

## **Athletes heart and exercise related sudden cardiac death: Across the age span**

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**ATHLETES HEART AND EXERCISE RELATED SUDDEN CARDIAC DEATH:  
ACROSS THE AGE SPAN**

**MATHEW G. WILSON MPhil**

A thesis submitted in partial fulfilment of the  
requirements of the University of Wolverhampton  
for the degree of Doctor of Philosophy

This research programme was carried out in collaboration with the  
**CRY Centre for Sport Cardiology, Olympic Medical Institute,  
Cardiovascular Disease and Sports Cardiology Centre, St George's Hospital, London,**  
and  
**Department of Cardiac Magnetic Resonance, Royal Brompton and Harefield NHS  
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## ABSTRACT

**Background** - Regular exercise reduces the risk of cardiovascular disease and subsequent sudden cardiac death (SCD). However, a small, but notable proportion of athletes die suddenly due to inherited or congenital disorders of the heart that predispose to malignant ventricular arrhythmias. Such tragedies are highly publicised, particularly when high-profile athletes are involved. To date, limited evidence for the efficacy of cardiovascular pre-participation screening exists outside of the Italian experience. Furthermore, limited data exists examining the impact of ethnicity on cardiac adaptations to physical training. Whilst the cardiovascular benefits of exercise are well known, the impact of life-long endurance exercise is less well understood. Long term high-intensity endurance exercise is associated with changes in cardiac morphology together with electrocardiographic alterations that are believed to be physiologic in nature. Recent data however, has suggested a number of deleterious adaptive changes in cardiac structure, function and electrical activity in response to life-long endurance activity.

**Aims and Objectives** - The aims of this PhD were; 1) To find an effective preparticipation screening method that would successfully identify pre-existing cardiovascular abnormalities, 2) To identify the prevalence of hypertrophic cardiomyopathy and Long QT syndrome in elite UK athletes; 3) To examine the impact and significance of ethnicity upon left ventricular remodelling in elite athletes, and 4) To examine the acute and chronic impact of ultra-endurance exercise across the life-span in male endurance athletes.

**Major Results and Conclusions** – 1) Study 2 sought to confirm the efficacy of resting 12-Lead ECG ‘alongside’ personal/family history questionnaires and physical examinations as collective tools to identify diseases that have the potential of causing sudden death within a cohort of elite junior athletes (n=1074) and physically active school children (n=1646). Nine participants were identified with a positive diagnosis of a disease associated with SCD. None of those diagnosed with a disease associated with SCD were symptomatic or had a family history of note. Thus, personal symptoms and family history questionnaires alone are inadequate in the identification of individuals with diseases associated with SCD. In conclusion, resting 12-Lead ECG is paramount when screening for diseases that have the potential of causing sudden death in the young.

2) Study 3 examined 3,500 asymptomatic elite athletes (75% male) with a mean age of  $20.5 \pm 5.8$  years with 12-lead ECG and 2-dimensional echocardiography. None had a known family history of HCM. Of the 3,500 athletes, 53 (1.5%) had LVH (mean  $13.6 \pm 0.9$ mm, range 13 to 16mm), and of these 50 had a dilated LV cavity with normal diastolic function to indicate physiological left ventricular hypertrophy. Three (0.08%) athletes with LVH had a non-dilated LV cavity and associated deep T-wave inversion that could have been consistent with HCM. However, none of the 3 athletes had any other phenotypic features of HCM on further non-invasive testing and none had first-degree relatives with features of HCM. In conclusion, the prevalence of HCM in elite athletes is significantly less than in the general population; with the demands of strenuous exercise on the cardiovascular system selecting out most individuals with HCM.

Study 4 examined 2000 elite athletes in order to identify the prevalence of Long QT syndrome. Three athletes had a QTc value of  $>500$  ms and all exhibited one of: paradoxical prolongation of QTc during exercise, a confirmatory genetic mutation, or prolonged QTc in a first-degree relative. In contrast, none of the athletes with a QTc value of  $<500$  ms had any

other features to indicate LQTS. Accordingly, the prevalence of a prolonged QTc interval in elite British athletes is 0.4%.

3) Study 6 examined 300 nationally ranked UK black male athletes (mean age 20.5 years) in comparison to 150 black and white sedentary individuals and 300 highly-trained white male athletes. Black athletes exhibited greater LV wall thickness and cavity size compared with sedentary black and white individuals. Black athletes had greater LV wall thickness compared with white athletes. A minority of black athlete's exhibit LVH  $\geq 15$  mm; proposing that in the absence of cardiac symptoms or a family history of HCM, an LV wall thickness  $\geq 15$  mm in black athletes may represent physiologic LVH when the LV cavity is enlarged and diastolic indexes are normal. 7 black athletes (12%) with LVH displaying deep T-wave inversions in leads V1 to V4. In conclusion, in the absence of obvious pathology, these electrical anomalies in black athletes likely represent a normal spectrum of ECG changes in response to physical training.

4) Study 8 examined 17 male participants (age  $33.5 \pm 6.5$  years, 26–40 years) using cardiac magnetic resonance (CMR) and echocardiography before and after a marathon to investigate the relationship between systolic function and diastolic function against biomarkers of cardiac damage. Results demonstrates biomarkers of myocardial cell damage following an acute bout of prolonged exercise are not associated with either systolic or diastolic functional measures, and do not seem to be associated with any detectable myocardial inflammation, oedema, or scarring using either gold standard techniques of gadolinium enhanced CMR or echocardiography respectively. The impact of multiple episodes of prolonged exercise, as experienced by highly trained veteran endurance athlete is not fully understood.

5) Study 10 examined the cardiac structure and function of 12 life-long, competitive endurance veteran athletes ( $> 50$  yrs, mean  $\pm$  SD marathons  $178 \pm 209$  (range 20 – 650)) against 17 young male endurance athletes ( $<40$  yrs) using echocardiography and CMR with late gadolinium enhancement (LGE) to assess myocardial fibrosis. Lifelong veteran athletes had smaller LV and RV end-diastolic and end-systolic volumes ( $p < 0.05$ ) but maintained LV and RV systolic function compared with young athletes. In 6 (50%) of the veteran athletes LGE of CMR indicated the presence of myocardial fibrosis; no LGE in the young athletes. The prevalence of LGE in veteran athletes was not associated with the number of competitive marathons or ultra-endurance marathons ( $>50$  miles) completed, age, LV and RV end-diastolic volumes or LV mass ( $p > 0.05$ ). In conclusion, there is limited evidence at present demonstrating that cardiovascular re-modelling following lifelong endurance exercise leads to long-term disease progression, cardiovascular disability or SCD.

**KEY WORDS:** sudden cardiac death, preparticipation screening, hypertrophic cardiomyopathy, long QT syndrome, myocarditis, veteran athlete, endurance, arrhythmia, and fibrosis.

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## **CHAPTER ONE**

### **1.1. Introduction**

The cardiovascular benefits of regular physical exercise have been well documented (Paffenbarger *et al.* 1997), with overwhelming evidence from epidemiological and intervention studies, suggesting that cardiovascular disease is largely a disease associated with physical inactivity (Leung *et al.* 2008; Loomba and Arora 2008). Exercise plays a beneficial role in the prevention and treatment of cardiovascular disease (Lobos *et al.* 2008), with epidemiologic studies supporting an inverse and robust relationship between physical activity and mortality risk, even after adjusting for potential confounding factors (Kokkinos 2008; Singer 2008). Indeed, the beneficial effects of exercise are not just observed within older individuals. Several investigations have reported significant improvements in cardiovascular fitness, fasting insulin tolerance, lean body mass, and systolic blood pressure with physical activity interventions in obese children, importantly, without the need for pharmaceutical treatment (Carrel *et al.* 2005; Zahner *et al.* 2006).

Long term high-intensity endurance exercise is associated with cardiac morphological changes, mainly being a left ventricular (LV) enlargement, together with electrocardiographic alterations including, most commonly, resting bradycardia, repolarisation abnormalities and increased R- or S-wave voltage suggestive of LV hypertrophy (Pluim *et al.* 2000; Pelliccia *et al.* 2002; Whyte *et al.* 2004; Whyte *et al.* 2004; Pelliccia *et al.* 2008). Establishment of upper normal limits of physiological enlargement in response to physical training is important in the differentiation of physiological and pathological LV hypertrophy. An examination of 306 International British male athletes identified 11 (2.5%) with a wall thickness >13 mm,

commensurate with a diagnosis of hypertrophic cardiomyopathy. Furthermore, 18 (5.8%) presented with a left ventricular internal diameter during diastole (LVIDd) of >60 mm, with an upper limit of 65 mm (Whyte *et al.* 2004). This British experience is in line with previous data (Pelliccia *et al.* 1999; Pelliccia *et al.* 2002) promoting concern for individuals with extreme LV remodelling mimicking hypertrophic cardiomyopathy.

With such overwhelming evidence to support the promotion of physical activity within the community, the death of an athletic individual (young or veteran) is a tragic and highly publicised event. For the past decade, our research team has been examining the causes of young sudden cardiac death and more recently, the causes of death and rhythm disturbances within the veteran athlete. Approximately 80% of non-traumatic sudden deaths in young athletes (under the age of 35) are caused by inherited or congenital structural and functional cardiovascular abnormalities, which provide a substrate for arrhythmias predisposing to sudden cardiac death (SCD) (Maron *et al.* 1986). Inherited or congenital cardiac pathologies include; hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), idiopathic concentric left ventricular hypertrophy, congenital anomalous coronary arteries, wolff-parkinson white syndrome (WPW), Long QT syndrome and marfan's syndrome (Maron 1996; Sharma *et al.* 1997; Maron 1998; Maron 2003; Corrado *et al.* 2005).

The steady trickles of SCD's in young athletes have called for the implementation of organised screening programmes by most major sporting governing bodies, including the International Olympic Committee (IOC) and Fédération Internationale de Football

Association (FIFA). The purpose of preparticipation screening is to provide medical clearance for participation in sport through routine systematic evaluations intended to identify pre-existing cardiovascular abnormalities and thereby reduce the potential for adverse events and loss of life (Pelliccia and Maron 1995; Corrado *et al.* 1998; Maron 2003; McGrew 2003; Corrado *et al.* 2005; Corrado *et al.* 2006).

Cardiac screening protocols have been broad ranging, from elite Olympic athletes to general population sport screening (Baggish and Thompson 2009). The American College of Cardiology and the American Heart Association recommend screening via a medical history and physical examination alone with further testing reserved for athletes with abnormalities detected during this process (Maron *et al.* 2007). However, the European Society of Cardiology recommends alongside history and physical examination the inclusion of a resting 12-lead electrocardiogram (ECG) (Corrado *et al.* 2005; Bille *et al.* 2006).

Controversy exists within the sporting medical community regarding the sensitivity of electrocardiography, whereby the high frequency of ECG alterations observed in athletes are normal variants of the athletes heart (Maron *et al.* 2007). Furthermore, echocardiography is generally accepted as the 'gold standard' method of assessment within cardiac screening programmes owing to its ability to diagnose HCM, the commonest cause of sudden cardiac death (SCD) in young athletes (Sharma *et al.* 1997); but has a large cost implication for mass screening. Screening antagonists use the false positive debate from 12-Lead ECG based programmes as the main reason for not supporting cardiac screening, citing increased follow up medical expenditure and increased levels in patient anxiety.

Whilst cardiovascular adaptations to exercise have been documented in the young athletes for over 20 years, it is only recently that the veteran athlete has gained popularity in the scientific and lay press. Recent data has documented an increased prevalence of supraventricular, complex ventricular, and profound bradyarrhythmias in endurance-trained athletes, predominantly occurring in veteran athletes (Jensen-Urstad *et al.* 1998; Ector *et al.* 2007; Whyte *et al.* 2007; Whyte 2008; Mont *et al.* 2009). Several forms of idiopathic ventricular arrhythmia (VA) have been identified in athletes, which, by definition, originate in hearts without structural abnormalities (Anselme 2003). The clinical significance of these arrhythmias remains to be fully elucidated. Debate continues as to whether changes in cardiac morphology and function, together with electrocardiographic changes persist in veteran endurance athletes, even after detraining (Pelliccia *et al.* 2002; Baldesberger *et al.* 2008), transforming from a physiological entity into a pathological phenomena. This transference may represent the initial expression of an underlying cardiomyopathy that may not be evident until many years later (Pelliccia *et al.* 2008).

This thesis is divided into two distinct but interrelated sections; Part 1) athletes heart, sudden cardiac death and pre-participation screening in young athletes (<35 years) and Part 2) the acute and chronic impact of ultra-endurance exercise across the lifespan (<35 and >50 years). Chapter Two examines the cardiac remodelling that occurs with prolonged and intensive exercise, so called 'athletes heart'. Chapter Three examines the inherited and congenital diseases that may lead to sudden cardiac death in athletes. Chapter Four attempts to find an effective preparticipation screening protocol that successfully identifies pre-existing cardiovascular abnormalities, thereby

reducing the potential for sudden cardiac death. Furthermore, Chapter Four examines the prevalence of hypertrophic cardiomyopathy and Long QT syndrome in elite athletes, concluding with diagnostic difficulties facing preparticipation screening programmes including ethnicity. Chapter Five examines the acute and chronic impact of ultra-endurance exercise upon cardiovascular structure and function. It also provides a systematic review of the cardiac structure and function in lifelong veteran endurance athletes. Finally, Chapter Six attempts to identify the impact of life-long, repetitive bouts of arduous endurance exercise on the heart focussing on fibrotic replacement of the myocardium. In conclusion, Chapter Seven addresses potential areas for future investigations to increase our knowledge of the impact of endurance exercise on the young and aged cardiovascular system and exercise related sudden cardiac death.

## **CHAPTER TWO – THE ATHLETES HEART**

### **2.1. Cardiac Remodelling with Prolonged Intensive Exercise**

Regular participation in systematic physical training demands substantial, and often sustained, increases in cardiac output. The physiological cardiac adaptation to chronic increases in preload and afterload on the heart lead to a form of reversible cardiac remodelling comprising of left and/or right ventricular hypertrophy, increases in cardiac chamber size and enhanced diastolic ventricular filling, which permits an increase in stroke volume (Sharma 2003). For over 50 years, these cardiac manifestations have been termed “athletes heart”, with early cardiac observations of highly trained athletes<sup>1</sup> demonstrating a displaced and forceful cardiac apical impulse on physical examination, large QRS complexes, sinus bradycardia, first- and second-degree heart block on the 12-lead ECG and an increased cardio-thoracic ratio on plain chest radiographs (Beckner and Winsor 1954; Winsor and Beckner 1955; Blomqvist and Saltin 1983).

### **2.2. Cardiac dimensions in athletes**

Since the introduction of M-mode echocardiography in the late 1970’s and subsequent 2-dimensional echocardiography in the 1980’s, there is a plethora of conclusive evidence documenting the cardiac structure and function of highly trained athletes (Oakley 1984; Pelliccia *et al.* 1991; Pelliccia *et al.* 1993; Spirito *et al.* 1994; George *et al.* 1995; Pelliccia *et al.* 1996; Pelliccia and Maron 1997; Pelliccia *et al.* 1999; Whyte *et al.* 1999; Pluim *et al.* 2000; George *et al.* 2001; Sharma *et al.* 2002; Whyte *et al.*

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<sup>1</sup> A highly trained athlete is defined in this thesis as an individual who engages in regular organised physical training within a particular sporting discipline and competes at county, national or international level.

2004; Whyte *et al.* 2004; Rawlins *et al.* 2009). The majority of investigations have been cross-sectional in design, comparing cardiac dimensions in athletes (mainly Caucasian) aged between 18 and 35 years during the competitive season, against age and sex-matched non-athletic sedentary individuals. Most investigations have determined LV wall thickness (LVWT) by measuring the interventricular septum and the LV wall in diastole and LV cavity size (usually measured below the level of the mitral valve leaflets) (Sharma 2003). Due to numerous cavity trabeculations and the crescent shape of the right ventricle (RV), reproducible measurements of RV dimensions and function using echocardiography are often difficult to obtain in healthy individuals (Foale *et al.* 1986), thus making the association between RV dimensions and exercise in highly trained athletes tenuous at best. Recent advances in cardiac magnetic resonance (CMR) allow a detailed interrogation of the RV however, studies to date are limited (Scharhag *et al.* 2002).

Early echocardiographic studies of cardiac dimensions in athletes revealed a large overlap with matched non-athletic control participants (Maron 1986) (Table 1). In absolute terms, cardiac dimensions in athletes are very slightly increased compared with non-athletes (Sharma 2003). Whilst the difference is small, it does reach statistical significance and amounts to a 15–20% greater LV wall thickness (LVWT) and 10 % greater LV cavity size compared with non-athletes. These modest increases in LVWT and LV cavity size are often the result of a marked increase in LV mass (in the order of 50%).

Table 1: Absolute cardiac dimensions in athletes and matched non-athletes

<b>Echocardiographic Variable</b>	<b>Controls</b>	<b>Athletes</b>	<b>Difference (%)</b>
Septal thickness (mm)	9.1	10.4	14.3
Posterior wall thickness (mm)	9.0	10.7	18.9
LV end-diastolic cavity (mm)	49.1	53.9	9.8
LV mass (g.m <sup>-2</sup> )	175	256	45
RV end-diastolic cavity (mm)	17.7	22.0	24.3

Results of echocardiographic studies in more than 1000 male athletes (Maron 1986). LV, left ventricular; RV, right ventricular.

Differentiation between a physiological or pathological remodelling process is important, as significant cardiac enlargement may be an expression of underlying cardiac disease, placing the athlete at risk of sudden cardiac death (Maron *et al.* 1986; Corrado *et al.* 2005). Pluim *et al.* (2000) published a meta-analysis of 66 echocardiography studies comparing 1,451 athletes with 813 control participants. Athletes were grouped into 3 similarly sized groups based upon the differing physiological loads of each type of exercise, i.e., endurance, power, or a combination of power and endurance. In endurance sports, volume loading of the heart predominates, with cardiac output increasing as much as 8-fold and only moderate increases in systemic blood pressure. In power sports, blood pressure can increase spectacularly (up to 480/350 mm Hg, for example) (MacDougall *et al.* 1985), whereas only a moderate increase in cardiac output occurs. In combined sports (such as cycling and rowing), there is a substantial increase in both volume and pressure loading. In all groups, athletes had significantly larger LV diameters and greater LV hypertrophy (LVH) than control patients. Although the modelling was progressively more eccentric in athletes performing endurance training, most athletes maintain relatively concentric hypertrophy (Douglas *et al.* 1997).

It is important to note, that whilst prolonged and sustained resistance training results in mild LVH, the largest reported gains in LV wall thickness measures are often seen in endurance and team game trained athletes. This is both true for male (Pelliccia *et al.* 1991; Pelliccia *et al.* 1993; Pelliccia *et al.* 1999; Pelliccia *et al.* 2005) and female athletes (Crouse *et al.* 1992; George *et al.* 1995; Pelliccia *et al.* 1996; Henriksen *et al.* 1999). Endurance exercise elicits a significant elevation in venous return for prolonged durations, leading to increased LV end-diastolic volume, resulting in dilation of the LV cavity. The increase in end-diastolic volume leads to a mechanical stretch (Law of LaPlace) resulting in an increase in LV wall thickness to normalise such wall stress (Whyte *et al.* 2004). Furthermore, endurance exercise is also associated with an increased afterload in response to various stimuli dependent upon mode of exercise (Fagard 1997). For example, during rowing, momentary elevations in systolic blood pressure (>200 mmHg) have been documented during the catch phase of the stroke (Clifford *et al.* 1994), whilst during cycling, a higher isometric strain, in both the upper and lower limbs, leads to an increased afterload for considerable periods of time (up to 7 hours) (Rodriguez Reguero *et al.* 1995).

More recently, cardiac magnetic resonance (CMR) has become the reference standard for the assessment of ventricular dimensions, function and mass in terms of accuracy and reproducibility. Measurements are highly accurate and unlike echocardiography, no geometrical assumptions need to be made about the ventricle (Bellenger *et al.* 2000; Bellenger *et al.* 2000). Whilst CMR is extensively used in the clinical identification of pathological conditions such as hypertrophic cardiomyopathy (HCM), few studies have used CMR to confirm echocardiographic measurements of “athlete’s heart”.

Scharhag *et al.* (2002) examined LV and RV mass, volume, and function in 21 male endurance athletes against and 21 sedentary participants using CMR. Results demonstrated that LV and RV masses were significantly larger in athletes than controls participants ( $p < 0.001$ ). LV and RV end-diastolic volumes, and stroke volumes were significantly greater in athletes than control participants ( $p < 0.001$ ), whereas LV and RV ejection fractions and LV-to-RV ratios were similar between groups. This landmark paper confirmed previous echocardiographic studies of athlete's heart, and further demonstrated that regular and extensive endurance training results in similar changes of LV and RV mass, volume, and function, as demonstrated by the constant ratios of the determined parameters. Scharhag *et al.* (2002) concluded that the endurance athlete's heart is a balanced (LV and RV) enlarged heart.

In contrast to endurance athletes who present an eccentric LV and RV hypertrophy, cardiac adaptations and dimensions in strength athletes are still under debate. Using CMR, Scharhag *et al.* (2009) examined 13 well trained strength athletes (age:  $28 \pm 7$  yr; height:  $182 \pm 6$  cm; weight:  $88 \pm 9$  kg; lean body mass (LBM):  $74 \pm 8$  kg; body surface area (BSA):  $2.09 \pm 0.14$  m<sup>2</sup>) against 13 control participants (age:  $30 \pm 6$  yr; height:  $182 \pm 5$  cm; weight:  $88 \pm 10$  kg; LBM:  $70 \pm 7$  kg; BSA:  $2.09 \pm 0.12$  m<sup>2</sup>). When indexed to LBM, no significant differences between strength athletes and control participants could be demonstrated for LV mass, RV mass, LV end-diastolic volume and RV- end-diastolic volume. The authors conclude that the strength athlete's heart is characterised by a mild biventricular eccentric hypertrophy, which can be attributed to the higher lean body mass, and demonstrates a normal RV and LV function, but importantly demonstrates no signs of LV or RV concentric hypertrophy.

### **2.3. Electrocardiographic changes in athletes**

Not only does the heart remodel structurally with prolonged intensive exercise, athletes also demonstrate a spectrum of alterations in the 12-lead electrocardiogram (ECG), including a marked increase in precordial R-wave or S-wave voltages, ST segment or T-wave changes suggestive of left ventricular hypertrophy (LVH), that may raise the suspicion of a pathologic heart condition (Van Ganse *et al.* 1970; Zeppilli *et al.* 1981; Zehender *et al.* 1990; Oakley 1992; Pokan *et al.* 1994; Pelliccia *et al.* 2000; Pelliccia and Maron 2001; Pelliccia *et al.* 2002; Plonska *et al.* 2006). The spectrum and unknown prevalence of ECG alterations is the main argument for cardiac screening antagonists, citing follow-up cost and false positive considerations as major barriers to the implementation of pre-participation cardiovascular screening programmes (Myerburg and Vetter 2007). If young athletes demonstrate abnormal ECG patterns, they would require additional diagnostic testing to confirm (or exclude) the presence of underlying cardiovascular disease (Maron 2005).

To address this dilemma, Pelliccia *et al.* (2007) assessed the prevalence and the spectrum of ECG abnormalities in a large and unselected population (32,652 participants; 26,050 or 80% were males) of young athletes ( $22.3 \pm 12.5$  years) undergoing preparticipation screening incorporating 12-lead electrocardiography. The ECG patterns were considered normal in the vast majority of athletes (28,799 of the 32,652; 88.2%), with abnormal patterns being identified in the remaining 3853 participants (11.8%). The spectrum of ECG abnormalities found in the overall study population is reported in Table 2. The most frequent abnormalities included prolonged

PR interval, incomplete RBBB and early repolarisation pattern, which together accounted for 59.19% of all anomalies (and the 7% of the overall study population).

Table 2: Prevalence of ECG abnormalities in an unselected population of 32,652 young individuals undergoing the pre-participation cardiovascular screening (Pelliccia *et al.* 2007).

<b>ECG abnormalities</b>	<b>Athletes, n (%)</b>
Negative T-waves in precordial/standard leads	751 (2.3)
RBBB	351 (1.0)
Increased R/S wave voltages (suggestive of LVH)	247 (0.8)
Left anterior fascicular block	162 (0.5)
Pre-excitation pattern	42 (0.1)
LBBB	19 (0.1)
Prolonged corrected QT interval	1 (0.003)
Others (incomplete RBBB, prolonged PR interval, early repolarisation pattern)	1 (0.003)

RBBB, right bundle branch block; LVH, left ventricular hypertrophy; LBBB, left bundle branch block.

The prevalence of ECG abnormalities was higher in males than in females (12.4 vs. 9.6%;  $P = 0.001$ ). The prevalence of ECG abnormalities was also different in respect to age, with proportion of prolonged PR interval, incomplete RBBB, and early repolarisation pattern being larger in the younger individuals, and inverted T-waves in precordial and/or standard leads, increased R/S wave voltages suggestive of LVH, and cardiac conduction disorders more frequent in adults. Interestingly, cyclists had a larger proportion of increased R/S wave voltages, ventricular conduction delays and inverted T-wave patterns in comparison with other sporting populations.

Finally, a minority of athletes ( $n = 1170$ ; 3.6%) demonstrated rhythm disturbances on the baseline 12-lead ECG. A large proportion ( $n = 340$ ; 1.0%) consisted of marked sinus bradycardia; other abnormalities included supraventricular ectopic beats ( $n = 377$ ; 1.1%) or ventricular ectopic beats (VEBs) ( $n = 349$ ; 1.1%). Far less commonly, supraventricular tachycardia ( $n = 29$ ; 0.09%), atrial flutter/fibrillation ( $n = 5$ ; 0.02%),

polymorphic VEBs (n = 40; 0.1%), or non-sustained ventricular tachycardia (n = 3; 0.01%) were observed.

Similar ECG alterations have been reported in 1000 elite British junior (15.7 ± 1.4 years) athletes (Sharma *et al.* 1999). When compared to age-, body surface area-, and gender matched controls, athletes had a significantly higher prevalence of sinus bradycardia and sinus arrhythmias. The PR interval, QRS, and QT duration were more prolonged in athletes than non-athletes. LVH was more common in athletes, as was criteria for left and right atrial enlargement. Importantly, none of the athletes with voltage criteria for LVH had left axis deviation, ST segment depression, deep T wave inversion, or pathological Q waves.

Although caution is warranted when comparing Pelliccia *et al.* (2007) and Sharma *et al.* (1999) investigations (Table 3), it is evident the largest proportion of ECG abnormalities in all athletes comprised those changes (i.e. incomplete RBBB, prolonged PR interval, and early repolarisation pattern) which are now believed to be innocent expressions of the ‘athlete's heart’.

Table 3: Comparative proportions of ECG abnormalities observed in Pelliccia *et al.* (2007) vs. Sharma *et al.* (1999) athletic populations, in relation to age and level of achievement.

	<b>Young amateur athletes (n = 32,652) % (Pelliccia <i>et al.</i> 2007)</b>	<b>Junior elite athletes (n = 1000) % (Sharma <i>et al.</i> 1999)</b>
Incomplete RBBB, prolonged PR interval, early repolarisation	7	43
Voltage criteria for LVH	0.8	45
Negative T-waves in precordial/standard leads	2.3	4

The most commonly cited paper regarding ECG alterations in athletes came from Pelliccia *et al.* (2000). Their examination of 1005 consecutive athletes (aged  $24 \pm 6$  years; 75% male) participating in 38 sporting disciplines, concluded that abnormal ECG patterns occurred in *ca.* 40% of the athletic population (Table 4); usually indicative of physiological cardiac remodelling. In contrast, a small but important subgroup of athletes without cardiac morphological changes showed striking ECG abnormalities that suggested cardiovascular disease. These changes were likely an innocent consequence of long-term, intense athletic training and, therefore, another component of athlete's heart, however; such false-positive ECG's may represent a potential limitation to routine ECG testing as part of preparticipation screening.

Table 4: Common and Less Common and Significant ECG Abnormalities

<b>Common Benign ECG Abnormalities (7%)</b>	<b>Less Common and Potentially Significant ECG Abnormalities (4.8%)</b>
Sinus bradycardia	Left atrial enlargement
First-degree atrioventricular block or increased PR interval	ST-segment depression Pathological Q waves
Incomplete right bundle branch block	Wolff-Parkinson-White pattern
Early repolarisation	Inverted T waves in $\geq 2$ leads
	Increased R/S voltages (left ventricular hypertrophy)
	Right bundle-branch block
	Left bundle-branch block
	Prolonged QTc interval

Recently, the European Society of Cardiology (ESC) 'sports group' (Corrado *et al.* 2010) published an updated classification of 'common' and 'uncommon' ECG characteristics for young (<35 years) athletes (table 5). Its aim was to improve the ECG accuracy in the evaluation of trained athletes, lowering the proportion of total false positive and false-positive results, hopefully leading to a considerable cost saving in the context of mass pre-participation screening.

Table 5: Classification of abnormalities of the athlete's ECG (Corrado *et al.* 2010)

<b>Common and training-related ECG changes</b>	<b>Uncommon and training-unrelated ECG changes</b>
Sinus bradycardia	T-wave inversion
First-degree AV block	ST-segment depression
Incomplete right bundle branch block	Pathological Q-waves
Early repolarisation	Left atrial enlargement
Isolated QRS voltage criteria for left ventricular hypertrophy	Left-axis deviation/left anterior hemiblock
	Right-axis deviation/left posterior hemiblock
	Right ventricular hypertrophy
	Ventricular pre-excitation
	Complete Left or right bundle branch block
	Long- or short-QT interval
	Brugada-like early repolarisation

#### **2.4. Athletes with cardiac dimensions exceeding predicted values**

Whilst the majority of previous echocardiographic studies have examined small cohorts of athletes, a seminal paper examining 947 elite Italian athletes (all male) from 25 sports was published by Pelliccia *et al.* (1991). Results suggested that an LV wall thickness >13 mm was unusual (16 of the 947 athletes; 1.7 %); and were predominantly confined to athletes participating in rowing, canoeing (n = 15) and cycling (n = 1). All athletes with LV walls greater than or equal to 13 mm thick also had enlarged LV end-diastolic cavities (dimensions, 55 to 63 mm). Furthermore, the upper limit of physiological hypertrophy of ventricular walls and internal diameter was reported as 16 mm and 66 mm respectively. Therefore, athletes with a wall thickness greater than 16 mm and a non-dilated LV cavity may indicate pathology, and should be investigated for, primary forms of pathologic hypertrophy, such as hypertrophic cardiomyopathy (HCM).

More recently, Whyte *et al.* (2004) examined 442 elite British athletes (306 male, 136 female) from 13 different sports confirming the Italian experience. Eleven (2.5%) athletes, competing in a range of sports including judo, skiing, cycling, triathlon,

rugby and tennis, presented with a wall thickness >13 mm, commensurate with a diagnosis of HCM. Eighteen (5.8%) male athletes presented with a LV internal diameter during diastole (LVIDd) >60 mm, with an upper limit of 65 mm. For males, the authors conclude that the upper normal limits for LV wall thickness and LVIDd are 14 mm and 65 mm for elite male British athletes.

Importantly, Whyte *et al.* also included 136 elite female athletes. None were found to have a maximum wall thickness >11 mm. LV cavity dimensions were <60 mm in all female athletes. The reasons underpinning the observed gender difference in wall thickness may be associated with reduced levels of anabolic sex hormones in female athletes and anthropometric differences (Whyte *et al.* 2004). Allometric scaling techniques have demonstrated a relationship between height, body mass and fat free mass and heart size in elite athletes (Batterham *et al.* 1999; George *et al.* 2001). The lower body surface areas and fat free masses observed within female athletes compared with their equivalent male counterparts, offers an explanation for the lower wall thickness values (Whyte *et al.* 2004). In conclusion, the upper normal limits for LV wall thickness and LVIDd are 11 mm and 60 mm for elite female British athletes, and 15 mm and 65 for elite male British athletes, respectively.

## **2.5. Effect of age on cardiac adaptation to regular intensive exercise**

Most studies evaluating athletes have been performed in adults aged between 18 and 35 years. However, there have been a small number of studies in younger athletes which suggest that age has an effect on cardiac adaptation to regular intensive physical training. Most studies confined to pre-pubertal athletes (Hollmann *et al.* 1986; Telford *et al.* 1988; Rowland *et al.* 1994; Manolas *et al.* 2001) indicate only

modest clinical evidence of 'athletes heart' compared to their adult counterparts. Potential reasons for blunted cardiovascular adaptations to training in children remain unclear, since maturational differences in the physiological mechanisms for athlete's heart have not been investigated. Children may demonstrate lower catecholamine responses to exercise than adults, perhaps reflecting differences in autonomic regulation of the heart. The lower levels of testosterone before puberty may explain the absence of an increased heart size with training. It is also possible that relatively reduced skeletal muscle bulk in prepubertal athletes may prevent them from training at the high workloads required to increase cardiac dimensions (Sharma 2003).

