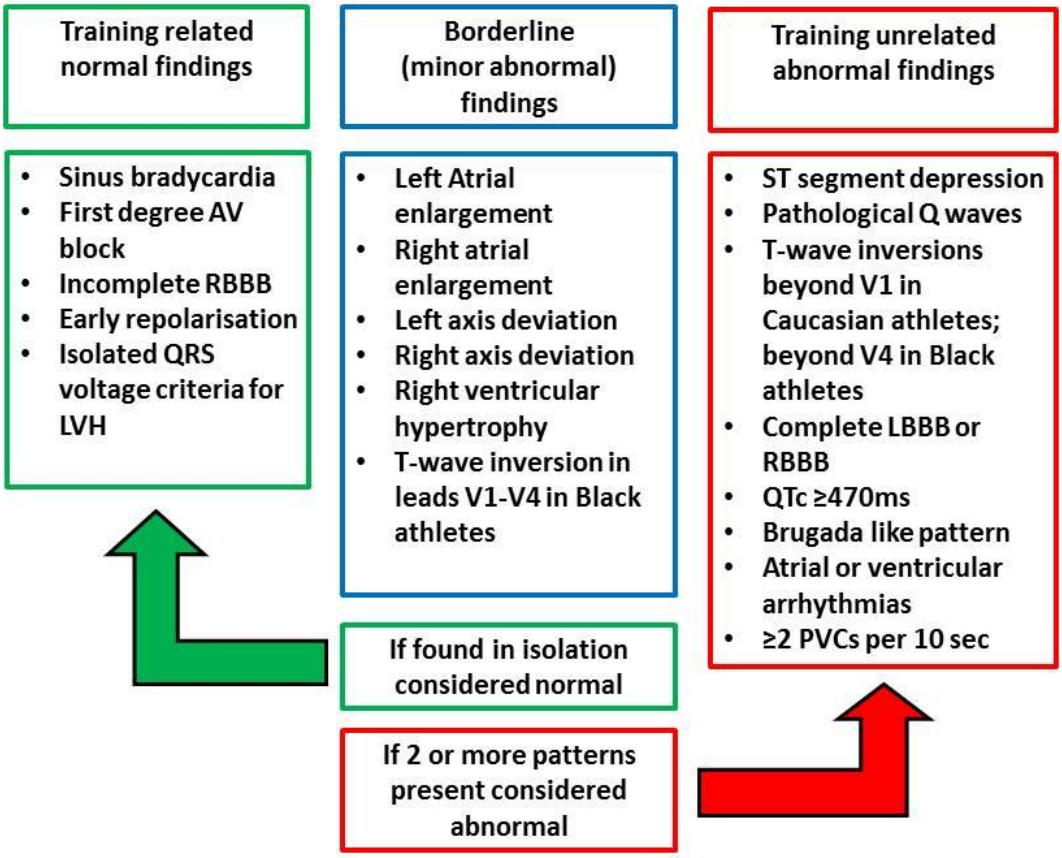


Figure 2. Definition of an abnormal ECG, using the Sheikh Refined criteria.

3.3 Echocardiography

Echocardiography was performed throughout the data collection period of November 2010 to January 2014 by two experienced sports cardiologists using the commercially available Phillips ie33 (U.S.A). Standard 2D, continuous, colour and pulsed-wave Doppler and pulsed tissue Doppler echocardiographic parameters were obtained from parasternal, apical, subcostal and suprasternal windows. Consistent echocardiographic protocols have been adopted throughout

the data collection process, with all data analysed offline and a minimum of 3 cardiac cycles were averaged for all indices. The FIFA echocardiographic protocol states a total of 33 measures should be taken in the pre-participation examination of the athlete. Each of these measures was taken among football players but the investigation of other athletes consisted of an abridged version of this, focusing on key parameters. The measures utilised and adopted in the write up of the forthcoming articles will be outlined below.

3.3.1 Aortic and atrial measurements

Throughout the articles presented in chapters 4 and 5, the measure of aortic dimension has been documented. Specifically, this referred to the Aortic root measures which were taken at the level of the sinus of Valsalva, and was measured inner edge to inner edge, using the 2D image in the parasternal long axis window. Investigation of the aorta is necessary given the potential to find anomalies such as the bicuspid aortic valves, aortic aneurysms, dissections, and coarctation. Left atrial dimension were recorded at ventricular systole in this window and using the same measurement technique. Left atrial volume however is taken in both the apical 4 chamber and apical 2 chamber views. This allows for its calculation using the biplane area-length method. The measurements for the right atrial area were acquired in apical 4 chamber view.

3.3.2 Left ventricular measures

Left ventricular wall thickness measures consisted of those taken at both the interventricular septum (anteroseptal measure) and posterior wall. End diastolic and end-systolic measures were taken in the parasternal long axis acoustic window, at the level of the mitral valve tip. To

corroborate these findings, septal and inferolateral thickness was measured in the short axis view at the mitral valve and mid-papillary level. Left ventricular diameters were also measured from the parasternal long axis window at the level of the mitral valve tip. Left ventricular volumes are calculated using the Simpsons biplane method. It requires accurate identification and subsequent manual tracing of the endocardial borders in both apical 4 chamber and 2 chamber views. This approach allows no assumptions to be made regarding the geometry, and is quantified by assuming the LV is a stack of elliptical discs. With this information the ejection fraction is also determined, via the adoption of the equation: $EF = (EDV-ESV)/EDV$. Left ventricular mass was calculated using the formula of Devereux (Devereux, 1987): $LV\ mass = 0.8x\ (1.04\ [(LVID+PWTd+SWT)^3 - (LVID)^3]\ +0.6\ g$. While not utilised in the articles presented, the discussion details the impact of ethnicity upon relative wall thickness. This was calculated using the formula: $RWT = (IVSdx\ PWTd)/LVIDd$. Concentric remodelling was distinguished by a RWT >0.42, and eccentric remodelling as ≤0.42.

Left ventricular diastolic function was determined by both early, passive filling of the left ventricle (E) and the active filling of the atrial contraction (A), in addition to their ratio E: A. These measures were achieved using pulsed-wave Doppler recordings from apical 4-chamber orientations with the transmitral flow sample volume placed at the tip of the mitral valve.

Diastolic function was also evaluated with the determination of mitral annular velocities, using tissue Doppler subsequently allowing for the assessment of E' (peak early diastolic tissue myocardial velocity). While measured during assessment, the values of A' and S', were not represented within the data presented. The apical 4-chamber orientation was once again utilised

and a 2 mm sample volume was positioned at both the septal and lateral wall aspect of the mitral valve annulus ensuring the best alignment between wall motion and the ultrasound beam. The nyquist limit was set between 10 and 35 $cm \cdot s^{-1}$. While acknowledging that current recommendations require the average of both lateral and medial myocardial velocity in early diastole (E'), for continuity and consistency in the published data we calculated the E/E' relationship solely using the lateral measure of E'.

3.3.3 Right ventricular (RV) measurements

The structural and functional investigation of the RV using transthoracic echocardiography has traditionally been restricted due to the position of the heart beneath the sternum, and the complex crescent shape of the RV being incompletely visualised in any given 2D echocardiographic view. Until recently measures of the RV of the heart have not been systematically recorded in our department. With this in mind, only RV internal diameter during diastole has been documented within the articles presented in the thesis. This dimension corresponds to the first measure of the right ventricular outflow tract taken in the parasternal long axis window.

3.3.4 Further testing

Athletes demonstrating symptoms, a family history of sudden cardiac death, and echocardiographic and/or ECG abnormalities considered to represent pathology were investigated further with 24h ECG, maximal exercise testing, and cardiac magnetic resonance imaging to evaluate the broader phenotype of common cardiomyopathic processes such as hypertrophic cardiomyopathy (HCM) and arrhythmogenic right ventricular cardiomyopathy

(ARVC). The pathway of clinical investigations was in accordance with Aspetar policy, outlined in Figure 3.

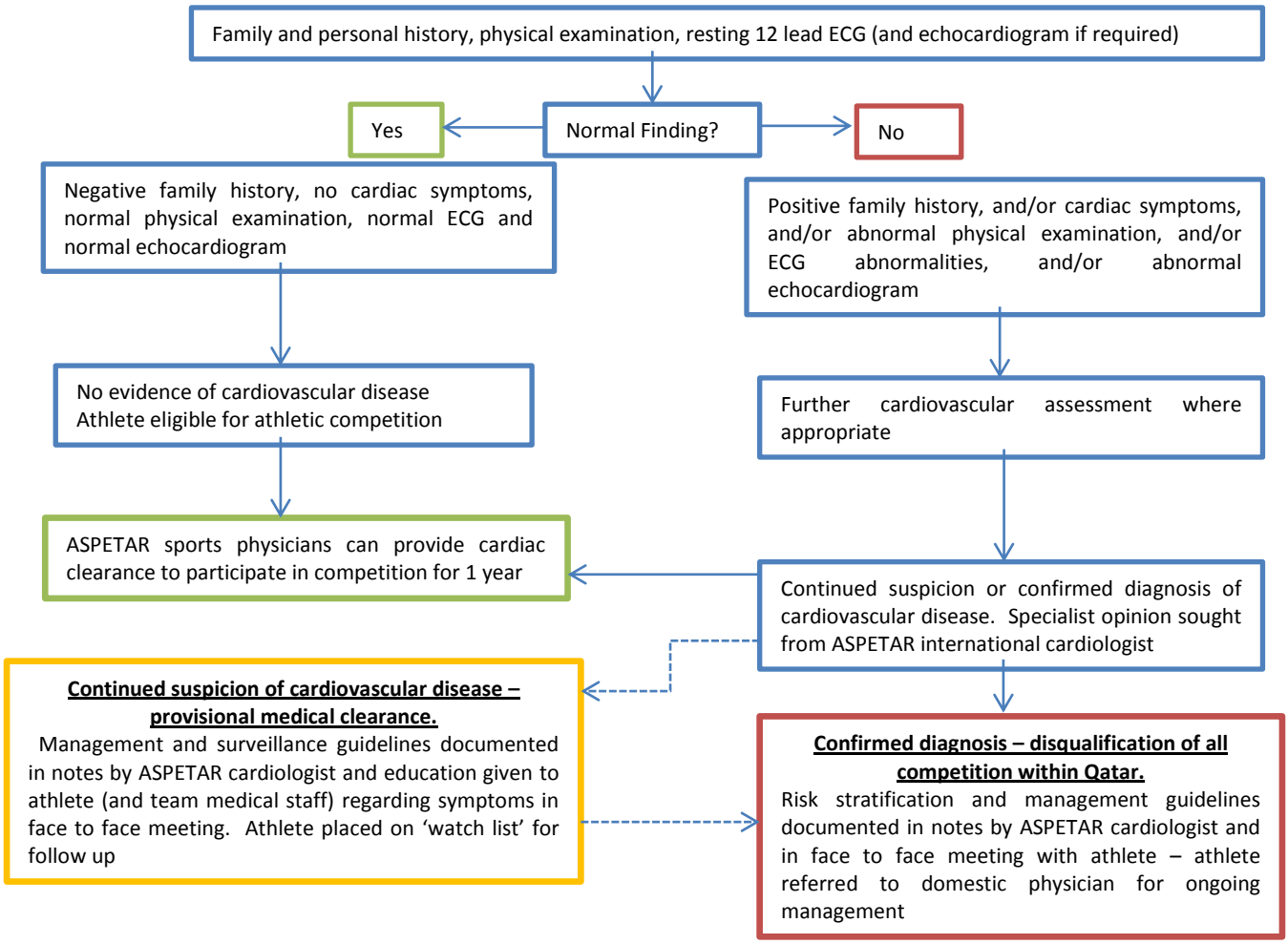


Figure 3. Clinical pathway and decision tree based upon the results of primary cardiovascular screening for athletes presenting at our institution.

CHAPTER FOUR

STUDY ONE: Electrocardiographic and morphologic adaptations in Arabic athletes: Are the European Society of Cardiology's recommendations for the interpretation of the 12-Lead ECG appropriate for this ethnicity?

Riding, N. R., Salah, O., Sharma, S., Carre, F., George, K. P., Farooq, A., Hamilton, B., Chalabi, H., Whyte, G. P. & Wilson, M. G. 2013. ECG and morphologic adaptations in Arabic athletes: are the European Society of Cardiology's recommendations for the interpretation of the 12-lead ECG appropriate for this ethnicity? *Br J Sports Med*. 48: 15, 1138-1143.

4.0 INTRODUCTION

Regular and sustained intensive physical activity is associated with a number of electrophysiological and structural cardiac adaptations, all of which enhances diastolic filling. These spectral modifications are collectively referred to as the 'Athlete's Heart'. The majority of studies investigating the 'Athletes Heart' are based on cohorts of Caucasian athletes. However, there is mounting evidence that an athlete's ethnicity has an important effect on the electrical and structural cardiovascular adaptations to prolonged and intensive exercise.(Basavarajaiah et al., 2008a, Di Paolo et al., 2012a, Papadakis et al., 2011a, Wilson et al., 2012b)

The 2012 London Olympics saw 13 Arabic nations participate in the games. Whilst both the International Olympic Committee (IOC), Fédération Internationale de Football Association (FIFA) and the European Society of Cardiology (ESC) recommend cardiovascular screening before undertaking competitive sport, there is little data on the impact of the Arabic ethnicity

upon the cardiac manifestations of the athlete's heart.(Wilson et al., 2012b) This lack of ethnic specific data (Uberoi et al., 2011b)increases the risk of generating false-positive diagnoses and unnecessary disqualifications from competitive sport, when attempting to differentiate physiological adaptation from inherited cardiac pathology associated with sudden cardiac death (SCD). Thus, the aim of the study was to examine the cardiac structure and function of high-level Arabic athletes when presenting for pre-participation cardiovascular screening, using electrocardiography and echocardiography.

4.1 METHODS

Ethical approval was obtained from the Shafallah Medical Genetics Centre ethics committee, with all athletes completing informed consent in either Arabic or English.

4.1.1 Participants

Between November 2010 and June 2012, 1175 high-level male athletes (exercising≥6 h/week) presented at our institution for preparticipation cardiac screening, of which 600 were Arabic, 415 Black African and 160 Caucasian. As previously described (Wilson et al., 2012b), the term "West-Asian" denotes individuals of Gulf or Middle-Eastern descent, and "Black African" denotes individuals of African descent. For ease of reference, West-Asian athletes will be termed Arabic from this point onwards. Arabic athletes were recruited from 7 Gulf States (Qatar, Bahrain, Oman, UAE, Kuwait, Yemen and Saudi Arabia) and 5 Middle-Eastern countries (Egypt, Jordan, Palestine, Iraq and Lebanon). Black African athletes from 9 predominantly West African countries (Sudan, Somalia, Ghana, Nigeria, Chad, Ivory Coast, Senegal, Cameroon and Ethiopia) were also recruited alongside Caucasian athletes from the U.S.A, Canada, Australia,

Russia, Bosnia, Serbia and Croatia. All Arabic athletes were compared to a cohort of 201 male Arabic control participants, who were not sedentary, but exercised ≤ 2h/week. Strict exclusion criteria included individuals that had undergone previous cardiovascular screening with electrocardiography (ECG) and echocardiography. This was important as the population truly reflected those individuals who had not been excluded from competitive sport on the suspicion of harbouring an inherited cardiac pathology.

4.1.2 Pre-participation Cardiovascular Screening

All players were screened using a cardiovascular pre-competition medical assessment form. Players completed the questionnaire regarding family history and personal symptoms in collaboration with an Arabic, French or English speaking cardiac nurse. Measurement of height, body mass, left brachial artery blood pressure (BP), precordial auscultation in supine and standing positions, and assessment for any physical characteristics of Marfan's syndrome were undertaken by a Sports Medicine Physician.

4.1.3 Resting 12-Lead Electrocardiography (ECG)

A standard 12-Lead ECG was obtained using a GE Mac 5500 (New York, USA) after a period of five minutes rest in the supine position. All ECG's were reported independently by two experienced investigators (OS, MW) using criteria previously published (Wilson et al., 2012b); with third opinions sought from two international cardiologists (SS, FC). ECG characteristics were classified into 'common and training-related' and 'uncommon and training-unrelated' traits according to the recent 2010 ESC report.(Corrado et al., 2010)

4.1.4 Echocardiography

Echocardiographic examination was performed using a commercially available ultrasound system (Philips, USA). Images of the heart were obtained in the standard planes, as previously described (Tajik et al., 1978). The left ventricular (LV) wall thickness was measured from 2-dimensional short-axis views in end-diastole, with the greatest measurement within the LV wall defined as the maximal wall thickness (mLVWT). M-mode echocardiograms derived from 2-dimensional images in the parasternal long axis were used for the measurement of LV end-diastolic diameter (LVED), left atrial (LA) and aortic root (Ao) diameter according to American Society of Echocardiography standards (Sahn et al., 1978), with LV diastolic volume (LV vol D) derived using Simpson's biplane methodology. Left ventricular mass (LVM) was calculated using the formula of Devereux (Devereux, 1987), but was also scaled for body surface area (BSA). Left ventricular diastolic function was assessed using pulsed-wave Doppler recordings from apical 4-chamber orientations. All data was analysed offline and a minimum of 3 cardiac cycles were averaged for all indices. For the tissue Doppler assessment of E', the apical 4-chamber orientation was utilised and a 2 mm sample volume was positioned at both the septal and lateral wall aspect of the mitral valve annulus ensuring the best alignment between wall motion and the ultrasound beam. The nyquist limit was set between 10 and 35 $cm \cdot s^{-1}$. Peak early diastolic (E') tissue myocardial velocity was recorded and E/E' was calculated.

4.1.5 Further Evaluation and Follow-Up

Athletes demonstrating symptoms, a family history of sudden cardiac death, and echocardiographic and/or ECG abnormalities considered to represent pathological LVH were

investigated further with 24h ECG, maximal exercise testing, and cardiac magnetic resonance imaging to evaluate the broader phenotype of common cardiomyopathic processes such as hypertrophic cardiomyopathy (HCM) and arrhythmogenic right ventricular cardiomyopathy (ARVC). A diagnosis of disease was established using published criteria (Maron et al., 2003c). All athletes were tracked for a minimum of three years.

4.1.6 Statistical analysis

Data was analyzed using SPSS 19 (Illinois, USA); presented as mean ± SD (range) and percentage where appropriate. One-way Analysis of Variance (ANOVA), using Bonferrroni adjustments if applicable, was used to identify differences in anthropometric, ECG and echocardiographic characteristics between athlete ethnicities. Strength associations between cardiac structure against the athletes BSA, blood pressure and ECG characteristics were calculated via a Pearson's correlation coefficient (r). Where appropriate, an independent sample t-test or Chi-square test was used to assess the presence of confounders between participants with uncommon ECG findings and T-wave inversion against cardiac structure, BSA and blood pressure. Since no confounders were detected, Odds ratio and 95% confidence intervals (CI) were determined between ethnicities. A p-value <0.05 was considered significant.

4.2 RESULTS

4.2.1 Identified Cardiac Pathology

Nine athletes (0.7%) were identified with a cardiac pathology associated with sudden cardiac death (SCD), and were excluded from further analysis (Table 1). Two Arabic (0.3%) and five

Black African (1.2%) were diagnosed with HCM; with Black Africans having a prevalence of HCM 4-times greater than Arabic athletes. Four athletes were referred to a specialist cardiologist in their respective home countries, and three remain under the management of our international cardiologists (SS, FC). Two Arabic athletes demonstrated ECG's diagnostic of Wolff-Parkinson-White syndrome and underwent electrophysiological study. Both were ablated as a result of electrophysiological findings, and returned to full competition following a 2-month post-operative recovery period.

Table 1: Outcomes for nine athletes identified with a cardiac disease associated with sudden cardiac death.