There have been even fewer studies in adolescent athletes (i.e. aged between 14 and 18 years), in whom sudden death from cardiomyopathy is most prevalent (Maron *et al.* 1996). Sharma *et al.* (2002) echocardiographically examined 720 adolescent elite athletes ( $15.7 \pm 1.4$  years) participating in 10 different sporting disciplines compared to 250 age-, sex- and size-matched sedentary control participants. The authors reported that adolescent athletes had greater absolute LVWT compared with controls ( $9.5 \pm 1.7$  mm vs.  $8.4 \pm 1.4$  mm;  $p < 0.0001$ ). Maximal LVWT exceeded predicted upper limits in 38 athletes (5%); however, no female athlete had a LVWT  $>11$  mm and only 3 athletes had absolute LVWT  $>12$  mm (0.4%). Each of the 38 athletes with a LVWT exceeding predicted limits also showed enlarged LV cavity dimension ( $54.4 \pm 2.1$  mm; range 52 to 60 mm).

In light of the parity of data in adolescent athletes, Study One in this thesis examined the cardiac structure and function in a large cohort of elite adolescent tennis players. The British Lawn Tennis association was the first elite sporting organisation in the

UK to adopt cardiovascular screening of all their national junior athletes for conditions predisposing to sudden cardiac death; performing cardiovascular evaluation on all junior national tennis players since 1996. Study one aimed to identify physiological upper limits of cardiac enlargement in junior tennis players to help facilitate the differentiation between physiological and pathological cardiac enlargement

### **2.5.1. STUDY ONE (Appendix 1)**

Basavarajaiah, S., **Wilson, M.**, Naghavi, R., Whyte, G., Turner, M. and Sharma, A. Physiological upper limits of left ventricular dimensions in highly trained junior tennis players. *Br J Sports Med* 2007; 41:784–788.

### **2.5.2 Methods – Athletes**

Between August 1996 and May 2003, 259 elite, adolescent tennis players from the British Lawn Tennis Association underwent 12-lead ECG and 2-dimensional echocardiography preceded by a full cardiovascular evaluation during the peak competitive season. All athletes competed at regional level and trained for an average of  $10.1 \pm 3.8$  hrs per week (range 5 – 24 hrs). The athletes were aged 13–19 years (mean  $\pm$  SD;  $14.8 \pm 1.4$  years). A total of 152 athletes (59%) were male and 107 (41%) were female. Body surface area (BSA) among the athletes was  $1.6 \pm 0.2$  m<sup>2</sup> (range 1.2 to 2.2 m<sup>2</sup>). None of the athletes had symptoms of underlying cardiovascular disease or a family history of premature sudden death (aged <50 years) from heart disease. Written consent for cardiovascular evaluation was obtained from subjects aged >16 years and from a parent/guardian in those aged <16 years old. All subjects were judged to be peri-pubertal based upon the onset of menstruation in female and

deepening of voice or the presence of obvious secondary sexual characteristics (facial and body hair) in males. Ethical approval for the study was granted by the Harrow Research Ethics Committee.

### **Controls**

The control population comprised of 86 healthy adolescent volunteers who were students at two large secondary education boarding schools. All individuals selected had a relatively sedentary lifestyle, defined as <2 h of organised physical activity a week. The controls were matched with athletes with respect to age ( $15.7 \pm 1.4$  years), gender (66% male) and BSA ( $1.7 \pm 0.2$  m<sup>2</sup>).

### **2.5.3. Results**

#### **LV wall thickness**

Athletes had significantly greater interventricular septal (IVSd) and LV-posterior wall thickness (LVPWd) during diastole compared with controls. However, in terms of absolute measurements, the difference in IVSd thickness and LVPWd between tennis players and controls was only (7%) and within resolution limits of echocardiography. The absolute wall thickness measurements in tennis players ranged from 6–12 mm. Male tennis players had greater wall thickness measurements compared with female tennis players (Table 6). None of the control group or female tennis players had a wall thickness >11 mm (6–11 mm).

A wall thickness >11 mm was considered to represent left ventricular hypertrophy (LVH). Only three male athletes (1.2%), all aged >15 years, had a LV wall thickness >11 mm (Table 7).

Table 6: Comparison between male and female adolescent tennis players

	<b>Male</b>	<b>Female</b>	<b>P value</b>
IVSd (mm)	9.4 ± 1.2 (6–12)	8.3 ± 1.0 (6–11)	<0.001
LVPWd (mm)	9 ± 1.3 (6–12)	8.5 ± 1.1 (6–11)	<0.001
LVEDd (mm)	49.9 ± 3.8 (40–59)	47.5 ± 3.5 (32–58)	<0.001
LVESd (mm)	32.5 ± 4.2 (22–40)	30.4 ± 3.7 (22–42)	<0.001
LVM (g)	226.6 ± 69 (141–323)	176.2 ± 51 (101–260)	<0.001

Values are mean ± SD and (range). HR, heart rate; IVSd, interventricular septal end diastolic dimension; LVPWd, left ventricular end diastolic posterior wall dimension; LVEDd, left ventricular end diastolic dimension; LVESd, left ventricular end systolic dimension; LVM, left ventricular mass.

Table 7: Distribution of LV wall thickness in different age groups of male and female tennis players

<b>Age (yrs)</b>	<b>No of players</b>	<b>Male</b>	<b>Female</b>	<b>Male LVWTd (mm)</b>	<b>Female LVWTd (mm)</b>
13	53	28	25	8.5 ± 1.3 (7-11)	7.9 ± 1.1 (7-10)
14	66	36	30	9.2 ± 1.2 (8-10)	8.2 ± 0.9 (7-10)
15	66	34	32	9 ± 1.4 (6-11)	8 ± 1.1 (7-10)
16	42	33	9	9.6 ± 1 (8-12)	7.9 ± 0.7 (7-9)
17	19	13	6	10 ± 0.7 (9-11)	8.8 ± 0.9 (8-10)
18	11	9	2	10 ± 0.6 (9-12)	9 ± 0.8 (9-11)
19	2	1	1	-	-

LVPWd, left ventricular end diastolic posterior wall dimension

The pattern of LVH observed in the 3 athletes was symmetrical, with no athlete showing a difference of >2 mm in left ventricular wall thickness measurements between contiguous segments of the wall. All 3 athletes had an enlarged LV cavity and normal indices diastolic function on Doppler studies, implying the hypertrophy was physiological rather than HCM.

## LV cavity size

Athletes had a significantly greater end diastolic LV cavity size as compared with the control group (48.9 vs. 47.9 mm,  $p < 0.05$ ). None of the control group had LV cavity size  $> 54$  mm, However 6 (3.9%) male and 2 (1.9%) female athletes had a LV cavity exceeding 54 mm. All 8 athletes with increased LV cavity size had preserved systolic function. Distribution of LV cavity size in male and female tennis players divided according to different age group are shown in Table 8. No athlete aged  $< 14$  years had a LV cavity dimension  $> 54$  mm. A multivariable linear model that was used to assess the relation between LV dimensions and other demographic variables (age, gender and body surface area) demonstrated an independent association between the two.

Table 8: Distribution of LV cavity size in different age groups of male and female tennis players

Age (yrs)	No of players	Male	Female	Male LVWTD (mm)	Female LVWTD (mm)
13	53	28	25	$45.4 \pm 3.6$ (41.4–52.7)	$45.3 \pm 3.3$ (39–51)
14	66	36	30	$48.8 \pm 3.5$ (40–59)	$47.9 \pm 2.4$ (43.8–54)
15	66	34	32	$50 \pm 4.1$ (40.5–56.7)	$47.7 \pm 3.8$ (32–55)
16	42	33	9	$51.08 \pm 3.2$ (44–59)	$48.6 \pm 4.7$ (45–58)
17	19	13	6	$53.1 \pm 2.5$ (49–59)	$49.2 \pm 2$ (45–51)
18	11	9	2	$53 \pm 2.2$ (49–55)	$50 \pm 2.8$ (48–52)
19	2	1	1	-	-

LVPWd, left ventricular end diastolic posterior wall dimension

## Electrocardiography

The Sokolow–Lyon voltage criterion for LVH was present in 117 (45%) of athletes and 20 (23%) of non-athletes. Of the 117 athletes with Sokolow–Lyon voltage criteria for LVH, only 3 (2.5%) had echocardiographic criteria for LVH. None of the non-athletes had echocardiographic evidence of LVH. The voltage criterion for LVH was

positive in all individuals with echocardiographically proven LVH. No athletes had minor or deep T-wave inversions or ST-segment depression in the lateral leads (V5–V6, I or aVL), to indicate pathological LVH. There was a poor correlation between LV mass and the amplitude of R wave on the 12-lead ECG.

#### **2.5.4. Discussion**

Regular participation in systematic physical training is associated with a modest increase in cardiac dimensions (Pelliccia *et al.* 1991; Pelliccia *et al.* 1999; Sharma *et al.* 2002; Makan *et al.* 2005). A small proportion of adult athletes develop substantial LVH or cavity enlargement simulating the diagnosis of hypertrophic or dilated cardiomyopathy, respectively (Maron *et al.* 1995). There are few data evaluating upper limits of cardiac dimensions in adolescent tennis players but data derived from adult athletes cannot be extrapolated to younger athletes who are physically less mature and have trained for shorter periods. Study one revealed that tennis players have modestly increased cardiac dimensions compared with non-athletes. These findings are not dissimilar to those identified in adolescent football players but are slightly smaller when compared with adolescent rowers (Sharma *et al.* 2002; Makan *et al.* 2005). In absolute terms, however, almost all tennis players had cardiac dimensions within normal limits for the general population. Only 3 athletes were considered to have LVH, defined as a LV wall thickness  $>11$  mm, however none of the 3 athletes had wall thickness  $>12$  mm. All 3 athletes were male and aged  $>15$  years indicating that gender and age were important determinants of cardiac dimensions in adolescent athletes. Therefore, the magnitude of hypertrophy was significantly less than that usually observed in individuals with HCM. Furthermore the 3 athletes with LVH had symmetric hypertrophy, enlarged LV size, and normal

indices of diastolic function supporting physiological (athlete's heart) hypertrophy as opposed to HCM, which is characterised by a non-dilated LV cavity and impaired myocardial relaxation.

A significant proportion of male athletes fulfilled Sokolow–Lyon voltage criteria for LVH, a finding that is common in young male athletes and has poor correlation with echocardiographic LVH. The most probable explanation for the high QRS voltages in males is the thin chest walls resulting in reduced distance between the myocardium and the chest wall surface. None of the athletes exhibited pathological Q waves, ST segment depression or deep T wave inversions to indicate cardiac pathology. A slightly higher proportion of tennis players had an enlarged LV cavity, which has also been reported in adolescent football players, swimmers, rowers and rugby players and probably represents a large isotonic component to the sporting discipline. A total of 3% of athletes were considered to have an enlarged LV cavity size but none had a LV cavity exceeding 60 mm or associated impairment of systolic function to indicate the diagnosis of dilated cardiomyopathy. This study relied on absolute measurements of LV dimensions (rather than values normalised to body surface area) so that the observations could be placed directly in the context of clinical cardiovascular diagnosis. Nevertheless, multivariable analysis defined body surface area, age and gender to be independent determinants of LV dimensions.

#### **2.5.5. Study One Conclusions**

Junior elite tennis players exhibit modest increases in LV wall thickness and cavity size. Absolute values rarely exceed predicted normal upper limits and do not generally resemble those seen in individuals with cardiomyopathy affecting the LV.

## **CHAPTER THREE – SUDDEN CARDIAC DEATH**

### **3.0. Inherited or Congenital Diseases that may lead to SCD**

In young ( $\leq 35$  years) athletes, SCD can largely be attributed to a number of inherited (structural or electrical) or congenital cardiac pathologies, these include; hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), concentric left ventricular hypertrophy, congenital anomalous coronary arteries, wolff-parkinson white syndrome (WPW), Long QT syndrome, Brugada syndrome and marfan's syndrome (Sharma *et al.* 1997). A clear and concise informative background will be given to the three main categories of conditions that are the main causes of SCD; 1) heart muscle disorders, 2) electrical disorders, and 3) congenital disorders.

#### **3.1. Hypertrophic Cardiomyopathy (HCM)**

In 1958, pathologist Donald Teare first described asymmetric hypertrophy in the hearts of 9 adolescents and young adults who had died suddenly (Teare 1958). Shortly afterwards, Braunwald *et al.* (1964) documented the clinical characteristics and the familial nature of the condition, terming it Hypertrophic Cardiomyopathy (HCM). HCM is a complex primary and genetically transmitted cardiac disease with a diverse clinical course that includes a benign or stable clinical course over many years, progressive congestive symptoms requiring therapeutic intervention, and the possibility of sudden and unexpected death (Wigle *et al.* 1985; Wigle *et al.* 1995; Maron 1997; Maron *et al.* 2000). Since the late 1970's, the definition of HCM has changed little. It is defined as an idiopathic cardiac muscle disorder characterised by a hypertrophied and non-dilated left and/or right ventricle in the absence of a cardiac or systemic cause (Maron and Epstein 1979; Goodwin 1982).

HCM may occur in many forms and may involve the left, right or both ventricles. Within the RV, hypertrophy is usually symmetric (McKenna *et al.* 1988), but in the LV it may be symmetric or asymmetric, involving the septum, posterior wall or occasionally isolated to the distal ventricle (Maron *et al.* 1981; Maron *et al.* 1981; Shapiro and McKenna 1983). Structural abnormalities of the mitral valve are observed in up to 60% of HCM patients (Klues *et al.* 1992). HCM has distinctive histology (Davies 1984), whereby affected areas of the myocardium demonstrate considerable interstitial fibrosis with gross disorganisation of the muscle bundles, resulting in a characteristic whorled pattern (Maron *et al.* 1981). Furthermore, myocardial cells show considerable organisational disarray, together with internal disorganisation of the myofibrillar architecture (Ferrans *et al.* 1972). Affected myocardial cells are short and wide, with the foci of disorganised cells often interspersed among areas of hypertrophied muscle cells that are otherwise normal in appearance. It is this myocardial cell disarray that may provide a substrate for electrical instability (McKenna *et al.* 1990).

Systolic and diastolic functional abnormalities are often observed in HCM patients (Goodwin and Krikler 1976; Bonow *et al.* 1981; Lorell 1985; Pearce *et al.* 1985). Hyperdynamic systolic function with rapid, early and near complete ventricular emptying is common (Braunwald *et al.* 1964; Bonow *et al.* 1981). Isovolumic periods (end systole to early diastole) are often prolonged, with slow filling and the proportion of filling volume that results from atrial systolic contraction may be increased.

HCM is familial, with autosomal dominant transmission and a high degree of penetrance (Clark *et al.* 1973; Maron *et al.* 1984; Greaves *et al.* 1987). Gene penetrance is quite often age related, with adolescence proving to be the age for clinical feature manifestation. Variable expression of the disease is common, even amongst members of the same family with the same gene defect. Mutations in any of 10 genes encoding sarcomeric contractile proteins have been identified as a cause of HCM (Maron *et al.* 2003). Mutations in the DNA encoding  $\beta$  cardiac myosin heavy chain (chromosome 14) (Jarcho *et al.* 1989; Geisterfer-Lowrance *et al.* 1990; Tanigawa *et al.* 1990),  $\alpha$  tropomyosin (chromosome 15) (Thierfelder *et al.* 1993; Thierfelder *et al.* 1994), and cardiac troponin T (chromosome 1) (Watkins *et al.* 1993; Thierfelder *et al.* 1994) have been identified, as well as an additional locus on chromosome 11 (Carrier *et al.* 1993).

HCM may be diagnosed at post-mortem examination in some young high-profile athletes dying suddenly during sport. Whether all such deaths are based on the identification of myocyte disarray, the histologic hallmark of HCM, is uncertain, but reliance on macroscopic appearance and cardiac weight alone has the potential for a false diagnosis of HCM in an athlete with physiological hypertrophy (Basavarajaiah *et al.* 2008). The Italian pathologists from the centre of excellence in the Veneto region have consistently reported fewer cases of HCM in athletes dying suddenly during sport compared with other nations, even before their screening program (Corrado *et al.* 1990). A protagonist for HCM being the most common cause of death in athletes would argue that there is a lower cluster of the HCM gene pool in the Mediterranean region; however, an antagonist may argue that a thorough histological examination of the heart by a cardiac pathology expert excludes HCM and identifies

an alternative cause such as arrhythmogenic right ventricular cardiomyopathy or an accessory pathway.

### **3.2. Arrhythmogenic right ventricular cardiomyopathy (ARVC)**

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a myocardial disease characterised by fibrofatty replacement and ventricular arrhythmias (Basso *et al.* 2009). The first comprehensive clinical description of the disease was reported in 1982 in adults with ventricular tachyarrhythmias of left bundle branch block morphology (Marcus *et al.* 1982), whilst also demonstrating the characteristic epsilon wave (Fontaine *et al.* 1984). A familial disease in at least 50% of cases, ARVC is typically transmitted as an autosomal dominant trait with variable penetrance (Nava *et al.* 1988). Data from clinical and pre-participation screening programmes, estimate the prevalence of ARVC to range from 1 in 1000 to 1 in 5000 (Nava *et al.* 2000; Peters *et al.* 2004; Corrado *et al.* 2006).

The replacement of the RV myocardium by fibrofatty tissue is progressive, starting from the epicardium or midmyocardium and then extending to become transmural. Progression then leads to wall thinning and aneurysms, typically located at the inferior, apical, and infundibular walls, the hallmark of ARVC (Fontaine *et al.* 1984; Basso *et al.* 1996; Corrado *et al.* 1997). The fibrofatty replacement interferes with electrical impulse conduction, and is the key cause of epsilon waves, right bundle branch block, late potentials, and re-entrant ventricular arrhythmias (Corrado *et al.* 1997; Basso and Thiene 2005). Histological examination reveals islands of surviving myocytes interspersed with fibrous and fatty tissue.

The presence of replacement-type fibrosis and myocyte degenerative changes are essential to make a clear-cut diagnosis of ARVC, in addition to substantial fat replacement. A certain amount of intramyocardial fat is present in the RV in a normal healthy heart and increases with age and bodyweight (Basso and Thiene 2005). For is the reason, fatty infiltration of the RV alone is not considered a sufficient morphological hallmark of ARVC.

Clusters of myocytes can also be seen to be dying at histology, providing evidence of the acquired nature of myocardial atrophy. These changes are frequently associated with inflammatory infiltrates, which probably play a major part in triggering life-threatening arrhythmias (Fontaine *et al.* 1984; Thiene *et al.* 1991; Basso *et al.* 1996; Corrado *et al.* 1997; Thiene and Basso 2001); with cardiotropic viruses being reported in the myocardium of patients with ARVC, supporting an infective pathogenesis (Bowles *et al.* 2002; Calabrese *et al.* 2006).

The disease affects more men than women and becomes clinically overt usually from the second to the fourth decade of life (D'Aliento *et al.* 1995; Baucé *et al.* 2008). Symptoms and signs do not usually appear before puberty or beyond the age of 60 years. Diagnosis in the early stages of ARVC can be challenging because of the non-specific nature of clinical findings. There is no single gold standard and the best strategy consists of combining information from several diagnostic tests. The diagnosis of ARVC is currently based on the presence of major and minor standardised Task Force Criteria including ECG, ventricular arrhythmias, RV function and morphology, histopathology, and family history. Diagnosis is established

when two major, one major plus two minor, or four minor criteria from different groups are fulfilled (Table 9) (McKenna *et al.* 1994).

Genetic mutation analysis of known ARVC genes can detect genetic abnormalities in at least 40–50% of probands (Corrado and Thiene 2006; Sen-Chowdhry *et al.* 2007). The causative genes encode proteins of mechanical cell junctions (plakoglobin, plakophilin, desmoglein, desmocollin, desmoplakin) and account for intercalated disk remodeling. Familiar occurrence with an autosomal dominant pattern of inheritance and variable penetrance has been proven (Thiene *et al.* 2007)

Ventricular arrhythmias range from premature ventricular complexes to sustained VT or ventricular fibrillation (VF) leading to cardiac arrest (Cox *et al.* 2008). The distinctive QRS morphology of ventricular arrhythmias is left bundle branch block, which indicates an origin from the RV. VF is the mechanism of instantaneous sudden death in young people and athletes with ARVC, who are often previously asymptomatic. In this subset of patients, VF is most likely related to a phase of disease progression, due to acute myocyte death and reactive inflammation (Basso *et al.* 1996). Prevention of sudden death is the most important management strategy of ARVC. Retrospective analysis of clinical and pathological series identified several risk factors such as previous cardiac arrest, syncope, young age, malignant family history, participation in competitive sports, VT, severe RV dysfunction, LV involvement, and QRS dispersion of 40 ms or more (Turrini *et al.* 2001; Corrado *et al.* 2003). However, only palliative therapy is available and consists of antiarrhythmic drugs, catheter ablation and implantable cardioverter defibrillator (Thiene *et al.* 2007).

Table 9: Task Force Criteria for diagnosis of ARVC (McKenna *et al.* 1994).

<p><b>I. Global and/or regional dysfunction and structural alterations*</b></p> <p><i>Major</i></p> <ul style="list-style-type: none"><li>• Severe dilatation and reduction of right ventricular ejection fraction with no (or only mild) left ventricular impairment</li><li>• Localised right ventricular aneurysms (akinetic or dyskinetic areas with diastolic bulging)</li><li>• Severe segmental dilatation of the right ventricle</li></ul> <p><i>Minor</i></p> <ul style="list-style-type: none"><li>• Mild global right ventricular dilatation and/or ejection fraction reduction with normal left ventricle</li><li>• Mild segmental dilatation of the right ventricle</li><li>• Regional right ventricular hypokinesia</li></ul> <p><b>II. Tissue characterisation of wall</b></p> <p><i>Major</i></p> <ul style="list-style-type: none"><li>• Fibrofatty replacement of myocardium on endomyocardial biopsy</li></ul> <p><b>III. Repolarisation abnormalities</b></p> <p><i>Minor</i></p> <ul style="list-style-type: none"><li>• Inverted T waves in right precordial leads (V2 and V3) (people aged &gt;12 years, in absence of right bundle branch block)</li></ul> <p><b>IV. Depolarisation/conduction abnormalities</b></p> <p><i>Major</i></p> <ul style="list-style-type: none"><li>• Epsilon waves or localised prolongation (&gt;110 ms) of the QRS complex in right precordial leads (V1–V3)</li></ul> <p><i>Minor</i></p> <ul style="list-style-type: none"><li>• Late potentials (signal-averaged ECG)</li></ul> <p><b>V. Arrhythmias</b></p> <p><i>Major</i></p> <ul style="list-style-type: none"><li>• Arrhythmias listed below plus T-wave abnormalities—see III Repolarisation abnormalities</li></ul> <p><i>Minor</i></p> <ul style="list-style-type: none"><li>• Left bundle branch block type ventricular tachycardia (sustained and nonsustained) (ECG, Holter, exercise testing)</li><li>• Frequent ventricular extrasystoles (&gt;1000/24 hr on Holter).</li></ul> <p><b>VI. Family history</b></p> <p><i>Major</i></p> <ul style="list-style-type: none"><li>• Familial disease confirmed at necropsy or surgery</li></ul> <p><i>Minor</i></p> <ul style="list-style-type: none"><li>• Family history of premature sudden death (&lt;35 years) due to suspected ARVC</li><li>• Family history of ARVC (clinical diagnosis based on present criteria)</li></ul>
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ARVC, arrhythmogenic right ventricular cardiomyopathy.\*Detected by echocardiography, angiography, magnetic resonance imaging, or radionuclide scintigraphy.

Sports activity has been shown to increase the risk of sudden death in people with ARVC by five-fold, since acute volume overload and stretching of the RV (Thiene *et al.* 2007) and sympathetic stimulation during exercise are major triggers of life-threatening arrhythmias (Corrado *et al.* 2003). Moreover, excessive mechanical stress, such as during competitive sports activity and training, can aggravate the underlying myocardial lesion and accelerate disease progression. Detection of symptom-free individuals at preparticipation screening for sport eligibility has been a lifesaving strategy. After implementation of systematic screening in Italy, including 12-lead ECG, there was a sharp decline in sudden death in young competitive athletes, from 3.8 per 100,000 people a year to 0.4 per 100,000 a year in 24 years, mostly due to identification and disqualification of those affected by cardiomyopathies, including ARVC (Corrado *et al.* 2006).

### **3.3. Ion channelopathies that may cause SCD**

At least 4% of sudden deaths are unexplained at autopsy [sudden arrhythmic death syndrome (SADS) as apposed to SCD] (Behr *et al.* 2003) and a quarter may be due to inherited cardiac disease (Corrado *et al.* 2001; Behr *et al.* 2008). Behr *et al.* (2008) investigated 57 consecutively referred families with an recent experience of SADS death, to examine if a comprehensive clinical investigation of SADS families would identify more susceptible individuals and identify causes of death in those individuals whose autopsy was inconclusive for a cardiac cause. Families underwent evaluation including resting 12 lead, 24hr and exercise ECG and 2D echocardiography. Other investigations included signal averaged ECG, ajmaline testing, CMR imaging, and mutation analysis.

First-degree relatives [184/262 (70%)] underwent evaluation, with 13 (7%) reporting unexplained syncope. Seventeen (30%) families had a history of additional unexplained premature sudden death(s). Thirty families (53%) were diagnosed with inheritable heart disease: 13 definite long QT syndrome (LQTS), three possible/probable LQTS, five Brugada syndrome, five ARVC, and four other cardiomyopathies. One SCN5A and four KCNH2 mutations (38%) were identified in 13 definite LQTS families, one SCN5A mutation (20%) in five Brugada syndrome families and one (25%) PKP2 (plakophilin2) mutation in four ARVC families.

Post mortem identification of ion channelopathies is problematic, as cardiac morphology is probably normal. Behr et al's. (2008) investigation demonstrates that over half of SADS deaths were likely to be due to inherited heart disease, namely ion channelopathies, and are more prevalent than previously thought.

#### **3.4. Congenital long QT syndrome and Brugada syndrome**

The congenital long-QT syndromes (LQTS) are responsible for a significant proportion of SCD's in young people without structural heart disease, estimated to have an incidence of approximately 1 in 2500 (Moss *et al.* 1991; Schwartz 1997; Roden 2008). The identification between 1995 and 1996 (Roden *et al.* 1996; Priori *et al.* 1999; Priori *et al.* 1999; Priori *et al.* 1999) of 3 of the genes responsible for the congenital long-QT syndrome (LQTS) (Schwartz *et al.* 1975; Schwartz 1985; Zareba *et al.* 1998) and the realisation that they all encode ion channels involved in the control of repolarisation (Moss *et al.* 1991; Schwartz 1997; Roden 2008) fostered the

concept that LQTS may represent a unique model for the study of genotype-phenotype correlation in hereditary arrhythmogenic disorders.

Interest in this correlation has been further stimulated by the demonstration that the mutations identified in these genes produce either gain or loss of function, resulting in an excess of late inward sodium current or in reduced outward potassium current (Moss *et al.* 1991; Schwartz 1997; Roden 2008). These ionic alterations lengthen action potential duration and produce the characteristic ECG signal of QT-interval prolongation and T-wave abnormalities.

The QT interval corrected for heart rate (QTc) can range from 370 to >700 ms, clearly overlapping that of normal individuals, and a single ECG may not manifest the stereotypical features (Monnig *et al.* 2006; Vyas *et al.* 2006; Vaglio *et al.* 2008). Some patients have a normal or borderline QTc at rest but prolongation with exertion or  $\beta$  adrenergic stimulation. Provocative testing with exercise or catecholamine infusion may improve the sensitivity of LQTS clinical detection (Vincent *et al.* 1991; Monnig *et al.* 2006)

The definitive clinical diagnosis of congenital LQTS can be complex (Ackerman 2004). Debate continues as to what QTc constitutes the upper limit of normal. An increasing proportion of asymptomatic individuals with genetically proven LQTS are found to have a normal resting ECG with a QTc by Bazett's formula of less than 460 ms (genotype positive/phenotype negative LQTS). In addition, a QTc of 440 ms, used in the past as an upper limit of normal, is present in far too many normal individuals (greater than 25%) to serve as a meaningful upper limit cut-off value. In general, a

QTc of 470 ms or more in males and 480 ms or more in females requires further investigation as to the presence of congenital (or acquired) causes of QT prolongation. A patient with LQTS and a resting QTc of 500 ms or more is generally considered at increased clinical risk for a significant arrhythmia (Priori *et al.* 2003). One approach to the diagnosis of congenital LQTS is to utilise the "Priori-Schwartz" score that incorporates QTc, T-wave morphology, symptomatic presentation, and family history into the diagnostic algorithm (Priori *et al.* 2003). A "Priori-Schwartz" score of 4 or more suggests high clinical probability for LQTS. In addition, genetic testing for the five cardiac ion-channel genes responsible for 75% of LQTS (LQT1, LQT2, LQT3, LQT5, and LQT6) is now available.

Physical activity (particularly swimming) appears to be a common trigger for ventricular arrhythmias in LQT1, whereas individuals with LQT2 seem more at-risk to auditory/emotional triggers, and patients with LQT3 may be at greater risk during rest and inactivity (Schwartz *et al.* 2001; Choi *et al.* 2004). However, exceptions to these genotype-phenotype correlations hinder genotype-specific tailoring of competitive sports recommendations. The entire personal and family phenotype must be incorporated before any eligibility or disqualification decision is rendered.

### **3.5. Brugada syndrome**

Brugada syndrome is characterised by RBBB primarily in leads V1 through V3, with ST-segment elevation, often followed by a negative T-wave and an R prime, and a propensity for sudden cardiac death, typically occurring with mild activity or during sleep (Brugada and Brugada 1992; Brugada *et al.* 2003). Several studies have linked the genetic basis of Brugada syndrome to mutations in the gene that encode the  $\alpha$

subunit of the sodium channel (Chen *et al.* 1998). More recent studies have linked the syndrome to mutations in genes that encode the  $\alpha$  and  $\beta$  subunits of the calcium channel (Brugada *et al.* 2003; Antzelevitch *et al.* 2007) and the gene that encodes glycerol-3-phosphate dehydrogenase 1-like enzyme (GPD1L) (London *et al.* 2007). The 4 genes thus far identified are estimated to account for approximately 28% of Brugada syndrome probands. Accordingly, 72% of cases remain accounted for by genotype.

Individuals with Brugada syndrome and no previous cardiac arrests may have a high risk of sudden death if they have inducibility of ventricular arrhythmias and a previous history of syncope (Sumitomo *et al.* 2003). Hyperthermia can potentially unmask the Brugada ECG pattern in patients with Brugada syndrome, who can then display fever-induced polymorphic VT.

### **3.6. Repolarisation changes in young athletes vs. ion channelopathies**

Minor repolarisation abnormalities, including mild elevation of the J point associated with mild ST segment elevation in the anterior chest leads and mild T wave inversion ( $< 0.2$  mV) in V1–2 and the inferior leads are a frequent finding in young athletes. A significant proportion of young athletes also possess minor interventricular conduction abnormalities such as incomplete RBBB (Firoozi *et al.* 2003).

With better understanding of the long QT and Brugada syndromes, it is becoming clearer that in some cases of these conditions, repolarisation changes similar to those commonly seen in young athletes are present. For example, it is recognised that in some subtypes of the long QT syndrome, abnormalities of T wave morphology, T wave microalternans, and small U waves in the proximity of the terminal portion of

the T wave are present (Zhang *et al.* 2000). Similarly, in the Brugada syndrome, the characteristic electrocardiographic abnormality is the presence of ST segment elevation along with RBBB in the anterior leads (Brugada and Brugada 1992). These features raise the possibility of misdiagnosing normality in a young athlete and allowing competitive participation in the face of a potentially lethal cardiac disorder. Furthermore, both the long QT and Brugada syndromes do express incomplete penetrance (Brugada and Brugada 1992) with latent ECG changes, and therefore relying on the ECG for their diagnosis would lead to false negatives. In some other cases the ECG changes may be subtle and there may be a need for provocation tests to confirm the diagnosis. These difficulties are highlighted by the relative lack of exposure and consequent unfamiliarity with these conditions in most cardiologists' daily practice. In cases of uncertainty, the presence of a history of syncope or a family history of premature sudden death should raise the level of suspicion and lead to expert help being sought (Firoozi *et al.* 2003).

### **3.7. Wolff–Parkinson–White syndrome (WPW)**

WPW syndrome is a cardiac conduction system abnormality, where supplementary electrical pathways can lead to re-entrant supraventricular tachyarrhythmias, which may trigger ventricular fibrillation (Sharma *et al.* 1997; Basilico 1999). SCD may occur with the development of atrial fibrillation with rapid atrioventricular conduction via the bypass tract, resulting in a prompt ventricular response (>300 bpm), concluding with ventricular fibrillation and SCD (Klein *et al.* 1979; Sarubbi 2006). Prevalence of WPW is exceptionally low, affecting only 0.15% to 0.20% of the general population, with a smaller risk (0.1%) of SCD (Winget *et al.* 1994). Affected individuals show rapid palpitation, pre-syncope or syncope. WPW can also be

identified by delta waves upon the resting ECG, along with a slurred QRS complex (Sharma *et al.* 1997; Basilico 1999). The most widely used treatment is the use of radiofrequency ablation of the accessory pathway. This has proved beneficial for athletes whose high sympathetic drive renders anti-arrhythmic drugs ineffective (Warin *et al.* 1989).

### **3.8. Congenital coronary artery anomalies (CAA's)**

Exercise related SCD can strike as a complication of anomalous insertion of the coronary arteries, when the left main coronary artery originating from the right anterior sinus of Valsalva (Roberts *et al.* 1982; Corrado *et al.* 1990; Sharma *et al.* 1997; Futterman and Myerburg 1998; Zeina *et al.* 2009), or when the right coronary artery arises from the left sinus of Valsalva (Basilico 1999; Cittadini *et al.* 2009). The mechanism behind SCD is attributed to the exit angle of the left main coronary artery from the right sinus of Valsalva. This sharp angle creates a narrowing of the coronary ostium, which with exercise induced aortic dilation, further exaggerates the exit angle of the left main coronary artery (Futterman and Myerburg 1998). During exercise, coronary ischaemia arises due to the impingement of the coronary artery between the aorta and the pulmonary trunk (Figure 1) (Basilico 1999).

CAA is the second most common cause of SCD in young athletes (17% of SCD cases) and is also thought to be the second most common cause of SCD in the USA (Maron *et al.* 2009). Detection of CAA's frequently often relies on personal symptom questionnaire and standard echocardiography; however, more recently three-dimensional magnetic resonance coronary angiography (MRCA) has been increasingly used to detect the presence and anomalous course of CAA's.

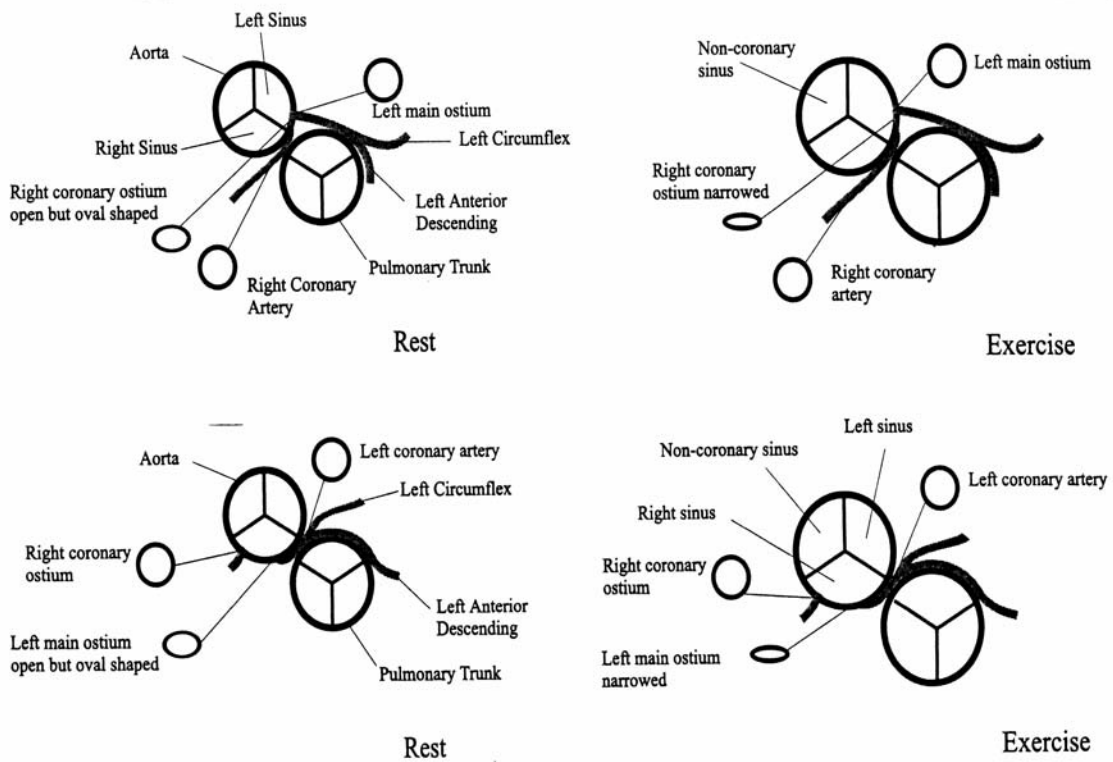


Figure 1: Diagram documenting proposed means of ischemia of anomalous right (upper level) and left (lower level) coronary arteries. Upon exercise, the aorta and pulmonary trunk enlarge, creating torsion and constriction of the ostium of the anomalous artery (Basilico 1999).

Whilst offering precise information about already suspected CAA's, MRCA can also identify anomalies previously not suspected (Casolo *et al.* 2005). Generally, diseased individuals are asymptomatic, but some demonstrate symptoms prior to SCD; these include syncope, angina, and dyspnea (Kumpf *et al.* 2006). The possibility of a CAA's should always be considered in young individuals with a history of chest pain or syncope, particularly if the episodes are triggered by exercise (De Rosa *et al.* 2005).

## **CHAPTER FOUR - PRE-PARTICIPATION SCREENING**

### **4.1. Preparticipation Screening**

The purpose of preparticipation screening is to provide medical clearance for participation in sport through routine systematic evaluations intended to identify pre-existing cardiovascular abnormalities and thereby reduce the potential for adverse events and loss of life (McGrew 2003). Approximately 80% of non-traumatic sudden deaths in young athletes are caused by inherited or congenital structural and functional cardiovascular abnormalities, which provide a substrate for arrhythmias predisposing to SCD (Maron *et al.* 1986). Previous demographic data on SCD in 134 deceased young athletes revealed that cardiovascular abnormalities were suspected in only 3% of examined athletes through the use of standard history and physical examination, with less than 1% receiving a confirmed diagnosis (Maron *et al.* 1996). The death of a young athletic individual is a tragic and highly publicised event that causes great debate within the lay community, as exercise is viewed as being highly beneficial for general health. The steady trickles of SCD's in young athletes have called for the implementation of systematic screening programmes by most major sporting governing bodies. Preparticipation screening for diseases that cause SCD is theoretically attractive because it has the ability to identify subjects whose risk for SCD might be reduced by intervention.

Whilst the prevalence of inherited or congenital conditions are rare, modern cardiovascular diagnostic technology can identify said conditions with a high degree of accuracy and reliability, lending further weight to preparticipation screening to ascertain pathology (Pelliccia and Maron 1995; Corrado *et al.* 1998; Maron 2003; McGrew 2003; Corrado *et al.* 2005; Corrado *et al.* 2006; Nistri *et al.* 2007). Both the

American College of Cardiology, the American Heart Association (ACC/AHA) and the European Society of Cardiology (ESC) recommend screening for occult cardiovascular disease before athletic participation, but their screening protocols differ significantly (Baggish and Thompson 2009). Since 1996, the ACC/AHA recommend screening via a medical history and physical examination alone with further testing reserved for athletes with abnormalities detected during this process (Maron *et al.* 2007). The 2007 ACC/AHA consensus update delineate a 12-element (eight medical history questions, four physical examination procedures) screening protocol. However, the ESC and subsequently the International Olympic Committee (IOC) also recommend screening with a history and physical examination, but also instruct the inclusion of a resting 12-lead electrocardiogram (ECG) (Corrado *et al.* 2005; Bille *et al.* 2006). Furthermore, the ESC and IOC also suggest a more comprehensive medical history (34 questions) and physical examination (six procedures).

Supporting data for ECG inclusive screening protocols have emerged from reports of the Italian experience, whereby since 1971, Italian law mandated medical protection for athletes participating in organised sport, which included a 12-Lead ECG and a sub-maximal exercise test (Pelliccia and Maron 1995). From 1979 to 1996, a total of 33, 735 young athletes have been systematically screened with 1058 athletes being disqualified from physical activity, of which 621 (58.7%) were associated with a cardiovascular cause (Corrado *et al.* 1998). From this cohort, the most frequent cardiovascular disorder to warrant disqualification was rhythm and conduction abnormalities (38.3%). It is noteworthy that initial screening in Italy is based upon electrocardiography. Only 3016 (8.9%) young athletes required echocardiography

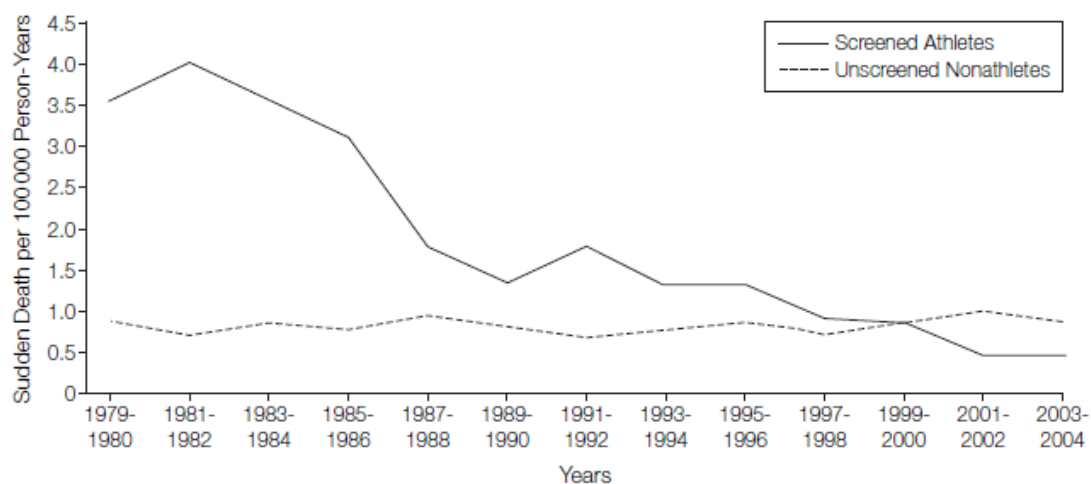
due to suspicions of HCM, whereby 22 were subsequently diagnosed. Thus, less than 10% of the population underwent echocardiographic evaluation, saving a substantial expenditure. The authors concluded that ECG based screening was effective in reducing the incidence of HCM-related SCD. However, controversy exists within the sporting medical community regarding the sensitivity of electrocardiography, whereby the high frequency of ECG alterations observed in athletes are normal variants of athletic training (Sharma *et al.* 1997), leading some authors to suggest that electrocardiography should be excluded in favour of personal and family history questionnaires (Maron *et al.* 1996).

Additional long-term observational data from Italy has recently been published and provides further support for an ECG based screening protocol. Corrado *et al.* (2006) examined the incidence rates and cardiovascular causes of SCD in young competitive athletes in relation to preparticipation screening in athletic and non-athletic populations (12 to 35 years) in the Veneto region of Italy between 1979 and 2004. Furthermore, a parallel study examined trends in cardiovascular causes of disqualification from competitive sports in 42,386 athletes undergoing preparticipation screening (22,312 in the early screening period [1982-1992] and 20,074 in the late screening period [1993-2004]).

During the study period, 55 SCD's occurred in screened athletes (1.9 deaths per 100,000 person-years) and 265 SCD's in unscreened non-athletes (0.79 deaths per 100,000 person-years). The annual incidence of SCD in athletes decreased by 89% (from 3.6 per 100,000 person-years in 1979-1980 to 0.4 per 100,000 person-years in 2003-2004;  $p < 0.001$ ), whereas the incidence of SCD among the unscreened non-

athletic population did not change significantly (Figure 2). Furthermore, most of the reduced mortality was due to fewer cases of sudden death from cardiomyopathies (from 1.5 per 100,000 person-years in the pre-screening period to 0.15 per 100,000 person-years in the late screening period;  $p < 0.002$ ).

Figure 2: Annual Incidence Rates of Sudden Cardiovascular Death in Screened Competitive Athletes and Unscreened Non-athletes Aged 12 to 35 Years in the Veneto Region of Italy (1979-2004) (Corrado *et al.* 2006).



During the study period, the annual incidence of sudden cardiovascular death decreased by 89% in screened athletes ( $P < 0.001$ ). In contrast, the incidence rate of sudden cardiovascular death did not demonstrate consistent changes over time in unscreened non-athletes (Corrado *et al.* 2006).

A total of 879 athletes (2.0%) were disqualified from competition due to cardiovascular causes; 455 (2.0%) in the early screening period and 424 (2.1%) in the late screening period. The proportion of athletes who were disqualified for cardiomyopathies increased from 20 (4.4%) of 455 in the early screening period to 40 (9.4%) of 424 in the late screening period ( $p = 0.005$ ). Finally, no deaths occurred during long term follow-up among athletes with HCM who were disqualified from competitive sports, suggesting that screening may prevent SCD (Corrado *et al.* 1998). The authors conclude that the incidence of SCD in young competitive athletes

substantially declined since the introduction of a National systematic screening programme, with a mortality reduction predominantly due to a lower incidence of sudden death from cardiomyopathies that paralleled the increasing identification of athletes with cardiomyopathies at preparticipation screening.

In conclusion, Study Two sought to confirm the efficacy of resting 12-Lead ECG 'alongside' personal/family history questionnaires and physical examinations as collective tools to identify diseases that have the potential of causing sudden death within a cohort of elite junior athletes and physically active school children.

#### **4.1.1. STUDY TWO (Appendix 2)**

**Wilson, M.G.,** Basavarajaiah, S., Whyte, G.P., Cox, S., Loosemore, M., Sharma, S. Efficacy of personal symptom and family history questionnaires when screening for inherited cardiac pathologies: the role of electrocardiography. *Br J Sports Med.* 2008; 42(3):207-11.

#### **4.1.2. Methods**

##### **Participants**

Written informed consent was obtained from all participants following ethical approval from Lewisham ethics committee. A total of 2720 individuals (under 35 years of age) were examined between September 2000 and February 2006. One thousand and seventy four National and International junior athletes ( $15.8 \pm 0.7$  years, range 10-27) and 1646 physically active school children ( $16.1 \pm 2.1$  years, range 14-20) were screened using personal and family history questionnaires, physical examination and resting 12-Lead ECG.

Elite athlete screenings were organised through their team doctors and the athletes were told to abstain from all physical activity for at least 3 hours prior to screening. In the school group, a standard letter was distributed through their school administration inviting students to attend the screening if they were interested in their cardiac health. Participants made appointments with the investigators once they had absorbed and understood the background information about risks and benefits of an ECG investigation. Parental consent was given in those individuals below the age of 16 years. Participants were not allowed to make an appointment within 48 hours of receiving the information and without signing the informed consent documents.

#### **4.1.3. Physical Examination and Questionnaire Consultation**

Measurement of height (cm), body mass (kg), brachial artery blood pressure in the seated position (mmHg), precordial auscultation in both supine and standing positions and recognition of the physical characteristics of Marfan's syndrome was undertaken by a consultant cardiologist with extensive experience of the athlete's heart and conditions predisposing to SCD in young athletes.

#### **4.1.4. Personal and Family History Questionnaire**

Participants were asked to complete a questionnaire (Table 10) prior to attending the ECG screening. If family history of sudden death or cardiac disease was unknown by the participant, they were asked to investigate with 1<sup>st</sup> and 2<sup>nd</sup> degree relatives until complete. Obtaining this information was problematic in a small number of participants who were either adopted or orphaned at an early age. Athletes with symptoms, and/or abnormalities on physical exam, and/or electrocardiographic

abnormalities (Table 10 and 11) underwent further detailed cardiovascular investigation with appropriate investigations which included any one of, or a combination of echocardiography, 24hr ECG Holter and integrated exercise cardiopulmonary stress test. Symptoms considered to be suggestive of a possible underlying cardiovascular disorder include repetitive syncope during exercise, prolonged periods of palpitations, sustained chest pain and unexplained sudden death in a 1<sup>st</sup> degree relative under the age of 35 years.

Table 10: Personal Symptoms and Family History Questionnaire.

1. Have you ever fainted?	During Exercise	Yes / No
	Following Exercise	Yes / No
	Unrelated to Exercise	Yes / No
2. Do you experience dizzy turns?	During Exercise	Yes / No
	Following Exercise	Yes / No
	Unrelated to Exercise	Yes / No
3. Do you experience palpitations	Yes / No	
4. Do you experience chest pain, heaviness or tightness?	During Exercise	Yes / No
	Following Exercise	Yes / No
	Unrelated to Exercise	Yes / No
5. Do you feel that you are more breathless or more easily tired than your team mates?	Yes / No	
6. Is there a family history of heart disease?	Yes / No	
7. Has there been unexplained death or deaths due to heart disease in young family members	Yes / No	

Table 11: A list of ECG patterns considered to represent a potentially serious cardiac disorder

<b>ECG Pattern</b>
Inverted T waves (more negative than -0.2 mV) in any lead except aVR, V1 and lead III
Left ventricular hypertrophy (Romhilt-Estes)
ST segment depression
Voltage criteria for increased LA
Left axis deviation and one other abnormality
Pathological Q wave patterns
Prolonged QT interval
Epsilon Waves
Right ventricular hypertrophy with ST segment depression in leads V1 to V3
Complete bundle branch block

#### 4.1.5. Results

Table 12: The number of positive answers given by junior athletes and school children to the personal symptom and family history questionnaire.

<b>Personal Symptom and Family History Questions</b>	<b>Junior Athletes (n= 1047)</b>	<b>School Children (n = 1646)</b>
Have you ever fainted during exercise?	14 (1.3%)	55 (3.3%)
Have you ever fainted following exercise?	15 (1.4%)	27 (1.6%)
Have you ever fainted un-related to exercise?	112 (10.7%)	265 (16.1%)
Do you experience dizzy turns during exercise?	67 (6.4%)	162 (9.8%)
Do you experience dizzy turns following exercise?	44 (4.2%)	55 (3.3%)
Do you experience dizzy turns un-related to exercise?	123 (11.7%)	217 (13.2%)
Do you experience palpitations?	41 (3.9%)	205 (12.5%)
Do you experience chest pains, heaviness or tightness during exercise?	65 (6.2%)	285 (17.3%)
Do you experience chest pains, heaviness or tightness following exercise?	52 (4.9%)	190 (11.5%)
Do you experience chest pains, heaviness or tightness un-related exercise?	68 (6.5%)	285 (17.3%)
Do you feel that you are more breathless or more easily tired than your team mates?	103 (9.8%)	277 (16.8%)
Is there a family history of heart disease?	313 (29.9%)	586 (35.6%)
Has there been unexplained death or deaths due to heart disease in young family members?	30 (2.9%)	158 (9.6%)

Junior athletes generally demonstrated fewer symptoms compared to school children. 29.9% of athletes reported a family history of heart disease, however only 2.9% reported an unexplained death or deaths due to heart disease in young family members. When asking the same two questions to school children, the results were 35.6% and 9.6% respectively.

Table 13: The number of participants screened with the number of follow ups, the reasons for follow up and the prevalence of diseases that may have the potential of causing SCD.

	<b>Junior Athletes</b>	<b>School Children</b>
Number Screened	1074	1646
Number requiring further cardiological evaluation after the initial screening	45	62
Percentage needing further evaluation	4.2%	3.8%
Number with an abnormal ECG	25	15
Percentage screened with an abnormal ECG	2.3%	0.9%
Number with serious symptoms and/or Family History of SCD	20	47
Percentage screened serious symptoms and/or Family History of SCD	1.8%	2.9%
Number diagnosed with a disease associated with SCD	5	4
Percentage of patients diagnosed with a disease associated with SCD	0.5%	0.2%
Prevalence	1 in 215	1 in 412

ECG; electrocardiogram, SCD; sudden cardiac death.

Four percent of all participants screened required further examination associated with an abnormal ECG and/or a positive questionnaire as documented in table 13. The prevalence of junior athletes diagnosed with a cardiac disease was over twice (0.5%) that of school children (0.2%). Junior athletes also had the highest number of ECG abnormalities (2.3% vs. 0.9%), but tended to report the fewest personal symptoms and/or family history of SCD (1.8% vs. 2.9%). None of the participants diagnosed with a disease associated with SCD were symptomatic. The present investigation identified 7 cases of electrical diseases associated with SCD, 1 case of arrhythmogenic right ventricular cardiomyopathy and 1 case of right ventricular outflow tract ventricular tachycardia.

All patients identified with a cardiac disorder that were deemed serious (Table 14) underwent further investigation for the purposes of diagnostic clarity and risk stratification prior to therapeutic intervention.

Table 14: Nine participants with a positive diagnosis of a disease associated with SCD.

<b>Patient Number</b>	<b>Gender</b>	<b>Abnormal ECG</b>	<b>Symptomatic</b>	<b>Family History of SCD</b>	<b>Diagnosis</b>
1	Female	Yes	No	No	Long QT syndrome – Type 1
2	Male	Yes	No	No	Wolff-Parkinson White
3	Male	Yes	No	No	Wolff-Parkinson White
4	Male	Yes	No	No	Long QT syndrome – Type 1
5	Female	Yes	No	No	Right Ventricular Outflow Tract Ventricular Tachycardia
6	Male	Yes	No	No	Wolff-Parkinson White
7	Male	Yes	No	No	Arrhythmogenic Right Ventricular Cardiomyopathy
8	Male	Yes	No	No	Long QT syndrome – Type 1
9	Male	Yes	No	No	Wolff-Parkinson White

#### **4.1.6. Discussion**

Study two concludes that personal symptoms are poor predictors of cardiovascular abnormalities. Furthermore, ominous symptoms, such as repeated syncope during exercise, all produced negative findings; most likely mis-reported or misdiagnosis of syncope, i.e. ‘exercise associated collapse without frank syncope’. Study two identified 9 individuals with potentially serious cardiovascular conditions, resulting in further investigations, appropriate risk stratification and potentially life saving therapeutic intervention. The programme involved the UK’s leading experts in

athlete's heart and inherited cardiovascular diseases, limiting our further investigations to 4% compared to 10% in the Italian experience (Corrado *et al.* 1998). Certain personal symptoms, such as atypical chest pain without other major symptoms, were excluded from further investigation by our cardiologists on the day of screening lowering further investigation rates.

The 12-Lead ECG is abnormal in over 90% of patients with HCM, with HCM being reported as the commonest cause of SCD in young athletes (Sharma *et al.* 1997). The present investigation did not identify a single case of HCM. The majority of athletes diagnosed with cardiovascular disease had ion channel or electrical abnormalities that would not have been identified at post mortem. Furthermore, the 12-lead ECG will identify patients with WPW syndrome and the majority of patients with Ion channelopathies, both of which cannot be detected with imaging tests (Sharma *et al.* 1997). Sorbo *et al.* (1995) examined 116,452 ECG's belonging to a cohort of 18-year old boys. The investigation identified 173 cases of overt WPW pattern (short PR interval, delta wave, anomalous configuration of QRS complex) with a calculated incidence of 1.48/1000. Interestingly, only sixty patients (34.6%) of the 173 were symptomatic (palpitations, near syncope and dizziness), suggesting 113 cases of false negative diagnoses with the use of personal symptoms and family history based questionnaires alone. The results imply that without a positive personal and family history questionnaire, 113 asymptomatic individuals would not have been diagnosed with WPW if an ECG had not been carried out and identification had relied on a questionnaire alone.

The role of symptom based questions within the questionnaire is to identify individuals presenting with symptoms suggestive of cardiovascular disease, specifically syncope during exercise, seizures and prolonged periods of palpitations. Firoozi *et al.* (2003) stated that unexplained syncope in a young athlete in the context of exercise should be considered to be an aborted sudden death until proved otherwise. This investigation found 20 and 47 positive cases of troublesome symptoms in junior athletes and school children respectively that required further examination. Within school children there were more follow up examinations due to positive personal symptom and family history questionnaires than positive ECG's. The present investigation found that those individuals presenting with symptoms or family history of cardiac disease were entirely healthy. The false positive rate is higher for personal symptom and family history questionnaires than that of ECG examination alone in school children.

Study two only identified 25 athletes with an abnormal ECG warranting further examination with a spectrum of methods including echocardiography. Such ECG alterations are most likely the consequence of athletic conditioning and represent another potential component of the athlete's heart syndrome (Pelliccia *et al.* 2002). However, further examination rates in the present study are low because of the extensive experience in the interpretation of the athlete's ECG by our cardiologists. It is imperative that only cardiologists with substantial experience of the athlete's heart and diseases associated with young sudden cardiac death should perform ECG examination, ultimately reducing the likelihood of recording false-positive or false-negative ECG findings.

Study two concedes the potential for false negatives using ECG alone without the use of echocardiography exists, even though the 12-Lead ECG is abnormal in over 90% of patients with HCM and in the majority of patients with ARVC (Sharma *et al.* 1997). Furthermore, congenital coronary artery anomalies include a variety of abnormal anatomical variations of the right and left coronaries could be missed in the absence of imaging techniques (McGrew 2003). In favour, we have follow up data over 6 years with no deaths, indicating a robust screening approach.

#### **4.1.7. Conclusion**

Whilst the exact number of young SCD is unknown, the incidence is low. Study two documents that personal symptoms and family history questionnaires alone are inadequate in the identification of individuals with diseases associated with SCD, and supports the recommendations of a number of bodies including the International Olympic Committee, European Society of Cardiology, and the Fédération Internationale de Football Association (FIFA). In conclusion, resting 12-Lead ECG is paramount when screening for diseases that have the potential of causing sudden death in the young.

#### **4.2. Prevalence of HCM in Elite Athletes**

According to epidemiologic studies based on echocardiographic identification of the disease phenotype, HCM has been reported to occur in about 1 in 500 patients in the general population (Maron *et al.* 1986; Maron *et al.* 1995; Maron 2002; Adabag *et al.* 2006; Maron 2007). Although the prevalence of HCM in the general population is 0.2% (Maron *et al.* 1995), the precise prevalence of HCM in the most highly trained athletes is unknown (Basavarajaiah *et al.* 2008). Calculations based on the Italian pre-

participation screening programme involving over 34,000 athletes indicate that the estimated prevalence of HCM in individuals participating in regular organized sporting activity is approximately 0.07% (Corrado *et al.* 1998). However, HCM is a leading cause of young sudden death, and accounts for one third of all sudden cardiac deaths in young competitive athletes (Van Camp *et al.* 1995; Maron *et al.* 1996).

Maron *et al.* (1995) statistical analysis of HCM prevalence of 1 in 500 is widely used in the scientific literature and lay press. However, for over 13 years, the CRY Centre for Sports Cardiology within the Olympic Medical Institute and the Inherited Cardiac Muscle Disorder's Clinic within Kings College Hospital has rarely documented cases of HCM within young athletes. Study three set out to determine the prevalence of HCM in some of the most highly ranked athletes in the United Kingdom to aid in justification for or against screening for HCM in this cohort.

#### **4.2.1. STUDY THREE (Appendix 3)**

Basavarajaiah, S., Wilson, M., Whyte, G., Shah, A., McKenna, W., Sharma, S. Prevalence of hypertrophic cardiomyopathy in highly trained athletes: relevance to pre-participation screening. *J Am Coll Cardiol.* 2008; 51(10):1033-9.

#### **4.2.2. Background**

Although there is no formal government-sponsored preparticipation screening program in the United Kingdom, certain sporting bodies such as the British Lawn Tennis Association, the Premiership football and rugby league, and the national swimming and boxing squads have adopted mandatory self-funded preparticipation screening programs for athletes comprising personal, family, and drug history;

physical examination; 12-lead ECG; and echocardiography with a view to further investigations if necessary. Dr. Sanjay Sharma has been responsible for performing cardiovascular evaluation in elite athletes in these sporting disciplines since 1996 at St George's Hospital Medical School, Olympic Medical Institute (Northwick Park Hospital), University Hospital Lewisham, and King's College Hospital.

#### **4.2.3. Methods**

Between 1996 and 2006, 3,500 asymptomatic elite athletes between 14 years and 35 years (mean age 20.5 years) underwent 12-lead ECG and 2-dimensional transthoracic echocardiography as a part of pre-participation screening for HCM. Of these, 2,625 (75%) were male and 875 (25%) were female. Just over 98% of athletes were Caucasian; the remainder were of West African descent. The athletes had a mean body surface area of  $1.86 \pm 0.16 \text{ m}^2$  (range 1.36 to 2.29  $\text{m}^2$ ). Written consent was obtained from individuals older than 16 years and from a parent or guardian for those younger than 16 years. The athletes participated in 15 different sporting disciplines, but the vast majority of the study group (71%) represented football, rugby, tennis, and swimming. The term 'elite' was used in relation to achievements in the athletic arena; all athletes competed at the regional level and approximately 60% at the national level during the study period. Ethical approval for the study was granted by Harrow Research Ethics Committee.

#### **4.2.4. Criteria for consideration of the diagnosis of HCM in athletes**

Athletes with a LV wall thickness  $>12 \text{ mm}$  were considered to have LVH (Maron 1986; Pelliccia *et al.* 1991; Sharma *et al.* 2002). Athletes with LVH and a relatively non-dilated LV in terms of athletic training ( $<56 \text{ mm}$ ) (Maron *et al.* 1995) 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.* 2005); 3) LV outflow obstruction caused by systolic anterior motion of the anterior mitral valve leaflet (Klues *et al.* 1993); 4) left bundle branch block (Savage *et al.* 1978); 5) ST-segment depression or deep T-wave inversions (<0.2 mV) in 2 contiguous leads (except V1 and V2 in athletes age <16 years old) (Maron *et al.* 1983; Sharma *et al.* 1999) on the ECG; and 6) a family history of HCM in first-degree relatives.

Athletes with a family history of HCM or those showing the echocardiographic and/or ECG abnormalities considered to represent pathological LVH were investigated further with 48-hr ECG (Monserrat *et al.* 2003), cardiopulmonary exercise test (Sharma *et al.* 2000), and cardiac magnetic resonance imaging (Moon *et al.* 2004) to evaluate the broader phenotype of HCM and to assess risk of SCD (Elliott *et al.* 2000). The 48-hr ECG was performed to check specifically for non-sustained ventricular tachycardia. The cardiopulmonary test was performed to identify abnormalities in exercise blood pressure response, exercise arrhythmias, and estimation of peak oxygen consumption. The cardiac MRI scan was performed to exclude apical HCM. In athletes with persisting diagnostic uncertainty after the investigations above, first-degree relatives were invited for screening for HCM and/or attempts were made to persuade the individual to detrain for 3 months followed by repeat evaluation (Ehsani *et al.* 1978; Maron *et al.* 1993).

#### **4.2.5. Results**

None of the athletes in the study had a family history of HCM in first-degree relatives, and none had experienced angina, breathlessness disproportionate to the amount of exercise performed, or exertional syncope. The diagnosis of HCM was excluded by echocardiography in 3,447 (98.5%) 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.

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

Of the 3,500 athletes, 53 (1.5%) showed a maximal LV wall thickness exceeding 12 mm and were considered to have LVH (Figure 3) (Maron *et al.* 1995). All 53 athletes were male and represented a variety of ball, racket, and endurance sporting disciplines, and all 53 participated in sport at the national level. None of the athletes with LVH had indexes of diastolic dysfunction, an enlarged left atrial diameter, or systolic anterior motion of the anterior mitral valve leaflet and associated LV outflow obstruction. Fifty of the 53 athletes with LVH had an associated dilated LV and normal systolic function, consistent with physiological LVH (Pelliccia *et al.* 1991; Sharma *et al.* 2002).

Twenty athletes in this cohort had deep T-wave inversions in at least 2 contiguous inferior and/or lateral leads. None of the athletes with LVH had left bundle branch block or ST-segment depression in 2 or more contiguous ECG leads.

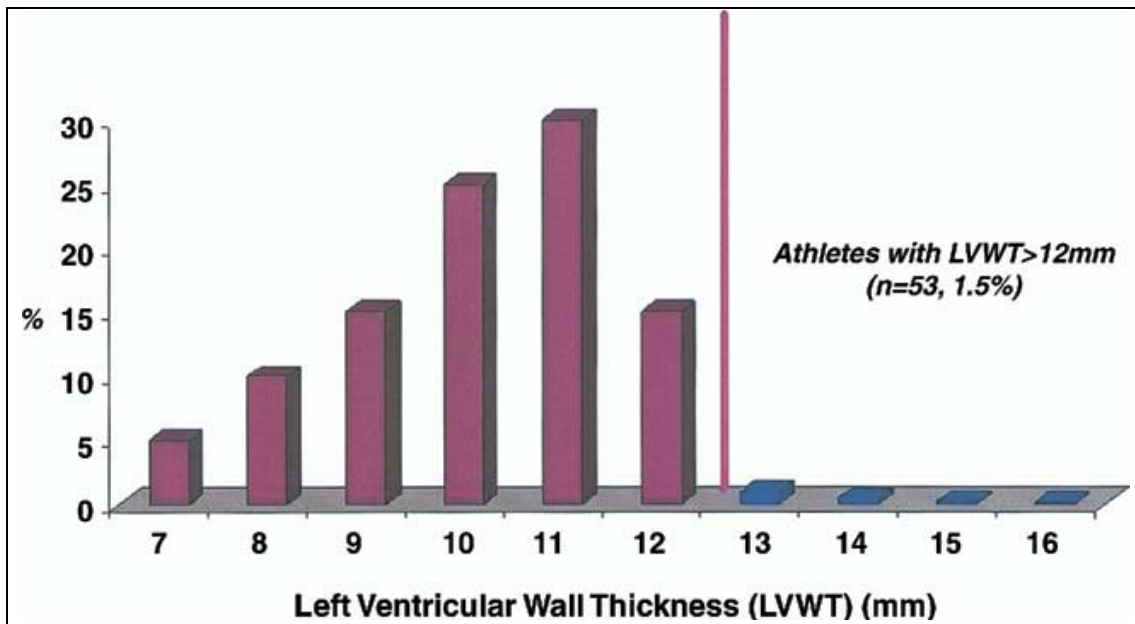


Figure 3: Distribution of LVWT in 3500 Elite Athletes

We found that 1.5% of elite athletes showed a wall thickness >12 mm. LVWT; left ventricular wall thickness.