Athlete	Ethnicity	Sport	Symptoms	FH of SCD (<35yr)	Abnormal ECG	Abnormal ECHO	Abnormal GXT	Abnormal 24h Holter	Abnormal CMR	Abnormal 1st degree relatives	Diagnosis
1	Arabic	Football	No	No	Yes	Yes	No	No	Yes	Yes	HCM – disqualified
2	Arabic	Football	No	No	Yes	No	No	No	Yes	Yes	HCM – disqualified
3	Black African	Football	Yes	Yes	Yes	No	Yes	No	Yes	-	HCM – disqualified
4	Black African	Basketball	No	No	Yes	Yes	No	No	Yes	-	HCM – disqualified
5	Black African	Basketball	No	No	Yes	Yes	No	No	Yes	-	HCM – disqualified
6	Black African	Basketball	No	Yes	Yes	Yes	No	No	-	Yes	HCM – disqualified
7	Black African	Football	Yes	No	Yes	Yes	Yes	No	-	-	HCM – disqualified
8	Arabic	Football	No	No	Yes	No	Yes	No	-	-	WPW – returned to competition
9	Arabic	Football	No	No	Yes	No	Yes	No	-	-	WPW – returned to competition

HCM; hypertrophic cardiomyopathy, WPW; Wolff-Parkinson-White syndrome, dash (-) means investigation was not carried out.

4.2.2 Demographics

Detailed demographics of the remaining athletes and controls are presented in Table 2. Athletes competed in a range of competitive sports (n=23), with high-intensity intermittent sports dominating [soccer (60%), volleyball (8.8%), handball (8.8%) and basketball (8.5%)]. Arabic athletes were significantly younger, smaller and lighter; resulting in a reduced BSA than their Black African and Caucasian counterparts. Arabic athletes presented with a greater incidence of a family history of SCD (<35 years) than Black African and Caucasian athletes (7.4% vs. 3.9 and 2.5%, $p<0.05$). Despite Arabic athletes demonstrating significantly lower systolic BP's than Black African and Caucasian athletes, 17 football players were given a 24hr BP Holter monitor due to systolic BP value > 140mmHg at initial screening. There was no ethnic distinction in prevalence, with all subsequently reported as normal and returning to full competition.

Table 2:Comparison of demographic, personal symptoms and family history parameters between Arabic, Black African Caucasian athletes and Arabic controls.

Parameter	Arabic (n=596)	Black African (n=410)	Caucasian (n=160)	Arab Controls (n=201)
Age (years)	22.7 ± 5.9* (13-40)	24.6 ± 4.7† (13-40)	24.4 ± 5.4† (15-36)	24.7 ± 8.6 (15-45)
Height (cm)	176 ± 8.9* (126-204)	182.9 ± 11.0† (160-210)	188.2 ± 11.4†§ (157-211)	173.8 ± 6.5 (152-197)
Body Mass (kg)	72.7 ± 13.8 (29-158)	80.4 ± 14.8† (46-126)	86.1 ± 13.9†§ (56-123)	71.1 ± 15.4 (43-153)
BSA (m^2)	1.88 ± 0.2* (1-2.57)	2.02 ± 0.2† (1.48-2.69)	2.12 ± 0.23†§ (1.60-2.61)	1.82 ± 0.26 (1.48-2.62)
Left Systolic BP (mmHg)	120 ± 13 (85-150)	125.2 ± 10.9† (97-150)	126.4 ± 11.8† (94-145)	118.1 ± 14.9 (86-158)
Left Diastolic BP (mmHg)	71 ± 9 (43-109)	73.6 ± 8.4 (44-107)	74.5 ± 10.1 (42-100)	72.1 ± 11.7 (42-97)
Murmur	2.3%	2.7%	1.3%	4.0%
Chest pain at rest or during exercise	3.4%	2.0%	1.9%	3.0%
Shortness of breath during exercise	2.8%	2.0%	0.6%	1.5%
Palpitations at rest or during exercise	3%	2.2%	3.8%	5.5%
Dizziness during exercise	9.2%	4.6%†	5%†	7.0%
Syncope	1.5%	0.5%	0%	0%
FH of SCD (<35yrs)	7.4%	3.9%†	2.5%†	4.5%
FH of Marfan	0.2%	0.2%	0.0%	0.0%

BSA - body surface area, BP - blood pressure, FH – family history, SCD – sudden cardiac death.

*Statistically significant between Arabic athletes vs. Arabic controls.

† Statistically significant between Arabic athletes vs. Black African and Caucasian athletes.

§ Statistically significant between Caucasian athletes vs. Black African and Arabic athletes

4.2.3 Ethnic Differences in Cardiac Structure and Function

Arabic athletes had a significantly greater ($p<0.05$) Ao, LA, LVED, mLVWT, LVM (LVM scaled) and E/A compared to controls (Table 3). However, Arabic athletes were

significantly ($p<0.05$) smaller in all absolute cardiac structural parameters than both Black African and Caucasian athletes. The percentage of athletes demonstrating LVH (≥ 12mm) was not significantly different between Arabic, Black African and Caucasian populations (0.5%, 0.5% and 0.6%, respectively), with no athlete exceeding a mLVWT of 14mm (Arabic - 14mm, Black African – 14mm and Caucasian – 13mm; Figure 1). Caucasian athletes demonstrated a significantly ($p<0.05$) greater LVED, LV diastolic volume and LVM than both Arabic and Black African athletes; with no difference in mLVWT between Black African and Caucasian athletes. Whilst E/E' was significantly reduced in Caucasian athletes versus Arabic and Black African, all athletes across ethnicities demonstrated normal diastolic function. For all three ethnicities, there was a significant association between resting systolic BP and BSA, LVED, mLVWT and LVM ($p<0.001$).

Table3: Comparison of echocardiographic parameters between Arabic, Black African and Caucasian athletes and Arabic controls.

Parameter	Arabic (n=596)	Black African (n=410)	Caucasian (n=160)	Arab Controls (n=201)
Ao (mm)	26.8 ± 2.4* (18-39)	27.4 ± 2.6† (21-36)	28.2 ± 2.6†§ (22-34)	25.9 ± 2.7 (21-34)
LA (mm)	33.4 ± 3.9* (20-47)	34.4 ± 3.7† (22-45)	34.4 ± 3.8† (24-48)	31.5 ± 4.0 (18-42)
LA vol D (ml)	46.0 ± 14.2* (12-117)	52.8 ± 16.0† (20-118)	50.8 ± 16.8† (15-101)	37.8 ± 11.9 (15-77)
RA area (mm^2)	15.6 ± 2.9* (7-27)	17.8 ± 3.2† (10-29)	17.5 ± 3.6† (10-27)	13.9 ± 3.2 (8-37)
LVED (mm)	52.7 ± 4.2* (39-65)	53.9 ± 3.9† (41.1-63)	55.8 ± 3.7†§ (40-63)	49.4 ± 4.1 (41-60)
LV vol D (ml)	122 ± 25 (40-236) *	130 ± 24† (60-209)	143 ± 29†§ (81-271)	106 ± 22 (47-175)
mLVWT (mm)	8.9 ± 0.9* (5.7 – 14)	9.3 ± 1.1† (6.3 – 14)	9.2 ± 0.8† (7 – 13)	8.6 ± 0.9 (6.3 – 12)
mLVWT ≥ 10 mm	12%*	25%[#]	14%	6%
mLVWT ≥ 12 mm	0.5%	0.5%	0.6%	0%
LVM (g)	164 ± 34* (54-262)	182 ±38† (71-291)	193 ± 32†§ (96-276)	143 ± 33 (78-286)
LVM/BSA (g/m^2)	86.8 ± 14.3*	89.7 ± 14.8	90.8 ± 13.3	77.3 ± 14.8
E/A	2.07 ± 0.42*	2.07 ± 0.38	2.05 ± 0.41	1.97 ± 0.46
E/E'	4.8 ± 0.8	4.9 ± 0.9	4.6 ± 0.7§	5.1 ± 0.9

Ao - Aortic diameter, LA - left atrial diameter, LVED – left ventricular end diastolic diameter in diastole, mLVWT – maximal left ventricular wall thickness in diastole, LVM – LV mass, BSA – body surface area, LV vol D – left ventricular volume in diastole, LA vol – left atrial volume, RA area - right atrial area.

*Statistically significant between Arabic athletes vs. Arabic controls. † Statistically significant between Black African and Caucasian athletes vs. Arabic athletes. § Statistically significant between Caucasian athletes vs. Black African and Arabic athletes.
[#] Statistically significant between Black African athletes vs. Caucasian and Arabic athletes

4.2.4 Ethnic Differences in Electrocardiographic Features

In terms of common and training-related ECG changes, Arabic athletes demonstrated a greater frequency ($p<0.05$) of sinus bradycardia, 1st degree AV block, incomplete RBBB, voltage criteria for LVH and early repolarisation than controls (Table 4). Apart from an increased incidence of pathological Q-waves (> 3 mm in depth in two or more leads (except III and aVR); 4% vs. 1%, $p<0.05$), Arabic athletes did not differ in the prevalence of uncommon and training-unrelated ECG changes compared to controls. There was also no difference between Arabic and Caucasian in the frequency of an uncommon and training-unrelated ECG. However, a significantly higher prevalence of uncommon and training-unrelated ECG's were observed in Black African than Arabic and Caucasian athletes (20% vs. 8.4% and 6.9%, $p<0.001$), specifically more RAE, LAE and T-wave inversion. Accordingly, Black African athletes were significantly more likely to have uncommon and training-unrelated ECG changes than Arabicand Caucasian athletes [(OR) 2.65, 95% (CI) 1.81 to 3.9, $p<0.001$ and 3.3, 95% (CI) 1.7 to 6.35, $p<0.001$)].

Table 4: Comparison of electrocardiographic parameters between Arabic, Black African and Caucasian athletes, and Arabic controls

Parameter	**Arabic** (n=596)	**Black African** (n=410)	**Caucasian** (n=160)	**Arab Controls** (n=201)
Sinus Bradycardia	69%*	77%†	80%†	60%
PR duration (ms)	163 ± 26 (98-300)	179 ± 31 (104-328)	165 ± 28 (116-294)	155 ± 23 (72-244)
1st degree AV block	8%*	24%#	12%	3%
QRS duration (ms)	99 ± 9 (66-130)	99 ± 8 (76-124)	103 ± 9 (82-124)	96 ± 9 (66-120)
QTc duration (ms)	404 ± 22 (343-490)	405 ± 21 (351-478)	405 ± 22 (343-458)	402 ± 24 (335-499)
QTc>470 ms	0.8%	0.2%	0%	0.5%
IRBBB	36%*	36%	61%§	22%
RBBB	0%	0%	0%	0%
LBBB	0%	0%	0%	0%
RAE	2%	5%#	2%	2%
LAE	1%	5%#	1%	1%
RAD	0.3%	0%	0.6%	0%
LAD	0.5%	0.5%	0.3%	0.5%
LVH	59%*	64%#	53%	43%
RVH with RAD	0%	0%	0%	0%
ST-elevation	82%*	88%†	88%†	73%
ST-depression	0%	0%	0%	0%
T-Wave inversion	2%	13%#	1%	2%
Pathological Q-Waves	4%*	2%	3%	1%
Mobitz Type-1	0%	0.2%	1%	0%
PVC	1%	0.5%	0%	0.5%

AV; atrioventricular, IRBBB; incomplete right bundle branch block, RBBB; right bundle branch block, ILBBB; incomplete left bundle branch block RAE; right atrial enlargement, LAE; left atrial enlargement, RAD; right axis deviation, LAD; left axis deviation, RVH; right ventricular hypertrophy, PVC – premature ventricular contraction.

*Statistically significant between Arabic athletes vs. Arabic controls.

† Statistically significant between Black African and Caucasian athletes vs. Arabic athletes.

§ Statistically significant between Caucasian athletes vs. Black African and Arabic athletes.

Statistically significant between Black African athletes vs. Caucasian and Arabic athletes

4.2.5 Ethnic Differences in Repolarisation Changes

Arabic athletes demonstrated a higher prevalence of early repolarisation than controls (82% vs. 73%, $p<0.05$) (Table 5). Black African and Caucasian athletes demonstrated a greater prevalence of early repolarisation than Arabic athletes (88% and 88% vs. 82%, respectively), with no difference between Black African and Caucasian athletes.

There was no difference in the prevalence of T-wave inversion between Arabic and controls (2% vs. 2%), or between Arabic and Caucasian athletes (2% vs. 1%, Figure 2). However, Black African athletes demonstrated a significantly ($p<0.001$) greater prevalence of T-wave inversion than Arabic and Caucasian (13% vs. 2% and 1%, respectively). The most common pattern was T-wave inversion isolated to V1-V4 (11% vs. 1% and 1%, respectively). However, Black Africans also demonstrated significantly ($p<0.001$) more isolated inferior (n=14; 3%), isolated lateral (n=10; 2%), and inferolateral T-wave inversion (n=8; 2%) than Arabic and Caucasian athletes; with 5 Black Africans also demonstrating deep ($\geq$ -0.2mV) inferolateral T-wave inversion. Accordingly, athletes of Black African descent were significantly more likely to have T-wave inversion than Arabic and Caucasian athletes, respectively [(OR) 8.33, 95% (CI) 4.17 – 16.61, $p<0.001$ and ((OR) 11.22, 95% (CI) 2.7 – 46.67, $p<0.001$].

Table 5: Comparison of electrocardiographic repolarisation parameters between Arabic, Black African and Caucasian athletes, and Arabic controls

Parameter	**Arabic** (n=596)	**Black African** (n=410)	**Caucasian** (n=160)	**Arab Controls** (n=201)
T-wave inversion	2%	13%#	1%	2%
T-wave inversion isolated in V1-V4	1%	11%#	1%	1%
T-wave inversion in inferior leads	0.7%	3%#	2%	0.5%
T-wave inversion in lateral leads	0.3%	2%#	0.6%	0%
T-wave inversion in inferolateral leads	0.2%	2%#	0.6%	0%
Deep T-wave inversion	0.5%	9%#	0.6%	0.5%
Deep T-wave inversion in inferolateral leads	0%	1.2%#	0.6%	0%
ST-elevation	82%*	88%†	88%†	73%
ST-depression	0%	0%	0%	0%

*Statistically significant between Arabic athletes vs. Arabic controls. † Statistically significant between Black African and Caucasian athletes vs. Arabic athletes. # Statistically significant between Black African athletes vs. Arabic and Caucasian athletes

4.2.6 Further Cardiovascular Examination

All 65 athletes (10 Arabic, 53 Black African and 2 Caucasian) and 3 Arabic controls with T-wave inversion, and 3 athletes (1 Arabic and 2 Black African) with an mLVWT ≥ 13mm, underwent maximal exercise testing and 24h Holter monitoring, which were normal. Special consideration was paid to 10 asymptomatic athletes (1 Arabic, 8 Black African and 1 Caucasian) with inferolateral T-wave inversion. Despite normal echocardiograms, 24h Holter monitoring and exercise tests, all 10 underwent CMR imaging with gadolinium. None demonstrated any structurally abnormalities or late enhancement to indicate an underlying cardiomyopathy, and were given medical

clearance to compete. Given the uncertainty regarding the long-term significance of inferolateral T-wave inversion we have recommended yearly evaluation and advised the athletes to seek immediate medical attention in the event of cardiac symptoms.

4.3 DISCUSSION

The correct differentiation of physiological cardiac adaptation due to exercise from an inherited or congenital cardiac pathology is paramount, to identify athletes at risk of SCD. This study examines the electrophysiological and structural cardiac adaptations associated with exercise in 600 high-level Arabic male athletes, competing in a wide variety of sporting disciplines, compared to cohort of high-level Black African and Caucasian athletes.

4.3.1 Prevalence of Hypertrophic Cardiomyopathy

Our study identified 9 athletes (0.7%) with a disease associated with SCD; with the prevalence of HCM in Black African (1.2%) 4-times greater than Arabic (0.3%) athletes. HCM is cited as the leading cause of sudden death in young athletes.(Maron et al., 1996a) However, the prevalence of HCM in Black African and Arabic athletes is approximately 13-times and 3-times greater respectively, than that observed in previous studies among Caucasian athletes; estimated at approximately 0.1% (Basavarajaiah et al., 2008b). This higher prevalence is supported by a previous ECG-only screening study in Arabic and Black African athletes that reported a SCD disease prevalence of 0.5% and 1% respectively.(Wilson et al., 2012b) Data collected in our facility suggests that up to 60%

of our Black African athletes have never seen a physician before presenting for pre-participation screening. This in part may explain the unusually high prevalence of HCM in this previously unexamined and unselected population.

4.3.2 Ethnic Differences in Cardiac Structure and Function

The present study revealed that Arabic athletes have significant, yet modest increases in cardiac dimensions compared to controls; yet all cardiac dimensions in all parameters are significantly smaller than Black African and Caucasian athletes. In all Arabic athletes, absolute values did not exceed predicted normal upper limits, and are in line with data established from Caucasian athletes.(Basavarajaiah et al., 2008b) The prevalence of LVH (mLVWT $\geq$ 12mm) in athletes was comparable between all three ethnicities. Our study did not observe the greater frequency of LVH that has previously been reported in athletes of Black African ethnicity (Papadakis et al., 2009), with Black African athletes demonstrating a LVH prevalence comparable within their Arabic and Caucasian counterparts (0.5%, 0.5% and 0.6%, respectively). However, when examining the prevalence of a wall thickness $\geq$ 10 mm, Black African athletes demonstrated a trend for significantly ($p<0.001$) greater wall thicknesses that Arabic and Caucasian athletes (25% vs. 12% and 14%, respectively), supporting the concept that certain Black African athletes may gravitate towards a physiologically thicker LV wall.

4.3.3 Ethnic Differences in Electrocardiographic Features

Uncommon and training-unrelated ECG changes raising the suspicion of structural heart disease were reported in 12% of the athletes. Supported by previous data from an ECG-only investigation in Arabic athletes, there was no significant difference between the frequency of uncommon and training-unrelated ECG changes between Arabic and Caucasian athletes (8.4 % vs. 6.9%).(Wilson et al., 2012b) However, Black African ethnicity continues to be positively associated with frequencies of uncommon ECG findings (20%), with Black African descent an independent predictor of uncommon ECG findings when compared to Arabic (2.7:1) and Caucasian (3.3:1) athletes. Specifically, Black African athletes demonstrate more RAE, LAE and T-wave inversion than both Arabic and Caucasian athletes.

4.3.4 T-wave Inversion Conundrum

The presence of T-wave inversion is of major concern, as these ECG alterations are a recognised manifestation of HCM and ARVC. In total, 65 athletes and 3 controls displayed T-wave inversion (a prevalence of 5.6%). Similar to previous studies (Papadakis et al., 2009), the most common pattern was T-wave inversion isolated to V1-V4 (11% Black African vs. 1% Arabic and 1% Caucasian), that was morphologically asymmetric or biphasic and proceeded by convex ST-segment elevation, but never ST-segment depression. Further work is required to understand the clinical significance behind the increased prevalence of isolated inferior and lateral T-wave inversion in Black African, and its relationship with inherited cardiac pathology.

Deep T wave inversions in the inferolateral leads are common in HCM. The present study observed 10 asymptomatic athletes without a family history of SCD (0.9%; 1 Arabic, 8 Black African and 1 Caucasian) demonstrating inferolateral T-wave inversions with normal echocardiograms. Subsequent investigation including CMR, failed to identify phenotypic features of HCM or AVRC in any athlete. Comparison of T-wave morphology in black patients with HCM demonstrates that T-wave inversions are usually confined to the lateral leads (80% of cases); whereas as T-wave inversion in leads V1-V4 are only observed in 3-4% of HCM patients.(Papadakis et al., 2011a) Accordingly, we advise caution and request annual follow-up in the asymptomatic athlete who presents with inferolateral T-wave inversion but normal or inconclusive imaging.(Wilson et al., 2012a)

4.3.5 Clinical Implications for Arabic Athletes

The present study demonstrates that the upper limits of physiological LVH established within Caucasian athletes (Basavarajaiah et al., 2008b), are clinically relevant to Arabic athletes. Accordingly, any Arabic athlete who presents values in excess of 12 mm should be viewed with caution, and should prompt further investigation to identify the underlying mechanism. Finally, the prevalence of an uncommon and training-unrelated ECG is comparable between Arabic and Caucasian athletes. Thus, the ESC guidelines for the interpretation of an athlete's ECG, based upon data derived from Caucasian athletes, are applicable to the Arabic athletic population.(Corrado et al., 2010) Consequently, the

equivalent rate of false positive ECG's between Arabic and Caucasian athletes should be considered acceptable for the establishment of a pre-participation cardiovascular screening programme in athletes of Arabic ethnicity.