#### **Athletes with LVH and a non-dilated LV**

Only 3 of the 53 athletes with LVH had a non-dilated LV, which could be considered to represent morphologically mild HCM. None of the athletes had any other echocardiographic features of HCM. All 3 athletes also showed deep T-wave inversions in inferior and/or lateral leads (Figure 4). The 48-hr Holter monitoring did not reveal any episodes of non-sustained ventricular tachycardia or paroxysmal atrial fibrillation in any of the 3 athletes. All 3 athletes exercised to the point of volitional exhaustion and achieved >95% of the predicted heart rate for age. All 3 athletes showed an adequate blood pressure response to exercise and achieved high peak oxygen consumption and anaerobic threshold values. Cardiac magnetic resonance scans using gadolinium-diethylenetriamine pentacetate (0.1 mmol/kg) in all 3 athletes revealed normal left and right ventricular structure and function. In relation to the

diagnosis of HCM, there was no evidence of apical HCM, marked hypertrophy of anterolateral free wall, or myocardial fibrosis.

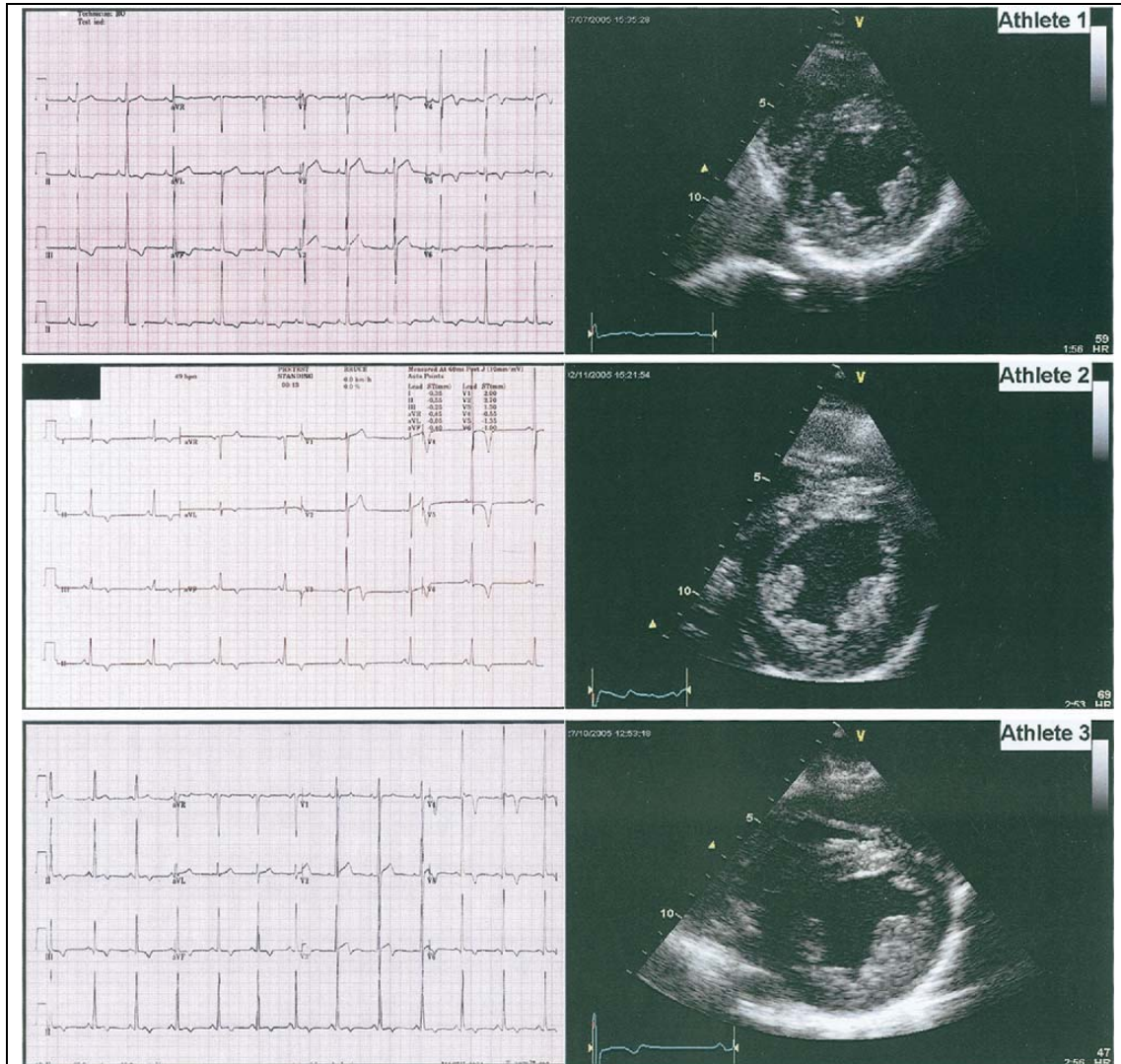


Figure 4: Electrocardiograms and Parasternal Short-Axis Views of the LV at the Level of Papillary Muscle of the 3 Athletes with LVH and a Non-dilated LV Cavity.

All 3 athletes showed left ventricular hypertrophy (LVH) associated with a non-dilated left ventricular (LV) cavity and inferior and lateral leads.

Both parents and siblings of all 3 athletes accepted invitations for screening for HCM with 12-lead ECG and 2-dimensional echocardiography, which did not reveal any conventional diagnostic features of the disorder to indicate familial disease. Only 1 of the 3 athletes was persuaded to detrain for 3 months, after which there was regression of LV hypertrophy on echocardiography and resolution of the deep T-wave inversion

on the ECG (Figure 5) (Basavarajaiah *et al.* 2006). The 2 remaining athletes declined detraining through fear of team deselection and continued to exercise. Both athletes agreed to be genotyped for known HCM-causing sarcomeric contractile protein gene mutations, which did not yield a diagnosis.

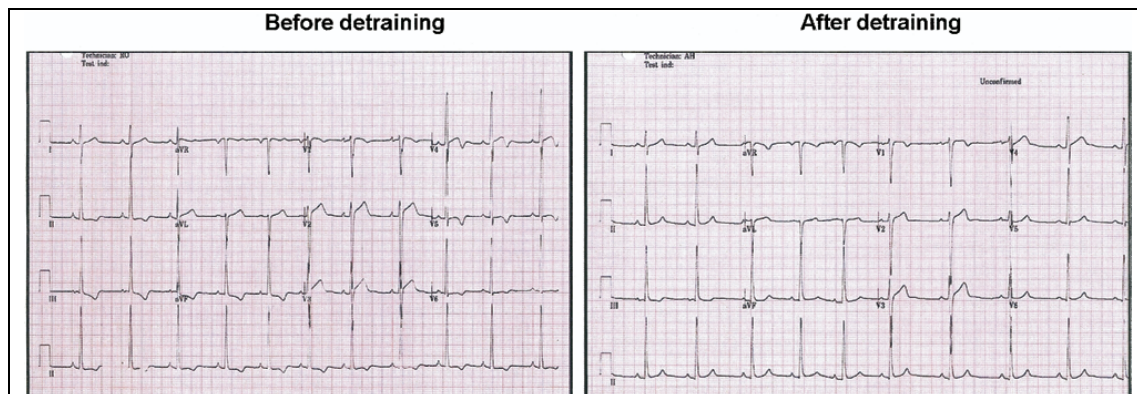


Figure 5: Electrocardiograms of a Swimmer with LVH and Inferolateral T-Wave Inversions Before and After Detraining for 12 Weeks.

Detraining was associated with regression of left ventricular hypertrophy (LVH) on echocardiography and normalization of deep T-wave inversions after detraining.

### **Athletes with other cardiac abnormalities on ECG and echocardiography**

Twenty-six athletes (0.7%) had cardiac diagnoses other than LV hypertrophy, including Wolff- Parkinson-White ECG pattern (n = 6), isolated long QT interval (>460 ms) (n = 9), mitral valve prolapse (n = 5), atrial septal defect (n = 2), bicuspid aortic valve (n = 3), and cor triatriatum (n = 1).

Thirty-five (1%) athletes showed deep T-wave inversions in contiguous leads. Of these, 20 had LV hypertrophy (17 with a dilated LV and 3 with a non-dilated LV). The remaining 15 (0.4%) athletes had deep T-wave inversions in the absence of LV hypertrophy.

#### **4.2.6. Discussion**

#### **4.2.7. Prevalence of HCM in elite athletes**

HCM is a leading cause of young sudden death, and accounts for one third of all sudden cardiac deaths in young competitive athletes (Van Camp *et al.* 1995; Maron *et al.* 1996). Study 3 shows that the prevalence of HCM in elite British athletes is extremely low. Of the 3,500 athletes studied, only 3 (0.09%) athletes had LV morphology that could have been regarded to be consistent with mild HCM after initial evaluation with ECG and echocardiography. However, in 1 of the 3 athletes, the diagnosis was excluded after demonstration of regression of LVH on echocardiography and associated resolution of repolarisation changes on ECG (see Study 5 (Basavarajaiah *et al.* 2006)). The remaining 2 athletes had mild LVH and an associated non-dilated LV, but neither had any other morphologic features of HCM or the broad phenotype of the disorder on 48-hr ECG monitoring and exercise stress testing. Outside the context of familial disease, neither athlete could be regarded as having unequivocal diagnostic features of HCM.

Interestingly, both athletes were of West African decent, which may have had a bearing on the magnitude of hypertrophy in response to exercise and repolarisation changes on the ECG (Lewis *et al.* 1989). The 2 athletes in question also showed high peak oxygen consumption and anaerobic threshold, indicating the ability to generate and sustain a large cardiac output for prolonged periods. In contrast, most individuals with HCM (Jones *et al.* 1998), including those participating in regular physical activity (Sharma *et al.* 2000), have been shown to have low peak oxygen consumption irrespective of symptomatic status or magnitude of LVH.

Genetic testing failed to identify a disease causing mutation in both athletes, but based on the genetic heterogeneity of HCM, the investigators concede that the diagnosis of HCM cannot be excluded with certainty by a negative genetic test. Even if a diagnosis of HCM were entertained in the 2 athletes of West African ancestry above, the prevalence of HCM in elite athletes is no more than 0.06%, compared with 0.2% in the general population. The pathophysiological manifestations of HCM, notably LVH, non-dilated LV, impaired myocardial relaxation, myocardial ischemia, dynamic LV outflow obstruction, and mitral regurgitation, are probably not conducive to achieving substantial increases in cardiac stroke volume in most affected individuals. We suspect that most individuals with HCM are selected out from competing in high-level sport where physical endurance is a major component.

There were a significant number of athletes with LVH, but all had a dilated LV cavity, indicating physiological LVH. Although LV dilatation is also recognised in HCM, it is usually a manifestation of end-stage disease and is associated with New York Heart Association functional class III or IV (Harris *et al.* 2006).

#### **4.2.8. Screening for HCM in elite athletes**

Screening for HCM specifically with echocardiography in elite athletes is not cost effective because several thousand athletes would have to be screened to identify one with HCM. The investigators concede that HCM shows marked morphologic and functional heterogeneity allowing a very small fraction of affected individuals to compete at national and international levels (Maron and Klues 1994); however, this cannot justify large-scale screening for HCM with echocardiography in all elite athletes. Furthermore, certain genetic mutations show age-related penetrance,

therefore the absence of LVH in adolescence or young adulthood does not rule out the possibility of developing HCM in the future (Maron *et al.* 2001).

Ironically the study identified 15 individuals with either the Wolff-Parkinson-White ECG pattern (n = 6) or a long QT interval (n = 9), which are considered rare causes of SCD in young athletes (Maron 2003) but may claim more lives in athletes than originally thought. Neither disorder precludes cardiac function and would not necessarily be selected out by intense physical exertion. All athletes with the Wolff-Parkinson-White pattern had an identifiable accessory pathway that was ablated, permitting resumption of competitive sport. Of the 9 athletes with a long QTc interval, 3 were diagnosed with unequivocal long QT syndrome based on a Schwartz points score of 4 (n = 2) (Schwartz *et al.* 1993), evidence of disease in a first-degree relative (n = 2), or a positive genetic diagnosis (n = 1) and were disqualified from competitive sports. Diagnostic uncertainty persists with the remaining 6, who have continued to compete for a mean period of 3 years without adverse cardiac events. Eleven athletes (0.3%) with a normal ECG showed minor congenital structural abnormalities that were not hemodynamically significant and did not result in disqualification from sport.

In agreement with Study 2, Study 3 suggests that screening elite athletes using an ECG is more likely to identify individuals with other conditions implicated in SCD and also to identify those who may have pathological LVH. The absence of ST segment depression, deep T-wave inversions, and left bundle branch block will exclude almost all cases of HCM as shown by longitudinal follow-up of previously screened Italian athletes (Pelliccia *et al.* 2006).

#### **4.2.9. Conclusion and Limitations**

The prevalence of HCM in elite athletes is significantly less than in the general population; the demands of strenuous exercise on the cardiovascular system select out most individuals with HCM. Screening all elite athletes with echocardiography, the accepted gold-standard investigation for HCM, has a poor yield, with many thousand athletes needing to be screened to identify a single individual with HCM. The ECG is useful in identifying individuals who may have pathological LVH and other congenital electrical disorders that may prove fatal. Based on the British experience of systematic cardiovascular screening of elite athletes, Study 3 proposes that echocardiography in athletes to screen for HCM should be reserved only for athletes with symptoms suggestive of underlying cardiovascular disease, a murmur indicative of LV outflow obstruction, family history of HCM 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 (Sharma *et al.* 1999; Corrado and McKenna 2007). Study 3 reveals that only 1% of athletes in this study would be expected to undergo echocardiography to exclude HCM based on the proposed recommendations, which has a massive cost-saving implication, particularly for financially less endowed sporting clubs.

Almost all of the athletes in this study were Caucasian. Of the small proportion of athletes of West African origin, 2 had features that could have been consistent with HCM; however, subsequent evaluation was more suggestive of physiological LVH. Future work should look to detail the cardiac structure and function in this particular

ethnic group to permit accurate cardiovascular evaluation and minimize the risk of a false-positive diagnosis of HCM.

#### **4.3. Prevalence and significance of an isolated long QT interval in elite athletes**

Previous research has documented a prevalence of Long QT syndrome in elite UK athletes (Basavarajaiah *et al.* 2008; Wilson *et al.* 2008). Through an ECG based cardiac screening programme, Wilson *et al.* (2008) identified 9 individuals with a positive diagnosis of a disease associated with sudden cardiac death; of which 3 were confirmed with a diagnosis of Long QT syndrome (Study 2). Basavarajaiah *et al.* (2008) identified a further 9 athletes with a long QTc interval. Three were diagnosed with unequivocal long QT syndrome based on a Schwartz points score of 4 (n = 2) (Schwartz *et al.* 1993), evidence of disease in a first-degree relative (n = 2), or a positive genetic diagnosis (n = 1) and were disqualified from competitive sports. Diagnostic uncertainty persisted in the remaining 6, who continued to compete for a mean period of 3 years without adverse cardiac events.

Congenital long-QT syndromes (LQTS) are recognised as a cause of adrenergic-mediated polymorphic ventricular tachycardia (VT) and have been implicated in exercise related sudden cardiac deaths in young athletes (Maron *et al.* 1996; Corrado *et al.* 2001; Behr *et al.* 2003; Basavarajaiah *et al.* 2007). The identification of a prolonged QT interval corrected for heart rate (QTc) in an athlete raises the potential diagnosis of congenital LQTS and issues relating to disqualification from competitive sporting disciplines involving moderate- and high-intensity strenuous exertion (Zipes *et al.* 2005; Basavarajaiah *et al.* 2007), however, an isolated prolonged QTc interval per se does not fulfil the proposed criteria for congenital long-QT syndrome (Moss

1986). Although there are numerous electrocardiographic studies relating to athletes (Sharma *et al.* 1999; Pelliccia *et al.* 2000; Biffi *et al.* 2002), the prevalence, and more importantly, the significance, of a prolonged QTc interval has never been addressed in elite athletes.

Study Four set out to identify the prevalence of prolonged QTc interval in a large cohort of elite British athletes and to evaluate the significance of prolonged QTc interval utilizing Holter monitoring, exercise testing, cardiovascular evaluation of first-degree relatives, and genetic testing in consenting individuals.

#### **4.3.1. STUDY FOUR (Appendix 4)**

Basavarajaiah, S., **Wilson, M.**, Whyte, G., Shah, A., Behr, E. and Sharma, S. Prevalence and significance of an isolated long QT interval in elite athletes. *Eur Heart J.* 2007. 28(23); 2944–2949.

#### **4.3.2. Methods**

##### **Athletes**

Between 1996 and 2006, 2000 elite athletes aged between 14 and 35 years (mean, 20.2 years) were evaluated as part of mandatory pre-participation cardiovascular screening; of which, 1260 (70%) elite athletes were males and 540 (30%) were females. The athletes participated in 15 different sports, but the vast majority of the study group (70%) represented football, rugby, tennis, and swimming. All athletes competed at least at regional level and ~50% of them were playing at a National level during the study period.

## **12-Lead Electrocardiography – QTc criteria**

The QT interval was measured in all leads from the onset of QRS complex to the end of T wave, defined as the intersection of iso-electric line and the tangent of the maximal downward limb of the T wave (Al-Khatib *et al.* 2003). The U-wave was excluded during the measurement of the QT interval, except when the T wave was biphasic or in the presence of T–U complexes where the identification of the termination of the T wave was difficult. In such cases, the U-wave was included if it exceeded 50% of the T-wave amplitude. In the presence of biphasic T waves, we have also assessed the QT interval in other leads that did not exhibit biphasic T waves. The lead with the longest QT interval was used to obtain an average QT over three to five consecutive beats. The QTc values were derived using Bazett's formula, which has been most widely used in all large studies evaluating patients with LQTS. All ECG's were analysed independently by three independent cardiologists with a clinical and academic interest in LQTS. According to internationally accepted guidelines, males with a QTc value of >440 ms and females with a QTc value of >460 ms were considered to have an abnormally prolonged QTc interval (Corrado *et al.* 2005).

## **Further investigations**

Athletes with a prolonged QTc interval were detrained for 6 weeks and underwent repeat ECG and further assessment with 48 h ECG monitoring and exercise stress testing to identify additional phenotypic features of congenital LQTS.

## **48hr ECG and Exercise Stress Testing**

Athletes were encouraged to continue with usual (non-athletic) life activities while undergoing ECG monitoring. The 48hr ECG recordings were analysed specifically for

episodes of polymorphic VT. An upright exercise stress test was performed in accordance with the standard Bruce Protocol and athletes were encouraged to the point of achieving maximal age-predicted heart rate (maximal heart rate of 220 - age). Continuous 12-lead ECG recordings were obtained throughout the test looking for episodes of polymorphic VT. ECG tracings were printed for the QTc calculation at heart rate increments of 10 beats per minute up to a heart rate of 130 beats per minute during exercise and heart rate decrements of 10 beats per minute from a heart rate of 130 beats per minute to baseline heart rate during recovery. The QT interval was not measured at heart rates above 130 beats per minute, as the Bazett's correction is deemed inaccurate at high heart rates.

#### **Assessment of first-degree relatives and Genetic Testing**

The first-degree relatives of the athletes with prolonged QTc intervals (parents and siblings) were invited to undergo 12-lead ECG to help identify evidence of familial disease. All athletes with prolonged QTc interval were offered genetic testing for all genetic mutations commonly implicated in LQTS type 1–3 (*KCNQ1*, *HERG*, and *SCN5A*). Genetic testing was performed following counselling and after obtaining informed consent. Mutations were identified using standard genetic tests (Curran *et al.* 1995; Wang *et al.* 1995; Wang *et al.* 1996).

#### **4.3.3. Results**

The mean QTc interval in 2000 athletes measured  $397 \pm 28$  ms and ranged from 346 to 570 ms. Of the 2000 athletes, seven (six male and one female) had a prolonged QTc interval amounting to a prevalence of 0.4%. The mean heart rate in these seven athletes was 58 beats per minute (range, 47–68 beats per minute) and the QTc ranged

from 460 to 570ms. Of the seven athletes, three had a baseline QTc value of >500 ms (Figure 1). All seven athletes were asymptomatic; none were taking regular medications that could be associated with a prolonged QTc interval and had family history of congenital LQTS, premature SCD, unheralded syncope, or epilepsy. None of the athletes had sensorineuronal deafness (Schwartz *et al.* 1975; Moss 1986). The characteristics of all athletes with prolonged QTc interval are shown in Table 15.



Figure 6: Panel showing the 12-lead ECG's of three athletes with QTc > 500 ms.

Table 15: Characteristics of the seven athletes with prolonged QTc intervals

Athlete	Age	Sport	QT interval (ms)	RR interval (s)	QTc interval (ms)	Positive ETT	Affected first-degree family members	Genetic testing
1	17	Swimming	568	1.066	550	Yes	Yes	Negative
2	19	Rugby	540	0.897	570	Yes	No	Negative
3	16	Swimming	582	1.277	515	No	Yes	Positive (LQT1)
4	15	Football	436	0.898	460	No	No	Declined
5	19	Rugby	492	1	492	No	No	Declined
6	15	Tennis	466	0.966	474	No	No	Negative
7	18	Tennis	467	0.908	490	No	No	Negative

## 48hr ECG and Exercise Stress Testing

All athletes with a prolonged QTc interval successfully completed the 48hr ECG monitoring. None of the athletes showed evidence of polymorphic VT during the recording. All athletes achieved at least 90% of their age-predicted heart rate during the test. None of the athletes developed episodes of polymorphic VT; however, two athletes exhibited prolongation of the QTc interval during the initial stages of exercise and immediately post exercise (Figure 7). Both athletes had a baseline QTc value of >500 ms.

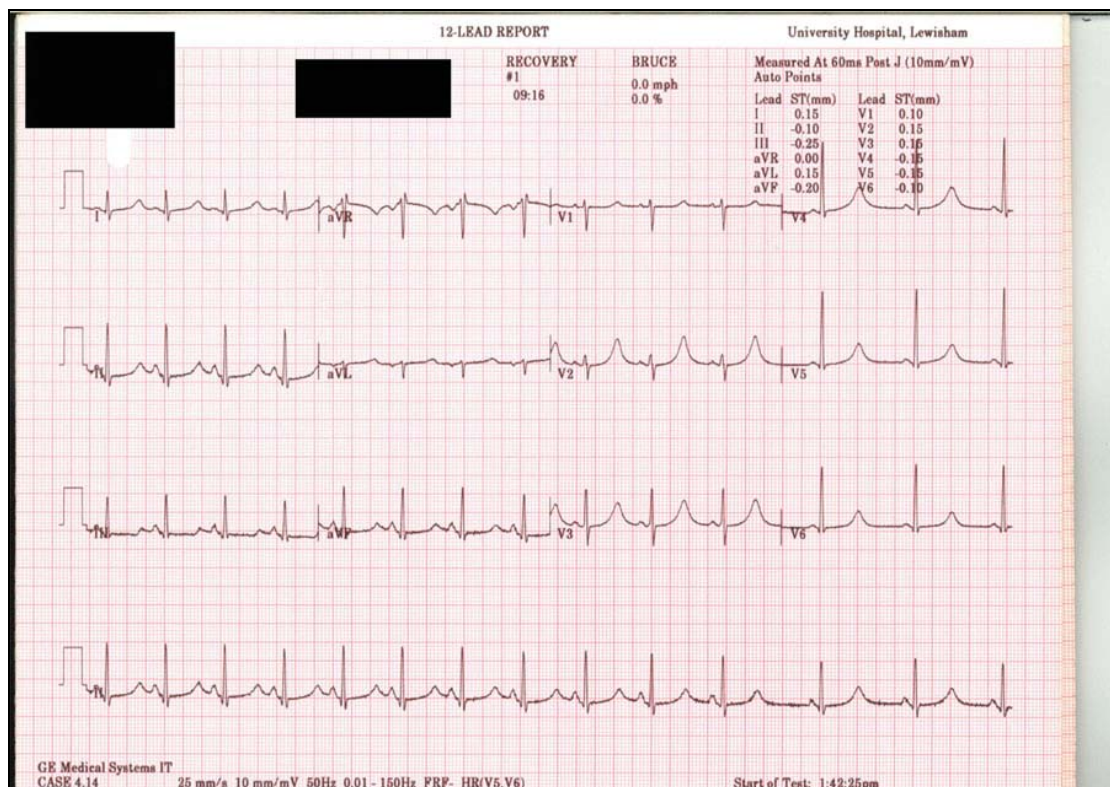


Figure 7: 12-Lead ECG of an athlete (athlete 1) demonstrating paradoxical prolongation of the QTc during the recovery phase of exercise.

## 12-Lead ECG screening of first-degree relatives

Both parents and all siblings of each of the seven athletes agreed to be evaluated with 12-lead ECG. One athlete had three siblings, two athletes had two siblings, and four athletes had one sibling. Two athletes had a first-degree relative with a long QTc. In

each case, one parent and one sibling were affected (Figure 8). Both athletes had a baseline QTc value of >500 ms.

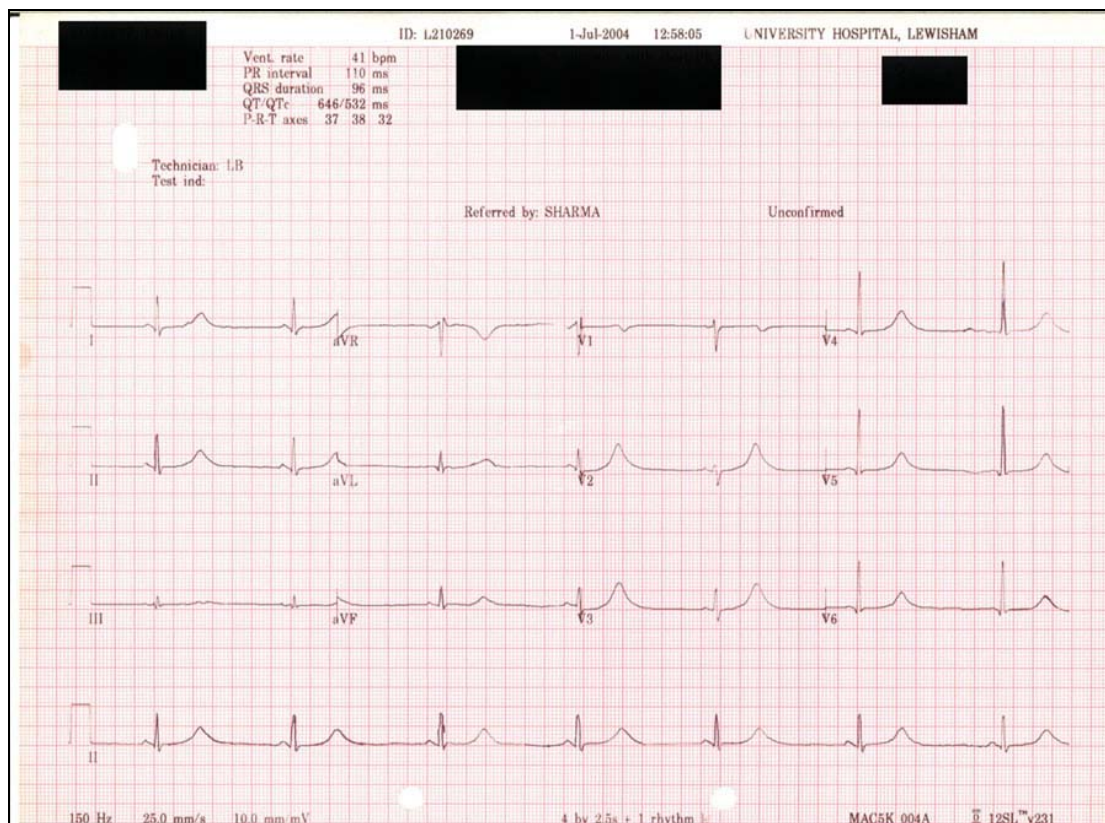


Figure 8: 12-Lead ECG of the brother of an athlete (athlete 3) with a long QTc.

### Genetic testing

Of the seven athletes, two declined genetic testing after counselling. The results from the genetic tests were not available before 4 months in any athlete and up to 12 months in one athlete. Only one of the five (20%) athletes who underwent genetic testing had a positive genetic diagnosis. The athlete in question had C to T nucleotide substitution at position c.691 of the *KCNQ1* gene, resulting in an amino acid exchange of arginine (R) to cysteine (C) at codon 231 (p.R231C) and his baseline QTc value of >500 ms. A genetic diagnosis was not possible in the other four athletes after screening for all the known mutations capable of causing LQT1-3.

#### **4.3.4. Discussion**

#### **4.3.5. Prevalence of isolated long QTc interval on a 12-lead ECG in athletes**

The diagnosis of congenital LQTS is based on the triad of prolonged QTc interval, unheralded syncope or polymorphic VT and a family history of SCD or LQTS (Schwartz *et al.* 1975; Moss 1986). On the basis of this triad, the prevalence of LQTS is between 1 in 2500 to 1 in 10,000 (Schwartz 1997). However, genotype–phenotype correlation studies in patients with congenital LQTS show that a significant number of gene positive individuals may manifest as a prolonged QTc interval in isolation.

Study 4 reveals that the prevalence of a prolonged QTc interval in elite athletes is 0.4%. This figure is not dissimilar to Mobitz type 1 first-degree AV block, wandering atrial pacemaker and right bundle branch block that are regarded as normal variants in athletes (Sharma *et al.* 1999). The Italian preparticipation screening programme comprising of over 34,000 athletes reported disqualification (0.69%) of all athletes based on the identification of a prolonged QTc interval (>440 ms in males and >460 ms in females) (Corrado *et al.* 2006). The results of both studies could be interpreted to indicate a higher prevalence of LQTS in athletes than other disorders, such as HCM, commonly implicated in exercise-related SCD in athletes (Corrado *et al.* 1998). If consideration is given to the fact that up to 40% of individuals with LQTS will not be identified on a single ECG, the prevalence of LQTS could be even higher (Napolitano *et al.* 2005).

However, the current data on SCD in young athletes (<35 years) indicate that deaths in the absence of a structural cardiac abnormality are implicated in no more than 2–

4% of cases (Maron *et al.* 1996; Corrado *et al.* 2001; Behr *et al.* 2003; Maron 2003; Basavarajaiah *et al.* 2007). In relation to the relatively high prevalence of a prolonged QTc interval on the 12-lead ECG in athletes, the low death rates suggest either that the vast majority of causal mutations may be relatively benign or that most athletes with an isolated long QT interval do not actually have LQTS.

#### **4.3.6 Significance of an isolated long QT interval in an athlete**

The significance of an isolated prolonged QTc interval in an athlete has never been studied previously. Although the Italian pre-participation programme identified a long QTc in 0.69% athletes, there is no data relating to subsequent investigations to confirm or refute the diagnosis of congenital LQTS in these athletes (Corrado *et al.* 2006). An isolated long QT interval in an athlete may represent the effect of delayed repolarisation as a result of increased left ventricular mass (Tanriverdi *et al.* 2005) or the fact that the Bazett's formula may not hold true in individuals with very slow heart rates (Funck-Brentano and Jaillon 1993; Malik *et al.* 2002). Conversely, it may be the only phenotypic manifestation of a potentially fatal ion channel disorder in whom abstinence from sport of a moderate- to high-intensity nature may be compulsory to minimise the risk of SCD.

Study 4 aimed at eliminating the effects of physical training (increased LV mass and slow heart rates) by re-evaluating all athletes with a prolonged QTc interval following a 6-week period of detraining based on the previous studies in athletes demonstrating regression of LV mass (Maron *et al.* 1993) and our own experience (Basavarajaiah *et al.* 2006). Study 4 evaluated potentially affected asymptomatic athletes (n = 7) for the broader phenotypic features of the disorder and evidence of familial disease. All

athletes had QTc intervals that would be considered to be representative of a diagnosis of LQTS with intermediate probability according to the Schwartz score (Schwartz *et al.* 1993). Detailed evaluations proved useful in the identification of additional phenotypic features of LQTS or evidence of familial disease and provided diagnostic clarification in three out of seven (43%) athletes.

Interestingly, all three athletes with a baseline QTc value of >500 ms either exhibited paradoxical prolongation of the QT during exercise, an additional phenotypic manifestation of LQT1 and 2 (Swan *et al.* 1999) or had a first-degree relative with a prolonged QTc interval. Two of the athletes scored four points on the Schwartz LQT diagnosis scoring system indicating a high probability of LQTS (Schwartz *et al.* 1993) and one had evidence of a disease causing mutation. These observations suggest that the demonstration of a QTc value of >500 ms in an athlete is indicative of unequivocal LQTS and warrants disqualification from most sports to minimise the risk of exercise related SCD. In such cases, subsequent genetic testing may be useful in confirming the genotype and facilitating cascade screening if applicable.

#### **4.3.7. The grey zone**

In contrast, none of the athletes with a QTc value of <500 ms (460, 474, 490, and 492 ms) had any features of congenital LQTS on exercise testing and Holter monitoring or any family members with a prolonged QTc interval. Similarly, none scored >4 points on the Schwartz scoring system to indicate a high probability of underlying LQTS (Schwartz *et al.* 1993). Indeed, risk stratification in probands with LQTS suggests that males with QTc value of <500 ms generally represent a low-risk group (Priori *et al.* 2003). However, according to the 36th Bethesda guidelines, the three athletes with a

QTc value of  $\geq 470$  ms would have been restricted from participating in their sporting disciplines (Zipes *et al.* 2005). A clinical decision was made to allow these athletes to continue to participate in competitive sport and all four athletes remain well after a mean follow-up of almost 3 years. Study 4 indicates that the significance of an isolated prolonged QTc interval of  $< 500$  ms in athletes remains unknown but represents a low probability of LQTS or a benign group in whom close monitoring rather than disqualification may be more appropriate in the absence a genetic diagnosis.

#### **4.3.8. Limitations**

Study 4 was unable to comment on the usefulness of genetic testing in the assessment of athletes with a long QT interval and could not utilise genotyping for risk stratification purposes, since two of the seven athletes declined the test and only one tested positive for the disorder. Nevertheless, the results of this study provide convincing evidence that a QTc value of  $\geq 500$  ms is diagnostic of LQTS in elite athletes; subsequent genotyping may influence decision making relating to on-going participation in sport.

#### **4.4. Diagnostic Difficulties facing Preparticipation Screening Programmes**

The inclusion of non-invasive diagnostic tests will undoubtedly aid in the process of identifying young athletes with inherited and/or congenital cardiac defects (Maron *et al.* 1996). Two-dimensional echocardiography is generally considered the modality of choice for clinical recognition of HCM, demonstrating otherwise unexplained LV wall thickening (Wigle *et al.* 1985). However, debate continues to divide the medical community over the follow-up implementation of diagnostic cardiac examination

when athletes with a personal and family history and/or a 12-Lead ECG are positive for a condition that may cause SCD.

The differentiation of physiological LVH from HCM can prove challenging for even the most experienced cardiologists. Cardiovascular adaptation to intense physical training itself can cause significant LVH that may mimic HCM, both structurally and electrically (Pelliccia *et al.* 1991; Maron *et al.* 1995). A common and challenging scenario involves the differentiation of physiological LVH (so called “athlete’s heart”) from HCM. Study five presents a case report of a 17 year old elite male swimmer who was referred following an abnormal 12-Lead electrocardiogram (ECG) picked up during cardiovascular screening by the present author.

#### **4.4.1. STUDY FIVE (Appendix 5)**

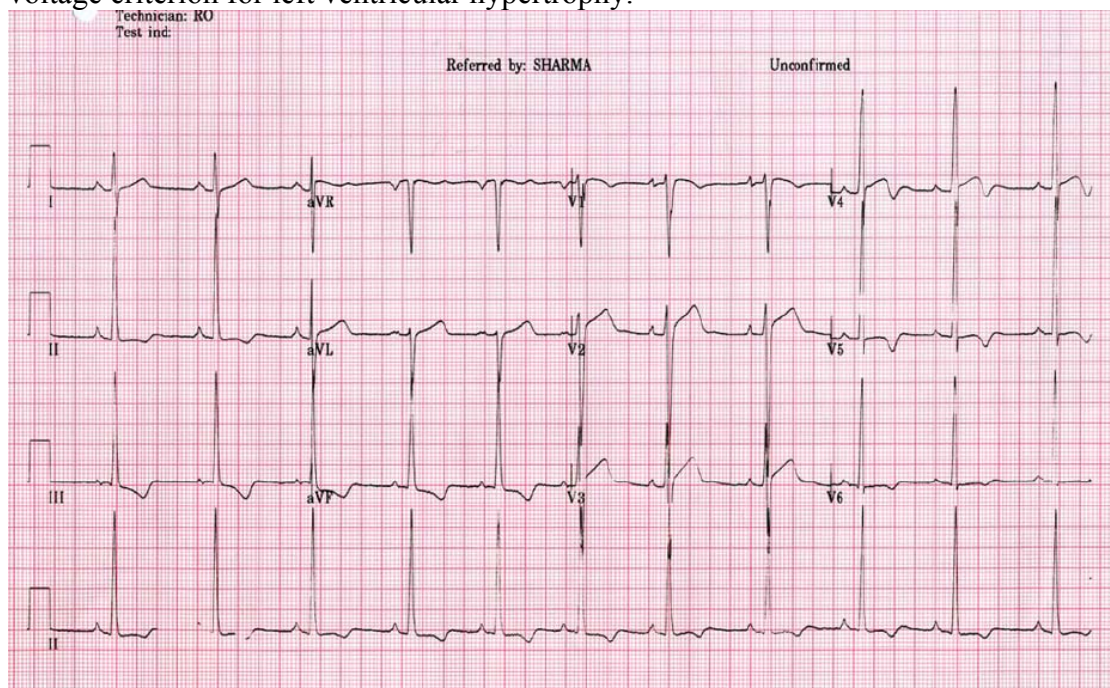
Basavarajaiah, S., **Wilson, M.G.**, Junagde, S., Jackson, G., Whyte, G.P. and Sharma, S. Physiological left ventricular hypertrophy or hypertrophic cardiomyopathy in an elite adolescent athlete: role of detraining in resolving the clinical dilemma. *Br J Sports Med* 2006; 40:727–729.

#### **4.4.2. Case Report**

The athlete trained for about 14 hours and swam 16 miles a week. He was asymptomatic. There was no history of illicit drug abuse or a family history of premature sudden cardiac death. Blood pressure measured 110/70 mmHg, and cardiovascular examination was normal.

The 12-Lead ECG showed voltage criteria for left ventricular hypertrophy and deep T wave inversions ( $>0.2$  mV) in the inferior and lateral leads (Figure 9). A two dimensional echocardiogram revealed significant concentric LVH with a maximal left ventricular wall thickness of 14 mm. The left ventricular cavity size was normal measuring 48 mm in end diastole. Indices of systolic and diastolic functions were normal (E wave 0.9 m/s; A wave 0.36 m/s; E/A 2.63; E deceleration time 226 milliseconds). The valves and right ventricle appeared normal.

Figure 9: A 12-Lead ECG from a 17 year old swimmer showing sinus rhythm with deep T wave inversion ( $>0.2$  mV) in inferior and lateral leads and isolated Sokolow voltage criterion for left ventricular hypertrophy.

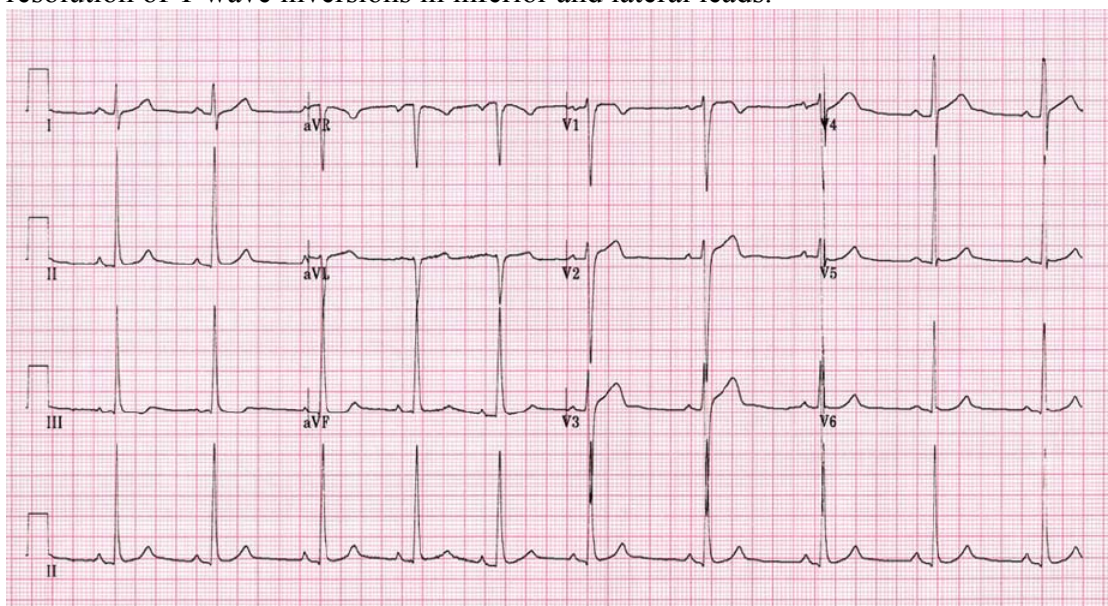


The differential diagnosis was between HCM and athlete's heart. The distinction between the two entities is crucial as a false diagnosis of HCM in an athlete calls for disqualification from competitive sport, conversely a false diagnosis of athlete's heart could jeopardise a young life. CMR imaging excluded apical HCM. A 12-Lead ECG and echocardiography performed on both parents and two siblings were normal. Although this excluded familial HCM, it did not rule out the possibility of a sporadic

disease causing mutation. During a cardiopulmonary exercise stress test, the athlete achieved a peak oxygen consumption of  $68 \text{ ml.kg}^{-1}.\text{min}^{-1}$  (141% of predicted). The blood pressure response to exercise was normal with the systolic blood pressure rising from 110 mmHg at rest to 180 mmHg at peak exercise. A 48 hour Holter monitor failed to reveal any pathological ventricular arrhythmias.

The athlete was persuaded to detrain for eight weeks, and three cardiovascular evaluations were performed in the interim, during which two consecutive ECG's revealed a gradual but complete resolution of the T wave inversions (Figure 10). A subsequent echocardiogram showed regression of LVH from 14 mm to 11 mm. The normalisation of the ECG and echocardiographic abnormalities after detraining confirmed that the changes observed in our athlete reflected extreme physiological adaptation to exercise, rather than HCM. The patient has resumed training and continues to compete at regional level.

Figure 10: A 12-Lead ECG from the same athlete after detraining showing complete resolution of T wave inversions in inferior and lateral leads.



#### 4.4.3. Discussion

The distinction between physiological LVH from HCM is crucial, especially when one considers that HCM accounts for approximately one third of all exercise related sudden cardiac death in young athletes. The athlete presented in Study five had some ECG and echocardiographic features suggestive of HCM based on two large studies performed in adolescent athletes. An ECG study of 1000 highly trained adolescent athletes suggested that deep T wave inversions ( $>0.2$  mV), in any lead and even minor T wave inversions in the lateral leads are generally absent in adolescent athletes (Sharma *et al.* 1999). An echocardiographic study of 720 athletes showed that LVH was present in 4% of adolescent athletes. However, in terms of absolute values, a wall thickness  $>12$  mm was rare and present in just two ( $<0.5\%$ ) athletes. Furthermore, adolescent athletes with a LVH also had an enlarged left ventricular cavity size, with measurements of 52–60 mm (Sharma *et al.* 2002), whereas our athlete had a non-dilated left ventricular cavity.

However, unlike patients with HCM, this athlete had normal indices of diastolic function and a high peak oxygen consumption, indicating that the LVH may be physiological. Patients with HCM have low peak oxygen consumption irrespective of symptoms (Sharma *et al.* 2000). The mechanisms include impaired myocardial relaxation and failure to augment stroke volume effectively during exercise. On the other hand, elite athletes have efficient left ventricular filling and can augment stroke volume even at rapid heart rates. In general, a peak oxygen consumption of  $>50$  ml.kg<sup>-1</sup>.min<sup>-1</sup> or  $>120\%$  of that predicted for age and size favours physiological LVH (Sharma *et al.* 2000).

In summary, the athlete in Study five had some objective evidence to suggest the diagnosis of HCM and others to indicate athlete's heart. Given the persistence of diagnostic uncertainty and the potential implications of a false diagnosis, he was persuaded to detrain for a period of eight weeks, which resolved the dilemma.

Detraining is a definitive method of differentiating physiological LVH from HCM. It is well recognised that physiological LVH in athletes regresses after a short period of detraining (Ehsani *et al.* 1978; Maron *et al.* 1993). Unfortunately, most athletes who are striving to achieve honours in competitive sport are not willing to detrain, as it compromises fitness and may prove costly for team selection. Study five shows the importance of implementing detraining to resolve diagnostic uncertainty in adolescent athletes with ECG and echocardiographic features suggestive of HCM. In the absence of routine availability of genetic testing for HCM, detraining enables a correct diagnosis and prevents subjective diagnostic errors with potentially serious consequences.

#### **4.5. Ethnicity and cardiac adaptation to regular intensive exercise**

Almost all studies of athlete's heart have been performed on Caucasian individuals (including Studies two, three and four within this thesis), hence there is limited data on the cardiac response to exercise in relation to ethnicity. There is evidence suggesting that there are racial differences in the response of the heart to certain pathological conditions such as hypertension (Arnett *et al.* 1994). For example, it is well recognised that Afro-Caribbean patients with systemic hypertension demonstrate a more significant increase in LV mass than Caucasian individuals (Dunn *et al.* 1983). Thus, increases in preload and/or afterload or the increases in systolic blood pressure

during prolonged exercise in Afro- Caribbean individuals may give rise to more marked morphological changes as part of the normal physiological adaptation process.

Early investigations by Lewis *et al.* (1989) evaluating 265 collegiate black athletes as part of a cardiac screening programme, reported that 13% of competitive black athletes had a LVWT of > 12 mm and 1.1 % (three athletes) had a LVWT of 16–18 mm. All of these individuals were normotensive and all denied drug abuse, but formal drug testing was not performed. Therefore, 13 % of athletes had a LVWT exceeding the upper limits for the general population and 1.1 % had findings, which could be consistent with HCM. The exact stimulus to the exaggerated LVH observed in Afro-Caribbean athletes remains unknown; however, an increased blood pressure response to exercise has been demonstrated in black athletes in one study (Ekelund *et al.* 1990), which provides one possible mechanism for the differences in LVWT measurements between black and white athletes.

As the majority of recognised data on the upper limits of LV wall thickness are derived in Caucasian (white) athletes, it is uncertain whether extrapolation of conclusions relating to LV wall thickness measurements derived from white athletes can be applied accurately to confirm or refute the presence of HCM in black athletes.

Sudden death from HCM in the U.S. is more common in black athletes compared with white athletes (Maron *et al.* 2003), underscoring the need for developing upper limits for LVH in black athletes to facilitate accurate differentiation between physiologic LVH and HCM. The scarcity of data on cardiovascular adaptation in black athletes

has the potential of generating false-positive diagnoses of HCM and unnecessary disqualification from competitive sport (Basavarajaiah *et al.* 2008). Study Six aimed to evaluate ethnic differences in cardiovascular adaptation to intensive exercise between black and white athletes.

#### **4.5.1. STUDY SIX (Appendix 6)**

Basavarajaiah, S., Boraita, A., Whyte, G., **Wilson, M.**, Carby, L., Shah, A. and Sharma, S. Ethnic differences in left ventricular remodeling in highly-trained athletes relevance to differentiating physiologic left ventricular hypertrophy from hypertrophic cardiomyopathy. *J Am Coll Cardiol.* 2008. 51(23):2256-62.

#### **4.5.2. Methods – Black Athletes and Controls**

The term “black” was used to denote individuals of African or Afro-Caribbean descent (Dunn *et al.* 1983; Bhopal 2004). The ethnicity assigned to each black athlete and control relied purely on information provided on health questionnaires.

#### **Black Athletes**

Between 2003 and August 2007, 300 asymptomatic elite black male athletes underwent 12-lead electrocardiogram (ECG) and 2-dimensional echocardiography during the peak competitive season. Athletes had a mean age of  $20.5 \pm 5.8$  years (range 14 to 35 years) and a mean body surface area (BSA) of  $1.94 \pm 0.16$  m<sup>2</sup> (range 1.3 to 2.29 m<sup>2</sup>). Athletes were Afro-Caribbean (42%), West African (40%), or East African (18%) in origin. Athletes of East African origin had a lower BSA compared with other black athletes ( $1.89 \pm 0.15$  m<sup>2</sup> vs.  $1.97 \pm 0.16$  m<sup>2</sup>;  $p < 0.001$ ). Athletes trained for an average of  $14 \pm 7$  h (range 10 to 46 h) per week, and all had competed

at the national level in the 4-year period. The athletes participated in 6 different sporting disciplines [football, n = 90 (30%); boxing, n = 60 (20%); basketball, n = 55 (18%); track sprinting, n = 21 (7%); long-distance running, n = 39 (13%); rugby, n = 29 (10%); and tennis, n = 6 (2%)]. Written consent for evaluation was obtained from individuals >16 years and from a parent/guardian for those <16 years of age.

### **Control participants**

Control participants comprised of 150 black and 150 white sedentary males and 300 white male elite athletes of similar age and BSA. Sedentary control participants were recruited from large secondary schools. Elite white athletes were recruited from the same sporting disciplines/clubs that provided black athletes for the study and therefore endured similar training programs.

### **Exercise stress testing and 48 hr ECG monitoring**

Athletes with LVH underwent upright exercise stress testing and 48-h Holter monitoring to check for the broader phenotype of HCM. An upright stress test was performed using the standard Bruce Protocol (Bruce 1971). The ECG and blood pressure (BP) were recorded at 1-min intervals. Athletes were exercised to volitional exhaustion and assessed specifically for the development of ischemic changes, abnormal or flat BP response (Frenneaux *et al.* 1990), and tachyarrhythmias. The 48hr ambulatory ECG monitoring was performed to check specifically for supraventricular and/or ventricular tachyarrhythmias. Athletes were encouraged to continue usual day-to-day life activities, including exercise, during the investigation.

### **4.5.3. Results**

#### **Sedentary control participants**

Black and white control participants were of similar age ( $19.4 \pm 6.4$  years vs.  $20.5 \pm 5.8$  years) and BSA ( $1.89 \pm 0.5 \text{ m}^2$  vs.  $1.82 \pm 0.2 \text{ m}^2$ ). There were no differences in LV wall thickness or LV cavity between black and white sedentary control participants ( $9.0 \pm 1.2$  mm vs.  $8.8 \pm 1.3$  mm and  $49 \pm 5.2$  mm vs.  $48 \pm 4.0$  mm, respectively). None of the control subjects exhibited a LV wall thickness  $>12$  mm or LV cavity size  $>55$  mm.

#### **Cardiac dimensions in black athletes versus black control participants and white athletes**

Black athletes and white athletes exhibited a greater LV wall thickness, cavity size, and left atrial diameter compared with black control subjects. Both black athletes and white athletes displayed enhanced diastolic LV filling ( $E'$  and  $E/E'$ ) compared with black control subjects on TDI (Table 15). Black athletes demonstrated a greater magnitude of LV wall thickness and LV mass compared with white athletes, amounting to a 12% and 13% difference, respectively (Table 16). There were no differences in the LV cavity size, left atrial diameter, baseline LV function, and BP between black athletes and white athletes.

#### **Black athletes with LVH**

In absolute terms, 54 black athletes (18%) had LV wall thickness  $>12$  mm (LVH) compared with 12 white athletes (4%) ( $p < 0.001$ ). The maximal LV wall thickness

measured in any black athlete was 16 mm, compared with 14 mm in any white athlete. Nine black athletes (3%) exhibited substantial LV wall thickness  $\geq 15$  mm.

Table 16: Comparison between black athletes, white athletes, and black control participants.

	<b>Black Athletes (n = 300)</b>	<b>White Athletes (n = 300)</b>	<b>Black Control Participants (n = 150)</b>	<b>p value</b>
Age (yrs)	20.5 $\pm$ 5.8 (14–35)	20.2 $\pm$ 4.9 (14–35)	19.4 $\pm$ 6.4 (14–35)	NS
BSA (m <sup>2</sup> )	1.93 $\pm$ 0.2	1.89 $\pm$ 0.3	1.87 $\pm$ 0.5	NS
LVWTd (mm)	11.3 $\pm$ 1.6* (8–16)	10.0 $\pm$ 1.5 (7–14)	9.0 $\pm$ 1.2 (6–12)	<0.001
LVIDd (mm)	53 $\pm$ 4.4† (44–64)	53.6 $\pm$ 4.1 (42–66)	49 $\pm$ 5.2 (28–55)	<0.001
LA diam (mm)	36 $\pm$ 4† (20–48)	36 $\pm$ 4 (24–47)	31 $\pm$ 4 (23–41)	<0.001
LVM (g)	286 $\pm$ 78* (113–618)	250 $\pm$ 62 (113–489)	225 $\pm$ 60 (110–360)	<0.001
E' (m/s)	0.22 $\pm$ 0.2† (0.16–0.29)	0.23 $\pm$ 0.1 (0.17–0.29)	0.16 $\pm$ 0.01 (0.13–0.19)	<0.001
A' (m/s)	0.05 $\pm$ 0.01† (0.03–0.08)	0.05 $\pm$ 0.01 (0.01–0.09)	0.07 $\pm$ 0.01 (0.04–0.09)	<0.001
E'/A'	2 $\pm$ 0.4† (1.7–4.6)	2 $\pm$ 0.5 (1.6–4.7)	1.6 $\pm$ 0.23 (1.1–2.4)	<0.001
E/E'	4.6 $\pm$ 1.3† (3.2–7.5)	4.5 $\pm$ 1.4 (3.4–7.2)	5.1 $\pm$ 1.2 (4.1–9.7)	<0.001

A', late annular diastolic peak velocity; ANOVA, analysis of variance; BSA, body surface area; E', early diastolic annular peak velocity; LA diam., left atrial diameter; LVIDd, maximal left ventricular cavity dimension in end-diastole; LVM, left ventricular mass; LVWTd, maximal left ventricular wall thickness in end-diastole. Data expressed as mean  $\pm$  standard deviation (range). \*More significant compared with black control participants and white athletes. †More significant compared with black control participants but not with white athletes.

### Demographics

Black athletes with LVH had a larger BSA compared with black athletes without LVH (2.0  $\pm$  0.2 m<sup>2</sup> vs. 1.92  $\pm$  0.2 m<sup>2</sup>; p<0.01). There were no differences between the 2 groups in relation to age or intensity of training, but all black athletes with LVH were age >16 years. In terms of ancestral origin of black athletes, 50 (20%) of the 246

athletes of West African ancestry (including Caribbean individuals) exhibited LVH versus 4 (7%) of 54 athletes of East African origin ( $p < 0.01$ ).

LVH was predominantly seen in black athletes participating in boxing, basketball, soccer, and sprinting, most of whom were of West African ancestry. In contrast, relatively few white athletes of similar age and BSA, participating in the same sporting disciplines, exhibited LVH. Black athletes participating in sprinting, boxing, and basketball exhibited a significantly greater magnitude of LVH compared with black athletes in other sporting disciplines ( $p < 0.01$ ). None of the long distance black runners, who were all East African, exhibited LVH.

### **Cardiac structure and function**

The pattern of LVH in black and white athletes was homogeneous, with no athlete showing  $> 2$  mm difference in LV wall thickness measurements between contiguous segments. All athletes with LVH also exhibited an enlarged LV cavity size ranging between 55 and 66 mm and normal indexes of diastolic function on transmitral Doppler and TDI, and none displayed systolic anterior motion of the mitral valve and associated LV outflow obstruction.

### **ECG in black athletes with LVH**

Black athletes with LVH exhibited a higher prevalence of voltage criteria for LVH compared with white athletes with LVH (37 [68%] vs. 5 [40%];  $p < 0.001$ ). Black athletes with LVH also displayed a higher prevalence of repolarisation changes, specifically ST-segment elevation (46 [85%] vs. 7 [62%];  $p < 0.001$ ) and deep T-wave inversions (7 [12%] vs. none [0%];  $p < 0.0001$ ) compared with white athletes with

LVH. Deep T-wave inversions ( $>0.2$  mV) in black athletes were confined to leads V1 to V4 and present in 4 of the 9 athletes with substantial LVH  $\geq 15$  mm. Deep T-wave inversions were not an ECG manifestation in white athletes with LVH. None of the athletes exhibited deep T-wave inversions in the inferior or lateral leads, baseline ST-segment depression, left atrial enlargement, pathologic Q waves, left bundle branch block, or leftward axis.

#### **Exercise stress testing and 48hr ECG monitoring**

Athletes with LVH underwent exercise stress testing and achieved  $>85\%$  of the predicted target heart rate and adequate BP responses. None of the athletes exhibited ST-segment depression or arrhythmias during the exercise protocol. There were no differences in the mean peak systolic BP between black athletes and white athletes ( $189 \pm 18.4$  mm Hg vs.  $183 \pm 15.8$  mm Hg). None of the athletes with LVH showed episodes of non-sustained ventricular tachycardia or supraventricular tachyarrhythmias over a 24hr period.

#### **4.5.4. Discussion**

Study six revealed that almost one-fifth of black athletes exhibited LVH compared with just 4% of white athletes. Furthermore, a significant minority (3%) of black athletes (but none of the white athletes) had substantial LVH ( $\geq 15$  mm), which could have been consistent with morphologically mild HCM. These results are striking compared with the Italian Olympian athletes, in which only 0.08% of 738 men exhibited LVH  $\geq 15$  mm (Pelliccia *et al.* 1991), indicating a racial predilection to developing LVH in response to the increased pre- and after-load associated with intensive exercise. 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. In the present study, basal and exercise related BP responses in both groups of athletes did not differ and could not explain the increased magnitude of LVH in black athletes.

With the exception of sprinting, where black athletes dominate, Study six investigated sporting disciplines in which both black and white athletes participate in large numbers and excel equally, revealing that more black athletes than white athletes exhibited LVH in almost every sporting discipline examined. Disciplines such as cycling and rowing, which are associated with substantial LVH in white athletes, were not examined, because the lack of participation and, more importantly, failure to attain athletic excellence by black athletes in these disciplines would not enable direct comparisons.

#### **4.5.5. Differentiating physiologic LVH from HCM in black athletes**

The differentiation between physiologic LVH and HCM is crucial, because diagnostic errors have potentially grave consequences. In this regard, conclusions derived from LV wall thickness measurements in white athletes (Pelliccia *et al.* 1991; Maron *et al.* 1995; Sharma *et al.* 2002) may have resulted in a diagnosis of HCM and disqualification from competitive sport in 9 black athletes (3%) with LVH  $\geq 15$  mm. However, none of the 9 athletes exhibited other morphologic features suggestive of HCM. Specifically, none exhibited a non-dilated LV cavity (Maron *et al.* 1995), enlarged left atrium  $>50$  mm (Pelliccia *et al.* 2005), LV obstruction (Lewis *et al.* 1992), or evidence of impaired myocardial relaxation (Lewis *et al.* 1992; Cardim *et al.* 2003).

Indeed, all of the black athletes with LVH, including the 9 athletes with substantial LVH, exhibited a large LV cavity (>55 mm) compared with individuals with HCM. LV cavity size in HCM is <50 mm, even in affected individuals participating in regular sport against medical advice (Sharma *et al.* 2000). An LV cavity >55 mm in HCM is due to progressive myocardial fibrosis and is associated with myocardial thinning, systolic dysfunction (Harris *et al.* 2006).

All black athletes with LVH also exhibited enhanced LV filling and normal left atrial pressures ( $E/E' < 7$ ) on TDI, supporting physiologic adaptation rather than HCM. In contrast, TDI studies in HCM have convincingly identified LV filling abnormalities in gene-positive HCM individuals, even before the development of LVH (Nagueh *et al.* 2003).

Upright exercise testing and ambulatory ECG in athletes with LVH failed to identify abnormalities in BP responses to exercise (Barley *et al.* 1996) or nonsustained ventricular tachycardia (Monserrat *et al.* 2003), which constitute the broad spectrum of the HCM phenotype in a substantial number of affected individuals (Elliott *et al.* 2000).

#### **4.5.6. ECG in black athletes with LVH**

In contrast to white athletes, 7 black athletes (12%) with LVH, including 4 with LVH  $\geq 15$  mm, displayed deep T-wave inversions in leads V1 to V4, a recognized ECG manifestation in HCM and arrhythmogenic right ventricular cardiomyopathy (ARVC). In keeping with the recommendations of the 36th Bethesda guidelines

(Maron *et al.* 2005) and the European Society of Sports Cardiology (Pelliccia *et al.* 2005), we were compelled to investigate all 7 black athletes with cardiac magnetic resonance imaging (outside of the scope of the study) and failed to identify apical HCM, marked hypertrophy of the anterolateral wall (Rickers *et al.* 2005), myocardial fibrosis, or characteristic right ventricular morphology associated ARVC in any athlete (Sen-Chowdhry *et al.* 2004). In the absence of obvious pathology, we suspect these electrical anomalies (deep T-wave inversions in leads V1 to V4) in black athletes probably represent a normal spectrum of ECG changes in response to physical training (Balady *et al.* 1984), but we concede that long-term longitudinal studies are required to assess the precise significance of such repolarisation changes in all athletes.

#### **4.5.7. Diagnostic algorithm for differentiating physiologic LVH from HCM in black athletes with substantial LVH**

Study six provides foundations for developing a pragmatic clinical algorithm for differentiating physiologic LVH from HCM in black male athlete's age  $\geq 16$  years using readily available and independently interpretable cardiac investigations. As previously shown in white athletes (Maron *et al.* 1995), black athletes with physiologic LVH exhibit enlarged LV cavity  $>55$  mm, a left atrial diameter  $\geq 50$  mm, and normal indexes of diastolic function on pulse Doppler and TDI in contrast to most individuals with HCM. Only black athletes age  $\geq 16$  years exhibited LVH (Maron *et al.* 1995); therefore, age is also pertinent when differentiating physiologic adaptation from HCM.

Although genetic testing is the most specific method of diagnosing HCM, the diverse genetic heterogeneity of HCM and incomplete knowledge of all causal mutations do not currently allow a timely genetic diagnosis (>6 months) in athletes striving for honours or competing for team selection. Unfortunately, failure to identify an abnormality after screening for known mutations for HCM cannot currently be regarded as exclusion of disease.

Based on standard objective assessment we could not assign an LVH  $\geq 15$  mm in black athletes to be representative of inheritance of HCM-causing gene mutations in any athlete. Figures relating to the actual prevalence of HCM in the general population are also relevant in this regard, because the prevalence is only 0.2% (Maron *et al.* 1995) and certainly less in the athletic population (Basavarajaiah *et al.* 2008); therefore, it is improbable on statistical grounds that 3% of all black athletes in the present study had HCM.

The substantial LVH identified in some athletes could have been attributed to the possible use of performance enhancing drugs (Payne *et al.* 2004), but we were constrained on professional, ethical, and financial grounds from probing into drug abuse. However, all athletes had competed at the national level and were subject to random anti-doping investigations.

#### **4.5.8. Conclusion**

Black athletes constitute a large proportion of athletes participating at the national level in the U.S. and United Kingdom. A substantial minority of black athletes also exhibit LVH  $\geq 15$  mm. Study six proposes that in the absence of cardiac symptoms or

a family history of HCM, an LV wall thickness  $\geq 15$  mm in black athletes may represent physiologic LVH when the LV cavity is enlarged and diastolic indexes are normal. Recommendations based on our observations should permit a more accurate evaluation of black athletes with LVH.

#### **4.6. PART ONE CONCLUSION**

The cardiovascular benefits of regular physical exercise have been well documented, with overwhelming evidence from epidemiological and intervention studies, suggesting that cardiovascular disease is largely a disease associated with physical inactivity. Exercise plays a beneficial role in the prevention and treatment of cardiovascular disease, with epidemiologic studies supporting an inverse and robust relationship between physical activity and mortality risk, even after adjusting for potential confounding factors. Indeed, the beneficial effects of exercise are not just observed within older individuals. Several investigations have reported significant improvements in cardiovascular fitness, fasting insulin tolerance, lean body mass, and systolic blood pressure with physical activity interventions in obese children, importantly, without the need for pharmaceutical treatment.

With scientific support the promotion of physical activity within the community, the death of a young athletic individual is a tragic and highly publicised event. Approximately 80% of non-traumatic sudden deaths in young athletes (under the age of 35) are caused by inherited or congenital structural and functional cardiovascular abnormalities, which provide a substrate for arrhythmias predisposing to SCD. Inherited or congenital cardiac pathologies include; hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), idiopathic

concentric left ventricular hypertrophy, congenital anomalous coronary arteries, wolff-parkinson white syndrome (WPW), Long QT syndrome and marfan's syndrome.