4.3.6 Limitations

All athletes with T-wave inversion were followed for only 3 years. Yet the precise significance of such repolarisation changes, especially the high prevalence of inferolateral T-wave inversion in Black African athletes, remains unresolved. There is no 'gold standard' test for the diagnosis of the presence (or absence) of heart diseases in these athletes. Although genetic testing is the most specific method of diagnosing HCM, the diverse genetic heterogeneity of HCM and incomplete knowledge of all causal mutations lend poor sensitivity to this diagnostic tool.

4.4 CONCLUSION

Arabic athletes have significant, yet modest increases in cardiac dimensions compared to Arab controls; yet all cardiac dimensions in all parameters were significantly smaller than Black African and Caucasian athletes. There was no significant difference between the frequency of uncommon and training-unrelated ECG changes between Arabic and Caucasian athletes. Therefore, the use of the ESC guidelines for the interpretation of an athlete's ECG, both established from data derived from Caucasian athletes, are clinically relevant and acceptable for use within Arabic athletes.

CHAPTER FIVE

STUDY TWO: Do big athletes have big hearts? Impact of extreme anthropometry upon cardiac hypertrophy in professional male athletes

Riding, N. R., Salah, O., Sharma, S., Carre, F., O'hanlon, R., George, K. P., Hamilton, B., Chalabi, H., Whyte, G. P. & Wilson, M. G. 2012. Do big athletes have big hearts? Impact of extreme anthropometry upon cardiac hypertrophy in professional male athletes. *Br J Sports Med*. 46: i90-i97.

5.0 INTRODUCTION

As we demonstrated within chapter 4 with the differential cardiac remodelling between Arabic athletes and matched Arabic controls, we can support the well-established notion that regular and prolonged intensive exercise is associated with cardiac morphological adaptation, together with electrocardiographic alterations.(Whyte et al., 2004b, Pluim et al., 2000a, Pelliccia et al., 2002, Whyte et al., 2004c) Significant cardiac enlargement may be an expression of underlying cardiac disease, placing the athlete at a greater risk of sudden cardiac death (SCD).(Corrado et al., 2005a) In rare cases, the degree of physiological adaptation in cardiac morphology can mimic that of a number of pathological disease states, most notably hypertrophic cardiomyopathy (HCM).(Baggish and Wood, 2011) Differentiation between a physiological or pathological remodelling process is, therefore, extremely important. Consequently, establishing the upper normal limits of physiological enlargement in response to physical training is an important focus for clinicians and scientists.

Fourteen and 65 mm have been established as the physiological upper limits for maximal wall thickness and LV internal diameter during diastole, respectively. These limits come

from three large scale studies examining approximately 4,800 elite athletes (predominantly male), who observed that a small minority (1.5 - 4%) demonstrate left ventricular hypertrophy (LVH) > 13mm and 4 - 6% have an LV end-diastolic dimension > 60mm. What this minority of athletes with pronounced LVH have common is an enlarged BSA (approximate mean BSA 2.1m^2).(1991a, 2004c, Basavarajaiah et al., 2008b). Within chapter 4, we could see this phenomenon in practice, in so much as the athletes with the smallest hearts, i.e. those of Arabic descent were also those with the smallest body surface areas. However, despite recognising that the largest maximal wall thicknesses are observed in those with the largest BSA's, there is limited data examining the impact of extreme body anthropometry (BSA >2.3 m^2) upon cardiac morphology in professional athletes. This is important as it is widely recognised that LV dimensions are influenced by body anthropometry.(Batterham et al., 1999b, George et al., 2009)Pluim et al. (Pluim et al., 2000a) was the first to recognise the importance of BSA when undertaking pre-participation screening, suggesting that the probability of false positive HCM identification would be exacerbated in athletes with a BSA> 2m^2. Basketball, handball and volleyball are three such sports whereby some male athletes may exceed the stereotypical anthropometry for an athlete; with heights and body mass's reaching 220 cm and 150 kg, respectively [14, 34]. Magalski et al (Magalski et al., 2008) electrocardiographic examination of 1,959 American Football players was one of the largest studies to undertake pre-participation screening in athletes with large anthropometry (mean BSA; 2.4 ± 0.3 m^2). Regrettably, only 203 American Football players received an echocardiogram following a referral due to an abnormal ECG, family history or clinical examination, with the BSA of this cohort unreported.

The aim of the present study was to investigate the cardiac structure and function in professional male athletes with extreme anthropometry (≥ 2.3 m^2), to confirm if the established upper limits of physiological cardiac adaptation to intensive and sustained physical activity are applicable for this unique population.

5.1 METHODS

Ethical approval was obtained from the Shafallah Medical Genetics Centre ethics committee, with all athletes completing informed consent.

5.1.1 Participants

Eight hundred and thirty six asymptomatic professional male athletes (age 25 ± 8 yrs), exercising ≥ 6h per week in 15 high-intensity intermittent sporting disciplines (e.g. Soccer, n=586; basketball, n=75; volleyball, n=41; handball, n=35) presented at our institution for pre-participation cardiac screening (Table 1). Athletes were categorised into three distinct groups according to their body surface area (DuBois and DuBois, 1916); Group 1) BSA >2.3 m^2 (n = 100, 197 ± 9 cm and 105 ± 12 kg); Group 2) BSA 2 to 2.29 m^2 (n = 244, 184 ± 6 cm and 83 ± 6 kg); and Group 3) BSA <1.99 m^2 (n = 492, 172 ± 6 cm and 66 ± 8 kg).Strict exclusion criteria included athletes whom had undergone previous pre-participation cardiovascular screening with electrocardiography and echocardiography, and those athletes currently experiencing symptoms suggestive of cardiovascular disease and/or demonstrating an early family history of SCD. This was important as the population truly reflected those individuals who had not been excluded

from competitive sport on the suspicion of harbouring an inherited cardiac pathology. As previously described (Wilson et al., 2012b, Wilson et al., 2011c), the term "West-Asian" denotes individuals of Gulf or Middle-Eastern descent, and "Black African" denotes individuals of African descent. West Asian athletes were recruited from 7 Gulf States (Qatar, Bahrain, Oman, UAE, Kuwait, Yemen and Saudi Arabia) and 6 Middle-Eastern countries (Egypt, Jordan, Palestine, Iraq and Lebanon). Black athletes from 7 African countries (Sudan, Somalia, Ghana, Nigeria, Ivory Coast Senegal, Cameroon and Ethiopia) were also recruited alongside Caucasian athletes from the U.S.A, Canada, Australia, Russia, Bosnia and Croatia.

Table 1: Demographic data of all athletes categorized by body surface area (BSA)

	Group 1 BSA>2.3m^2 (n=99)	**Group 2 BSA 2-2.29m^2 (n=244)**	**Group 3 BSA <1.99m^2 (n=492)**
Age (years)	26.0 ± 5.8 (15-35)	25.1 ± 6.2 (14-35)	23.5 ± 6.2$^{\#}$ (13-37)
Height (cm)	196.8 ± 8.6* (170-217)	183.7 ± 6.2† (168-207)	172.5 ± 7.6 (153-191)
Weight (kg)	105.1 ± 12.1* (85-156)	82.8 ± 5.9† (66-110)	66.2 ± 7.5 (41-88)
Ethnicity			
West-Asian	31%	55%	76%
Black African	46%	35%	19%
Caucasian	23%	10%	5%
Sport			
Football	11.1%	68.6%	83.0%
Basketball	40.4%	8.7%	2.6%
Handball	18.2%	7.0%	0.8%
Volleyball	23.2%	7.4%	0.0%
Other	7.1%	8.3%	13.4%

*Significant difference between BSA>2.3m^2 and other two groups (P<0.05). †Significant difference between BSA2-2.29m^2 and BSA<1.99m^2 (P<0.05), $^{\#}$Significant difference between both BSA>2.3m^2 and BSA2-2.29m^2 from BSA<1.99m^2 (P<0.05).

5.1.2 Physical Examination

The physical examination was based on the ESC sport's cardiology section consensus statement.(Corrado et al., 2005c) Players completed the questionnaire regarding family history and personal symptoms in collaboration with an Arabic, French or English speaking Sports Medicine Physician and Nurse. Measurement of height (SECA 264, Hamburg, Germany), body mass (Detecto 6129KGM, Missouri, USA), brachial artery blood pressure (GE Dinamap Pro 400V2, New York, USA) in the supine position (both left and right arms) after a period of five minutes rest, precordial auscultation in supine and standing positions, and assessment for any physical characteristics of Marfan's syndrome were undertaken by a Sports Medicine Physician.

5.1.3 Resting 12-Lead Electrocardiography (ECG)

A standard 12-Lead ECG was obtained using a GE Mac 5500 (New York, USA) after a period of five minutes rest in the supine position. All ECG's were reported independently by two experienced investigators (OS, MW) using the recent 2010 ESC recommendations for interpretation of 12-lead electrocardiogram in the athlete (Corrado et al., 2010), with third opinions sought from 2 international cardiologists (SS, FC) for difficult cases.

5.1.4 Echocardiography

A 2D, M-mode and Doppler and tissue Doppler echocardiographic examination was performed in the left lateral decubitas position by a consultant cardiologist using a commercially available ultrasound system (Philips, USA). Images of the heart were obtained in the standard parasternal long-axis and short-axis and apical 4-chamber planes, as previously described (Tajik et al., 1978), in order to identify subtle focal regions of abnormal LV hypertrophy. The LV wall thickness was measured from 2-dimensional short-axis views in end-diastole, with the greatest measurement within the LV wall defined as the maximal wall thickness. M-mode echocardiograms derived from 2-dimensional images in the parasternal long axis were used for the measurement of LV end-diastolic diameter (LVIDd) and -systolic (LVIDs) dimensions, left atrial diameter, and aortic root diameter according to American Society of Echocardiography standards (Sahn et al., 1978), with LV volumes (diastolic and systolic) derived using Simpson's biplane methodology. Left ventricular mass was calculated using the formula of Devereux.(Devereux, 1987) Three to 5 consecutive measurements were taken, and the average was calculated. Left ventricular diastolic function was assessed using pulsed-wave Doppler recordings from apical 4-chamber orientations. A 4 mm sample volume was placed at the tips of the mitral leaflets in diastole and transmitral flow was acquired to obtain peak early (E) and atrial (A) flow velocities. All data was analysed offline and a minimum of 3 cardiac cycles were averaged for all indices. For the tissue Doppler assessment of E', the apical 4-chamber orientation was utilised and a 2 mm sample volume was positioned at both the septal and lateral wall aspect of the mitral valve annulus ensuring the best alignment between wall motion and the ultrasound beam. The high pass filter was bypassed and gains set to a minimal value to obtain the

best signal to noise ratio. The nyquist limit was set between 10 and 35 $cm \cdot s^{-1}$. Peak early diastolic (E') tissue myocardial velocity was recorded and E/E' was calculated.

5.1.5 Criteria for consideration of the diagnosis of pathological LVH in athletes

Based on previous publications and our own experience of an athlete's heart, athletes with a LV wall thickness >12 mm were considered to have LVH.(Pelliccia et al., 1991a, Maron, 1986, Sharma et al., 2002) Athletes with LVH and a relatively non-dilated LV in terms of athletic training (<56 mm) (Maron et al., 1995c) in association with any one of the following were considered to have findings that could be consistent with pathological LVH rather than physiological hypertrophy: 1) impaired diastolic function (Lewis et al., 1992); 2) enlarged left atrial diameter >45 mm in athletes <18 years old (Basavarajaiah et al., 2006) and up to 50 mm in older athletes (Pelliccia et al., 2005b); 3) LV outflow obstruction (Klues et al., 1993); 4) left bundle branch block (Savage et al., 1978); and 5) ST-segment depression or deep T-wave inversions (<-0.2 mV) in ≥ 2 contiguous anterior, inferior or lateral leads (but not aVR, and III) (Maron et al., 1983) on the ECG. Athletes demonstrating echocardiographic and/or ECG abnormalities considered to represent pathological LVH were investigated further with 48-h ECG (Monserrat et al., 2003), cardiopulmonary exercise test (Sharma et al., 2000a, Sharma et al., 2000b), and cardiac magnetic resonance imaging (Maron, 2012) to evaluate the broader phenotype of common cardiomyopathic processes such as HCM and arrhythmogenic right ventricular cardiomyopathy, in addition to assessing risk of SCD.(Elliott et al., 2000).

5.1.6 Statistical analysis

All data was presented as mean ± SD and (range), and analyzed using SPSS (Statistical Package for Social Sciences 17, Illinois, USA). Data was analysed using a two-way between subjects ANOVA, with paired wise comparisons, used to identify any significant differences in athlete anthropometrics and echocardiographic characteristics between the three BSA groups, together with athlete anthropometrics and echocardiographic characteristics between Black African, West-Asian and Caucasian ethnicity in the >2.3m^2 BSA group. Relationships between data indices of echocardiographic measures of cardiac structure and function against the athletes BSA together with their resting systolic blood pressure were examined via Pearson's product–moment correlation analysis. A p-value <0.05 was considered significant.

5.2 RESULTS

None of the athletes experienced angina, breathlessness disproportionate to the amount of exercise performed, or exertional syncope. The diagnosis of HCM was excluded by echocardiography in 819 (98%) on the basis of a LV wall thickness <12 mm, absence of systolic anterior motion of the anterior mitral valve leaflet causing LV outflow obstruction, and normal diastolic function.

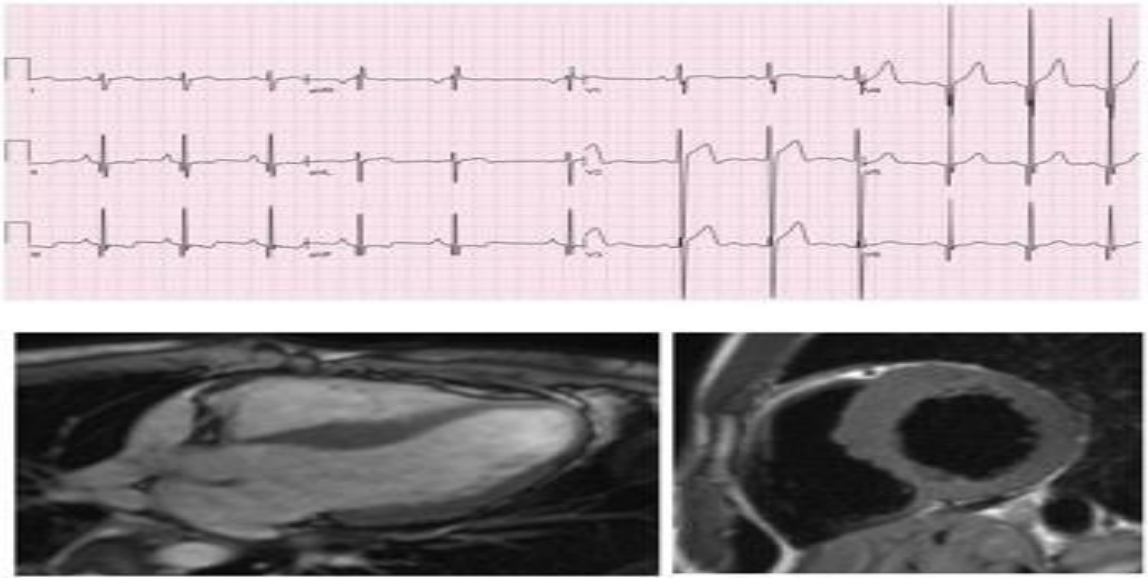
5.2.1 Athletes with an LV wall thickness >12 mm (LVH)

Of the 836 athletes, 17 (2%) showed a maximal LV wall thickness exceeding 12 mm and were considered to have LVH.(Maron et al., 1995c) Twelve (12%) of these athletes demonstrating

LVH came from the >2.3 m^2 BSA cohort, compared with just 3 (1.2%) and 2 (0.4%) from Groups 2 and 3, respectively. All 17 athletes with LVH had an appropriate (≥45mm) LV chamber dimension (mean 56 ± 4mm, [range 49 - 63]), normal systolic and diastolic function, an enlarged left atrial diameter, and no systolic anterior motion of the anterior mitral valve leaflet or LV outflow obstruction.

5.2.2 Athletes with an LVH >12 mm and an abnormal ECG

Of the 17 athletes with LVH, only 2 (0.2%) demonstrated a wall thickness that exceeded 13 mm (Table 2; athletes 1 and 2). However, both athletes also demonstrated ECG's highly suspicious of HCM (Figure 1a and 1b). Following extensive further investigation, both athletes were diagnosed with a cardiomyopathy and were eventually disqualified from competitive sport. Both athletes were removed from any further group analysis.



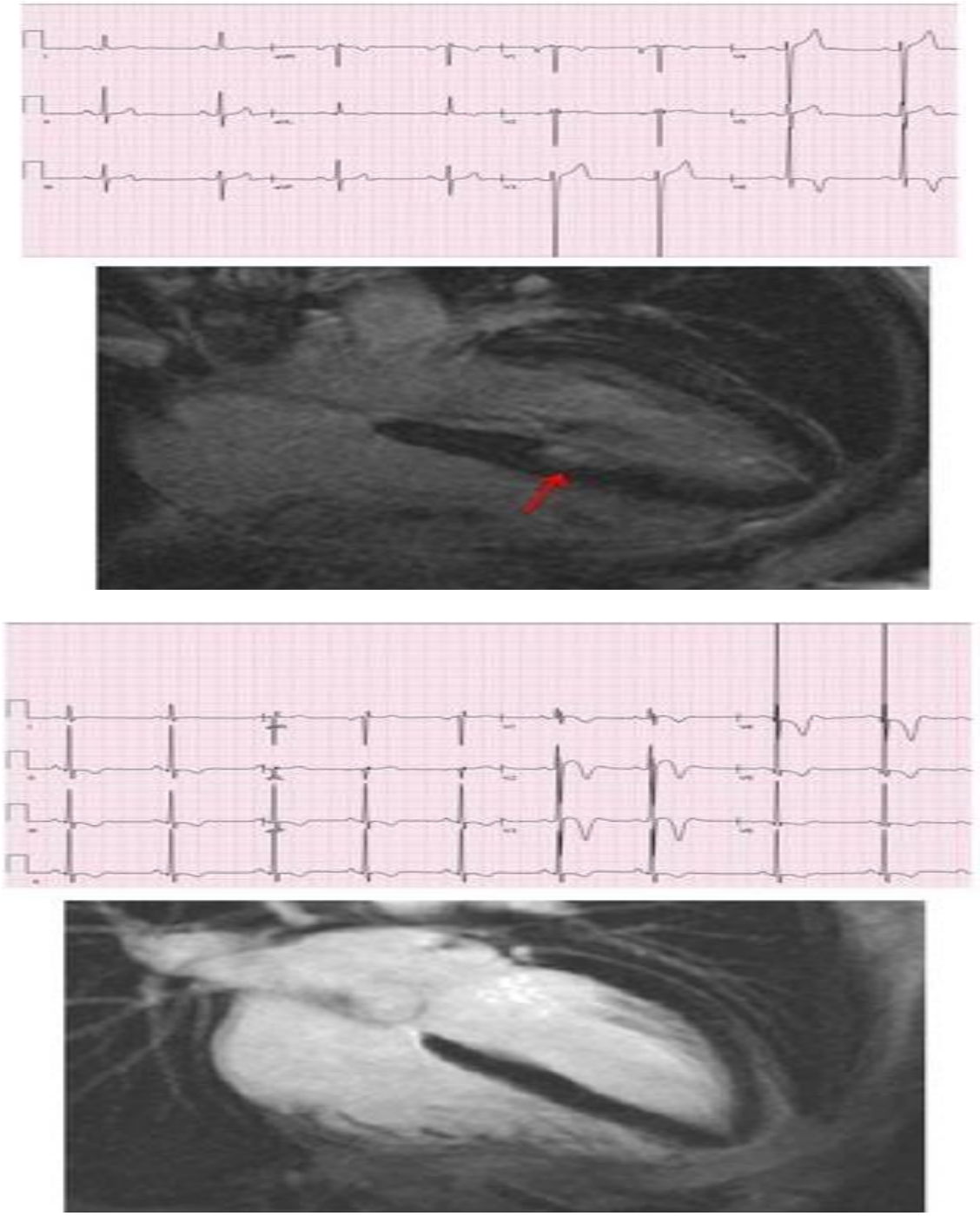


Figure 1 (A)–(C) Twelve-lead ECG and cardiac magnetic resonance images of two athletes (1 and 2) with a maximal wall thickness greater than 13 mm, and one athlete (3) with a maximal wall thickness of 8.2 mm on echocardiography, yet apical segments do not show normal tapering pattern and are disproportionately thickened on CMR imaging. Arrow (athlete 2) points to localised fibrosis of the septal wall at the mid-cavity level. This figure is only reproduced in colour in the online version.