The purpose of preparticipation screening is to identify unsuspected cardiovascular disease and prevent SCD in athletes by appropriate intervention. Whilst the prevalence of inherited or congenital conditions are rare, modern cardiovascular diagnostic technology can identify potential SCD conditions with a high degree of accuracy and reliability, lending support to the establishment of preparticipation screening programmes to ascertain pathology. There is, however, considerable controversy relating to the efficacy, cost-effectiveness and the impact of false positive results of preparticipation screening. Cardiac screening protocols have been broad ranging, from elite Olympic athletes to general population sport screening.

Most studies evaluating athletes have been performed in adults aged between 18 and 35 years, with Whyte *et al.* (2004) documenting that the upper normal limits for LV wall thickness and LVIDd are 11 mm and 60 mm for elite female British athletes, and 15 mm and 65 for elite male British athletes, respectively. Study 1 examined the cardiac structure and function in a large cohort of elite adolescent tennis players (13-19 years), in order to identify the physiological upper limits of cardiac enlargement in junior tennis players, aiding in the differentiation between physiological and pathological cardiac enlargement. Importantly, Study 1 reported that IVSd, LVEDd and LVPWd in tennis players were significantly higher than in controls (8.9 mm vs 8.3 mm  $p<0.001$ , 48.9 mm vs 47.9 mm  $p<0.05$  and 9 mm vs 8.3 mm  $p<0.001$  respectively), however in absolute terms, the difference did not exceed 7%. None of

the tennis players had a wall thickness exceeding 12 mm or a left ventricular cavity size exceeding 60 mm. Study 1 demonstrates that junior elite tennis players exhibit only modest increases in LV wall thickness and cavity size. Absolute values rarely exceed predicted normal upper limits and do not generally resemble those seen in individuals with cardiomyopathy affecting the LV.

Preparticipation screening for diseases that cause SCD is theoretically attractive because it has the ability to identify subjects whose risk for SCD might be reduced by intervention. Study 2 sought to confirm the efficacy of resting 12-Lead ECG ‘alongside’ personal/family history questionnaires and physical examinations as collective tools to identify diseases that have the potential of causing sudden death within a cohort of elite junior athletes (n=1074) and physically active school children (n=1646). Study 2 identified 9 participants with a positive diagnosis of a disease associated with SCD. None of the participants diagnosed with a disease associated with SCD were symptomatic or had a family history of note. Thus, Study 2 clearly demonstrates that personal symptoms and family history questionnaires alone are inadequate in the identification of individuals with diseases associated with SCD, and supports the recommendations of a number of bodies including the International Olympic Committee, European Society of Cardiology, and the Fédération Internationale de Football Association (FIFA). In conclusion, resting 12-Lead ECG is paramount when screening for diseases that have the potential of causing sudden death in the young.

According to epidemiologic studies based on echocardiographic identification of the disease phenotype, HCM has been reported to occur in about 1 in 500 patients in the

general population. Although the prevalence of HCM in the general population is 0.2%, the precise prevalence of HCM in the most highly trained athletes is unknown. This is important as HCM is a leading cause of young sudden death, and accounts for one third of all sudden cardiac deaths in young competitive athletes. Study 3 examined 3,500 asymptomatic elite athletes (75% male) with a mean age of  $20.5 \pm 5.8$  years with 12-lead ECG and 2-dimensional echocardiography. None had a known family history of HCM. Of the 3,500 athletes, 53 (1.5%) had LVH (mean  $13.6 \pm 0.9$ , range 13 to 16), and of these 50 had a dilated LV cavity with normal diastolic function to indicate physiological left ventricular hypertrophy. Three (0.08%) athletes with LVH had a non-dilated LV cavity and associated deep T-wave inversion that could have been consistent with HCM. However, none of the 3 athletes had any other phenotypic features of HCM on further non-invasive testing and none had first-degree relatives with features of HCM. One of the 3 athletes agreed to detrain for 12 weeks, which showed resolution of ECG and echocardiographic changes confirming physiologic LVH. In conclusion, Study 3 documents that the prevalence of HCM in elite athletes is significantly less than in the general population; with the demands of strenuous exercise on the cardiovascular system selecting out most individuals with HCM. Screening all elite athletes with echocardiography, the accepted gold-standard investigation for HCM, has a poor yield, with many thousand athletes needing to be screened to identify a single individual with HCM. In corroboration with Study 2, the ECG is useful in identifying individuals who may have pathological LVH and other congenital electrical disorders that may prove fatal. Based on the British experience of systematic cardiovascular screening of elite athletes, Study 3 proposes that echocardiography in athletes to screen for HCM should be reserved only for athletes with symptoms suggestive of underlying cardiovascular disease, a murmur indicative

of LV outflow obstruction, family history of HCM 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 .

Congenital long-QT syndromes (LQTS) are recognised as a cause of adrenergic-mediated polymorphic ventricular tachycardia and have been implicated in exercise related SCD in young athletes. Since Studies 2 and 3 documented a prevalence of Long QT syndrome in elite UK athletes ( $QTc > 460$  ms), Study 4 set out to examine 2000 elite athletes (mean age, 20.2 years) using 12-lead ECG and 2-D echocardiography in order to identify the prevalence of Long QT syndrome. The QT interval was corrected for heart rate ( $QTc$ ). Three athletes had a  $QTc$  value of  $>500$  ms and all exhibited one of: paradoxical prolongation of  $QTc$  during exercise, a confirmatory genetic mutation, or prolonged  $QTc$  in a first-degree relative. In contrast, none of the athletes with a  $QTc$  value of  $<500$  ms had any other features to indicate LQTS. Study 4 reveals that the prevalence of a prolonged  $QTc$  interval in elite British athletes is 0.4% The study eliminated the effects of physical training by re-evaluating all athletes with a prolonged  $QTc$  interval following a 6-week period of detraining based on the previous studies in athletes demonstrating regression of LV mass (Study 5), demonstrating that a  $QTc$  value of  $>500$  ms in an athlete is indicative of unequivocal LQTS and warrants disqualification from most sports to minimise the risk of exercise related SCD. However, Study 4 also indicates that the significance of an isolated prolonged  $QTc$  interval of  $<500$  ms in athletes remains unknown but represents a low probability of LQTS or a benign group in whom close monitoring rather than disqualification may be more appropriate in the absence a genetic diagnosis.

The distinction between physiological LVH from HCM is crucial, especially when one considers that HCM accounts for approximately one third of all exercise related sudden cardiac death in young athletes. Study 5 presents a case report of a 17 year old elite male swimmer demonstrating voltage criteria for left ventricular hypertrophy and deep T wave inversions ( $>0.2$  mV) in the inferior and lateral leads of a resting 12-Lead ECG suggestive of a cardiomyopathy. Echocardiography revealed significant concentric LVH with a maximal LV wall thickness of 14 mm, with normal systolic and diastolic function. CMR imaging excluded apical HCM. The athlete was persuaded to detrain for eight weeks, and three cardiovascular evaluations were performed in the interim, during which two consecutive ECG's revealed a gradual but complete resolution of the T wave inversions. A subsequent echocardiogram showed regression of LVH from 14 mm to 11 mm. In conclusion, Study 5 is a 'classic' example of sound basic medicine, showing the importance of implementing detraining to resolve diagnostic uncertainty in adolescent athletes with ECG and echocardiographic features suggestive of HCM. In the absence of routine availability of genetic testing for HCM, detraining enables a correct diagnosis and prevents subjective diagnostic errors with potentially serious consequences.

Almost all studies of athlete's heart have been performed on Caucasian individuals hence there is limited data on the cardiac response to exercise in relation to ethnicity. As the majority of recognised data on the upper limits of LV wall thickness are derived in Caucasian (white) athletes, it is uncertain whether extrapolation of conclusions relating to LV wall thickness measurements derived from white athletes can be applied accurately to confirm or refute the presence of HCM in black athletes.

This is important as sudden death from HCM in the U.S. is more common in black athletes compared with white athletes. Study 6 examined 300 nationally ranked UK black male athletes (mean age 20.5 years) with 12-Lead ECG and 2-dimensional echocardiography, in comparison to 150 black and white sedentary individuals and 300 highly-trained white male athletes matched for age, size, and sport. Black athletes exhibited greater LV wall thickness and cavity size compared with sedentary black and white individuals. Black athletes had greater LV wall thickness compared with white athletes. In absolute terms, 54 black athletes (18%) had LV wall thickness  $>12$  mm compared with 12 white athletes (4%), and 3% of black athletes exhibited LV wall thickness  $\geq 15$  mm compared with none of the white athletes. Study 6 also reports on 7 black athletes (12%) with LVH, including 4 with LVH  $\geq 15$  mm, displaying deep T-wave inversions in leads V1 to V4, a recognized ECG manifestation in HCM and ARVC. In the absence of obvious pathology, we suspect these electrical anomalies (deep T-wave inversions in leads V1 to V4) in black athletes probably represent a normal spectrum of ECG changes in response to physical training, but we concede that long-term longitudinal studies are required to assess the precise significance of such repolarisation changes in all athletes. In conclusion, Study 6 demonstrates that a substantial minority of black athlete's exhibit LVH  $\geq 15$  mm; proposing that in the absence of cardiac symptoms or a family history of HCM, an LV wall thickness  $\geq 15$  mm in black athletes may represent physiologic LVH when the LV cavity is enlarged and diastolic indexes are normal.

Recently, increases in awareness of conditions that may cause SCD have led to many more young athletic individuals with a family history of SCD identifying themselves for cardiac screening. It is imperative that only cardiologists with substantial

experience of cardiovascular adaptations to exercise together with specific knowledge to the broad phenotypic manifestations of inherited cardiac diseases which may cause SCD, should perform preparticipation examination, ultimately reducing the likelihood of recording false-positive or false-negative ECG findings. We concede the potential for false negatives when pre-participation screening, even though the 12-Lead ECG is abnormal in over 95% of patients with HCM and in the majority (80%) of patients with ARVC. Although imaging techniques were available such as in Studies 3, 4 and 6, Study 2 was an ECG lead screening protocol. Thus, congenital coronary artery anomalies including a variety of abnormal anatomical variations of the right and left coronaries may be missed in the absence of personal symptoms, such as recurrent atypical chest pain with exercise. However, in favour, we have follow up data over 15 years with no deaths, indicating a robust screening approach for both protocols.

In conclusion, mandating preparticipation cardiovascular screening and potential disqualification from sport are extremely contentious issues and present intrinsic difficulties and limitations related to efficacy and the impact of false positive results with ECG and ECG/echocardiographic driven protocols. The Italian screening programme has been shown to reduce death rates from cardiomyopathies, however, a program to screen several million physically active young individuals raises innumerable challenges in terms of organisation, implementation, and cost efficacy. If Government's are to be expected to provide funding for such programmes and with the continued financial strain placed upon NHS frameworks, Studies 1 to 6 provide sports cardiologists with definitive data regarding the upper limits of LV hypertrophy in adolescent athletes, the prevalence of HCM and Long QT syndrome in elite UK athletes, the ethnic differences in LV remodeling in highly-trained athletes and a

demonstration of a practically robust and financially viable 12-Lead ECG lead screening protocol.

## **CHAPTER FIVE - ACUTE AND CHRONIC IMPACT OF ULTRA-ENDURANCE EXERCISE**

### **5.1. The Veteran Athlete Introduction**

An important distinction in exercise related sudden death is made on the basis of age. Most sudden cardiac deaths (SCD) in young athletes (<35 years of age) are associated with inherited cardiac pathologies with cardiomyopathies presenting as the commonest cause. In contrast, sudden cardiac deaths in older athletes (>35 years) are caused predominately by atherosclerotic coronary artery disease (CAD) (Maron *et al.* 1980). Strenuous endurance activities, such as marathon running, may even lead to an increased risk of acute cardiac events, although the occurrence of coronary events during marathons is rare (Willich *et al.* 1993; Siegel 1997; Tunstall Pedoe 2004; Roberts and Maron 2005).

Over the past few decades, prolonged endurance events, such as marathon running have become more popular. In 2001, nearly 480,000 runners completed a marathon in the United States alone, with a shift toward older participants (Neilan *et al.* 2006). Specifically, runners aged 50 or more years may have a higher prevalence of subclinical cardiac disease, which may precipitate cardiac events (Mohlenkamp *et al.* 2006). The central and peripheral cardiovascular benefits of regular physical exercise have been well documented (Paffenbarger *et al.* 1997). Overwhelming evidence from epidemiological and intervention studies, suggest that cardiovascular disease is largely a disease associated with physical inactivity and that exercise plays a beneficial role in prevention and treatment (Kokkinos 2008; Leung *et al.* 2008; Loomba and Arora 2008; Singer 2008). Much of this work has focused on endurance exercise of moderate intensity, duration and frequency. In contrast, there is a burgeoning debate surrounding the cardiovascular benefits of endurance and ultra-

endurance exercise (Whyte 2008). With a growing population of veteran<sup>2</sup> endurance athletes regularly participating in endurance training and competition there is an emerging requirement to establish the impact of such exercise on the cardiovascular system.

Long term high-intensity endurance exercise is associated with changes in cardiac morphology together with electrocardiographic alterations that are believed to be physiologic in nature (Pluim *et al.* 2000; Pelliccia *et al.* 2002; Whyte *et al.* 2004; Whyte *et al.* 2004; Pelliccia *et al.* 2008). Recent data however has documented an increased prevalence of supraventricular, complex ventricular, and profound bradyarrhythmias in endurance-trained athletes, predominantly occurring in veteran athletes (Jensen-Urstad *et al.* 1998; Ector *et al.* 2007; Whyte *et al.* 2007; Whyte 2008; Mont *et al.* 2009). Furthermore, several forms of idiopathic ventricular arrhythmia have been identified in athletes, which, by definition, originate in hearts without structural abnormalities (Anselme 2003). The clinical significance of these arrhythmias remains to be fully elucidated. In support of the potential pathological changes in the cardiac electrical activity recent studies have reported an incomplete reversal of left ventricular hypertrophy in retired elite athletes suggesting, in part, a pathological remodelling process (Pelliccia *et al.* 2002; Naylor *et al.* 2005; Baldesberger *et al.* 2008). Debate continues as to whether changes in cardiac morphology and function, together with electrocardiographic changes persist in veteran endurance athletes, even after detraining.

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<sup>2</sup> A veteran athlete is defined as any individual greater than 50 years of age competing in endurance events

Studies of the vasculature indicate that ageing is associated with a progressive decline in conduit, resistance and microvascular endothelial function, along with remodelling in larger vessels (Green *et al.* 2004). Endothelial dysfunction is a strong independent prognostic index in patients with established cardiovascular disease and also asymptomatic apparently healthy individuals, so a decline in endothelial health with age may reflect the impact of other risk factors, or alternatively represent a causative link between ageing and cardiovascular risk. The mechanisms associated with endothelial deterioration with age are incompletely understood, but there is some evidence that they may be linked with elevated inflammation or oxidative stress (Green *et al.* 2004). Exercise training appears to ameliorate the detrimental impacts of ageing on the vasculature and is associated with enhanced endothelial function at all levels of the vasculature (Buijs *et al.* 1998; Ainslie *et al.* 2008; Demirkaya *et al.* 2008). The impact of chronic endurance exercise on vascular structure and function is less well understood.

A gradual decline in global cerebral blood flow (CBF) occurs between 20-80 years of age (Fazekas *et al.* 1952; Pantano *et al.* 1984; Grolimund and Seiler 1988; Buijs *et al.* 1998; Krejza *et al.* 1999; Scheel *et al.* 2000; Stoquart-Elsankari *et al.* 2007; Demirkaya *et al.* 2008). The reason for this age-related decline in CBF is not well understood; however a reduced cerebral metabolism both at a cellular and global level due to cerebral atrophy, as well as vascular alterations (e.g. atherosclerosis) have been implicated (Kety 1956; Jernigan *et al.* 2001; Ainslie *et al.* 2008). Regular physical activity is associated with an elevated CBF, thus individuals with a higher cardio respiratory fitness have higher cerebral blood flows than age matched sedentary individuals (Ainslie *et al.* 2008). A higher CBF, as observed in physically

active individuals may be protective against cerebrovascular disease (Hooker *et al.* 2008).

Accordingly, ageing is associated with deleterious changes in both the structure and function of the cardiovascular system. Using sedentary, age and gender matched controls, previous studies have described a positive effect of exercise in slowing the progressive decline with age. Care is warranted in the interpretation of such results given the multiple genetic and lifestyle factors that could affect the health of the ageing cardiovascular system particularly when employing cross-sectional designs. With this in mind, the Study Seven aims to provide a systematic review of the cardiac and vascular structure and function of the veteran athlete and examine whether the aetiology of these exercise induced changes are physiologic or pathologic in nature.<sup>3</sup> Of note, Study Seven will examine the link between mechanisms relevant to the limited evidence reporting an increased prevalence of supraventricular, complex ventricular and profound bradyarrhythmias in endurance-trained veteran athletes. It will conclude with potential areas for future investigations to increase our knowledge of the impact of endurance exercise on the aged cardiovascular system.

### **5.1.1 STUDY SEVEN (Appendix 7)**

**Wilson, M.,** O'Hanlon, R., Basavarajaiah, S., George, K., Green D., Ainslie, P., Sharma, S., Prasad, S., Murrell, C., Nevill, A. and Whyte, G. Cardiovascular Function and the Veteran Athlete. *European Journal of Applied Physiology*. (In Press).

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<sup>3</sup> The values presented in Study Seven are obtained under resting conditions unless specifically stated.

## 5.2 Cardiac Structure and Function in Veteran Endurance Athletes

### 5.2.1 Cardiac Output ( $\dot{Q}$ )

The decrease in peak exercise  $\dot{Q}$  in older individuals is in part due to a decrease in maximal heart rate (HR). Less well-known is the decline in peak exercise stroke volume (SV) in the older individuals (Kohrt *et al.* 1991). Ogawa *et al.* (1992) demonstrated that the decline in  $\dot{V}O_{2\max}$  with age in veteran athletes is related primarily to a lower maximal  $\dot{Q}$ . Although a lower maximal HR accounts for a portion of this effect, a smaller SV is also of importance. It is thought that compromised early LV filling is compensated partially by an increased contribution during late diastole (i.e., a higher A wave and a lower E/A) (Peterson *et al.* 2003).

Nussbacher *et al.* (1999) stated that in addition to a reduction in maximal HR with ageing, there is also an increase in LV afterload and preload. There are 4 main causes for this increase in LV afterload: increased systemic vascular resistance; reduced arterial compliance; increased inertance due to a larger volume of blood requiring acceleration at the onset of ejection associated with aortic dilatation and; increased pulse wave velocity (Lakatta 1993; Fleg *et al.* 1995).

### 5.2.2. Cardiac Systolic and Diastolic Function

Most data would suggest that global resting LV systolic function (normally represented by EF or fractional shortening) is largely unaltered in the “normal” ageing process (Goldspink 2005; Lumens *et al.* 2006). Conversely, it is well known that there is a “normal” age-related decrease in resting LV diastolic function that may reflect altered active relaxation, chamber compliance as well as changes in left atrial function

(Oxenham and Sharpe 2003; Oxenham *et al.* 2003; Hees *et al.* 2004). Whether years of endurance training in the veteran athlete may off-set an age-related decline in resting LV diastolic function has been the subject of some debate. Furthermore, whether such years of high-level training could augment LV diastolic and/or systolic function during exercise, when the LV faces significant hemodynamic loading, is also of interest. Indeed, the assessment of LV diastolic and systolic function in veteran endurance athletes effectively serves two functions: 1) to help determine if any structural changes in the heart have an impact on function and potentially, therefore, health, and; 2) to help determine if cardiac function in the older athlete is important in explaining the ability to attain an age-related supra-normal cardio-respiratory or endurance capacity (often assessed as  $\dot{V} O_{2max}$ ). Whilst  $\dot{V} O_{2max}$  declines with age in a similar manner regardless of activity status, the higher absolute cardio-respiratory capacities in veteran endurance athletes compared to age-matched controls is well documented (Hawkins *et al.* 2001).

A reduction in LV diastolic function commonly occurs in normal ageing, regardless of life-long physical activity (Nottin *et al.* 2004). Impairment of active and passive diastolic properties of the myocardium involves both muscular and interstitial components. Impaired  $Ca^{2+}$  uptake by the sarcoplasmic reticulum of the cardiomyocytes leads to slow and incomplete active ventricular relaxation (Nikitin *et al.* 2005), while expansion of the interstitium and alterations in collagen metabolism adversely affected the passive elastic properties of the myocardium (Villari *et al.* 1997). LV early diastolic filling rate progressively slows after the age of 20 years (Benjamin *et al.* 1992; Schulman *et al.* 1992; Swinne *et al.* 1992), so that by 80 years the rate is reduced, on average, up to 50%. Fibrotic changes within the LV

myocardium or residual myofilament  $\text{Ca}^{2+}$  activation from the preceding systole are presumed mechanisms for a reduced early diastolic LV filling rate. More filling occurs in late diastole, ultimately producing an exaggerated A wave (Lakatta and Levy 2003). This is thought to be due to a general increase in LV stiffness with ageing (Aronow 2001). During vigorous exercise, despite a reduction in the LV early diastolic filling rate (Schulman *et al.* 1992), the LV at end diastole in healthy older persons is not reduced, but rather is greater in older than in younger men. Whether the capacity for further acute dilation of the LV of veteran athletes is compromised is yet to be determined. Bouvier *et al.* (2001) demonstrated significantly better diastolic function (E/A ratio, isovolumetric relaxation time, and deceleration time) in healthy male veteran athletes (>70 years) at rest, compared with age-matched control sedentary participants.

LV EF, the most commonly used clinical measure of LV systolic performance, is usually preserved during healthy ageing (Lakatta and Levy 2003; Nikitin *et al.* 2005). The average value of EF is approximately 65%, and very few healthy, sedentary older individuals examined to exclude clinical and occult coronary disease have an EF <50% (Fleg *et al.* 1995), which is a value indicative of impaired LV systolic function (Vasan and Levy 2000). Nikitin *et al.* (2005) demonstrated global LV systolic function does not deteriorate at rest with normal ageing in healthy adults between  $40 \pm 13$  and  $73 \pm 8$  years of age. During exercise, EF has been shown to be significantly higher in veteran athletes (>70 years) than age-matched control participants (Bouvier *et al.* 2001).

Studies of LV function at rest in veteran endurance athletes have been generally limited to cross-sectional comparisons with age-matched sedentary groups and/or younger healthy subjects. An early non-invasive study of LV function in veteran athletes documented normal systolic function (fractional shortening) in 9 male endurance and 13 male sprint veteran athletes (Child *et al.* 1984). However, the sample sizes were small, of heterogeneous age (mean 54 and 46 years, respectively), no control group was studied and imaging technologies were limited as no Doppler assessment of LV diastolic function was performed. In a later study, Forman *et al.* (1992) employed flow Doppler assessment of early (E) and late (A) diastolic filling of the LV and reported that veteran endurance athletes had E filling velocities similar to younger controls but were significantly greater than older sedentary subjects suggesting some preservation of LV diastolic function due to exercise training into older age. As non-invasive echocardiography techniques have developed further insight has questioned such simple interpretation. Nottin *et al.* (2004) employed both flow Doppler and myocardial tissue Doppler velocity analyses of early and late LV diastolic function. Whilst early flow velocities were increased in older athletes compared to older controls they were still blunted compared to young sedentary controls. Myocardial tissue Doppler velocities, a less load-dependent measure of LV diastolic function (Sohn *et al.*, 2003), were not different in both older groups and significantly depressed compared to young sedentary controls. Nottin *et al.* (2004) concluded that long-term training did not reduce the age-related decline in LV relaxation properties and those factors such as lower HR and higher blood volumes may explain the higher E in veteran athletes. In partial support of Nottin and colleagues, Prasad *et al.* (2007) reported that maintenance of physical fitness with age did not prevent an age-related decrease in the rate of LV relaxation occurring before

the opening of the mitral valve or in the propagation of flow into the LV. In contrast diastolic function, reflecting myocardial relaxation after aortic valve closure and during early mitral inflow was higher in trained versus untrained older individuals. This was ascribed, at least in part, to the more compliant ventricles of fit older individuals (Arbab-Zadeh *et al.* 2004). A more recent study by D'Andrea *et al.* (2007) also assessed RV function and suggested that early RV diastolic function may be enhanced in veteran athletes and that this may be an independent determinant of cardiac performance during physical effort.

The study of Arbab-Zedah *et al.* (2004) was notable because it adopted invasive assessments of LV diastolic and systolic function in a protocol that included assessment during multiple changes in hemodynamic load on the LV. Loading was altered by rapid saline infusion and lower-body negative pressure which altered LV filling pressure and was correlated to simultaneous changes in stroke volume (SV). The increase in LV filling pressure with rapid saline infusion is partially akin to hemodynamic changes on the LV during exercise. In old endurance-trained individuals the filling pressure-SV curve was shifted upwards and to the left, relative to age-matched controls. In short, for the same filling pressure veteran athletes had greater SV and it was concluded that endurance training improved ventricular compliance.

Taken together, these studies suggest that exercise training may be associated with enhanced LV diastolic function that is most obvious when the LV is placed under some load. Veteran endurance athletes have normal intrinsic global LV systolic function. Exercise training into old age may maintain ventricular compliance that,

during exercise, could explain an augmented SV and thus elevated  $\dot{V} O_{2\max}$  compared to age matched sedentary subjects. Data gleaned from cross-sectional analysis of LV function at rest are more conflicting but suffer from self-selection biases and other confounders. For example, resting heart rate is inversely proportional to the E/A ratio (Galderisi *et al.* 1993), as a slower heart rate may reduce the atrial component of LV filling by lengthening the diastole filling period (Johannessen *et al.* 1991). Whether an intrinsic increase in relaxation or LV compliance occurs at rest is, therefore, difficult to interpret from cross-sectional athlete-control comparisons. Longitudinal studies may remove some of these technical issues but of course are highly problematic given a design that requires virtually life-long exercise training. In shorter aerobic training studies (6-12 months) in older individuals, it is interesting to note that EF at rest was unaltered (Ehsani *et al.* 1991; Stratton *et al.* 1994; Spina *et al.* 1996; Jungblut *et al.* 2000). Endurance training may offset some of the biochemical consequences of ageing that increase stiffness and reduce compliance (Lakatta and Yin 1982). Another possible mechanism may reflect a training induced improvement in calcium re-uptake by the sarcoplasmic reticulum that has been reported to decrease with healthy ageing (Capasso *et al.* 1983).

In summary, veteran athletes demonstrate maintenance in LV systolic function and may be able to partially off set the reduction in diastolic filling with regular and intensive endurance exercise. This is most obvious when the LV is placed under some physical load. Whilst some interesting data exist comparing LV function between veteran endurance athletes and age-matched controls further research is required. Studies with larger cohorts including women, e.g. (Hagmar *et al.* 2005) or a resistance-training stimulus, e.g. (Haykowsky *et al.* 2000; Haykowsky *et al.* 2000)

should be combined with newer imaging techniques (e.g. strain analysis) and different cardiac chamber assessment (e.g. RV, left atria). An extension of work with veteran endurance athletes could further our understanding of age and exercise interactions on major artery structure and function (e.g. stiffness, compliance) as well as cardiac autonomic control.

### **5.3. Cardiac Remodelling with Age**

Cross-sectional studies of participants without hypertension or clinically apparent cardiovascular disease indicate that LV wall thickness increases progressively with age in both sexes (Lakatta and Levy 2003). At the sub-cellular level, ageing is associated with changes in excitation–contraction coupling mechanisms and diminished  $\beta$ -adrenergic contractile response (Lakatta 1993). At the cellular level, cardiac ageing is characterised by a significant reduction of cardiomyocyte number with hypertrophy of remaining cells and an increase in interstitial tissue (Olivetti *et al.* 1991). Olivetti *et al.* (1995) reported cardiac myocyte enlargement, together with a decrease in the estimated myocyte number that was greater in males than in females.

### **5.4. Long Term Consequences of Cardiac Remodelling**

Henschen *et al.* (1889) first described the athlete's heart over a century ago using young cross country skiers. Henschen noted that “skiing causes an enlargement of the heart, and that this enlarged heart can perform more work than the normal heart. There is therefore, a physiologic enlargement of the heart, due to athletic activity” (Rost 1997). In the mid-1930's, Kirch (1935; 1936) presented data on 35 athletes who had died suddenly, reporting that cardiac hypertrophy was the result of ‘physical exercise’. Further work by notable Scandinavian scientists, such as Kjellberg *et al*

(1949) and Reindell et al. (1957) on the athlete's heart using radiological techniques developed the understanding between heart size and performance. However, it was the development of echocardiography and computed tomography scanning in the 1970's, which accelerated our understanding of the athlete's heart.

Establishment of upper normal limits of physiological hypertrophy in response to physical training is important in the differentiation of physiological and pathological LV hypertrophy. Whyte *et al.* (2004) examined 306 young, international British male athletes identifying 11 (2.5%, mean age:  $24.4 \pm 5.9$  years) with a wall thickness  $>13$  mm, commensurate with a diagnosis of hypertrophic cardiomyopathy. Furthermore, 18 (5.8%) presented with a LV internal diameter during diastole  $>60$  mm, with an upper limit of 65 mm. This British experience is in line with previous Italian data (Pelliccia *et al.* 1999; Pelliccia *et al.* 2002) promoting concern for individuals with extreme LV remodelling. It is worth noting that the majority of evidence for cardiac remodelling with prolonged and intensive exercise comes from endurance based populations. However, the 11 athletes identified in Whyte *et al.* paper with a wall thickness  $> 13$ mm, competed in a range of sports including judo, skiing, cycling, triathlon, rugby and tennis. Thus, different long-term training methods, such as resistance exercise (either strength and/or explosive power) may have different remodelling effects, both structurally and functionally, and on components such as arterial stiffness (Scharhag *et al.* 2009).

Incomplete reversal of extreme LV cavity dilatation with deconditioning has been documented with longitudinal echocardiographic examinations. Pelliccia *et al.* (2002) reported that substantial chamber enlargement persisted in 20% of retired and

deconditioned former elite athletes after 5 years. Miki *et al.* (1994) echocardiographic examination of 9 veteran cyclists 2-years post retirement demonstrated a significant reduction in LV dimension ( $p < 0.001$ ) but with no change in LV wall thickness or fractional shortening. The authors also noted a significant increase in E:A ratio ( $p < 0.05$ ), postulating that the abnormal increase in E:A ratio observed within retired veteran cyclists, may be induced by life-long high intensity exercise, resulting in LV diastolic dysfunction. Although observed in young athletes (mean 20 years), Naylor *et al.* (2005) documented that following a 6 week detraining period, athletes exhibited a significantly higher LV mass with a significant reduction in diastolic function compared to controls. Noteworthy was the normalization of diastolic function following return to training raising the possibility that diastolic function may be normal in athletes who exhibit LV hypertrophy in the presence of a training stimulus, whereas the absence of an ongoing training stimulus may be associated with decreased diastolic function in subjects who exhibit LV hypertrophy.

Conclusions in this area are difficult to draw however; Pelliccia *et al.* (2010) recently provided new insights into the risk/benefit relationship of long term exercise by reporting the results of a longitudinal cardiovascular evaluation in 114 Olympic endurance athletes (mean age  $22 \pm 4$  years) over a 4-17 year period. Global LV systolic function was unchanged whilst wall motion abnormalities were absent. In addition, LV volumes and LV mass index were unchanged, and LV filling patterns remained within normal limits, although left atrial dimension showed a mild increase. The authors concluded that intensive endurance conditioning over many years in Olympic athletes was not associated with inappropriate LV remodelling or dysfunction or with adverse clinical events, onset of symptoms, or new diagnosis of

cardiomyopathies. Importantly, Bhella and Levine (2010) point out, that 2 of these 114 athletes did have significant ventricular arrhythmias that required medical intervention. Whilst the Pelliccia *et al.* (2010) paper significantly contributes to our understanding of the long-term consequences of cardiac remodeling in trained athletes in the short-term (<17 years), the impact of life-long endurance exercise noted in veteran athlete's (>50 years) remains unclear. The application of modern imaging techniques, such as strain and cardiac magnetic resonance (to be discussed), longitudinally in both young and veteran athletes, may help resolve this debate.

### **5.5. Ultra-Endurance Exercise and Cardiac Structure and Function**

A large body of research has suggested that acute bouts of ultra-endurance exercise result in a depression in indices of global left ventricular (LV) diastolic and systolic function (Middleton *et al.* 2006) and the unrelated appearance of elevations in serum markers of cardiac myocyte damage (Shave *et al.* 2007) often above acute myocardial infarction cut-off levels. Despite such conclusions from recent meta-analyses, this is still a controversial research area (George *et al.* 2008) with many aspects of these phenomenon equivocal, lacking data or poorly understood. Two specific issues underpin the focus of future research. Firstly the assessment of changes in LV systolic and diastolic function after prolonged exercise has, almost uniformly, been completed using echocardiography. The changes observed in measures such as ejection fraction (EF) are often small and the resolving limits of echocardiography have been questioned. Cardiac magnetic resonance (CMR) is the reference standard for the assessment of ventricular dimensions, function and mass in terms of accuracy and reproducibility. Measurements are highly accurate and no geometrical assumptions need to be made about the ventricle (Bellenger *et al.* 2000; Bellenger *et al.* 2000). To

date there are no studies of cardiac function after prolonged exercise that has employed CMR.