5.2.3 Athletes with other cardiac abnormalities on ECG and echocardiography

One further athlete (Table 2; athlete 3) was diagnosed with amild variant of apical HCM, due to disproportionally thickened apical segments of the basal and septal walls upon cardiac MR imaging, following an abnormal ECG (Figure 1c) but normal echocardiogram (maximal basal LV wall thickness of 8 mm). This athlete was removed from any further group analysis. Four asymptomatic athletes without cardiac murmur were found to have trivial valve regurgitation (one mitral, one aortic and two tricuspid), not requiring further investigation after echocardiography. Finally, one asymptomatic player had an aortic root dimension at the upper limit of normal but given the borderline measure and normality of other parameters, was provided medical clearance and requested to attend yearly echocardiographic examination. These last five athletes remained in the group analysis.

Table 2. Follow-up results of three athletes presenting with an abnormal ECG on initial screening

Athlete	Symptoms	FH of SCD (<35yr)	ECG abnormality	Echocardiogram	Exercise Stress Test & 24hr Holter ECG	CMR	Screened 1st degree relatives	Diagnosis
ATHLETE 1 19 year old West Asian footballer	No	No	RAE, profound voltage (77mV), Q waves in II, III, aVF, T wave inversion in I, II, III, aVL, aVF and ST segment depression in II, III and aVF.	Sub-aortic IVSd bulge of 20 mm, without obstruction of the outflow tract.	No arrhythmia during exercise with appropriate BP response. Few monomorphic PVB on Holter monitoring.	Asymmetric septal hypertrophy with a maximal septal wall thickness of 20mm vs. lateral wall of 11 mm without obstruction. No LGE, oedema or systolic dysfunction.	Father's ECG and Echo confirmed HCM	Non-obstructive HCM
ATHLETE 2 29 year old Black African-American basketball player	No	No	Profound voltage in V3, Deep T-wave inversion in V6	Normal apart from max wall thickness of 13.6 mm	No arrhythmia during exercise with appropriate BP response. No arrhythmia on Holter	Mild asymmetric hypertrophy of IVSd without obstruction (basal 8 mm, mid 15 mm, apical 9 mm), associated with a significant mid-septum transmural fibrosis	Not available	Non-obstructive HCM
ATHLETE 3 27 year old West-Asian Futsal player	No	No	Profound voltage in V4 (59mV), T wave inversion in II, III, aVF, V2-V6 and ST segment depression in V4-V5	Normal (max wall thickness 8.2 mm)	No arrhythmia during exercise with appropriate BP response. No arrhythmia on Holter	Apical segments are disproportionally thickened, increased basal and septal wall thickness. No LGE, oedema or systolic dysfunction	Not available	Mild variant of apical HCM

RAE; right atrial enlargement, LVH; left ventricular hypertrophy, IVSd; intraventricular septum in diastole, BP; blood pressure, PVB; premature ventricular beats, LGE; late gadolinium enhancement, HCM; hypertrophic cardiomyopathy.

5.2.4 Impact of BSA upon cardiac structure and function

A significant and progressive increase in aortic, left and right atrial, as well as left and right ventricular dimensions and volumes was observed as BSA increased (Table 3; $p<0.05$). No athlete with a normal ECG demonstrated a maximal wall thickness > 13mm and an LVIDd> 65mm. A total of 36 athletes (4% overall) had an LVIDd> 60mm; of which 19 (19%) came from Group 1 compared to 13 (5%) and 4 (0.8%) from Groups 2 and 3, respectively. A significantly higher peak early diastolic mitral flow velocity was observed in Group 3 compared to the two other BSA groups ($p<0.05$). Furthermore, a peak early mitral annular velocity of the septal wall was significantly lower in Group 1 athletes than the other two BSA groups ($p<0.05$). No other cardiac functional measures were significantly different between BSA groups. Finally, a significant linear relationship ($r = 0.3$, $p<0.0001$) was observed between the athletes BSA and their systolic blood pressure (Figure 2), and between systolic blood pressure and IVSd ($r = 0.49$), LVIDd ($r = 0.54$), PWTd ($r = 0.51$) and LVM ($r = 0.69$, $p<0.0001$).

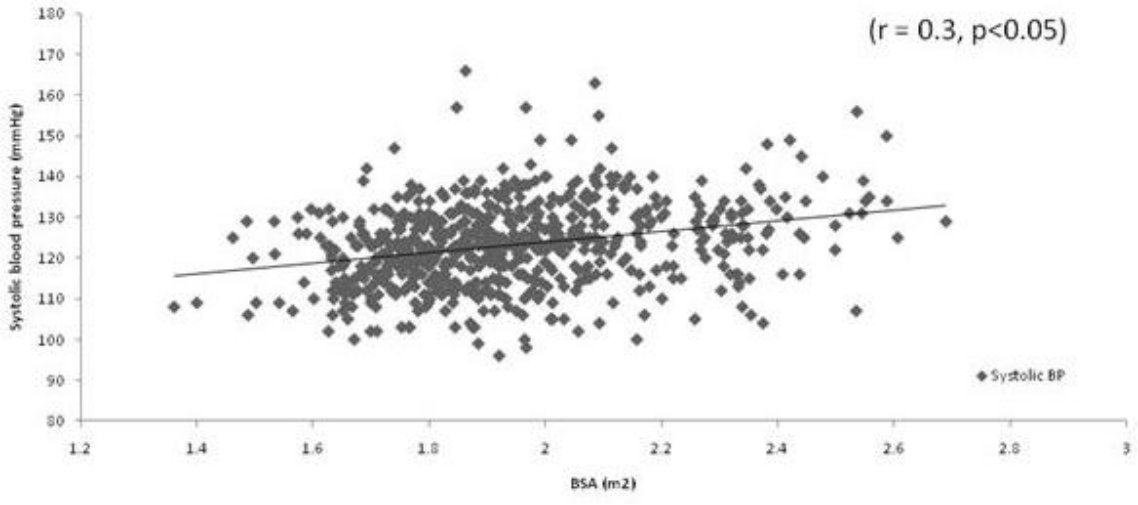


Figure 2 Relationship between the athlete's body surface area and their systolic blood pressure.

Table 3. Cardiac structural variables compared between BSA categories (mean±SD; range).

	Group 1 BSA>2.3m^2 (n=99)	**Group 2 BSA 2-2.29m^2 (n=244)**	**Group 3 BSA <1.99m^2 (n=492)**
Aortic diameter (mm)	30 ± 2* (25 – 35)	28 ± 2† (23 – 39)	26 ± 2 (19 – 33)
LA (mm)	37 ± 4* (28 – 48)	35 ± 3† (26 – 47)	32 ± 4 (21 – 42)
LA area (mm^2)	22 ± 4* (14 – 33)	20 ± 3† (13 – 31)	18 ± 4 (10 – 30)
LA vol (ml)	66 ± 17* (23 – 103)	58 ± 15† (26 – 118)	46 ± 12 (18 – 96)
Right atrial area (mm^2)	20 ± 3* (12 ± 28)	18 ± 3† (12 – 28)	15.6 ± 5.8 (8 – 26)
Right ventricular internal diameter in diastole (mm)	22 ± 5* (14 – 40)	19 ± 4† (4 – 34)	17 ± 3 (9 – 32)
Interventricular septum thickness in diastole (mm)	10 ± 1* (7 – 13)	9 ± 01† (7 – 12)	9 ± 1 (6 – 12)
Posterior wall thickness in diastole (mm)	9 ± 1* (7-13)	9± 1† (6 – 11)	8 ± 1 (5 - 11)
LVID in diastole (mm)	57 ± 3* (48 – 63)	55 ±3† (42 – 65)	52±4 (40 – 62)
LVID in systole (mm)	40 ± 5* (26 – 50)	39 ± 4† (27 – 47)	37 ± 4 (25 – 62)
LV end diastolic volume (ml)	155 ± 30* (88 – 271)	133 ± 23† (68 – 216)	114 ± 22 (11 – 196)
LV end systolic volume (ml)	50 ± 12* (22 – 111)	45 ± 10† (21 – 76)	38 ± 10 (14 – 98)
LV Mass (g)	223 ± 39* (140 – 348)	190 ± 28† (123 – 286)	157 ± 30 (66 – 241)

*Significant difference between BSA>2.3m^2 and other two groups (P<0.05). †Significant difference between BSA2-2.29m^2 and BSA<1.99m^2 (P<0.05).

LA, left atrial diameter; LVIDd, left ventricular internal diameter in diastole

5.2.5 Impact of ethnicity upon cardiac structure and function in athletes with a BSA >2.3m^2

Of the 99 remaining athletes in the BSA >2.3 m^2 cohort (31 West-Asian, 45 Black African and 23 Caucasian athletes), there were no significant differences in BSA between the three ethnicities. Black African athletes had a significantly thicker IVSd and PWTd than both West-Asian and Caucasian athletes ($p<0.05$). Black African athletes also had significantly larger LA volumes, RA areas and LV masses than West-Asian athletes ($p<0.05$). West-Asian athletes had a significantly larger LVIDd than Caucasian athletes ($p<0.05$). There were no significant differences between ethnicities in any diastolic or systolic parameter.

Table 4. Impact of ethnicity upon cardiac structure and function in athletes with a BSA>2.3m^2 (mean ±SD; range).

	West-Asian N=31	Black African N=45	Caucasian N=23
Height (cm)	189 ± 8 (170-206)	201 ± 7 (182-217)	199 ± 7 (180-210)
Body mass (kg)	109 ± 14 (91-150)	105 ± 12 (85-156)	101 ± 8 (87-117)
BSA (m^2)	2.4 ± 0.1 (2.3-2.6)	2.4 ± 0.1 (2.3-3.0)	2.4± 0.1 (2.3-2.6)
Ao (mm)	30 ± 2 (25-33)	30 ± 2 (26-35)	30 ± 2 (26-34)
LA (mm)	37 ± 4 (30-45)	37 ± 4 (28-45)	37 ± 4 (29-48)
LA area (mm^2)	22 ± 3 (14-30)	23 ± 3 (16-29)	22 ± 4 (14-33)
LA vol (ml)	61 ± 15 (23-91)	71 ± 16† (36-103)	60 ± 18 (31-98)
RA area (mm^2)	19 ± 4 (12-28)	21 ± 3† (12-28)	19 ± 3 (13-24)
IVSd (mm)	10 ± 1 (7-12)	11 ± 1* (8-13)	10 ± 1 (7-13)
LVIDd (mm)	60 ± 1# (48-60)	57 ± 1 (50-63)	58 ± 1 (54-63)
PWTd (mm)	9 ± 0.2 (7-12)	10 ± 0.2* (7-13)	9 ± 0.2 (8-10)
LVIDs (mm)	39 ± 5 (28-46)	40 ± 5 (26-50)	41 ± 3 (36-46)
LVEDV (ml)	147 ± 32 (88-236)	157 ± 24 (109-209)	161 ± 36 (120-271)
LVESV (ml)	48 ± 12 (22-76)	51 ± 10 (34-75)	54 ± 16 (30-111)
LVM (g)	208 ± 33 (140-276)	236 ± 43† (146-348)	217 ± 27 (164-266)

* Significant difference between Black athletes vs. West-Asian and Caucasian athletes ($p<0.05$).
† Significant difference between Black athletes vs. West-Asian athletes ($p<0.05$).
Significant difference between West-Asian athletes vs. Caucasian athletes ($p<0.05$).

5.3 DISCUSSION

The main finding of the current study was that the upper normal limits for maximal LV dimensions in professional male athletes with extreme anthropometric characteristics (BSA >2.3m^2) remains 14 mm for maximal wall thickness and 65 mm for LV internal diameter during diastole. Furthermore, for those athletes with the largest BSA's, Black African ethnicity was associated with larger cardiac dimensions than either West Asian or Caucasian ethnicity. Finally, in a sample of 836 athletes, 3 were diagnosed with a cardiomyopathy; 0.4% prevalence rate that in all cases, the ECG was vital for the initial identification and eventual diagnosis of the disease.

From four large scale echocardiographic studies examining a total of 5053 elite athletes (Pelliccia et al., 1991a, Whyte et al., 2004c, Basavarajaiah et al., 2008a, Basavarajaiah et al., 2008b), only 134 athletes (2.7%) demonstrated a maximal wall thickness greater than 12mm, with only a further 27 athletes (0.5%) presenting LVH>13 mm. However, out of these 5053 athletes the largest end of range BSA's in all four studies varied from 2.26-2.29 m^2, with only 1 athlete from Whyte et al. (Whyte et al., 2004c) study presenting a BSA of 2.52 m^2. This study presents 100 professional male athletes with a BSA >2.3 m^2 (mean 2.4 ± 0.1 m^2). Only one athlete from this cohort demonstrated LVH>13 mm, but he also exhibited a particular abnormal ECG suggestive of an inherited cardiac disease, and was eventually diagnosed with HCM via cardiac magnetic resonance. Of the remaining 99 asymptomatic athletes, 12 (12%) had a wall thickness greater than 12 mm and 18 (18%) had an LVIDd greater than 60 mm. However, in the presence of a normal ECG, absence of systolic anterior motion of the anterior mitral valve leaflet causing LV outflow obstruction, an appropriately dilated LV, and normal diastolic function, a

diagnosis of HCM was excluded in all athletes. This study suggests that irrespective of an athlete's enlarged BSA, the upper limit of physiological maximal wall thickness remains in the 13-16 mm range. Indeed, our data supports the more conservative approach limits suggested by Whyte et al. (Whyte et al., 2004c) such that regardless of extreme body anthropometry, the physiological upper normal limits of LV wall thickness and LVIDd are 14 mm and 65 mm, respectively.

It is still however important to note that while there are increased measures of left ventricular end diastolic volume (147ml ± 32ml) and left ventricular mass (223g ± 39g); when creating cut off values for this group of anthropometrically large athletes using 2 standard deviations, these values are beyond what is typically seen in the general athletic population (LVEDVd= 225ml; LVM=301g). Nevertheless with this athletic group presenting with no greater risk of pathology, then it suggests that these variables do not require further investigation and that the LVIDd cut off value of 65mm and maximal LVWT value of 14mm are still sufficient in detecting the physiological upper limit of normality.

Despite being referred for echocardiography due to a clinical suspicion of possible cardiac disease based upon an abnormal ECG, family history or clinical evaluation, two studies are worthy of mention that support our data in 'big' athletes. Abernethy et al. (Abernethy et al., 2003) investigated 156 asymptomatic American Football (NFL) players and reported mean maximal wall thickness and LVIDd to be 11.2 ± 0.2 mm and 53 ± 0.5 mm, respectively. Whilst, Magalski et al.[14] observed that from 203 referred NFL athletes, 197 (97%) demonstrated a maximal IVSd from 7 – 12mm, with 6 athletes (3%) presenting an IVSd from 13-14mm.

However, all 203 were considered not to have a cardiomyopic process due to no other echocardiographic abnormalities and normal Doppler inflow velocities.

It is well recognised that little account of body size is taken in the determination of 'apparently normal' cardiac dimensions in adult athletes, even though allometric scaling in the paediatric population is routine practice.(Dewey et al., 2008b) Despite the strong relationships between BSA and multiple LV measures in the current study, absolute upper normal limits are still clinically relevant. It may be that scaling, via an appropriate method and scaling variable, maybe be of more clinical value in those athletes with smaller BSA's.

Recent data suggests that an athlete's ethnic origin may have a significant impact on their cardiovascular response to exercise.(Basavarajaiah et al., 2008a, Rawlins et al., 2010b, Magalski et al., 2008) Despite no significant difference in BSA between ethnicities in the >2.3 m^2 cohort of athletes, Black African athletes presented significantly greater wall thicknesses, and resultant LV masses, than West-Asian and Caucasian athletes. It should be noted that regardless of ethnicity and the extreme BSA of this cohort, the established upper limits of cardiac structure and function are applicable to all three ethnicities. Previous data from our group has demonstrated that a minority (3%) of Black athletes (mean BSA 2.1m^2; 9 from 300) may present physiological LVH $\geq$ 15mm.(Basavarajaiah et al., 2008a) The present data set of 219 Black African athletes from a broad range of BSA's did not find an athlete with a normal ECG presenting a maximal wall thickness greater than 13mm. A limitation of the present study is that a data set of 46 Black African with a BSA > 2.3m^2 maybe too small to ascertain if this ethnicity with extreme anthropometry requires the upper limits of physiological LVH to be raised to

15mm; in spite of demonstrating significantly greater wall thicknesses and masses that their West-Asian and Caucasian counterparts. Interestingly, Basavarajaiah et al. (Basavarajaiah et al., 2008a) study demonstrated that basal and exercise related BP responses in both Black and Caucasian athletes did not differ and could not explain the increased magnitude of LVH in Black athletes. At the time we suggested that a combination of genetic (Barley et al., 1996), endocrine, and hemodynamic factors (Ekelund et al., 1990) probably accounts for the increased LVH in black athletes. Yet to date, no data has been published to confirm this postulation. Secondly, whilst professional basketball, handball and volleyball players were recruited, substantiation of the upper limits of physiological LVH is required in the small minority of athletes with extreme BSA's who compete in sports that induce the greatest amounts of cardiac remodelling; namely rowing, cycling, cross-country skiing, biathlon. Nevertheless, this will once again prove problematic for the Black African ethnicity whose participation in these endurance sports is limited.

Regardless of these limitations, our data supports the clinical utility of ECG in the initial identification of athletes suspected of harbouring an inherited cardiac disease. The present study diagnosed one athlete with a mild variant of apical HCM via cardiac magnetic resonance, following an abnormal ECG suggestive of an inherited cardiac disease. This was in spite of a normal echocardiogram (maximal LV wall thickness of 8 mm). In conclusion, marked repolarisation changes, ST depression, pathological Q waves and multiple ventricular ectopic's are a great concern, even when cardiac dimensions are within accepted limits.

5.4 CONCLUSION

In conclusion, irrespective of an athlete's extreme anthropometrical dimensions and ethnicity, the physiological upper normal limits of LV wall thickness and LV internal diameter during diastole due to intensive and sustained physical activity are 14 mm and 65 mm, respectively. Moreover, even when matched for extreme BSA (>2.3m^2), Black African athletes present significantly greater wall thicknesses and resultant LV masses than Arabic and Caucasian athletes.

CHAPTER SIX

STUDY THREE: Systematic echocardiography is not efficacious when screening an ethnically diverse cohort of athletes in West-Asia

Riding, N. R., Sharma, S., Salah, O., Khalil, N., Carre, F., George, K. P., Hamilton, B., Chalabi, H., Whyte, G. P. & Wilson, M. G. 2013. Systematic echocardiography is not efficacious when screening an ethnically diverse cohort of athletes in West Asia. *European Journal of Preventative Cardiology*. Online: 2047487313506549.

6.0 INTRODUCTION

The purpose of pre-participation cardiovascular screening is to provide medical clearance for sport through systematic evaluation aimed at identifying pre-existing cardiovascular abnormalities, and thereby reducing the potential for adverse events and sudden cardiac death (SCD). Despite methodological differences regarding the inclusion of a resting 12-Lead electrocardiogram (ECG) between American and European cardiological societies (Maron et al., 2007b, Corrado et al., 2005c), both agree that compelling justification for cardiovascular pre-participation screening exists based on medical, ethical and legal grounds. However several major sporting organisations including Fédération Internationale de Football Association (FIFA) also recommend systematic echocardiography to be included as part of cardiovascular screening protocol for high-level athletes.

Echocardiography is generally accepted as the primary modality for further examination following the identification of an 'abnormal or training un-related' ECG, owing to its enhanced ability to diagnose hypertrophic cardiomyopathy (HCM) (Rawlins et al., 2009a), the commonest

cause of SCD in young athletes. Yet, it is expensive, time consuming and requires highly skilled personal. Basavarajaiah et al. (Basavarajaiah et al., 2008b) examination of 3,500 high-level athletes (98% Caucasian), documented that screening for HCM specifically in this population with echocardiography was not cost effective because several thousand Caucasian athletes would have to be screened to identify one athlete with HCM. Despite conceding that HCM demonstrates marked morphological and functional heterogeneity, allowing a very small fraction of affected individuals to participate in high-intensity competitive endurance sport (Wilson et al., 2011b); the authors suggested that this cannot justify the inclusion of echocardiography in large-scale screening programmes for elite Caucasian athletes.

However, there is mounting evidence that ethnicity has a significant impact upon the cardiovascular adaptations associated with high-level sport. The most pronounced paradigm of ethnically distinct modifications stems from athletes of African/Afro-Caribbean descent, who exhibit a significantly higher prevalence of repolarization anomalies and left ventricular hypertrophy (LVH), posing significant challenges when differentiating physiological LVH from HCM (Papadakis et al., 2012, Kervio et al., 2012). While not to the same extent as athletes of African/Afro-Caribbean descent, in chapter 5 we demonstrated that among our Arabic athletes there was an increased prevalence of SCD related pathology. In this regard it is equally important to establish the cost implications of screening with echocardiography in this previously unrepresented population.

For two years, our insitution has followed the model of systematic echocardiographywhen screening all high-level athletes competing in Qatar (an ethnically diverse and heterogenous

population). Accordingly, we sought to confirm 1) the efficacy of systemtic echocardiography alongside the ECG, personal/family history questionnaires and physical examination, as collective tools to identify diseases with the potential to cause SCD within our population of athletes, and 2) provide a cost-analysis of a government funded pre-participation screening programme.

6.1 METHODS

Between November 2010 and October 2012, 1628 ethnically diverse athletes, exercising ≥6 h/week, presented at our institution for preparticipation cardiac screening. 85% of athletes came from 5 high-intensity intermittent sports [football (n=990, 61%), handball (n=117, 7.2%), volleyball (n=111, 6.8%), basketball (n=108, 6.6%) and martial arts (n=60, 3.7%)]. The remaining 15% came from sports such as athletics, cycling, sailing, swimming, tennis and weight lifting. Athletes came from 7 Gulf States (n = 595) 5 Middle-Eastern (n = 315), 9 African (n = 499), 6 Western/European (n = 180), 3 East-Asian (n = 16), 2 South-Asian (n = 19) and 10 South-American (n = 4) countries. For ease of reference, athletes of Gulf or Middle-Eastern descent will be termed Arabic from this point onwards. Furthermore, as previously described 'Black African' denotes individuals of African descent (Wilson et al., 2012b). Strict exclusion criteria included individuals that had undergone previous cardiovascular screening with ECG and ECHO. This was important as the population truly reflected those athletes who had not been excluded from competitive sport on the suspicion of harbouring an inherited cardiac pathology.

6.1.1 Pre-participation Cardiovascular Screening

All athletes completed the pre-competition medical assessment questionnaire regarding family history and personal symptoms in collaboration with an Arabic, French or English speaking cardiac nurse. Measurement of height, body mass, left brachial artery blood pressure (BP), precordial auscultation in supine and standing positions, and assessment for any physical characteristics of Marfan's syndrome were undertaken by a Sports Medicine Physician.

6.1.2 Resting 12-Lead ECG

A standard 12-Lead ECG was obtained using a GE Mac 5500 (New York, USA) after a period of five minutes rest in the supine position. All ECG's were reported independently by two experienced investigators (OS, MGW) using previously published criteria (Drezner, 2012); with third opinions sought for troublesome cases from two international experts in sports cardiology (SS, FC).

Before ECHO examination occurred, based upon the findings from the pre-competition medical assessment questionnaire and the ECG, athletes were separated (by MGW) into two categories; 1) those demonstrating "negative" cardiovascular signs and symptoms of a disease associated with SCD not requiring further examination, or 2) those demonstrating "positive" cardiovascular signs and symptoms suggestive of a disease associated with SCD, who require further cardiological examination(s) to rule out pathology.

6.1.3 Systematic echocardiography

Echocardiography was performed by an experienced sports cardiologist (OS) using a commercially available ultrasound system (Philips, USA), using protocols previously seen in chapter 5.

6.1.4 Further Cardiac Evaluation

Athletes demonstrating symptoms suggestive of cardiac disease, and/or family history of sudden cardiac death, and/or ECG and/or echocardiographic abnormalities suggestive of cardiac pathology were investigated further with either 24h ECG ambulatory monitoring, maximal exercise stress testing, cardiac magnetic resonance imaging or electrophysiological study, to evaluate the broader phenotype of common cardiomyopathic or ion channel processes. Careful consideration was given to athletes with a family history of sudden death and ECG abnormalities suggestive of HCM and arrhythmogenic right ventricular cardiomyopathy; notably deep T-wave inversions, ST-segment depression, pathological Q waves, or left bundle branch block. Even in the presence of a normal echocardiogram, athletes with these abnormal ECG features required 24h ECG ambulatory monitoring, maximal exercise stress testing, cardiac magnetic resonance imaging as a minimum in order to rule out the subtle forms of disease, such as mild apical HCM. Genetic testing may also be indicated when there is no family history of cardiac hereditary disease, but the athlete may present borderline cardiac abnormalities on ECG or echocardiography and/or symptoms, however not sufficient per se to confirm a diagnosis of a cardiomyopathy or primary cardiac arrhythmia. In such cases, where there is adequate evidence to consider the hypothesis of an inherited disease, genetic testing can be proposed directly to the

athlete (Richard et al., 2012a). However, before genetic testing occurs and in order for the athlete to fully understand the ramifications of a positive or negative genetic result, our group follows the 2010 ESC position statement on genetic counseling and testing in cardiomyopathies(Charron et al., 2010)**.**

6.1.5 Financial Analysis

Aspetar (Qatar Orthopaedic and Sports Medicine Hospital) is a FIFA accredited F-MARC medical centre of excellence. Its cardiovascular pre-participation screening programme is entirely government funded, without financial reliance upon charitable or public health sector institutions. For ease of interpretation, all monetary data is presented in United States dollars, as the exchange rate between the Qatar Riyal (QR) is fixed (3.64QR to $1). Aspetar's investment in man-power, infrastructure, consumables and cardiological/imaging equipment, together with economic inflation or equipment depreciation is not presented, due to the fact that the Aspetar pre-participation screening programme is just an element with the institutions cardiology scope of services.

Economic models were provided to evaluate the inclusion of systematic echocardiography as a routine examination procedure alongside the 12-Lead ECG (systematic echocardiography protocol), or its inclusion solely as a further examination modality (Echocardiography further examination protocol). In this case echocardiography is only utilized in the event of an athlete demonstrating "positive" cardiovascular signs and symptoms suggestive of a disease associated with SCD; who then requires echocardiography and/or other cardiological examinations to rule out pathology

6.2 RESULTS

6.2.1 Systematic echocardiography protocol

To screen 1628 high-level athletes with the inclusion of systematic echocardiography, a total cost of $811,730.00 USD was incurred (Table 1). Ten athletes were diagnosed with a cardiac pathology associated with SCD [8 HCM (0.5%) and 2 Wolff-Parkinson-White syndrome (0.1%, WPW); Table 2], with the cost per diagnosis at $81,173USD. The athletes diagnosed with HCM were disqualified from high-intensity competitive sports. Both athletes diagnosed with WPW had lesions ablated as a result of their electrophysiological findings; returning to full competition. All 10 athletes diagnosed with HCM or WPW presented abnormal ECGs, with 3 also presenting a positive family history of SCD or personal symptoms.

Sixteen athletes had a congenital abnormality not restrictive of competitive sport; 7 (0.4%) with a bicuspid aortic valve (BAV; 5 with murmur), and 8 (0.5%) with a trivial atrial septal defect (ASD; 1 with murmur). Echocardiography did not identify an athlete with a disease associated with SCD in ‘isolation’.

6.2.2 Echocardiography further examination protocol

If following a 12-Lead ECG led programme with echocardiography reserved as a further examination modality, 244 athletes (15%) would require further cardiological examination(s) to rule out pathology, due to “positive” cardiovascular signs and symptoms. Seventy seven athletes (4.7%) demonstrated an abnormal ECG, 184 (11.3%) presented with either an abnormal personal

symptom(s), a FH of SCD or an abnormal physical examination. Of these athletes, 17 (1%) were accounted for twice, by presenting with both an abnormal ECG and at least one of (a) symptoms, (b) a FH of SCD or (c) an abnormal physical examination. Accordingly, using echocardiography as a further examination modality, the screening programme cost would be reduced by 47% ($431,130.00 USD vs. $811,730.00 USD), with the cost per diagnosis reduced to $43,113.00 USD (Table 1). Despite this, 2 athletes with BAV, and 2 trivial ASD would have been missed without following the systematic echocardiography protocol, as all 5 were asymptomatic with an unremarkable physical examination and ECG.

Table 1: Cost of a government funded pre-participation screening programme using 1) systematic echocardiography, or 2) echocardiography utilised as a further examination modality

Procedure	Number of Tests Completed	Cost of Screening Modality (USD)	Systematic echocardiography protocol (USD)	Echocardiograpghy further examination protocol (USD)
Sports Medicine Consultation	1628	137	223,036	223,036
12-Lead ECG	1628	45	73,260	73,260
Systematic echocardiography Qatar	1628	275	447,700	-
Systematic echocardiography US	1628	1000	1,628,000	-
Systematic echocardiography Europe	1628	100	162,800	-
Echocardiography reserved as a follow up modality (15%) Qatar	244	275	-	67,100
Echocardiography reserved as a follow up modality (15%) US	244	1000		244,000
Echocardiography reserved as a follow up modality (15%) Europe	244	100		24,400
24hr Holter	38	330	12,540	12,540
GXT	62	375	23,250	23,250
CMR imaging	25	824	20,600	20,600
24hr BP	16	275	4,400	4,400
EP study	2	549	1,098	1,098
Genetic Test	2	2923	5,846	5,846
TOTAL COST			**$ 811,730.00 USD**	**$ 431,130 USD**

Table 2: Outcomes for ten athletes identified with a disease associated with sudden cardiac death

Athlete	Ethnicity	Sport	Symptoms	FH of SD (<35yr)	Abnormal ECG	Abnormal Echo	Abnormal GXT	Abnormal 24h Holter	Abnormal CMR	Abnormal 1st degree relatives	Diagnosis
1	Arabic	Football	No	No	Yes	Yes	No	No	Yes	Yes	HCM – disqualified
2	Arabic	Football	No	No	Yes	No	No	No	Yes	Yes	HCM – disqualified
3	Black African	Football	Yes	Yes	Yes	No	Yes	No	Yes	-	HCM – disqualified
4	Black African	Basketball	No	No	Yes	Yes	No	No	Yes	-	HCM – disqualified
5	Black African	Basketball	No	No	Yes	Yes	No	No	Yes	-	HCM – disqualified
6	Black African	Basketball	No	Yes	Yes	Yes	No	No	-	Yes	HCM – disqualified
7	Black African	Football	Yes	No	Yes	Yes	Yes	No	-	-	HCM – disqualified
8	Arabic	Football	Yes	No	Yes	Yes	No	No	Yes	-	HCM – disqualified
9	Arabic	Football	No	No	Yes	No	Yes	No	-	-	Ablated WPW – returned to competition
10	Arabic	Football	No	No	Yes	No	Yes	No	-	-	Ablated WPW – returned to competition

FH; family history, SD; sudden death, ECG; electrocardiography, ECHO; echocardiography, GXT; maximal graded exercise test, CMR; cardiac magnetic resonance, HCM; hypertrophic cardiomyopathy, WPW; Wolff-Parkinson-White syndrome, dash (-) means investigation was not carried out.

6.3 DISCUSSION

The main finding of the study is that including systemtic echocardiography to a cardiovascular pre-participation screening programme almost doubles the financial burden compared to a 12-Lead ECG led programme with echocardiography reserved as a follow up modality. Ten athletes were diagnosed with a cardiac pathology associated with SCD, with all 10 presenting abnormal ECGs. Echocardiography only assisted in the diagnosis of the majority of individuals with HCM, and failed to identify an inherited SCD associated pathology in isolation. The utilisation of echocardiography as a further examination modality, would have produced a 47% cost reduction to the overall programme ($811,730.00 vs. 431,130.00 USD), with a cost per diagnosis reduced to $43,113.00 from $81.173.00 USD.

6.3.1 Prevalance of cardiac disease

Our study identified 10 athletes (0.6%) with a disease associated with SCD; with the prevalence of HCM in black African's 3-times greater than Arabic athletes (1% vs. 0.3%, respectively). However, the prevalence of HCM in black African athletes is approximately 10-times greater than that observed in previous studies among Caucasian athletes; estimated at approximately 0.1% (Basavarajaiah et al., 2008b). This higher prevalence is supported by previous studies in Arabic and Black African athletes, that report a SCD disease prevalence of approximately 0.5% and 1% respectively (Wilson et al., 2012b, Riding et al., 2013); with previous investigations reporting HCM to be more prevalent in black athletes than Caucasians (Maron et al., 1996a). Anecdotal data collected in our facility suggests that up to 60% of our black African athletes (originating from Sudan, Somalia, Ghana, Nigeria, Chad, Ivory Coast, Senegal, Cameroon and

Ethiopia) have never seen a physician before presenting for pre-participation screening. This in part may explain the unusually high prevalence of HCM in this previously unexamined and unselected population; in addition to the high numbers of athletes requiring further examination (15%) with "positive" cardiovascular signs and symptoms suggestive of a disease associated with SCD, which required further cardiological examination(s) to rule out pathology.

Whilst our data implies that systematic echocardiography is not efficacious (both clinically and financially), an argument can be made for targeting certain sports and ethnicities. It is widely acknowledged that the prevalence of HCM is 1:500 for HCM (Maron et al., 1995a), yet we identified this to be 1:100 in our Black African athletes. Taken together that SCD is more common in Black African athletes competing in high-intensity, intermittent and dynamic sports (basket and football) (Maron et al., 2003b), a balanced approach to targeted screening may be possible if financially feasible. This is already the case for many sports medicine physicians working with basketball and volleyball regarding Marfan's syndrome. Furthermore, if echocardiography is requested, a secondary argument can also be made for examination at the entry point of an athlete's career and again, following significant anthropometrical maturation changes during the adolescent growth spurt. However, in our groups opinion, targeted screening contains many ethical issues (on top of the well-established arguments of the morality of pre-participation cardiovascular screening) in terms of mixed race athlete ethnicity and what sporting modality is actually a high-intensity, intermittent and dynamic sport.

Our data does however demonstrate that echocardiography did not identify a single HCM patient in isolation, with all HCM patients presenting with abnormal ECG's suggestive of cardiac

pathology. Our ethnically diverse screening data supports that of Pelliccia et al. (Pelliccia et al., 2006) in which no unequivocal cases of HCM were found after the echocardiographic re-evaluation of 4,500 previously medically cleared young competitive Caucasian athletes. Furthermore, our data supports Basavarajaiah et al. (Basavarajaiah et al., 2008b)examination of 3,500 high-level athletes (98% Caucasian), in which the authors propose that screening for HCM specifically in this population with echocardiography was not cost effective because several thousand Caucasian athletes would have to be screened to identify one athlete with HCM.

6.3.2 The conundrum of common congential cardiac malformations

Several studies have suggested the added value of including echocardiography as standard in the pre-participation screening of athletes (Stefani et al., 2008, Rizzo et al., 2012), citing the importance of trying to identify congenital cardiac malformations. The bicuspid aortic valve (BAV) is the most common congenital cardiac malformation, seen both in the general population and in athletes. Yet the impact of regular and intensive physical activity upon the BAV is not well documented. The physiological stress of exercise on the BAV may precipitate its early deterioration, instigating dilation of the initial aorta; however large cohort, longitudinal studies are lacking to corroborate this hypothesis. Whilst early identification of the BAV, with its subsequent annual echocardiographic review would be useful to identify early aortic valve degeneration and aortic root dilatation in athletes, systematic echocardiography for all athletes may be ideal but as our data show, it is currently impractical given the financial resources required and the low prevalence of congenital cardiac malformations predisposing to SCD in sport.

6.3.3 Repolarisation abnormalities with normal echocardiograms

This study also highlights the limitation of echocardiography in the diagnosis of subtle HCM phenotypes; with 2 out of the 7 HCM athletes demonstrating normal echocardiographic examinations despite presenting with inferolateral T-wave inversion on ECG (Table 2). Given the diagnostic uncertainty in these 2 athletes following echocardiography, this study also highlights the important role of including cardiac magnetic resonance (CMR) in the workup of athletes presenting with significant repolarisation abnormalities.

CMR provides a comprehensive assessment of both ischemic and non-ischemic cardiomyopathies supplying detailed precise information on cardiac anatomy, function, tissue characterisation, epicardial and microvascular perfusion, valvular flows, and coronary and peripheral angiography. Measurements of maximal wall thickness are highly accurate, as is the pattern definition of LV wall thickening (focal vs. mild concentric) and unlike echocardiography, no geometrical assumptions need to be made about the ventricle(Bellenger et al., 2000a, Bellenger et al., 2000b). Indeed, in some regions of the LV chamber, the extent of hypertrophy can be underestimated by echocardiography compared to CMR (Rickers et al., 2005, Maron et al., 2010), which is not diagnostically helpful in athletes presenting with ECG's suggestive of a cardiomyopic process. Finally, LGE provides a sensitive tool for the detection of myocardial fibrosis, abnormalities not typically seen in physiological LV hypertrophy, thus highlighting pathology (McCrohon et al., 2003, Moon et al., 2004, Popovic et al., 2008).

6.3.4 Financial Analysis

The secondary aim of this investigation was to provide an accurate cost-analysis of a government funded pre-participation screening programme. Our data demonstrates that to screen 1628 high-level athletes with the inclusion of systematic echcardiography it cost our facility a total of $811,730.00 USD. This would have been reduced to $431,130.00 USD if we followed a protocol of echocardiography reserved as a further examination modality. No calculation for Quality Adjusted Life Years (QUALY) was calculated for either protocol; simply the presentation of absolute monetary data. Whilst some authors have attempted to provide cost-effectiveness calculations for pre-participation screening programmes based upon published 'registry' data (Wheeler et al., 2010), others have demonstrated that past estimates of SCD incidence vary widely and often utilize limited methodology for case identification (Hamilton et al., 2012a, Drezner et al., 2011b). SCD incidence rates require a precise account of the number of SCD events during a specific period (a numerator) and an accurate estimate of the participating athletes per year (denominator). Harmon et al. (Harmon et al., 2011a) exemplified this by attempting to identify all cases of SCD in NCAA student-athletes during a 5-year period. Thirty-nine (87%) of the 45 SCD cases identified by the authors came from the NCAA database, while only 25 (56%) cases were identified by public media reports, and 9 (20%) from catastrophic claims data. In our opinion without accurate and robust numerators and denominators, financial extrapolation for national policy governance is not possible at this present time.