The elevation of cardiac troponin I or T (cTnI/cTnT) after prolonged exercise is widely reported (Shave *et al.* 2004; George *et al.* 2005; Neilan *et al.* 2006; Neilan *et al.* 2006; Shave *et al.* 2007; Middleton *et al.* 2008; Shave *et al.* 2008) and in a recent study, 78% of runners investigated following the completion of a competitive marathon presented evidence of minor cardiac damage (Shave *et al.* 2005). Despite this few studies have assessed the relationship between raised cTn and a depression in cardiac function after prolonged exercise. George *et al.* (2004; 2005) reported no correlation between post-marathon race changes in cTnT and depressed Doppler and tissue-Doppler measures of LV diastolic function. Conversely, Rifai *et al.* (1999) reported that triathletes with more abnormal wall segment motion, after completing an Ironman triathlon, had higher levels of cTnT than those athletes with fewer wall motion abnormalities. More recently, Neilan *et al.* (2006) at the Boston Marathon, linked the increase in biomarkers after marathon completion with post-race diastolic dysfunction. This specific issue remains controversial and requires the collection of more data.

Although the presence of cardiac troponins is pathognomonic of cardiac damage, the rapid return of cardiac troponins to baseline (<24 h) has led to the suggestion that this phenomenon is physiological and not pathological in nature. It is likely that acute elevations of cardiac troponins following endurance exercise are physiological owing to the low peak levels recorded and the rapid return to baseline; troponin release may simply be related to cardiac adaptation to exercise where transient myocardial injury

acts as a physiological signal for adaptation leading to enhanced structure and function (Whyte 2008). Animal studies have however demonstrated that endurance exercise can trigger the development of myocardial inflammation and fibrosis and a limited number of post mortem studies have demonstrated both replacement and interstitial fibrosis in the hearts of athletes who have died suddenly (Rowe 1992; Whyte *et al.* 2008). A possible mechanism underlying troponin release with exercise and transient cardiac dysfunction may be related to exercise induced myocardial inflammation. Using specialised imaging protocols, CMR can also image focal and global myocardial inflammation and oedema, owing to the relaxation properties of water, using T2-weighted techniques (Simonetti *et al.* 1996; Laissy *et al.* 2002; Abdel-Aty *et al.* 2005). Imaging after intravenous gadolinium can detect regional hyperemia secondary to inflammation and focal areas of myocardial fibrosis (Miller *et al.* 1989; Friedrich *et al.* 1998; Roditi *et al.* 2000). The utility of CMR to detect myocardial inflammation has been validated in numerous studies and the subject of a recent white paper from the American College of Cardiology (Friedrich *et al.* 2009).

Accordingly, Studies Eight aimed to examine the relationship between cardiac structure and function, using gold standard measurements of systolic function (CMR) and diastolic function (echocardiography), against serum biomarkers of cardiac damage following the completion of a competitive marathon. Secondly, Study Eight assessed the potential relationship between acute bouts of ultra endurance exercise leading to troponin release and the presence of myocardial inflammation and fibrosis using gadolinium enhanced CMR.

### **5.5.1. STUDY EIGHT (Appendix 8).**

**Wilson, M.**, O'Hanlon, R., Prasad, S., Wage, R., Smith, G., Oxborough, D., Dahl, A., Godfrey, R., Alpendurada, F., Wong, J., Shaw, A., Basavarajaiah, S., Sharma, S., Nevill, A., Gaze, D., George, K. and Whyte, G. Biological markers of cardiac damage are not related to measures of cardiac systolic and diastolic function using cardiovascular magnetic resonance (CMR) and echocardiography following an acute bout of prolonged endurance exercise. *British Journal of Sports Medicine*. (In Press).

### **5.5.2. Methods**

**Participants:** Following ethical approval from the Brompton, Harefield and NHLI research ethics committee, 17 recreational athletes provided written informed consent and volunteered to run a marathon (distance 42.2 km). Exclusion criteria included the presence of cardiopulmonary disease, including diagnosis and treatment for hypertension, angina, myocardial infarction and peripheral vascular diseases. Participants were asked not to run more than a total distance of 20miles in the week leading up to the marathon, with no training in the immediate 3 days prior to the marathon. During the marathon, participants were permitted to consume food and fluid *ad libitum*. On the day of the marathon, start times ranged from 0500-0700hrs. Maximum air temperature reached 10°C with *ca.* 40% humidity.

### **Design**

Echocardiographic, cTnI, NTproBNP levels and CMR data were collected at an initial assessment approximately 24 hrs prior to marathon completion. After immediate completion of the marathon, only echocardiographic, cTnI, and NTproBNP were collected. At 6hrs post-marathon, CMR data was collected along with echocardiography, cTnI, and NTproBNP.

### 5.5.3. Results

The participants included 17 men (mean  $\pm$  SD [range]: age  $33.5 \pm 6.5$  years [46-26 yrs], body mass  $80 \pm 9.2$  kg [100-63 kg], height  $1.81 \pm 0.06$  m [1.93-1.70 m]). All 17 runners returned for post-marathon evaluation having successfully completed the study protocol ( $209 \pm 19$  min; range, 171-240 min). The average time of 209 mins for the protocol completion, would have placed the participants in the top 17% (total runners; 23680) from the 2008 London Marathon<sup>©</sup>. Post-marathon testing commenced within 15 min of marathon completion in all participants. Body mass was significantly reduced post-marathon ( $80 \pm 9.2$  vs.  $78.8 \pm 8.6$  kg,  $p < 0.001$ ). Heart rate was significantly increased post-marathon ( $57 \pm 8$  vs.  $80 \pm 12$  beats.min<sup>-1</sup>;  $p < 0.001$ ), and remained significantly elevated 6 hrs post-marathon ( $68 \pm 11$  beats.min<sup>-1</sup>;  $p < 0.001$ ).

### Echocardiography

LVIDd was mildly but significantly reduced post-marathon ( $53.9 \pm 0.9$  vs.  $52.5 \pm 1.2$  mm,  $p < 0.001$ ). The mitral E wave was not reduced post-marathon, whereas A wave increased significantly post-marathon, remaining significantly elevated 6 hrs post-marathon. This resulted in a significant E/A reduction post-marathon ( $1.11 \pm 0.34$  vs.  $1.72 \pm 0.44$ ;  $p < 0.05$ ), that remained depressed 6 hrs post-marathon ( $1.49 \pm 0.43$ ;  $p < 0.05$ ). IVRT was not significantly increased immediately post-marathon, but became significantly reduced 6hrs post-marathon ( $76.2 \pm 4.6$  vs.  $66.1 \pm 4.3$ ;  $p < 0.008$ ). E deceleration time and E/E' were not significantly different immediately post- or 6hrs post-marathon (Table 17). No correlations were observed between BM and LVIDd and measures of diastolic function (E/A, IVRT, E deceleration time, E/E').

Table 17: Data indices for LV diastolic function pre-, post- and 6hr post-marathon. Values are expressed as mean (SD).

	<b>Pre-marathon</b>	<b>Post-marathon</b>	<b>6hr Post-marathon</b>	<b>P value</b>
HR (bpm)	57 ± 8	80 ± 12*	68 ± 11††	P<0.001
BM (kg)	80 ± 9.2	78.8 ± 8.6*	na	P<0.001
LVIDd (mm)	53.9 ± 0.9	52.5 ± 1.2*	53.4 ± 0.9	P<0.001
E (cm/s)	0.75 ± 0.04	0.69 ± 0.02	0.76 ± 0.03†	P<0.05
A (cm/s)	0.46 ± 0.1	0.67 ± 0.18*	0.54 ± 0.11††	P<0.05
E /A	1.72 ± 0.44	1.11 ± 0.34*	1.49 ± 0.43††	P<0.05
IVRT	76.2 ± 4.6	73.5 ± 4.2	66.1 ± 4.3*	P<0.008
E decel	204.4 ± 21	231 ± 95.5	220.2 ± 45.6	NS
E/E'	6.2 ± 0.4	6.6 ± 0.5	6.3 ± 0.3	NS

HR, heart rate, BM, body mass, LVIDd, left ventricular internal diameter during diastole, E, peak early diastolic filling; A, peak late diastolic filling; E/A, ratio of E to A; IVRT, isovolumic relaxation time; E decel, deceleration time of early filling velocity; E/E', the ratio of early diastolic transmitral E wave velocities to tissue Doppler mitral annulus early diastolic E' wave velocities; SV, Stroke volume; EF, ejection fraction.

\*Significantly different from pre-marathon values (p<0.05); † significantly different from post-marathon values (p<0.05); †† significantly different from pre- and post-marathon values (p<0.05).

### **CMR Systolic Function**

The LV end-diastolic and end-systolic volumes were reduced post marathon but the stroke volume was preserved (135.4 ± 20.7 vs. 135.5 ± 21.8 ml, P=1.000) and a corresponding small increase in LV EF 6 hrs post-marathon reached significance (64.4% ± 4.2% vs. 67.4% ± 5%; p<0.05). No significant difference in the RV volumes, RV SV or RV EF was seen post-marathon (Table 18).

Table 18: CMR Indices pre and post marathon.  
Values are expressed as mean (SD).

	Pre-marathon	6hr Post-marathon	P value
LVEDV (ml)	211 ± 34	201 ± 32	P<0.001
LVESV (ml)	75 ± 17	66 ± 16	P<0.001
LVSV (ml)	135 ± 21	135 ± 21	NS
LVEF (%)	64.4 ± 4	67.4 ± 5	P=0.014
RVEDV (ml)	219 ± 40	219 ± (39)	NS
RVESV (ml)	84 ± 22	82 ± 22	NS
RVSV (ml)	135 ± 22	137 ± 24	NS
RVEF (%)	62 ± 5	62.7 ± 6	NS

LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume, LVSV, left ventricular stroke volume; LVEF, left ventricular ejection fraction; RVEDV, right ventricular end diastolic volume; RVESV, right ventricular end systolic volume, RVSV, right ventricular stroke volume; RVEF, right ventricular ejection fraction. \*Significantly different from pre-marathon values (p<0.05).

No runner demonstrated focal or global myocardial oedema on pre and post marathon STIR imaging (Table 19 and Figure 11). Myocardial rGE pre and post contrast ratio was less than 45% in all, and none reached the rGE threshold of myocardium/skeletal muscle ratio of >4.0. Finally, no LGE was seen pre or post marathon.

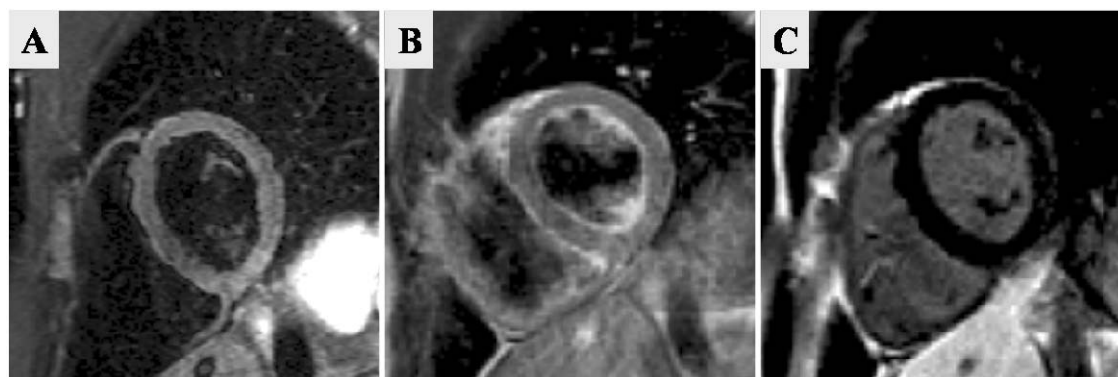


Figure 11: Representative images of CMR acquisitions to detect myocardial oedema/inflammation (STIR) (A), hyperaemia (rGE) (B), and myocardial fibrosis (LGE) (C).

Table 19: Myocardial oedema (STIR), hyperemia assessment (rGE), and fibrosis (LGE) pre and post marathon.

<b>CMR Index</b>	<b>Pre Marathon</b>	<b>Post Marathon</b>
Myocardial to Skeletal STIR Ratio	1.3 ± 0.3	1.4 ± 0.3
Percentage SI Increase in rGE Myocardium	30% ± 8%	31% ± 9.6%
rGE ratio Myocardium/Skeletal Muscle	2.1 ± 0.9	2.4 ± 1.0
LGE	Nil	Nil

### **Cardiac Biomarkers**

There were significant elevations in cTnI and NTproBNP immediately post marathon, which remained significantly elevated 6 hrs post marathon (Table 20). There were no correlations between elevations in cTnI and NTproBNP pre-marathon ( $r=0.186$ ,  $p=0.475$ ), post-marathon ( $r=0.281$ ,  $p=0.274$ ) and 6 hrs post-marathon ( $r=0.148$ ,  $p=0.570$ ). Eight participants were found to have cTnI elevations immediately post marathon above the cut off level for acute myocardial infarction (AMI;  $\geq 0.03$  ng/mL). cTnI was further elevated at 6 hrs post-Marathon in 15 of the 17 runners in this study, whilst NTproBNP remained significantly elevated above baseline values but was falling at 6 hrs post-Marathon.

Table 20: Data for indices of biological markers of cardiac damage pre-, post-, 6hr post-marathon. Values are expressed as mean (SD).

	<b>Pre-marathon</b>	<b>Post-marathon</b>	<b>6hr- Post-marathon</b>	<b>P value</b>
cTnI	0.00	0.04 ± 0.03*	0.07 ± 0.10*	P<0.05
NTproBNP	37.4 ± 24.15	59.34 ± 43.3*	68.07 ± 45.5*	P<0.017

cTnI, cardiac troponin-I; NTproBNP, N terminal pro B type natriuretic peptide  
\*Significantly different from pre-marathon values ( $p<0.05$ ).

### **Relationships between blood markers, LV function and inflammation**

There were no significant correlations between cardiac biomarkers (cTnI and NTproBNP) and measures of diastolic function (E, A, E/A, IVRT, E deceleration time and E/E') post-marathon or 6hr post-marathon. This included immediate post-marathon diastolic function against 6hr post marathon cTnI and NTproBNP results, and immediate post-marathon cTnI and NTproBNP results against 6hr post-marathon diastolic function (E, A, E/A, IVRT, E deceleration time and E/E'). Finally, there were no significant correlations between biomarkers of cardiac damage (cTnI and NTproBNP) and measures of CMR systolic function (SV or EF), myocardial inflammation, hyperemia, or myocardial fibrosis post-marathon or 6 hr post-marathon.

#### **5.5.4. Discussion**

Study eight observed a significant reduction in LV diastolic function (E/A ratio) immediately following a Marathon run that remained depressed 6 hours post-exercise. Data indices of systolic function using gold standard assessment, namely CMR, demonstrated a biologically significant increase in EF 6hrs post-marathon. A concomitant, but unrelated elevation in cardiac biomarkers (cTnI and NTproBNP) was observed immediately post-Marathon that remained elevated or increased further following 6 hours of recovery. Finally, study eight demonstrates that exercise induced cardiac biomarker release is not associated with changes in biventricular systolic function or indeed any detectable myocardial damage (inflammation, oedema, hyperemia, or fibrosis) using current gold standard imaging modalities.

The release of cardiac troponins (cTnT and cTnI) following prolonged exercise has been extensively documented (Shave *et al.* 2005). The high prevalence of cTnI and

NTproBNP in the current cohort is consistent with previous marathon studies (George *et al.* 2005; Neilan *et al.* 2006; Neilan *et al.* 2006). The relationship between cardiac biomarkers, systolic and diastolic function following prolonged exercise has been an area of controversy in the literature. A large number of studies have reported a lack of association between troponin release and diastolic functional changes, suggesting that they are distinctly separate phenomena (Whyte *et al.* 2005). Study eight data concurs with these studies demonstrating no significant relationship between cTnI and NTproBNP and measures of diastolic function (E, A, E/A, IVRT, E deceleration time and E/E') post-marathon or 6hr post-marathon. These data support the hypothesis that alterations in cardiac function and the presence of cardiac biomarkers are unrelated.

The majority of previous papers have examined cardiac biomarkers immediately post-exercise and/or 24 hours post-exercise. Our time course findings of cTnI immediately following a marathon contrasts research by Middleton *et al.* (2008) documenting a significant elevation in cTnI immediately post marathon, that remained significantly elevated 6hrs post-marathon (Table 20). Middleton *et al.* reported that during a marathon, between 60 and 120 min, cTnT increased in all participants. But at race completion, or within 1 hr of marathon completion, cTnT had returned to baseline values in all subjects. All but 1 subject showed a further release of cTnT within the 24 hr recovery period, with 5 of these subjects having an elevated cTnT 24hrs after exercise (Middleton *et al.* 2008). The reasons for the absence of cTnT at Marathon completion in this study are unclear however; it contrasts findings in the majority of previous studies.

In light of the continued rise of cTnI at 6 hours post-Marathon in the present study, in addition to examining concomitant time points for cardiac biomarkers and LV diastolic function we examined the relationship between cTnI measured 6 hours post-exercise with LV diastolic function immediately post-exercise. The rationale for this interrogation was the potential that a delayed release of cardiac troponin may be associated with alterations in LV diastolic function. Study eight suggests no relationship between cTnI and LV diastolic function at these time points therefore offering further support of a separate aetiology for these two phenomena.

The aetiology and clinical significance of post-exercise troponin release is yet to be elucidated. Shave *et al.* suggested that post-exercise release of troponin may represent either necrosis of cardiac myocytes leading to irreversible damage, or may be a transient and reversible change in membrane permeability of the myocyte (Shave *et al.* 2007). The mechanisms for troponin release may come from the unbound pool found in the cardiomyocyte cytoplasm and may reflect a physiologic as opposed to a pathologic process (Dawson *et al.* 2008). Importantly, our data demonstrated no correlation between peak troponin and NTproBNP release against diastolic function immediately post- or 6hrs post-marathon. Furthermore, no single participant was found to meet criteria for myocardial inflammation or fibrosis following the marathon run. It appears unlikely that the minor elevations in biomarkers of cardiac damage observed following prolonged endurance exercise indicate myocardial necrosis of sufficient magnitude to cause LV dysfunction. It is tempting to suggest that elevated cardiac troponins represent reversible cardiomyocyte membrane damage that may reflect part of a remodelling process however; further study is required to elucidate the mechanism(s) (Middleton *et al.* 2008).

Limited evidence for the relationship between cTnI and NTproBNP exists within the literature. Elevated concentrations of NTproBNP reflect elevated myocardial wall stress due to volume or pressure overload, usually observed within cardiac disease states. Our data corroborates that of Scharhag *et al.* (2005) whereby no correlation was observed between cTnI and NTproBNP following an acute bout of prolonged exercise. Differing from our data, Scharhag *et al.* observed a relationship between NTproBNP and exercise time ( $r=0.50$ ,  $p<0.001$ ). The authors postulated that the release of NTproBNP after prolonged exercise may not result from cardiac damage but may have a cytoprotective and growth regulating effect. Membrane damage, subsequent to an increased rate and force of cardiac contraction during endurance exercise, may provide a mechanism by which cytosolic troponin is released into the circulation (Shave *et al.* 2007). However, whilst NTproBNP was significantly elevated post-marathon, indicating increased wall stress, it was not correlated with cTnI, suggesting that another mechanism for troponin release should be considered. Few studies have examined NTproBNP release and diastolic function after prolonged endurance exercise. Neilan *et al.* (2006) document a significant relationship between NTproBNP and diastolic dysfunction following the Boston Marathon.

Interestingly,  $E/E'$  was not significantly different immediately post- or 6 hrs post-marathon (Table 16). Assuming TDI to be less dependent on load, the fact that both  $E$  and  $E'$  stayed the same is surprising as both should increase with an elevated HR. The lack of rise in both could reflect a "real" depression in both due to preload drop (although minor) or an alteration in relaxation and compliance.

To our knowledge, no studies have used the gold standard technique of assessing systolic function, namely CMR, together with standard assessment of diastolic function following a competitive marathon. A significant elevation in CMR EF ( $68.3 \pm 16.7$  vs.  $71.4 \pm 16.4$  %,  $p < 0.05$ ) was observed between pre- and 6hrs post-marathon, together with a preserved SV pre- and 6hrs post-marathon ( $131.9 \pm 26.9$  vs.  $131.9 \pm 27.01$  ml,  $P = 1.000$ ). Our CMR EF result is in contrast to numerous authors who have documented a reduction in EF following prolonged endurance exercise (Middleton *et al.* 2006; Neilan *et al.* 2006; Scott *et al.* 2009), or a maintenance (Neilan *et al.* 2006; Neilan *et al.* 2006) observed through standard echocardiography alone. The increase in EF 6hrs post-marathon is due to a significantly reduced LV dimension. In order to maintain SV (which was observed), EF must increase accordingly. Whether the elevation in EF 6hrs post-marathon is a systolic rebound or over-loading performance issue remains to be confirmed.

#### **5.5.5. Limitations**

Like many studies of this type, the numbers our cohort studied are small and the findings may not necessarily be applicable to larger populations. The spatial resolution of the CMR technique may also be insufficient to image small focal areas of myocardial inflammation or scarring caused by subclinical myocyte damage.

#### **5.5.6. Conclusions**

Study eight demonstrated that cardiac biomarkers suggestive of myocyte damage are elevated after a marathon, but these elevations are not associated with any detectable myocardial damage or acute changes in left or right ventricular function. cTnI and NTproBNP were significantly elevated immediately post-marathon completion, with

cTnI was further elevated at 6 hours post-Marathon in 15 of the 17 runners in this study. Whilst NTproBNP remained significantly elevated above baseline values it was falling at 6 hours post-Marathon. Evidence from the study eight found that biomarkers of myocardial cell damage following an acute bout of prolonged exercise are not associated with either systolic or diastolic functional measures, and do not seem to be associated with any detectable myocardial inflammation, oedema, or scarring using either gold standard techniques of gadolinium enhanced CMR or echocardiography respectively.

## CHAPTER SIX

### 6. Electrocardiography and the Veteran Endurance Athlete

#### 6.1. Cardiac autonomic function

Physical exercise has a beneficial effect upon cardiac autonomic activity. Regardless of age, endurance athletes demonstrate a higher parasympathetic modulation and have a particularly high global heart rate variability compared with sedentary individuals, indicating that endurance activity may have a favorable effect on the cardiac autonomic profile (Sztajzel *et al.* 2008). Veteran athletes demonstrate a decreased heart rate (HR) variability in both time and frequency domains suggesting an increased parasympathetic withdrawal during the autonomic control of post-exercise tachycardia (Brown and Brown 2007).

Pollock *et al.* (1997) conducted a 20-year review of veteran athletes documenting a linear decrease in maximal HR of 5-7  $\text{beat}\cdot\text{min}^{-1}\cdot\text{decade}^{-1}$  that was independent of continued high-intensity training. Early data suggested the decrease in maximal exercise HR with age was mainly due to the withdrawal of cardiac parasympathetic modulation and diminished  $\beta$ -adrenergic responsiveness. This weakened  $\beta$ -adrenergic responsiveness in older sedentary individuals appeared to contribute to an attenuated LV contractile response to exercise, regardless of a larger  $\beta$ -adrenergic stimulation (Schulman *et al.* 1992; Seals *et al.* 1994; Seals *et al.* 1994). Although, recent experiments with atropine administration demonstrate that there is no change in peak HR, suggesting that the reduction in peak HR was not due to parasympathetic withdrawal (Uusitalo *et al.* 1998; Stein *et al.* 2002). At present, the degree to which  $\beta$ -adrenergic responsiveness diminishes in veteran athletes has yet to be documented. However, the reduction in HR response to exercise is the reason why the maximum

acute cardiac output reserve in healthy individuals decreases, on average, by about 30% between ages 20 and 85 years (Lakatta and Levy 2003).

## **6.2. Electrocardiographic (ECG) changes**

ECG changes are common in elite athletes with up to 40% demonstrating minor changes (Pelliccia *et al.* 2000) including, most commonly, repolarisation abnormalities and increased R- or S-wave voltage suggestive of LV hypertrophy (LVH) (Bjornstad *et al.* 1991; Sharma *et al.* 1999; Pelliccia *et al.* 2000; Pelliccia *et al.* 2002; Pelliccia *et al.* 2008). In the majority of cases, these ECG alterations are considered an innocent and benign consequence of athletic training (Sharma *et al.* 1999). However, data from the Italian National pre-participation screening programme (Pelliccia *et al.* 2000), identified a small but important number of athletes (5% of 1005 athletes) demonstrating a particularly abnormal or bizarre ECG pattern, but with no evidence of structural cardiovascular abnormalities or an increase in cardiac dimensions. The long-term clinical outcome of this cohort as they progress through the ageing process, to veteran athletes, remains largely unknown.

Recently, from a database of 12,550 athletes, Pelliccia *et al.* (2008) reported on 81 athletes with diffusely distributed and deeply inverted T waves ( $\geq 2$  mm in at least three leads) who had no apparent cardiac disease and who had undergone serial clinical, ECG, and echocardiographic studies for a mean (SD) of  $9 \pm 7$  years (range, 1 to 27). From the 81 athletes, 63 with an abnormal repolarisation pattern (78%) were still engaged in regular competition and training. During serial follow up, ECG alterations remained essentially unchanged (or showed deeper T-wave inversion) in 54 athletes (67%). In the remaining 27 athletes, ECG patterns either normalised

completely (in 12) or became less abnormal (in 15) by showing reduced T-wave inversion. No changes in LV dimensions were observed in the 81 athletes during the follow-up period regardless of change in ECG patterns. Importantly, a diagnosis of cardiomyopathy was made in 5 (6%) of the 81 athletes who had no previous evidence of cardiac disease. Pelliccia *et al.* suggest that these abnormal ECG's may represent the initial expression of genetic cardiac disease, preceding by many years phenotypic expression and adverse clinical outcomes (Corrado *et al.* 2006).

### **6.3. Supraventricular, complex ventricular and profound bradyarrhythmias**

Together with a high vagal tone, life-long endurance athletes are also known to incur 'apparent' innocent arrhythmias and conduction alterations, such as sinus bradyarrhythmia, junctional rhythm, and first degree AV block. Recent data has documented an increased prevalence of substantial ectopy with frequent premature beats and complex ventricular tachyarrhythmias (including couplets and bursts of non-sustained ventricular tachycardia), predominantly occurring within endurance trained veteran athletes (Jensen-Urstad *et al.* 1998; Biffi *et al.* 2002; Biffi *et al.* 2004; Ector *et al.* 2007; Whyte *et al.* 2007; Whyte 2008; Mont *et al.* 2009). Biffi *et al.* (2008) reported that intensive endurance training may shift cardiovascular autonomic modulation from parasympathetic toward sympathetic dominance, thereby enhancing cardiovascular performance at peak training (Iellamo *et al.* 2002). However, the increased ventricular irritability, caused by predominance of sympathetic tone, might explain the clinical occurrence of ventricular arrhythmias in some veteran athletes (Chen *et al.* 2007).

#### **6.4. Paroxysmal and Lone Atrial Fibrillation**

Atrial fibrillation (AF) is characterised by rapid and chaotic electrical impulses (300–600 per minute) circulating within the atria and resulting in dysfunctional atrial activity and an irregular heart rate (Swanson 2006). AF is the most common sustained cardiac arrhythmia, which affects approximately 1.0–1.5% of the general population, and has a projected incidence that is markedly increasing (Miyasaka *et al.* 2006). Although many comorbidities and risk factors are known, (prevalence of AF doubles approximately every 10 years after age 50) (Kannel *et al.* 1998), the ultimate underlying cause(s) remain unknown. Obel and Davidson (2005) reported that studies using prolonged rapid atrial pacing (PRAP) as a method of inducing sustained AF in animal models, long periods of intense physical activity may result in a propensity to atrial tachyarrhythmia. Studies examining the effects of PRAP on the electroanatomic remodelling of the atria have shown that sympathetic hyperactivity occurs, which has a powerful influence on the maintenance of AF under such conditions. Interestingly, the authors provide evidence of a 53-year-old male endurance runner with symptomatic cardiac arrhythmias, including atrial ectopy and AF, but otherwise healthy. After 3 months of detraining, the patient's symptoms were ameliorated, atrial ectopy all but vanished, as did AF – these changes were sustained at a 6-month follow up.

Whilst there are over 16,000 AF articles indexed on Medline (Swanson 2006), few articles exist documenting the impact of life-long endurance exercise upon prevalence rates of AF in veteran athletes (Zeppilli *et al.* 1994). Although not considered veteran athletes for this review, Mont and co-workers (2002) reported 32 men out of 51 (63%) with lone AF (mean age 44) had been engaged in long term physical activity (av. 22

years) at least 3 hrs per week. Athletes started their episodes of AF at a younger age, they had a lower incidence of mild hypertension and their episodes of AF were predominantly vagal in contrast to the sedentary patients. When compared to healthy controls, and not sedentary participants, the athletes had greater atrial and ventricular dimensions and a higher ventricular mass. Karjalainen *et al.* (1998) postulated that enhanced vagal tone, atrial enlargement and LV hypertrophy, all characteristic of many endurance veteran athletes, may predispose normal hearts to AF.

Baldesberger *et al.* (2008) examined 62 former Swiss professional cyclists ( $66 \pm 7$  years), who completed the Tour de Suisse at least once during the years 1955–75, in comparison with 62 male golfers who had never engaged with high intensity endurance activity and were age, weight, hypertension, and cardiac medication matched. Former cyclists demonstrated a lower HR and a higher incidence of AF or atrial flutter (10 vs. 0%,  $P < 0.028$ ) and non-sustained ventricular tachycardia (VT). Mont *et al.* (2009) noted that the higher proportion of AF and flutter when compared with the study by Kaarjalainen (1998) is probably explained because the former cyclists were older, suggesting that incidence of AF and flutter further increases with aging in veteran athletes, as with any kind of AF.

Elosua *et al.* (2006) assessed former and current sport practice and the number of lifetime hours of sport practice in 51 men with lone AF (20 with vagal characteristics) in comparison to 109 general population control participants. Two important, yet cautious findings were reported: 1) the proportion of patients with lone AF who reported current sport practice was higher than in controls (31% vs. 14%), and 2) current practice of sport was associated with a higher prevalence of lone AF, with the

practice of more than 1500 lifetime hours of sport appearing to be the threshold for the observed association. Baldesberger *et al.* (2008) examination 62 former Swiss professional cyclists (noted above) corroborated these observations by reporting that former athletes with a very high number of previous bicycle years had a higher LV mass, larger atria, and a significant higher occurrence of AF or flutter correlating with previous bicycle years, indicating that there might be a threshold (volume) above which irreversible cardiac changes occur as another cause for AF or flutter.

### **6.5. Potential arrhythmic substrate(s) for AF**

In patients with hypertension or structural heart disease, AF may be the consequence of structural changes in the atria, dilatation and/or fibrosis, secondary to chronic volume and pressure overload (Mont *et al.* 2009). It would seem logical, that life-long endurance exercise may induce structural changes in the atrium (enlargement and/or fibrosis) that may create a favourable substrate for AF. Interestingly, Frustaci *et al.* (1997) found structural changes in a series of 12 patients with paroxysmal, recurrent, drug refractory lone AF. Inflammatory lymphomonuclear infiltrates, compatible with myocarditis, were documented in 66% of patients; a non-inflammatory cardiomyopathic process in 17%; and patchy fibrosis in the remaining 17%. Whilst numerous authors have examined myocarditis and its role within sudden cardiac death (Andersson *et al.* 2001; Durakovic *et al.* 2005; Chimenti *et al.* 2006; Basso *et al.* 2007; Durakovic *et al.* 2008), few have examined the link between myocarditis, fibrotic infiltrate and life-long endurance exercise in veteran athletes (Andersson *et al.* 2001).

### **6.5.1. STUDY NINE (Appendix 9)**

**Wilson, M.G.,** O'Hanlon, R., Prasad, S.K., Basavarajaiah, S., Stephens, N., Senior, R., Shaw, A., Sharma, S. and Whyte, G.P. Myocardial fibrosis in an endurance veteran athlete: Reminder of an important clinical lesson. *BMJ Case Reports*. 2009. doi:10.1136/bcr.12.2008.1345.

Study nine presents a 68 year old male veteran runner who had accurately recorded running a total distance of 148,561 miles, but was recently experiencing symptoms of sustained tachycardia, chest discomfort, dyspnoea and loss of competitive running performance. On questioning, the patient reported several periods of sustained intensive exercise whilst suffering with flu like symptoms to maintain his World Record attempt. On examination, resting 12-Lead electrocardiography, maximal cardiopulmonary exercise stress testing and echocardiography were normal. Cardiovascular magnetic resonance imaging (CMR) demonstrated no regional wall motion abnormality together with normal RV and LV wall thickness. However, a pattern of late gadolinium enhancement (LGE) which indicated myocardial scarring in the basal, lateral wall as a result of previous myocarditis was observed (Figure 12).