6.3.5 Limitations

Coronary artery anomalies are an important contributing mechanism for SCD, accounting for between 5-13% of all deaths (de Noronha et al., 2009b, Maron et al., 1996a). While we failed to find any, we concede that these abnormal anatomical variations may be missed in the absence of imaging techniques (Edwards et al., 2010). Furthermore, the potential for false negative screening results using the 12-lead ECG alone increases without systematic ECHO, even though ECG is abnormal in >90% of patients with HCM and in the majority of patients with ARVC (Wilson et al., 2012c). In favor of this technique, we have over 12 years of follow-up data with no deaths from an 12-ECG lead screening programme (Wilson et al., 2008b), indicating a robust screening approach.

We consider the pricing structure of our screening programme to be competitive, but realize that pricing varies globally. For example, a typical European echocardiogram may cost $100 USD vs. $1000 USD in North America. Thus using our data and financial models, the total cost in Europe following a systematic echocardiography protocol may be 1.5 times cheaper vs. North American that may be 2.5 times more expensive. Thus, extrapolation of our screening statistics to different currencies, should allow team physicians to undertake financial feasibility studies for their respective institutions/teams, in order to assess if privately funded pre-participation screening programmes are economically affordable.

6.4 CONCLUSION

In times of financial austerity and regardless of an athlete's ethnic background, we propose that when undertaking mass pre-participation screening, echocardiography should be reserved for

athletes with symptoms suggestive of underlying cardiovascular disease, a murmur indicative of LV outflow obstruction, a family history of SCD in first-degree relatives or specific ECG changes; notably deep T-wave inversions, ST-segment depression, pathological Q waves, left bundle branch block, or extreme leftward cardiac axis. Our study reveals that if following a 12-Lead ECG programme with echocardiography reserved for follow up to exclude a disease associated with SCD, 15% of athletes would be expected to undergo echocardiography with a cost saving of 47% to the overall programme.

CHAPTER SEVEN

STUDY FOUR: Comparison of three current sets of electrocardiographic interpretation criteria for use in screening athletes

Riding, N. R., Sheikh, N., Adamuz, C., Watt, V., Farooq, A., Whyte, G. P., George, K. P., Drezner, J., Sharma, S., & Wilson, M. G. 2014. Comparison of three current sets of electrocardiographic interpretation criteria for use in screening athletes. *Heart*. Published Online First.30/10/14. doi:10.1136/heartjnl-2014-306437

7.0 INTRODUCTION

In 2010, the European Society of Cardiology (ESC) produced 'revised' recommendations for the interpretation of electrocardiograms of athletes (Corrado et al., 2010). This was due to the increasing number of sporting governing bodies undertaking pre-participation cardiovascular screening reporting unacceptably high-levels of false positive ECGs arising from the overlap between physiological ECG patterns commonly observed in athletes, and those suggestive of cardiac pathology. To demonstrate improved specificity, the authors reanalysed the ECGs of 1,005 highly trained athletes previously reported a decade earlier (Pelliccia et al., 2000b). Originally, 402 athletes (40%) presented an abnormal ECG (so called 'Group 2' changes) which was lowered to 11% using the 2010 ESC recommendations. Work from our group and others has, however, demonstrated that certain black ethnic populations, such as African, African-Caribbean and Black Latin-American, continue to demonstrate a high prevalence of abnormal ECGs (circa. 20-40%) when using the 2010 ESC recommendations (Riding et al., 2013, Papadakis et al., 2011b, Magalski et al., 2011, Wilson et al., 2012b).

To address this issue, in 2012 an international team of experts produced the ‘Seattle Criteria’ (Drezner et al., 2013a); a revision of ECG interpretation guidelines for athletes, aimed to provide greater accuracy in identifying those with cardiac pathology, whilst also attempting to reduce the false positive rate. The Seattle Criteria have demonstrated favourable results over the ESC recommendations, with a reduction in the number of ECGs previously considered abnormal (17 to 4%) in a population of high-level athletes, whilst still identifying all athletes with cardiac pathology (Brosnan et al., 2013b). Furthermore, the Seattle Criteria considers specific ethnic ECG facets such as anterior (V1-V4) T-wave inversion (commonly observed in up to 13% of Black athletes (Papadakis et al., 2011b)), to represent an ethnically benign variant of the 'athlete's heart in those of Black ethnicity, helping to reduce false positive rates further.

Recently, Sheikh et al. (Sheikh et al., 2014b) published additional ‘Refined Criteria’ for ECG interpretation, based upon their experience of screening thousands of athletes utilising both the ESC recommendations and the Seattle Criteria. Sheikh et al. [9] demonstrated that the ECG patterns of isolated atrial enlargement (left and right), axis deviation (left and right) and right ventricular hypertrophy found in both the ESC recommendations and the Seattle Criteria provided an extremely low diagnostic yield for cardiac pathology. A unique feature of this investigation was a validation assessment in 103 young athletes with confirmed hypertrophic cardiomyopathy (HCM) where by the Refined Criteria identified 98.1% of HCM cases.

Whilst the ESC guidelines were initially considered acceptable for use within Arabic athletes (Riding et al., 2013), it is unknown if the Seattle Criteria or the Refined Criteria are clinically appropriate for differentiating physiological cardiac adaptation from inherited pathology associated with sudden cardiac death (SCD) in Arabic athletes. Consequently, the aim of this investigation was to assess the accuracy of the new 2014 Refined Criteria versus the 2013 Seattle Criteria and the 2010 ESC recommendations in a large cohort of Arabic, Black and Caucasian athletes when undertaking mass pre-participation cardiovascular screening.

7.1 METHODS

Ethical approval was obtained from Shafallah Medical Genetics Centre and the Qatar Anti-Doping Laboratory ethics committee, with all athletes completing informed consent in either Arabic or English.

7.1.1 Participants

Between November 2010 and January 2014, 2491 male athletes (exercising ≥6 h/week) presented at Aspetar Orthopaedic Sports Medicine Hospital for pre-participation cardiac screening; of whom 1367 were Arabic, 748 Black and 376 Caucasian. Ethnicity was self-determined by the athlete. Arabic athletes were recruited from seven Gulf States (Qatar, Bahrain, Oman, United Arab Emirates, Kuwait, Yemen and Saudi-Arabia) and seven Middle-Eastern countries (Egypt, Morocco, Algeria, Tunisia, Jordan, Palestine and Lebanon). Black athletes came from 9 African countries (Sudan, Somalia, Ghana, Nigeria, Chad, Ivory Coast, Senegal, Cameroon and Ethiopia), 3 Caribbean countries (Trinidad and Tobago, Jamaica and Cuba) and those that self-determined their ethnicity as Black from South America (Brazil, Colombia,

Ecuador and Uruguay). The vast majority of Caucasian athletes came from mainland Europe, Australia and North America with a small number from South America.

7.1.2 Pre-participation cardiovascular screening

All players were screened using a cardiovascular pre-competition medical assessment form. Athletes completed the questionnaire regarding family history and personal symptoms, together with measurements of height, body mass, left brachial artery blood pressure (BP) in collaboration with an Arabic, French or English-speaking cardiac nurse. Precordial auscultation in supine and standing positions, and assessment for any physical characteristics of Marfan's syndrome were undertaken by a Sports Medicine Physician. From 2491 athletes presenting for pre-participation cardiac screening, 1718 (68.7%) required both ECG and echocardiography as standard as part of sport or club requirements.

7.1.3 Resting 12-lead ECG

A 12 lead ECG was recorded on all athletes after a period of 5 minutes rest in the supine position using a GE Mac 5500 (New York, USA). A well-defined protocol for electrode placement was used throughout by a single physiologist. Six electrodes are placed on the chest in the following locations: V_1, fourth intercostal space at the right sternal border; V_2, fourth intercostal space at the left sternal border; V_3, midway between V_2 and V_4; V_4, fifth intercostal space in the midclavicular line; V_5, in the horizontal plane of V_4 at the anterior axillary line, or if the anterior axillary line is ambiguous, midway between V_4 and V_6; and V_6, in the horizontal plane of V_4 at

the midaxillary line. Four limb lead electrodes were placed on the arms and legs distal to the shoulders and hips.

7.1.4 Echocardiography

Echocardiographic examination was performed using a commercially available ultrasound system (Philips, USA). Images of the heart were obtained in the standard planes (Tajik et al., 1978), with cardiac structure and function evaluated with previously described criteria (Riding et al., 2013). All echocardiograms were obtained and reported by a single echocardiographer.

7.1.5 Further evaluation and follow-up

Athletes demonstrating symptoms, a family history of SCD, ECG abnormalities and/or echocardiographic abnormalities considered to represent pathology were investigated further. Subsequent studies included 24-hour ECG, maximal exercise testing and cardiac magnetic resonance imaging. A diagnosis of disease was established using published criteria (Maron et al., 2003c, Maron et al., 2005).

7.1.6 Retrospective ECG examination

All 2491 ECGs were analysed retrospectively using the ESC recommendations, followed by the Seattle Criteria and Refined Criteria. During analysis, first and last authors were blinded to pathological findings in all athletes, with MGW providing final judgement on ECG normality or

abnormality using each of the 3 ECG criteria. Electrocardiographic parameters used to define various ECG abnormalities for the 3 sets of criteria are presented in Table 1.

7.1.7 Refined Criteria

Differences between the ESC recommendations and the Seattle criteria can be observed in Table 1. Compared to the ESC recommendations and the Seattle Criteria, the unique aspect of the Refined Criteria is that athletes would not receive further cardiovascular evaluation when presenting with the following recognised training related ECG changes in isolation; 1) left atrial enlargement (LAE), 2) right atrial enlargement (RAE), 3) left axis deviation (LAD), 4) right axis deviation (RAD) and 5) Sokolow-Lyon voltage criteria for right ventricular hypertrophy (RVH). In line with the Seattle Criteria, a corrected (Bazett's formula) QT interval (QTc) ≥470 milliseconds (ms) in males and ≥480ms in females, and T-wave inversion preceded by convex ST-segment elevation in leads V1-V4 in asymptomatic Black athletes do not require further investigation. However, importantly, the presence of 2 or more of the above ECG patterns would warrant secondary investigation (Figure 1) (Sheikh et al., 2014b). It is worth noting that the Refined Criteria are not an evolution of the 2012 Seattle Criteria, but uses ECG parameters from both the 2010 ESC recommendations and the Seattle Criteria.

Table 1: Electrocardiographic parameters used to define various ECG abnormalities in the European Society of Cardiology recommendations, Seattle criteria and refined criteria. LBBB, left bundle branch block; mm, millimetres; msec, milliseconds; RBBB, right bundle branch block

ECG Abnormality	**European Society of Cardiology Recommendations**	**Seattle Criteria**	**Sheikh Refined Criteria**
Left atrial enlargement	Negative portion of the P wave in lead V1 ≥0.1mV in depth and ≥40msec in duration	Prolonged P wave duration of >120msec in leads I or II with negative portion of the P wave ≥1mm in depth and ≥40msec in duration in lead V1	As ESC
Right atrial enlargement	P-wave amplitude ≥2.5mm in leads II, III or aVF	As ESC	As ESC
Left QRS-axis deviation	-30^{O} to -90^{O}	As ESC	As ESC
Right QRS-axis deviation	$>115^{O}$	$>120^{O}$	As ESC

Right ventricular hypertrophy	Sum of R wave in V1 and S wave in V5 or V6 ≥10.5mm	Sum of R wave in V1 and S wave in V5>10.5mm and right axis deviation >120^{O}	As ESC
Corrected QT interval	>440msec (males) and >460msec (females)	>470msec (males) and 480msec (females)	As Seattle
Complete left bundle branch block	QRS ≥120msec predominantly negative QRS complex in lead V1 (QS or rS), and upright monophasic R wave in leads I & V6	As ESC	As ESC
Complete right bundle branch block	RSR' pattern in anterior precordial leads with QRS duration ≥120msec	Not relevant	As ESC
Intraventricular conduction delay	Any QRS duration >120msec including RBBB and LBBB	Any QRS duration ≥140msec or complete LBBB	As ESC
Pathological Q-wave	>4mm deep in any lead except III, aVR	>3mm deep and/or >40msec duration in ≥2 leads except III and aVR	≥40msec in duration or ≥25% of the height of the ensuing R-wave

Significant T-wave inversion	≥2mm in ≥2 adjacent leads (deep) or 'minor' in ≥2 leads	>1mm in depth in two or more leads V2−6, II and aVF or I and aVL (excludes III, aVR and V1)	As Seattle
ST-segment depression	≥0.5mm deep in ≥2 leads	As ESC	As ESC
Ventricular pre-excitation	PR interval <120msec with or without delta wave	PR interval <120msec with delta wave	As Seattle

7.1.8 Statistical analysis

Data was analysed using SPSS 21.0 (Illinois, USA); presented as mean ± SD (range) and percentage where appropriate. One-way Analysis of Variance (ANOVA) using Bonferrroni adjustments (if applicable) was used to identify differences in athlete anthropometry. A Chi-square test was used to compare the number of abnormal ECGs between the 3 ECG interpretation criteria and between athlete ethnicities. Specificity and sensitivity for the 3 criteria were calculated in those athletes who undertook both ECG and echocardiography as part of club requirements; following which positive and negative likelihood ratios were calculated. A McNemar Chi-square test was used to compare specificity and positive likelihood ratios between criteria. A p-value <0.05 was considered significant.

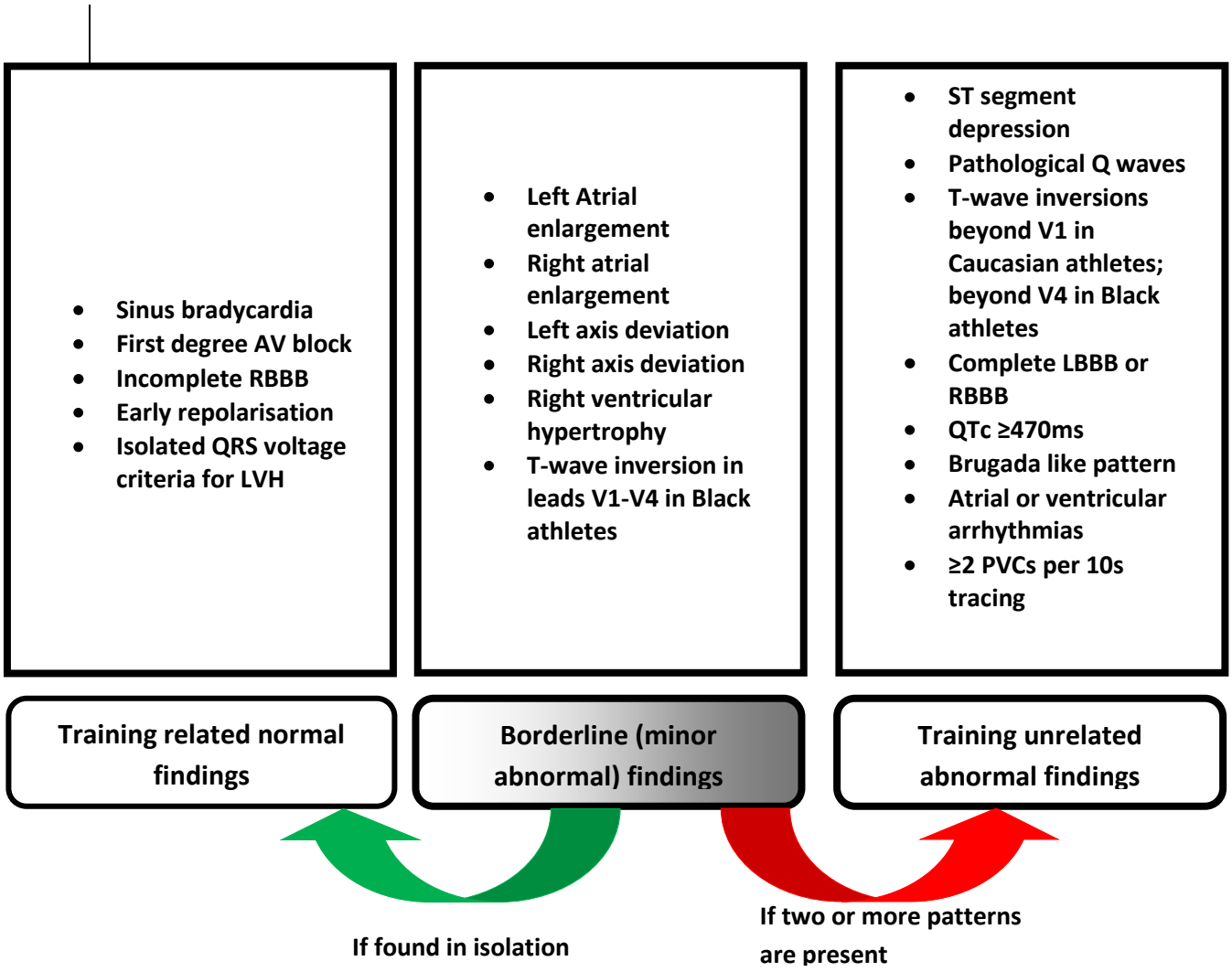


Figure 1. Definition of an abnormal ECG, using the Sheikh Refined criteria.

7.2 RESULTS

7.2.1 Athlete demographics

Overall, Arabic athletes were younger than both Black and Caucasian athletes (21.3 ± 5.4 vs. 24.1 ± 5.0 and 24.3 ± 5.4 years respectively; $p<0.05$). Arabic athletes had a smaller body surface area (BSA) than both Black and Caucasian athletes (1.87 ± 0.26m^2 vs. 2.00 ± 0.28m^2 vs. 2.14 ±

0.26 m^2, $p<0.05$). Caucasian athletes presented a larger BSA than Black athletes ($p<0.05$). Athletes competed in a range of competitive sports (n=27), with 4 high-intensity intermittent sports dominating participation rates [soccer (43.2%), handball (13.7%), volleyball (9.1%), and basketball (8.5%)].

7.2.2 Identification of cardiac pathology

Ten athletes (0.6%) were identified with a cardiac pathology associated with SCD; 7 with HCM (5 Black and 2 Arabic) and 3 Arabic athletes with Wolff-Parkinson-White syndrome (WPW). All athletes with HCM presented with an abnormal ECG, but were diagnosed with pathology via a combination of echocardiography, 24 hour Holter, exercise stress testing and cardiac MRI. The incidence of HCM in Black athletes (0.9%) was five-times greater than in Arabic athletes (0.2%). All athletes with HCM displayed T-wave inversion; 5 inferolateral, 1 isolated lateral and 1 with anterior-inferior. Six of the 7 HCM athletes demonstrated 'deep' (>0.3 mV) T-wave inversion, ST-segment depression and Sokolow voltage criteria for left ventricular hypertrophy, calculated as the amplitude of the S wave in V1 plus the amplitude of the R wave in either V5 or V6 ≥3.5mV (mean 4.53 mV). These 3 cases of WPW demonstrated a classical delta wave, a short PR interval together with a prolonged QRS duration. All 3 athletes underwent electrophysiological study and ablation, returning to full competition following a 2-month post-operative recovery period.

7.2.3 Comparison of 3 ECG interpretation criteria

The number of ECGs considered abnormal using the 3 criteria is presented in Table 2. From 2491 athletes, 555 (22.3%) were considered to have an abnormal ECG according to the ESC recommendations. The most common ECG abnormalities were a prolonged QT interval (26.1%), T-wave inversion (21.3%), right atrial enlargement (16.5%) and a short PR interval (12.4%). Black athletes were significantly more likely to present an abnormal ECG than Arabic and Caucasian athletes (29.9% vs. 19.1% and 18.6% respectively, $p<0.0001$).

Compared to the ESC recommendations, utilisation of the Seattle Criteria significantly reduced the number of abnormal ECGs from 22.3% to 11.6% (a 48% reduction ($p<0.0001$)). The main two ECG parameters that accounted for the majority of this improvement were an increase in the QTc cut-offs (≥470 ms males and ≥480 ms females) and the acknowledgement that isolated anterior T-wave inversion in asymptomatic Black athletes is benign. This spared 172 (6.9%) athletes from further investigation. From the remaining abnormal ECGs, 54.6% were considered abnormal due to either isolated RAE (31.8%), LAE (13.1%), left and right axis deviation (5.2% and 3.1%) and RVH (1.4%). Pathological Q waves (27.0%) and other locations of T-wave inversion (23.2%) were also highly prevalent. Black athletes were again significantly more likely to present an abnormal ECG than Arabic and Caucasian athletes (16.6% vs. 9.7% and 8.5% respectively, $p<0.0001$). Yet across all 3 ethnicities, the number of abnormal ECGs were significantly reduced compared to the ESC recommendations ($p<0.0001$).

Application of the Refined Criteria further reduced ($p<0.0001$) the number of abnormal ECGs in athletes to 5.3%. Compared to the ESC recommendations and the Seattle Criteria, this produced

a 76% and 54% reduction in the number of abnormal ECGs, respectively. However, Black athletes continue to present a significantly higher ($p<0.0001$) prevalence of abnormal ECGs compared to Arabic and Caucasian athletes (10% vs. 3.6% and 2.1%).

Table 2: Performance comparison of 3 ECG interpretation criteria (ESC recommendations vs. Seattle Criteria vs. Sheikh Refined Criteria)

	Combined (n=2491)	**Arabic (n=1367)**	**Black (n=748)**	**Caucasian (n=376)**
Prevalence of an abnormal ECG using ESC recommendations	555 (22.3%)	261 (19.1%)	224 (29.9%)	70 (18.6%)
Prevalence of an abnormal ECG using Seattle Criteria	289 (11.6%)	133 (9.7%)	124 (16.6%)	32 (8.5%)
Prevalence of an abnormal ECG using Sheikh Refined Criteria	132 (5.3%)	49 (3.6%)	75 (10%)	8 (2.1%)
Number of identified conditions associated with SCD	10 (7 HCM; 3 WPW)	4 (2 HCM; 2 WPW)	6 (5 HCM; 1 WPW)	0
FPR when using ESC recommendations	21.9%	18.8%	29.1%	18.6%
FPR when using Seattle Criteria	11.2%	9.4%	15.8%	8.5%

FPR when using Sheikh Refined Criteria	4.9%	3.3%	9.2%	2.1%

7.2.4 Sensitivity and specificity for the 3 ECG interpretation criteria

From 2491 athletes screened, 1718 (68.7%) were required to undergo both ECG and echocardiography due to club requirements. This cohort also contained all of the pathological cases (7 HCM and 3 WPW) and was consequently used to calculate the incidence of serious pathology together with the sensitivity and specificity of the 3 ECG interpretation criteria (Table 3). Compared to the ESC recommendations, the Seattle Criteria significantly improved specificity from 76.6% to 87.5%, whilst the Refined Criteria further improved specificity to 94.0%. Amongst Black athletes, the Refined Criteria offered 90.2% specificity, compared to 69.5% and 83.7% for the ESC recommendations and the Seattle Criteria respectively. This significant improvement in specificity was also seen in Arabic athletes. The Refined Criteria led to a significant improvement in specificity (95.6%), compared to 80.2% and 88.9% for the ESC recommendations and the Seattle Criteria respectively. However, there was 100% sensitivity for all 3 ECG interpretation criteria which detected all 7 cases of HCM and 3 cases of WPW.

Table3: Table representing the sensitivity and specificity and likelihood ratios of 3 ECG interpretation criteria

	ESC recommendations	**Seattle Criteria**	**Sheikh Refined Criteria**
Combined athletes (Arabic, Black and Caucasian)			
Positive predictive value (%)	2.44 (1.18 - 4.44)	4.48 (2.17 - 8.09)	8.93 (4.37 - 15.81)
Negative predictive value (%)	100 (99.72 - 100)	100 (99.75 - 100)	100 (99.7 - 100)
Sensitivity (%)	100 (68.97 - 100)	100 (68.97 - 100)	100 (68.97 - 100)
Specificity (%)	76.58 (74.5 - 78.57)	87.53 (85.87 - 89.1)	94.03 (92.80 - 95.1)
Positive likelihood ratio	4.27 (3.92 - 4.65)	8.02 (7.07 - 9.09)	16.75 (13.87 - 20.21)
Negative likelihood ratio	0	0	0
Black athletes			
Positive predictive value (%)	2.68 (1.00 -5.74)	4.84 (1.81 -10.24)	8.00 (3.01 -16.61)
Negative predictive value (%)	100 (99.29 -100)	100 (99.40 -100)	100 (99.45 -100)

Sensitivity (%)	100 (54.05 -100)	100 (54.05 -100)	100 (54.05 -100)
Specificity (%)	70.62 (67.20 -73.88)	84.10 (81.26 -86.66)	90.70 (88.38 -92.69)
Positive likelihood ratio	3.40 (3.04 to 3.81)	6.29 (5.33 to 7.42)	10.75 (8.59 to 13.46)
Negative likelihood ratio	0	0	0
Arabic athletes			
Positive predictive value (%)	1.53 (0.43 - 3.88)	3.01 (0.84 - 7.53)	8.16 (2.32 -19.62)
Negative predictive value (%)	100 (99.66 - 100)	100% (99.70 -100.00)	100 (99.72-100)
Sensitivity (%)	100 (40.23 - 100.00)	100 (40.23 -100.00)	100 (40.23 -100.00)
Specificity (%)	81.14 (78.96 - 83.19	90.54 (88.86 -92.04)	96.70 (95.61 -97.58)
Positive likelihood ratio	5.30 (4.75 to 5.92)	10.57 (8.97 to 12.45)	30.29 (22.72 to 40.37)
Negative likelihood ratio	0	0	0

7.3. DISCUSSION

The correct differentiation of physiological adaptation owing to sustained and intensive exercise from an inherited or congenital cardiac pathology is paramount, in order to correctly identify athletes at risk of SCD. The key finding from the current study is that the prevalence of an abnormal ECG was significantly reduced to 5.3% when using the 2014 Refined Criteria compared to the 2013 Seattle Criteria (11.6%) and the 2010 ESC recommendations (22.3%) respectively; whilst all 3 ECG interpretation criteria proved 100% sensitive, identifying all cases of serious cardiac pathology.

Our results demonstrate that when using the 2010 ESC recommendations, almost 1 in 5 Arabic, 1 in 3 Black and 1 in 5 Caucasian athletes would require further investigation due to an abnormal ECG. These high false positive rates certainly reinforce concerns voiced by the cardiovascular screening sceptics. Whilst the ESC recommendations are based upon consensus rather than scientific evidence, the Seattle Criteria modified its ECG interpretation criteria by applying evidence that 1) accounted for the impact of African-Caribbean ethnicity upon the electrocardiographic patterns seen in athletes (Papadakis et al., 2009, Papadakis et al., 2011b, Di Paolo et al., 2012a) and 2) by raising the QTc thresholds (≥470 ms men and ≥480 ms women) that would trigger further evaluation (Basavarajaiah et al., 2007a, Goldenberg et al., 2008). By incorporating these two electrocardiographic features, our study demonstrates that 172 (6.9%) of athletes would be spared further investigation, helping to lower ($p<0.0001$) the prevalence of abnormal ECGs by 48% compared to the ESC recommendations. This compares favourably with a recent investigation involving elite Caucasian athletes from Australia (Brosnan et al., 2013b). Our data, however, demonstrates that almost 1 in 10 Arabic, 1 in 6 Black and 1 in 11

Caucasian athletes would still require further investigation using the Seattle Criteria, primarily due to the presence of RAE (31.8%), LAE (13.1%), LAD (5.2%), RAD (3.1%) and RVH (1.4%), either in isolation or in association with a recognised training related ECG change.

Using HCM, ARVC and pulmonary hypertension populations as a comparison group, both Zaidi et al. (Zaidi et al., 2013b) and Gati et al. (Gati et al., 2013) have demonstrated that in asymptomatic athletes, the presence of RAE, LAE, LAD, RAD and RVH either in isolation or in association with a recognised training related ECG changes correlate extremely poorly with serious cardiac pathology. Despite this, consensus opinion for the inclusion of these ECG parameters in both the ESC recommendations and the Seattle Criteria comes from the fact that these anomalies, in particular LAE, are common ECG features in HCM. In HCM, however, they usually co-exist with multitude of other ECG abnormalities such as T-wave inversion, Q-waves and ST-segment depression (Gati et al., 2013). Excluding these ECG parameters forms the basis of the Refined Criteria improving specificity and reducing the prevalence of an abnormal ECG in our cohort to 5.3% overall. More strikingly, the Refined Criteria significantly improved the abnormal ECG prevalence in Black athletes to just 10% (vs. 29.9% ESC and 16.6% Seattle Criteria), whilst it was further reduced to 3.6% and 2.1% in Arabic and Caucasian athletes respectively.

7.3.1 Identification of Pathology

Our study identified 7 athletes (0.4%) with HCM; with the prevalence in Black athletes five-times greater than Arabic athletes (0.9 % vs. 0.2%). No Caucasian athlete was diagnosed with HCM. HCM is cited as the leading cause of sudden death in young athletes (Maron et al., 1996a), particularly within the Black population (Maron et al., 2003b). Importantly, all 3 ECG interpretation guidelines identified all 7 HCM athletes with 100% sensitivity. Our incidence

rates in the present study from a cohort of 1718 athletes who underwent systematic ECG and echocardiography are similar to those reported in previous screening studies involving Black and Arabic athletes, who report a disease incidence of 1% and 0.5% respectively (Wilson et al., 2012b). Whilst the incidence of HCM in Black athletes is still approximately 9-times higher than that observed in Caucasian athletes; our Arabic athletes now report similar HCM incidence rates to that of Caucasians, estimated at 0.1% (Basavarajaiah et al., 2008b).

A further 29 (1.2%) athletes were identified as having a congenital/valvular abnormality. Specifically, bicuspid aortic valve (n=7, 0.3%), mitral valve prolapse (n=3, 0.1%), mild aortic regurgitation (n=5, 0.2%), mitral regurgitation (mild) (n=2, 0.1%), atrial septal defect (n=6, 0.2%) and one case of dextrocardia (0.04%); all picked up through auscultation. None of these athletes was restricted from competition. Only one of these cases was identified via an abnormal ECG (dextrocardia). This poor sensitivity underscores the importance of a physical examination within the cardiovascular screening remit.

7.3.2 Limitations

Our results are based on observational cross-sectional data. The potential for a false negative result exists even though 90-95% of individuals with HCM and 80% with ARVC exhibit ECG abnormalities (Maron, 2002, Marcus, 2000). Furthermore, without serial examination over many years, it is near impossible to ascertain if asymptomatic athletes without a family history of SCD presenting with isolated LAD/RAD or LAE/RAE would later go onto develop a cardiomyopathy. Secondly, our population was exclusively male, limiting the application of our data to the female athletic population.

In the present study one athlete, a 27-year old black football player from South America died unexpectedly. At the time of pre-participation screening, the athlete reported no cardiovascular symptoms and no family history of SCD. ECG and echocardiography were strictly normal. The athlete self-presented to the emergency department complaining of severe abdominal pain and died several hours later. An autopsy was performed but the report has not been made available to the authors.

7.4 CONCLUSION

The 2014 Refined Criteria outperformed both the 2013 Seattle Criteria and the 2010 ESC recommendations by significantly reducing the number of false-positive ECGs in Arabic, Black and Caucasian male athletes whilst remaining 100% sensitive in identifying all athletes with cardiac pathology associated with SCD. The 2014 Refined Criteria can not only be successfully applied to Black and Caucasian athletes, but also to Arabic athletes, helping to reduce both further investigation rates and the potential for unnecessary disqualifications, whilst maintaining sensitivity for conditions that may predispose athletes to SCD.

CHAPTER EIGHT

8.0 STUDIES ONE - FOUR SYNPOSIS

The primary focus of this thesis was to establish whether differences exist in cardiac structure and function between Arabic athletes and those of other ethnic origins. A secondary focus was to evaluate these differences and examine their impact upon pre-participation cardiac screening protocols. By addressing these overarching goals, we were able to provide novel clinical findings that enhance the current body of knowledge for sports medicine physicians, health professionals and cardiovascular scientists working with athletes when attempting to prevent SCD.

8.1 Study One

Study one utilised a large cohort of high-level Arabic athletes, addressing the issue of ethnicity and its impact upon cardiac structure and function, i.e. the 'Arabic Athletes Heart'. Results demonstrated that while Arabic athletes displayed greater cardiac dimensions than Arabic controls, these values were significantly smaller than those of Caucasian and Black athletes. With regard to the electrocardiographic characteristics however, the Arabic athlete showed similar changes to those observed in the Caucasian athlete. The similarities between the two ethnicities were evident both among training related and training unrelated ECG findings. Ultimately, this close association with Caucasian athletes confirmed that the ESC guidelines for ECG interpretation in athletes are clinically applicable to the Arabic athletic population. Furthermore, Study 1 supported the ever increasing documentation of the divergent electrophysiological adaptation among Black athletes compared with Caucasian athletes. Contrary to recent publications however, the results refute, to some degree, the marked structural hypertrophy of Black athletes in comparison to other ethnicities.

8.2 Study Two

Study two was designed with the intention of informing and shaping clinical practice when encountering a further important group of athletes; anthropometrically large athletes. The primary finding was that among the cohort of athletes with a BSA >2.3m^2, despite showing a linear relationship between body size and cardiac size, no athlete displayed cardiac remodelling exceeding the previously established upper limits of physiological adaptation i.e. 14mm and 65mm for LVWT and LVIDd respectively. Despite remaining within the boundaries of physiological adaptation, Black athletes within this subgroup of anthropometrically large athletes showed a greater magnitude of cardiac remodelling, with greater maximal wall thicknesses. Importantly these findings could not be explained by resting blood pressure. A limitation of the study was the small number of sporting disciplines, especially the lack of sports combining endurance and strength such as rowing and cycling. However, these findings have already impacted policy, with the British Society of Echocardiography citing this paper within their echocardiographic guidelines for screening high-level athletes.

8.3 Study Three

Study three examined the current practice of cardiovascular pre-participation screening with echocardiography within a sports medicine institution. The key outcome of the study was identifying that echocardiography is not cost effective when screening an ethnically diverse cohort of athletes; failing to independently identify any cardiac pathology related to sudden cardiac death. Echocardiography did permit the detection of non SCD related conditions such as bicuspid aortic valve and atrial septal defects; however its inclusion almost doubled the financial burden compared with the use of echocardiography as a follow up investigation ($811,730 vs. $431.130). These findings have already elicited policy change within ASPETAR; whereby

echocardiography is no longer utilised as a primary tool in the systematic cardiovascular work up of an athlete presenting for pre-participation screening, and is only utilised when clinically indicated.

8.4 Study Four

Study four was conducted with the aim of assessing the performance of the newly published 'Refined' ECG interpretational criteria against the 2010 ESC guidelines and the 2012 'Seattle Criteria'. The results revealed that there has been a significant improvement in criteria specificity, reducing the number of unnecessary further tests or disqualifications, leading to a low number of false positive cases. Importantly, a sensitivity of 100% for pathology detection was maintained. With several sporting governing bodies including FIFA, UEFA and the IOC endorsing the ESC guidelines the results indicate significant improvements can be made with regards to their screening protocols by adopting the latest guidelines.

CHAPTER NINE

9.0 GENERAL DISCUSSION

9.1 Impact of ethnicity on cardiac structure and function

Within the field of sports cardiology, recent literature has indicated that ethnicity is a significant factor in both disease inheritance and physiological adaptation to exercise. Early work focused almost exclusively on Caucasian athletes, yet recent work has demonstrated that athletes of African/Afro-Caribbean descent are three times more likely to succumb to SCD than their Caucasian counterparts (Harmon et al., 2011b). Moreover, the morphologic and electrocardiographic adaptations of the physiologically derived 'athlete's heart' are also shown to demonstrate differences with respect to ethnicity. The athletic population is however not limited to these two ethnicities with an increasing number of athletes from the Middle East and West Asia performing at the highest level of international sport.

In accordance with the primary objective of the thesis, we demonstrated, for the first time, that while Arabic athletes present with larger hearts than Arabic control subjects, they typically have smaller hearts than athletes of Black and Caucasian ethnicities. Compared to other Asian groups (Gulf and Middle-Eastern are considered West-Asian), the results demonstrate significant differences i.e. Kervio et al (Kervio et al., 2012) found that despite Japanese athletes being significantly smaller and lighter than Caucasian and Black athletes, they had comparatively marked percentage of eccentric remodelling (Japanese: 30%; Caucasian: 13; Black: 7%); predominantly attributable to greater LVIDd dimensions. The number of Japanese athletes was

however small (n=68), confined to football players, and thus extrapolation to other Asian athletes should be done with caution.

From a structural perspective, Caucasian athletes in Study 1 showed greater cardiac remodelling with larger LVIDd, LV volume during diastole and LV mass than Arabic and Black athletes. The greater cavity dimensions and resultant LVM exhibited by the Caucasian athletes is not a new concept, and the extent of the remodelling corroborate those reported by Pelliccia *et al* (Pelliccia et al., 1999). LVWT failed to demonstrate any significant difference between Caucasian and Black athletes. This is interesting considering the previously reported increase in LVH among Black athletes compared with other ethnicities. Of note, Study 1 data shows that while Black athletes may not demonstrate significantly marked LVH, they had a greater percentage of athletes who had a wall thickness greater than 10 mm (Black: 25% vs. Caucasian: 14%; A: 12%). Moreover, our unpublished data shows that using relative wall thickness, Black athletes demonstrate a greater propensity for concentric remodelling than the other ethnicities ($p<0.001$), and consequently suggest potentially different mechanisms that may explain this altered cardiac remodelling.

The highly reported adaptation of left ventricular wall thickness is in response to the greater haemodynamic load placed upon the heart as a result of an increased afterload during exercise. It was originally put forward that the different blood pressure responses to stressors such as exercise may mediate the differential adaptation between Black and Caucasian athletes (Gottdiener et al., 1990, Hinderliter et al., 1992a). However, in response to exercise, Basavarajaiah *et al* (Basavarajaiah et al., 2008a) failed to demonstrate significant difference in blood pressure levels in Black athletes compared to their Caucasian counterparts. Despite this,

previous research demonstrates an accentuated left ventricular adaptation among Black individuals when compared to matched individuals of Caucasian ethnicity, both in normotensive and hypertensive populations (Beaglehole et al., 1975, Taylor et al., 1983, Hinderliter et al., 1992a). Moreover, the ethnic differences remained despite adjustment for factors such as fat mass, fat-free mass, systolic blood pressure, age, gender (Drazner et al., 2005, Hinderliter et al., 1992a). This may still however be explained in part by a greater haemodynamic burden. In comparison to matched Caucasian individuals, among apparently healthy young African-Americans, Hefernan *et al* (Heffernan et al., 2008) identified that despite demonstrating comparable brachial blood pressures, Black individuals had greater central blood pressures, diffuse macrovascular and microvascular dysfunction, increased stiffness of central elastic arteries and heightened resistance artery constriction/blunted resistance artery dilatation.

This study furthered work from an investigation in non-athletic normotensive black individuals (Lang et al., 1995). The authors demonstrated that in response to isoproterenol, forearm blood flow responses were markedly attenuated, indicative of a blunting of vasodilatation mediated by β_2-adrenergic receptors. When these factors were addressed in terms of its impact upon LV remodelling Hinderliter *et al* (Hinderliter et al., 2004) found a clear association. The authors measured various haemodynamic measures in addition to diurnal blood pressure variation and cardiac structural dimensions among 171 adults between the ages of 25-45 years. Importantly, it was observed that African American individuals presented with early concentric remodelling of the left ventricle. This may be mediated, in part, by hemodynamic influences, including a greater peripheral vascular resistance and a smaller nocturnal decline in BP, all of which significantly differed between ethnicities. Notably, ethnic differences in relative wall thickness

were no longer significant when adjusted for either indexed peripheral resistance or systolic blood pressure during sleep.

The demonstration of vascular dysfunction or at least divergent vascular adaptation in the presence of normal brachial artery blood pressure may pose a plausible explanation for the well-established finding of ventricular hypertrophy in normotensive Black athletes. With this in mind, it may support the hypothesis that exercise associated alterations in cardiac preload and afterload might exaggerate the degree of structural and electrical remodeling in Black athletes similar to that of hypertensive Black patients (Sheikh and Sharma, 2014).

9.2 The influence of body size upon the athlete's heart and the associated methodological considerations.

The key finding of study two was that no asymptomatic athlete without a family history of SCD had either an LVIDd greater than 63 mm or a maximal WT greater than 13 mm. The results provide a reassuring conclusion that even among large athlete's established criteria for the upper limits in cardiac structure are applicable. Thus, athletes with a maximal WT greater than 14 mm and a cavity dimension greater than 65 mm should be viewed with suspicion until proven otherwise. Despite this there was a significant correlation between cardiac dimensions and body size variables which suggest that across the body size range meaningful between individual/group comparisons should account for differences in body size.

As the data is not available we cannot exclude the training level/status as a potential reason for the exaggerated physiological remodelling in the Black athletes. However considering that the LVWT of our Arabic and Caucasian athletes was of a similar magnitude among those with a

BSA>2.3m^2, it seems plausible that body size is a critical factor upon cardiac structural development. Consequently, it raises the question of whether advanced scaling techniques (other than dividing the parameter by BSA) should be more routinely adopted in clinical practice, especially when analysing large anthropometrically heterogeneous cohorts.

The practice of scaling is widespread in paediatric cardiology and indeed among various other medical domains, yet remains underutilised in adult cardiology. In order to improve scientific validity and allow for more thorough investigation of inter-individual and inter-racial differences, scaling should ideally be implemented. It is especially pertinent when one considers the 'grey zone' between physiological adaptation and the demonstration of pathology. Despite this, when applied it is still imperative the correct methodology is used. Even in those studies that adopt scaling with the best intentions, the per ratio standard scaling is often inappropriately used, given that it assumes a linear relationship between body size and cardiac size, and moreover disagrees with the theory of geometric similarity.

The theory of geometric similarity (Schmidt-Nielsen, 1984) indicates that the relative geometries govern to some extent the relationship between the two variables. This becomes problematic when one-dimensional (wall thickness and chamber diameters) and three dimensional entities (chamber volume and muscle mass) are scaled against the one dimensional variable of height, the two dimensional body surface area (BSA) or the three dimensional body size and fat free mass. This has been supported by numerous studies (Gutgesell and Rembold, 1990, Batterham et al., 1997, Batterham and George, 1998). However, a body of evidence examining an elite athletic population is lacking. George and colleagues (George et al., 1998b) confirmed that the

dimensionality theory of an allometric scaling method was the most appropriate when 8 male weight lifters were compared against controls (George et al., 1998b); a conclusion further supported by the same authors in 15 elite female weight lifters (George et al., 1998a). Batterham et al (George et al., 2001) used the allometric approach when examining 464 highly trained junior athletes confirming that allometric scaling should be preferentially adopted over ratio scaling.

Of note, our data seemingly demonstrates that among a cohort of the largest sized athletes, screening is not warranted, with all athletes demonstrating cardiac adaptation within the limits of established normality. Nevertheless, while the establishment of the upper limits does provide all the clinically relevant information, the value of screening is highlighted should athletes of smaller body size be investigated. In this regard, should we hypothetically identify a young pre-pubescent gymnast with a wall thickness of 12mm, this may be deemed of physiological origin based upon the upper limits of normality. Should scaling be utilised it would be apparent that this is indeed outside the realms of normality. Importantly, the concept of scaling would be additionally useful in the long term follow up of athletes, where, as the young athlete develops the heart should develop accordingly and any deviation from this would be apparent in the scaled results.

9.3 The influence of ethnicity upon cardiac electrophysiology

From an electrocardiographic perspective, Arabic athletes have demonstrated greater levels of physiological adaptation than Arabic controls; however unlike that of structural adaptation, their findings mimicked Caucasian athletes, both with regards to training related (Caucasian: 98.1% vs. Arabic: 97.3%) and training unrelated ECG alterations (Caucasian: 6.9% vs. Arabic: 8.4%).

In turn, due to the development of the ESC guidelines in a Caucasian cohort of athletes, we were able to assert that these interpretational guidelines, the most current at the time of investigation, were applicable to our cohort of Arabic athletes. Whilst no pathology was identified in the Caucasian athletes (in part due to the small number of Caucasian athletes studied), the prevalence of SCD related disease in our Arabic athletes was 3-times higher than that of Caucasian athletes (Basavarajaiah et al., 2008b, Corrado et al., 1998, Averill et al., 1960); identifying two Arabic athletes with HCM (0.3%) and two with WPW (0.3%). The exact reasoning for a higher incidence of diseases associated with SCD in Arabic athletes remains unclear. Considering the low prevalence, this however may simply represent a coincidental finding of opportune screening. This is supported by the current ASPETAR screening database (at the time of writing April 2014), the incidence for both HCM and WPW was the same as previously documented (0.2%) and with no other reported findings, despite a further 800 Arabic athletes screened. In contrast, 5 Black African athletes were diagnosed with HCM (1.2%), with ASPETAR data remaining significantly higher than other centres around the world who examine Black athletes.

Whilst there is a relationship between electrophysiology and cardiac mechanics in HCM, whereby the electrical remodelling may elicit prolonged repolarisation, promote the spatial dispersion of repolarisation or alteration of the repolarisation sequence, manifesting itself as T-wave inversion on the ECG (Lin et al., 2013, Shipsey et al., 1997); the exact nature of the precordial T-wave inversion in the absence of any phenotypic expression of disease is yet to be elucidated. Indeed, with a predisposition for Black ethnicity, a genetic mechanism may play a significant role.

The first line of investigation for an athlete presenting for screening should indeed be inclusive of the ECG, and research has indicated that the ECG may be effective in detecting the early signs of pathology, even without any concomitant phenotypic expression. The notion that T-wave inversions may be an early indicator of underlying cardiac pathology was addressed by Pelliccia and colleagues (Pelliccia et al., 2008a). They tracked athletes with T-wave inversion over 9 ± 3 years and found that 6% of athletes went on to develop pathology. This suggests that genetic testing in such athletes may be warranted.

Nevertheless, the global efficiency of mutation screening in index cases is only around 30-65% in HCM, 30-70% in ARVC, 40-60% in LQT, and 20-30% in both DCM and Brugada syndrome (Richard et al., 2012b). Such variable performance of genetic testing thus represents an area of concern should such athletes with T-wave inversions undergo genetic testing. Genetic testing in such athletes, as recommended by Wilson et al 2012 (Wilson et al., 2012a) potentiates the athlete to the risk of false reassurances and a false negative diagnosis. Should a genetic mutation be detected, the presentation of the genotype positive-phenotype negative athlete and the associated implication on sporting clearance demonstrates the complex scenario faced by cardiologists.

Disqualification from sport for the diagnosed athlete should of course be the last resort; however opinion differs between European and North American policy in this regard. While the North American policy allows the engagement in sport (except in swimmers with LQT 1 mutation), the ESC approach is to disqualify all mutation carriers regardless of whether there is phenotypical expression (Maron et al., 2004a, Pelliccia et al., 2005a). The risk carried in such athletes is said

to be low, yet not negligible. It is for this reason the clearance or disqualification should be taken on a case-to-case basis and having considered several factors. These factors include: the type of gene and mutation found in the athlete, as some harbour more risk than others; the family history of the athlete, in particular the finding of any sudden deaths in the family; the sporting activity the athlete is currently engaged in; and any personal risk factors for SCD in the athlete (Richard et al., 2012b). This area is however clouded, especially when one considers the aspects of variable expressivity and penetrance of mutations, which in turn are suggestive of epigenetics and environmental factors influencing the phenotype (Schwartz et al., 2011). Future studies using genetic testing and larger, ethnically diverse cohort studies will help determine the true impact of the T-wave inversion.

9.4 What constitutes best screening practice?

Two of the papers within this thesis constitute the structural and functional remodelling of the athletes heart and how the heart of the Arabic athlete compares to those of other ethnicities. Ultimately the results facilitate cardiologists in the interpretation of ECG and echocardiography in Arabic athletes. It was then necessary to understand how this data impacts upon pre-participation screening. Firstly, by assessing whether the different cardiac adaptation among Arabic athletes leads to an increase in specificity and a reduced false positive rate, and secondly if systematic echocardiography for athletes is warranted in our population.

The implementation of screening in young athletes for the detection of the silent congenital conditions often linked to sudden cardiac death still generates controversy and debate among the cardiology community. Nevertheless, appreciating the fact that the athletes who succumb to

SCD could lose at least 50 years of life, and that the predisposing conditions are mostly detectable during life, the screening of athletes does appear to be warranted. In this regard, it is acknowledged that pre-participation cardiac screening is indicated based upon medical, legal and ethical grounds (Hamilton et al., 2012b).

After ascertaining the necessity of screening, data presented in this thesis offers the conclusion that pre-participation screening should be inclusive of personal symptom and family history questionnaire, ECG using the latest interpretational guidelines, and physical examination. After previous systematic implementation of the echocardiogram, our research has now impacted upon policy within the hospital, whereby the echocardiogram no longer remains in the routine screening of the athlete.

The utilisation of the echocardiogram within pre-participation screening has been scarce, predominantly a result of the increased cost and the need for qualified personnel to conduct the test. Nevertheless, FIFA are one sporting body which mandates all players competing in one of their affiliated competitions to undergo screening with an echocardiogram (Dvorak et al., 2009). The reasoning for this was to target their pre-competition medical assessment (PCMA) to be all encompassing, achieving maximal probability to detect SCD risk factors. Citing a low pre-test probability of exercise induced myocardial ischemia FIFA also advocated the use of ECG exercise testing, via bicycle ergometer; to establish a truly comprehensive screening process. Regardless of this thorough approach, a zero risk is still unattainable. Indeed, following the initial application at the 2006 FIFA world cup the use of the ECG exercise test was questioned and subsequently removed from the screening protocol of the authors (Thünenkötter et al., 2009).

Echocardiography, however, still remains as a mandatory inclusion in FIFA PCMA screening. Despite allowing for the potential identification of coronary artery anomalies and congenital cardiac malformations such as the bicuspid aortic valve; to answer the question whether including echocardiography constitutes best screening practice, it must be acknowledge that findings from Study 3 demonstrates that echocardiography in isolation fails to identify any athlete with underlying pathology in isolation, and it is best utilised as a tool to solely support other tests.

One component within pre-participation screening our data demonstrates has beneficial clinical utility is that of the ECG. The American Heart Association's standpoint of excluding the ECG within the screening remit is based upon the low prevalence of disease, poor sensitivity, high false positive rate, poor cost effectiveness, and a lack of clinicians to interpret the results (Maron et al., 2007b). Nevertheless the AHA offers a less specific method of screening and is at best simplistic and ultimately endangers athletes at risk of sudden cardiac death. The opposition to ECG screening based upon the argued high rate of false positive findings is particularly flawed considering the exaggerated false positive rate found if screening excludes the ECG (Wilson et al., 2008b). Indeed, no study monitoring sudden cardiac death has shown that screening via personal symptom and family history questionnaire and physical examination alone can prevent or detect athletes at risk (Drezner and Khan, 2008).

The experience among our cohort of athletes indeed suggests that the family history and personal symptom questionnaire constitutes a significant burden to the rate of false positive cases. This is demonstrated by a prevalence of pathology unrelated chest pain of 3%, palpitations 3.6%, and

dizziness at 6.5%. Incidentally, further consideration must be given to the personnel conducting the questionnaire, ie a medical doctor; the language of the questionnaire and its related correct interpretation; and the specific questionnaire in use as these aspects can significantly alter its validity and reliability.

To support the accommodation of the ECG within screening, Study 4 demonstrated the progressive trend of false positive rate reduction of the published interpretational guidelines. It was found that the latest 2014 guidelines from Sheikh et al (Sheikh et al., 2014a) reduced the rate of false positives to just 5%. Antagonists for ECG screening may claim that this still accounts to 50 athletes per 1,000, however when one considers that the identification of an abnormal finding simply leads to the athlete undergoing further tests including: echocardiogram; 24hr Holter; or stress test, significant distress is not placed upon the athlete. This notion is supported by research among 591 Norwegian professional football players, where 77% felt the need for screening, 64% feeling more confident while playing football and less than 3% experiencing distress (Solberg et al., 2012). Moreover, contrary to the 2007 AHA statement on cardiovascular screening(Maron et al., 2007b), a recent American based study of 952 young competitive high school athletes has shown that screening does not cause anxiety. They demonstrate that neither screening with or without ECG imposed anxiety on the athlete during screening, and no difference in anxiety values immediately after exercise. Indeed those who received an ECG were more satisfied with screening ($p<0.001$), felt safer during competition ($p<0.001$), and were more supportive of cardiovascular screening in athletes ($p<0.001$). Importantly the low levels of anxiety were consistent among the 220 athletes with a false positive finding ($p=0.775$). These athletes distress levels did not elevate in comparison to those who underwent screening without

ECG, despite the need for further testing (p=0.311), and would recommend screening to others. It must be noted both studies conducted further testing immediately after primary screening and this in itself may be a constituting factor behind the low anxiety demonstrated among athletes.

With regards to ethnicity, the rate of false positive findings was greater among Black athletes than other ethnicities, and still elicits a rate of 9.2% after using the latest Refined criteria. Although this may be an acceptable rate considering the prevalence of HCM in Black athletes is 1:100, introducing means to lower this false positive rate may potentially affect sensitivity of disease detection. With this rate differing significantly from that of Arabic and Caucasian athletes it may suggest that a form of selective screening be used in place for more potentially 'at risk' groups.

In addition to the known increased risk among Black athletes, Harman et al (Harmon et al., 2011b) identified that basketball was an independent risk factor for SCD (SCD rate of 1:11394), and certainly deaths are often most commonly seen in dynamic sport players. It has also been hypothesized that the combination of myocardial hypertrophy, impaired myocardial relaxation, myocardial ischemia and dynamic LVOT obstruction impede augmentation of stroke volume for long periods, selecting out endurance sports to those with the condition (Chandra et al., 2013). However, we know that Caucasian athletes and indeed endurance athletes do evidentially succumb to SCD; in turn it appears that it would raise serious moral and ethical questions to selectively screen in such a manner.

Accounting for all aspects of this discussion section, and the clear effectiveness of the ECG, it has been suggested that should one shift their attention away from the notion of mandatory screening or national screening programmes the idea of universal agreement on the correct screening practice would be closer. It would allow the clinician to focus upon what is scientifically justified and medically recommended and allow for a more pragmatic view of the benefits of screening with the ECG (Borjesson and Drezner, 2012).

9.5 Thesis Limitations

The primary aim of the thesis was to investigate the Arabic athlete's heart. A limitation of this thesis was the lack of any analysis and determination of the female athlete's heart within this unique ethnic population. The justification for exclusion of females was due to the limited number of female athletes presenting to the athlete screening department at ASPETAR. This is because of the GCC regions recent acceptance of females engaging in high-level sport.

ASPETAR athletes are predominantly confined to the high intensity, dynamic sports of football, basketball, handball and volleyball; those often associated with a greater risk of sudden cardiac death. A further limitation of the athletic population investigated was therefore the homogeneity of athletes tested and a lack of a significant number of endurance athletes, or indeed those combining both isometric and isotonic activity, such as rowers or swimmers, especially when deriving the upper physiological limits of for the athletes with the largest anthropometric values ($>2.3m^2$). An additional limitation in this regard was the lack of East African athletes within our cohort. We continually detail the presence of more pronounced cardiac remodelling among African/Black athletes yet within the thesis we predominantly refer to West-African athletes. An

important caveat among the literature related to the ethnic impact upon the athlete's heart is the generalisation of these athletes. It is evident that East Africans are most suited to endurance events such as marathon running, while West Africans to the more dynamic intermittent sports, and given it is likely that physiological differences are apparent here, more research must be done to distinguish these inter-ethnicity differences. Nevertheless the cohort utilised is a representation of the athletic population in Qatar and indeed the wider scope of the Middle East and thus justifies the lack of such endurance and strength/endurance athletes in the investigations.

There has been limited work determining the true cost effectiveness of screening, yet noteworthy studies by Wheeler et al (Wheeler et al., 2010) and Fuller (Fuller, 2000) identified that ECG led screening comes below the ceiling ratio deemed acceptable for medical interventions; with cost effectiveness ratios of $42,900 and $44,000 per life year saved respectively. Unfortunately without longitudinal data it is not possible to determine the true cost effectiveness of the ASPETAR screening protocol. The same limitation can be applied to the finding of 100% sensitivity rate for ECG led screening. We identified that screening with the echocardiogram was not efficacious based upon the identification of athletes with pathology. In this regard, the detection of a pathological process was missed in two athletes; one with apical hypertrophic cardiomyopathy, and the second with mid-inferolateral wall scaring following CMR investigation and in combination with a family history of SCD, syncope and rhythm disturbances was given a diagnosis. Given this limited duration of the follow-up period it cannot be confidently stated that the presence of a normal ECG and other screening tools is indicative of a true negative finding.

9.6 Future directions

After consistently reporting the significant level of abnormal findings among Black athletes, and acknowledging the diagnostic uncertainty of inferior, lateral and inferolateral T-wave inversions among otherwise normal healthy athletes, it is important to attempt to understand the underlying mechanisms and whether athletes with such repolarisation patterns have undetected genetic mutations predisposing the athlete to sudden cardiac death.

In a similar vein, we identified that Black athletes had greater levels of structural LVH. With research among the general population indicating there may be a link between eccentric LVH and haemondynamic loading, it seems important to assess the impact of these characteristics in Black athletes, and whether the increased stresses of exercise exacerbates this LV remodelling.

Further research could investigate the utilisation of scaling within the analysis of the athletes heart. Among the research presented within this thesis, there is an indication for adopting such practices. Moreover, the establishment of true best practice, identifying the most suitable scaling and body size variables may hopefully ensure its practice within the cardiological setting, allowing for consistent comparisons between cohorts.

9.7 Thesis Summary

The research presented in the thesis is the first to investigate the structure and function of the athletes heart in Arabic athletes and athletes with a BSA>2.3m^2. We identified that while Arabic athletes present significantly smaller cardiac dimensions than Black African and Caucasian athletes, there was no significant difference between the frequency of an uncommon and training

unrelated ECG between Arabic and Caucasian athletes. Therefore, an important message from this paper for practicing clinicians is that the use of ESC guidelines for the interpretation of an athlete's ECG is clinically relevant and acceptable for use within Arabic athletes. In another unique population we identified that regardless of extreme anthropometry, established upper limits for physiological cardiac hypertrophy of 14 mm for maximal wall thickness and 65 mm for LVIDd are clinically appropriate for all athletes. However, it must be stressed that the abnormal ECG is key to diagnosis and guides follow-up, particularly when cardiac dimensions are within accepted limits.

A second aspect to the thesis was looking at the effectiveness of current screening practice. When investigating the appropriateness of the echocardiogram in pre-participation screening, we found that all athletes diagnosed with a disease associated with SCD were identified via an abnormal ECG and/or physical examination, personal symptoms, or family history. Resultantly we concluded that screening athletes with systematic ECHO is not economically or clinically effective, increasing screening cost by47%. From this, we further supported the clinical utility of ECG screening. The 2014 Refined Criteria for athlete ECG interpretation outperformed both the 2013 Seattle Criteria and the 2010 ESC recommendations by significantly reducing the number of false-positive ECG's in Arabic, Black and Caucasian athletes to just 5%, all the while maintaining 100% sensitivity for serious cardiac pathologies.

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