Acute myocarditis is typically a viral or post-viral process, which may result in the acute onset of LV systolic dysfunction. It can range from mild and clinically undetectable to fulminant and fatal over a short time course. Clinically, patients with acute viral myocarditis present with tachycardia, hypotension and shortness of breath. The clinical course of myocarditis is highly variable with complete or near complete

resolution occurring in a few weeks. The majority will experience some degree of recovery of function but are often left with a degree of left ventricular dysfunction.

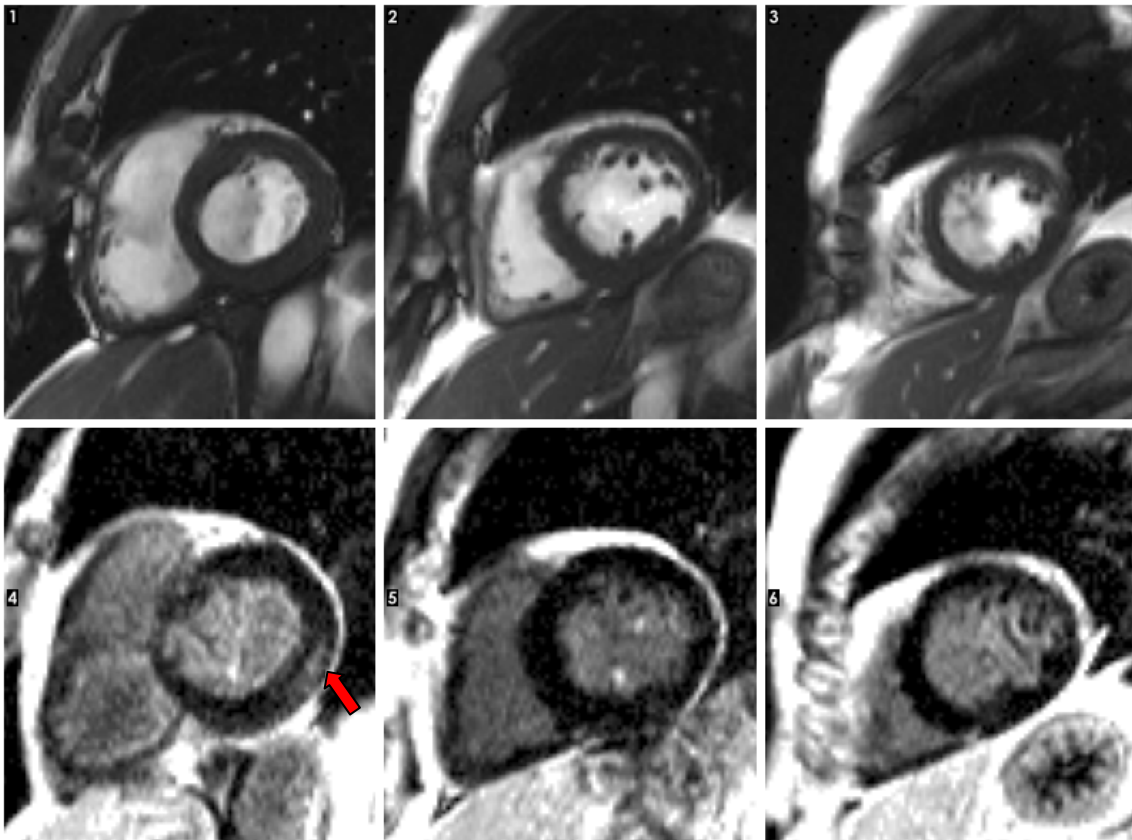


Figure 12: Myocardial scarring in the basal, lateral wall as a result of previous myocarditis. Arrow indicates scar in frame 4 (Wilson *et al.* 2009).

Myocarditis should be suspected in athletes with unexplained cardiac arrhythmias and dysfunction, especially if preceded by a flu-like syndrome. An early diagnosis is desirable in order to avoid the risk of fatal consequences, since physical activity can exacerbate the inflammatory process (Chimenti *et al.* 2006). In patients with acute or chronic myocarditis, arrhythmia may be the only clinical symptom in the natural course of the disease. Factors responsible for the increased incidence of cardiac arrhythmias include structural changes, ventricular hemodynamics, and vascular changes. The potentially malignant tachyarrhythmias and bradyarrhythmias caused by myocarditis are of particular concern. Acutely, inflammatory processes in the cardiac

myocytes and interstitium can lead directly to fluctuations in membrane potential, hence arrhythmogenesis (Babu-Narayan *et al.* 2007).

Sustained life-long endurance activity, provides ample opportunity for viral or post-viral infection to occur. Treatment is often difficult for highly competitive athletes to comprehend, as initial treatment for athletes with myocarditis should be complete absence from all physical activity for at least 6 months. Athletes should only resume training when ventricular function and cardiac dimensions return to normal and the clinically relevant arrhythmias disappear (Chimenti *et al.* 2006; Babu-Narayan *et al.* 2007). Adherence to such guidelines should be strongly advocated to reduce the potential of life-threatening arrhythmias or rapidly progressive cardiac dysfunction and the introduction of antiviral or an immunosuppressive treatment (Chimenti *et al.* 2006).

In summary, study nine demonstrates that veteran athletes are at increased risk of developing supraventricular arrhythmias. Likely reasons include changes in autonomic drive including increased parasympathetic modulation at rest and increased sympathetic modulation during exercise, increased atrial size and increased inflammation (Sorokin *et al.* 2009).

## **6.6. Ventricular arrhythmias**

Recent data has documented an increase in complex ventricular arrhythmias (VA), including couplets and bursts of non-sustained ventricular tachycardia, predominantly occurring within veteran athletes (Jensen-Urstad *et al.* 1998; Biffi *et al.* 2002; Biffi *et al.* 2004; Ector *et al.* 2007; Whyte *et al.* 2007; Baldesberger *et al.* 2008; Whyte 2008;

Mont *et al.* 2009). Debate continues to the clinical nature of VA and the specific outcome of high-level endurance athletes with frequent and complex ventricular arrhythmias (Heidbuchel *et al.* 2003). Indeed, VA's are sensitive to deconditioning in athletes with and without structural heart disease. Biffi *et al.* (2004) reported an 80% decrease in frequency and complexity of ventricular arrhythmias (from  $10,611 \pm 10,078$  to  $2165 \pm 4877$ ), as well as a 90% decrease in the occurrence of non-sustained ventricular tachycardia's with deconditioning. Using longitudinal data, the authors conclude that frequent and complex ventricular tachyarrhythmias are not ominous in trained athletes without cardiovascular abnormalities, and that these rhythm disturbances are another expression of the athlete's heart.

However, the specific outcome of high-level endurance athletes with frequent and complex ventricular arrhythmias remains unclear. Although examining younger athletes, Heidbuchel *et al.* (2003) reported on 46 high-level endurance athletes with ventricular arrhythmias (45 male; median age 31 years) followed-up for a median of 4.7 years. Right ventricular (RV) arrhythmogenic involvement was manifested in 59% of the athletes, and suggestive in another 30%. Thirty-seven athletes (80%) had ventricular arrhythmias with left bundle branch morphology, indicating an origin in the RV or the interventricular septum. The worst arrhythmia documented non-invasively at initial evaluation (12-lead ECG, Holter, exercise test) was sustained VT in 17 athletes (37%), non-sustained VT in 24 (52%), and only ventricular extrasystoles or couplets in five (11%). An invasive EP study induced sustained monomorphic VT in 15 out of 40 athletes, of whom 13 (87%) in the baseline state.

Eighteen developed a major arrhythmic event, with 9 sudden deaths. They were significantly younger than those without event (median 23 years vs. 38 years;  $P=0.01$ ). Importantly, the outcome could not be predicted by presenting symptoms, non-invasive arrhythmia evaluation or morphological findings at baseline. Only the induction of sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) during invasive electrophysiological (EP) testing was significantly related to outcome (RR 3.4;  $P=0.02$ ). The authors oppose longitudinal observations by Biffi *et al.* (2004) concluding that complex VA do not necessarily represent a benign finding in endurance athletes. Endurance athletes with arrhythmias have a high prevalence of RV structural and/or arrhythmic involvement, thus providing further evidence for the development and/or progression of the underlying arrhythmogenic substrate with high-intensity life-long endurance activity.

Recently, Biffi *et al.* (2008), examining young athletes, documented no significant relationship between LV mass (or mass index) and the grade or frequency of ventricular tachyarrhythmias. Athletes with more frequent ventricular arrhythmias did not show parallel increases in LV mass, and athletes with the greatest LV mass did not demonstrate more frequent ventricular arrhythmias than athletes with lesser or normal mass. Of particular interest, whilst not biologically significant, athletes with the most frequent and complex ventricular ectopy (those with >1,000 premature ventricular contractions) showed the smallest calculated LV masses and mass indexes. Biffi *et al.* observations demonstrate that ventricular tachyarrhythmias in trained athletes (without cardiovascular abnormalities) arise largely independent of training-related LV remodelling, meaning that the underlying determinants of ventricular tachyarrhythmias remain unresolved. However, whilst examining younger athletes,

Ector *et al.* (2007) noted that VA's in high-level endurance athletes frequently originate from a mildly dysfunctional right ventricle (RV). Studying 22 athletes with VA against 15 athletes without VA, the authors reported a RV EF of  $64 \pm 6\%$  in athletes without VA and a reduced RV EF ( $49 \pm 10\%$ ) in athletes with VA. Since both groups of athletes were engaged in the same intensity and frequency of exercise, this finding cannot be attributed to the presence of athlete's heart per se. The authors suggest that endurance exercise and volume overload subject the thin-walled RV to a greater increase in workload than the thick-walled LV with subsequent different remodelling. Indeed, animal models have demonstrated that chronic volume overload causes a greater mass increase in the RV than in the LV, resulting in an increased collagen deposition and selective growth factor activation restricted to the RV (Modesti *et al.* 2004). The origins and clinical significance of complex ventricular arrhythmias within veteran athletes remain to be fully elucidated and requires a robust methodological and longitudinal examination of a large number of life-long veteran athletes.

In summary, the relationship between ventricular arrhythmias and sudden cardiac death in athletes without evident heart disease is controversial. Furthermore, the origins and clinical significance of complex ventricular arrhythmias within veteran athletes remain to be fully elucidated and requires a robust methodological and longitudinal examination of a large number of life-long veteran athletes, especially those currently experiencing arrhythmia.

### **6.7. Idiopathic interstitial myocardial fibrosis**

The impact of multiple episodes of prolonged exercise, as experienced by highly trained veteran endurance athlete however is not fully understood. Whyte *et al.* (2007) propose that in the absence of any other cause, life-long, repetitive bouts of arduous endurance exercise may result in fibrous replacement of the myocardium, resulting in a pathological substrate for the propagation of arrhythmias. This proposed mechanism is supported in studies in non-ischaemic cardiomyopathy where myocardial damage leading to fibrosis has been implicated in myocardial re-entry leading to VA (Hsia and Marchlinski 2002). Furthermore, previous studies have supported the view that conduction system abnormalities and arrhythmias in athletes may be associated with myocardial damage (Bjornstad *et al.* 1993).

Evidence for Whyte *et al.* (2007) proposed theory that, life-long repetitive endurance exercise, resulting in fibrous replacement of the myocardium, comes from the same research group who recently observed idiopathic interstitial myocardial fibrosis at post-mortem in the heart of an athlete that died suddenly during marathon running (Whyte *et al.* 2008). The deceased had been running for 20 years, having completed multiple marathons, with a personal best time of 2 h 30 min. At autopsy, the weight of the heart was 480 g (above that expected for a 75-kg male - upper limit of 431 g), with widespread replacement fibrosis particularly in the lateral and posterior ventricular walls as well as interstitial fibrosis in the inner layer of the myocardium. Pre-mortem, the athlete was healthy and free from cardiovascular disease, and there was no documented evidence of diseases associated with widespread myocardial fibrosis. The cardiac pathologic findings were consistent with a LVH of indeterminate

causation (also known as “idiopathic left ventricular hypertrophy,” ILVH) in the presence of idiopathic interstitial fibrosis (Whyte 2008).

The presence of idiopathic interstitial fibrosis could act as a pathological substrate in the development of fatal arrhythmias resulting in sudden cardiac death. Limited evidence reporting idiopathic fibrosis exists in the literature, likely due to the absent histological examination of the hearts of veteran athletes’ post-mortem. Focal fibrosis of the papillary muscle in a highly trained endurance athlete has been reported previously (Rowe 1993) and lends support to this observation. ILVH has been previously documented in athletes at post-mortem and is associated with sudden cardiac death (Sharma *et al.* 1997; Seto 2003).

Changes to the myocardium with ageing are difficult to separate with diseases associated with ageing, namely hypertension (Lakhan and Harle 2008). An autopsy study of 230 non-cardiac patients demonstrated increased fibrosis and fat within the cardiac conduction system of elderly patients (Song *et al.* 1999), together with an age-related increase in right atrial fibrosis and a decrease in nerve plexus population (Burkauskiene *et al.* 2006). The causes of interstitial fibrosis are not well understood, however variable and dense interstitial fibrosis are observed in dilated cardiomyopathy (Marijjanowski *et al.* 1995), non-infarcted myocardium from hearts with ischaemic scars (Volders *et al.* 1993), dilated non-ischaemic myocardium (Brooks *et al.* 2003) and systemic hypertension (Pardo Mindan and Panizo 1993). An increased collagen content following sirius red FB3 staining of the myocardium is also observed in the presence of inflammatory and amyloid cells, and as a result of myocarditis. Wilson and co-workers (2002) suggested that myocardial ischemia

secondary to intramyocardial small-vessel coronary artery disease and the increased oxygen requirements of a hypertrophied myocardium, may contribute to the development of myocardial fibrosis, LV dysfunction and atrial and ventricular arrhythmias. However, from a biochemical-mechanical standpoint, Lakhan and Harle (2008) noted that myocardial fibrosis that occurs with normal aging should not be dependent upon the renin-angiotensin-aldosterone system or inflammatory mediators, as neither of these systems are activated in the healthy elderly patient. Even in the absence of overt hypertension, arterial vascular walls lose compliance with age, resulting in some degree of pressure overload with normal ageing. Whether this age-related pressure overload is severe enough to cause cardiac ischemia and fibrosis is unknown.

Gadolinium enhanced CMR provides a sensitive tool for detection of myocardial fibrosis, which is distinguished by bright late-enhancement regions where the contrast lingers in the extracellular spaces of scarred myocardium. (McCrohon *et al.* 2003). This technique relies on the difference in wash-in and wash-out kinetics and volume of distribution of Gadolinium in oedematous/fibrotic myocardium, and with increasing image resolution shows promise in other causes of myocardial fibrosis including sarcoid, systemic sclerosis, hypertrophic cardiomyopathy and dilated cardiomyopathy (McCrohon *et al.* 2003; Moon *et al.* 2004). In addition to the identification of interstitial fibrosis, work from our group has demonstrated the promising role in which late gadolinium enhanced CMR and STIR scans can identify possible myocardial inflammation in endurance athletes (Wilson *et al.* 2009). Myocardial inflammation may be a potential mechanism for the release of troponin and NTproBNP following a marathon. Wilson *et al.* (2009) performed CMR in 18

well trained athletes 24h pre and 6h post a marathon run. The authors documented that serum markers of myocardial cell damage post ultra-endurance exercise are not associated with CMR detectable levels of myocardial oedema, inflammation or scarring, suggesting lower degrees of myocardial damage than in patients with acute myocardial infarction, inspite of similar levels of troponin elevation (Study Eight).

Recent studies examining cardiac structure and function employing CMR in veteran endurance athletes are limited by recruitment of veteran participants who, whilst older and endurance trained, were not truly lifelong endurance athletes with poorly documented (ultra)-endurance histories (Jensen-Urstad *et al.* 1998; Ector *et al.* 2007; Whyte *et al.* 2007; Mohlenkamp *et al.* 2008; Whyte *et al.* 2008; Whyte 2008; Breuckmann *et al.* 2009; Yared and Wood 2009). Consequently, the impact of life-long episodes of intense prolonged exercise, as experienced by veteran endurance athletes is not fully understood. Accordingly, Study Ten aimed to examine the cardiac structure and function of a unique cohort of truly life-long, competitive veteran endurance athletes (> 50 years) using echocardiography and CMR imaging.

#### **6.7.1. STUDY TEN (Appendix 10)**

**Wilson, M.,** O'Hanlon, R., Prasad, S., Deighan, A., MacMillan, P., Oxborough, D., Godfrey, R., Smith, G., Sharma, S., Nevill, A., George, K. and Whyte, G. Diverse patterns of myocardial fibrosis in lifelong, veteran endurance athletes (In Press).

#### **6.7.2. Methods**

**Participants:** Following ethical approval from the Brompton, Harefield and NHLI research ethics committee, 17 young male athletes ( $31 \pm 4.5$  years) and 12 veteran male

athletes ( $56.3 \pm 6.2$  years) provided written informed consent, volunteered to participate, and underwent gadolinium CMR and 2D, M-mode, Doppler and tissue Doppler echocardiographic investigations. Individuals with significant co-morbidities including chronic cardiovascular disease (angina, previous MI, prior revascularisation, PVD, hypertension) and pulmonary disease were excluded. All veteran participants underwent maximal integrated cardio-pulmonary stress testing before inclusion in the study. All veteran participants were free from inducible arrhythmias during or post-exercise, with no ST segment changes indicative of myocardial ischemia. Blood pressure and heart rate response to exercise and recovery was normal for all veteran participants. All participants were asked not to run more than a total distance of 20 miles (32 km) in the week leading up to the study, with no training in the immediate 2 days prior to CMR investigations.

### **Recruitment**

All participants provided evidence of continuous lifelong competitive endurance training history (15 years of age to the present day). Veteran participants were recruited in two ways: 1) an advertisement placed in the United Kingdom's 100 Marathon running club newsletter - an organisation whereby membership is given to the proven completion of a minimum of 100 competitive marathons. 2) An advertisement placed in the British Olympic Association's 'Olympian' magazine – a quarterly magazine for past and present Olympians. Ten veteran athletes (83%) were categorised ultra-endurance marathon runners, with 2 veteran athletes (17%) considered rowers. Both rowers had run a minimum of 20 marathons each and had documented evidence of competitive 'age-group' rowing history for over 43 and 45 years, respectively. Young athletes were recruited through a previous CMR investigation (Wilson *et al.* 2009), but were also required to provide evidence of lifelong endurance competition (15 years of

age to present day). All young athletes were categorised as marathon runners or triathletes.

### 6.7.3. Results

#### Competitive History

For the first time, accurate diary recordings of the athletes training and competitive history have been documented. The data is unique in as much as the athletes are documented life-long endurance athletes; with both populations having continued to compete in intensive endurance events from the age of 15 years up until the present day. Many athletes in both populations have represented Great Britain in numerous World Championships (n = 35), with two athletes medalling at the Olympic Games (Rowing and Modern Pentathlon). There were no significant differences in height, body mass or BSA between young and veteran athletes, suggesting a morphological association between self selection and competitive endurance events (Table 21).

Table 21: Participant demographics including length of endurance career and competitive curriculum vitae. Values are expressed as mean  $\pm$  SD and (range).

	Young Athletes	Veteran Athletes
Age (yr)	31 $\pm$ 4.5 (26 – 40)	57.3 $\pm$ 6.2* (50 – 67)
Height (m)	1.81 $\pm$ 0.08 (1.70 – 1.93)	1.78 $\pm$ 0.06 (1.73 - 1.91)
Body Mass (kg)	80 $\pm$ 9.2 (61.8 – 99)	77.6 $\pm$ 10.1 (65 – 97)
BSA (m <sup>2</sup> )	2 $\pm$ 0.14 (1.74 - 2.3)	1.96 $\pm$ 0.14 (1.79 - 2.26)
Resting Heart Rate (bpm)	56.5 $\pm$ 7.8 (48 – 72)	55.8 $\pm$ 8.2 (44 – 69)
Years Competitive Training	18.4 $\pm$ 6.8 (11 – 31)	43 $\pm$ 5.7* (35 – 52)
Number of Marathons	2.3 $\pm$ 2.7 (0 – 10)	178 $\pm$ 209* (20 – 650)
Number of Ultra-Marathons	0.4 $\pm$ 1 (0 – 3)	65.1 $\pm$ 91.2* (0 – 257)
Number of Ironman Triathlons	1.1 $\pm$ 2.6 (0 – 10)	4 $\pm$ 12.3 (0 – 39)

BSA, body surface area, \*significantly different from young athletes ( $p < 0.05$ ).

### LV Diastolic Function

Veteran athletes revealed a significant reduction in LV diastolic function compared to young athletes (Table 22). The mitral E wave was significantly smaller in veteran athletes, leading to a significant reduction in E:A ( $1.72 \pm 0.44$  vs.  $1.41 \pm 0.48$ ;  $p < 0.05$ ). Furthermore, E' was significantly reduced in veteran athletes, whilst IVRT was significantly increased in veteran athletes compared to young athletes. Although the global diastology of the lifelong, ultra-endurance veteran athletes was smaller compared to young athletes, it was not impaired and was considered clinically normal for this aged population.

Table 22: Echocardiographic data indices for LV diastolic function. Values are expressed as mean  $\pm$  SD and (range).

Echo Variable	Young Athletes	Veteran Athletes
E decel (ms)	$204.4 \pm 21.05$ (176 – 241)	$205.5 \pm 36.6$ (165 – 285)
IVRT (ms)	$76.2 \pm 19$ (39 – 105)	$88 \pm 6.9^*$ (74 – 99)
E (cm/s)	$0.75 \pm 0.14$ (0.45 – 0.99)	$0.56 \pm 0.1^*$ (0.4 – 0.71)
A (cm/s)	$0.46 \pm 0.1$ (0.33 – 0.66)	$0.42 \pm 0.1$ (0.28 – 0.6)
E /A	$1.72 \pm 0.44$ (0.98 – 2.65)	$1.41 \pm 0.48^*$ (0.75 – 2.55)
E'	$12.8 \pm 3.7$ (8 – 20)	$10.4 \pm 2.4^*$ (7 – 13)
E/E'	$6.2 \pm 1.6$ (3.7 – 9.2)	$5.7 \pm 1.4$ (3.7 – 8.4)

E decel, deceleration time of early filling velocity; IVRT, isovolumic relaxation time; E, peak early diastolic filling; A, peak late diastolic filling; E/A, ratio of E to A; E/E', the ratio of early diastolic transmitral E wave velocities to tissue Doppler mitral annulus early diastolic E' wave velocities. \*Significantly different from young athletes ( $p < 0.05$ ).

### **Cardiac Morphology and Systolic Function**

Absolute and indexed left atrial volume, and peak wall thickness and left ventricular mass were matched between the young and veteran athlete groups (Table 23). Absolute LV and RV end-diastolic and end-systolic volumes were significantly smaller in veteran athletes compared to young athletes. Absolute and indexed LV stroke volume (SV) was significantly smaller in veteran athletes compared to young athletes. Differences in RV SV did not reach statistical significance despite being similar in magnitude to the LV. LV and RV ejection fractions (EF) were preserved in veteran athletes (LV EF:  $65.8 \pm 5.3\%$  & RV EF:  $66 \pm 5.1\%$ ) compared to young athletes (LV EF:  $64.5 \pm 4.3\%$  & RV EF  $62.1 \pm 5.5\%$  respectively). Finally, although LV and RV end-diastolic and end-systolic volumes were significantly smaller in veteran athletes, absolute and indexed LV mass was similar between young and veteran athletes (LV mass:  $151.2 \pm 22.6$  vs.  $148.4 \pm 15.6$ g,  $p < 0.05$ ).

### **Age and Cardiac Structure and Function**

There are significant negative correlations between age and LVEDV and RVEDV ( $r = -0.39$ ,  $p < 0.05$  and  $r = -0.45$ ,  $p < 0.05$  respectively), but not for LVSV and RVSV although a weak negative relationship existed ( $r = -0.264$ ,  $p = 0.16$  and  $r = -0.31$ ,  $p = 0.11$  respectively). LV EF and RV EF demonstrated a significant positive relationship with age ( $r = 0.4$ ,  $p < 0.05$  and  $r = 0.04$ ,  $p < 0.05$  respectively) (Figure 13).

Table 23: CMR data indices of LA, LV and RV volumes, mass and systolic function. Values are expressed as mean  $\pm$  SD and (range).

	Young Athletes		Veteran Athletes	
	Absolute	Absolute <sup>^</sup> BSA	Absolute	Absolute <sup>^</sup> BSA
LAEDV (ml)	71.5 $\pm$ 20.7 (43 – 117)	25.5 $\pm$ 6.8	69.8 $\pm$ 13 (52 – 92)	25.7 $\pm$ 5.6
LVEDV (ml)	211.4 $\pm$ 34.8 (162 – 272)	74.7 $\pm$ 9.6	181.6 $\pm$ 27.7* (142 – 232)	66.8 $\pm$ 11.3*
LVESV (ml)	75.7 $\pm$ 17.6 (47 – 111)	26.8 $\pm$ 5.6	62.5 $\pm$ 16.1* (42 – 90)	23 $\pm$ 6.4
IVSd (mm)	10.4 $\pm$ 0.7 (9 – 12)	7.4 $\pm$ 0.5 (6.6 – 8.5)	10.8 $\pm$ 1.3 (9 – 13)	7.8 $\pm$ 0.9 (6.6 – 9.5)
PWd (mm)	10.4 $\pm$ 0.9 (9 – 12)	7.3 $\pm$ 0.5 (6.5 – 8.5)	9.6 $\pm$ 1.2 (8 – 11)	6.9 $\pm$ 0.9 (5.8 – 8.2)
LV Length (mm)	97.4 $\pm$ 6.5 (89 – 112)	69.1 $\pm$ 3.1 (62.4 – 73.9)	88.1 $\pm$ 5.6* (78 – 97)	63 $\pm$ 4.5* (56.8 – 70)
LVmass (g)	151.2 $\pm$ 22.6 (119 – 210)	53.3 $\pm$ 5.2	148.4 $\pm$ 15.6 (120 – 167)	54.6 $\pm$ 6.7
RVEDV (ml)	214.9 $\pm$ 37.3 (143 – 276)	72.1 $\pm$ 21.5	181.4 $\pm$ 24* (150 – 227)	66.6 $\pm$ 9.4
RVESV (ml)	82.3 $\pm$ 21.7 (41 – 114)	26.8 $\pm$ 5.6	62.8 $\pm$ 15* (45 – 96)	23 $\pm$ 6.4
LVSV (ml)	135.6 $\pm$ 21.3 (104 – 183)	47.9 $\pm$ 5.4	119 $\pm$ 17.6* (101 – 163)	43.8 $\pm$ 6.9*
RVSV (ml)	132.6 $\pm$ 20.7 (97 – 154)	44.5 $\pm$ 12.6	118.8 $\pm$ 15.6 (102 – 174)	43.7 $\pm$ 6.4
LVEF (%)	64.5 $\pm$ 4.3 (56 – 74)	-	65.8 $\pm$ 5.3 (55 – 71)	-
RVEF (%)	62.1 $\pm$ 5.5 (53 – 73)	-	66 $\pm$ 5.1 (58 – 75)	-

LAEDV, left atrium end diastolic volume; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume; IVSd, intra-ventricular septum during diastole; PWd, posterior wall thickness during diastole; LV length, left ventricular length; LVmass, left ventricular mass; RVEDV, right ventricular end diastolic volume; RVESV, right ventricular end systolic volume; LVSV, left ventricular stroke volume; RVSV, right ventricular stroke volume; LVEF, left ventricular ejection fraction; RVEF, right ventricular ejection fraction.

\*Significantly different from young athletes (p<0.05).

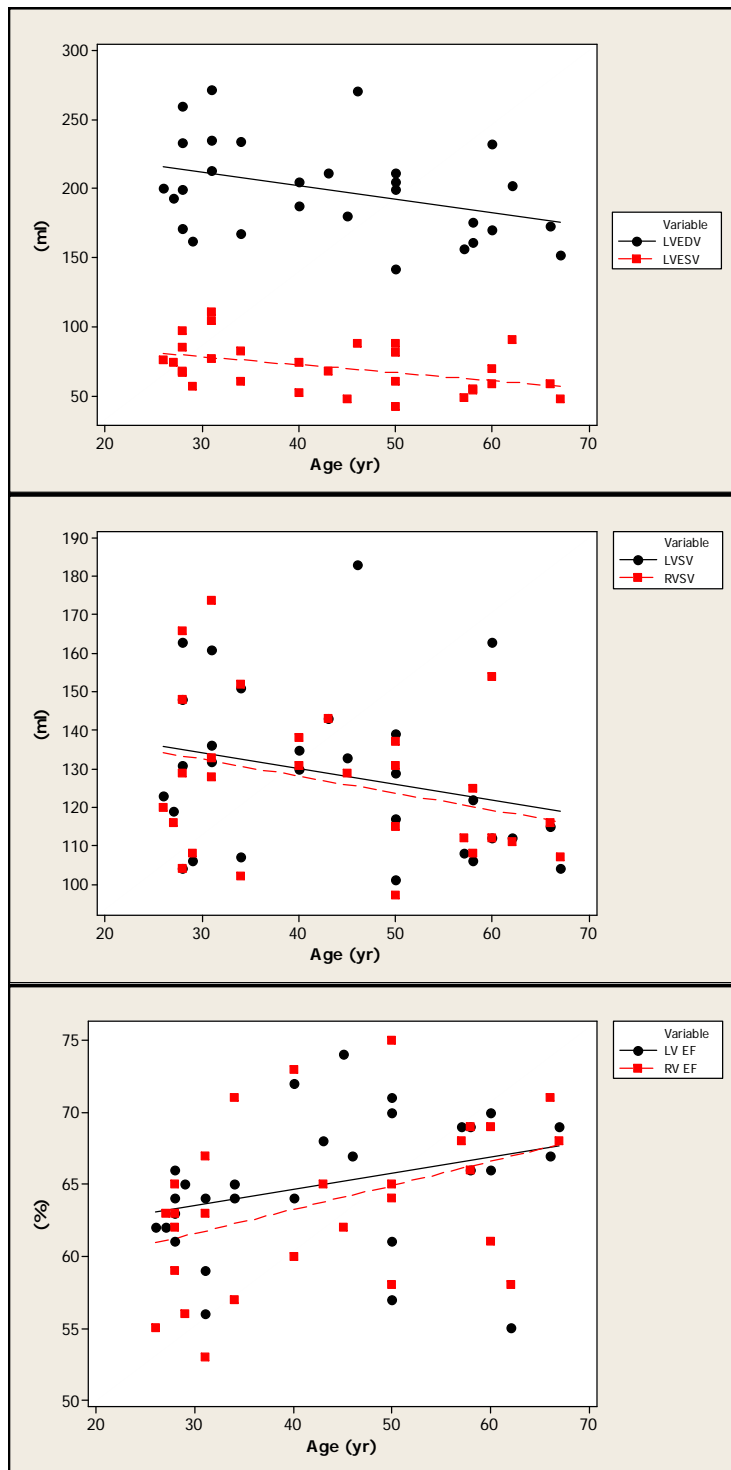


Figure 13: Correlations between athlete's age and LV and RV volumes and systolic function. LVEDV, left ventricular end diastolic volume; LSV, left ventricular stroke volume; LVEF, left ventricular ejection fraction; RVEDV, right ventricular end diastolic volume; RSV, right ventricular stroke volume; and RVEF, right ventricular ejection fraction.

### **STIR and Late Gadolinium Enhancement**

No young athletes or veteran athletes demonstrated focal or global myocardial oedema on STIR imaging. Myocardial rGE pre and post contrast ratio was less than 45% in all athletes, and none reached the rGE threshold of myocardium/skeletal muscle ratio of >4.0 (Young Athletes STIR ratio  $1.43 \pm 0.37$  vs. Veteran athletes STIR ratio  $1.52 \pm 0.24$ ). No LGE was observed in young athletes. In contrast, 6 ultra-endurance veteran athletes (50% of cohort) demonstrated LGE (Tables 24 & 25). The prevalence of LGE did not correlate ( $p = 0.67$ ) to the number of competitive marathons or ultra-endurance marathons (>50 miles) completed in the veteran athletes.

Table 24: CMR STIR and LGE data indices. STIR ratios are expressed as mean  $\pm$  SD and (range).

<b>CMR Index</b>	<b>Young Athletes</b>	<b>Veteran Athletes</b>
Myocardial to Skeletal STIR Ratio	$1.43 \pm 0.37$ (0.49 - 2.06)	$1.52 \pm 0.24$ (1.19 - 2.02)
LGE	Nil (0%)	6 (50%)

Regardless of positive or negative LGE scores, all 12 veteran athletes underwent perfusion imaging. Normal perfusion scores were noted in 11 veteran athletes, with only 1 veteran athlete (Participant 1) demonstrating a significant perfusion defect, who was immediately referred for computed tomographic (CT) angiography.

### **Diastology of Veteran Athletes with and without LGE**

Whilst statistical power is low, there is an observed depression in diastolic function in those veteran athletes presenting with positive LGE scores compared with veteran athletes without LGE (Figure 14).

Table 25: Location and extent of LGE in veteran athletes

Participant Number	Age (yr)	% of total LGE Mass (g)	LGE Pattern	Perfusion Defect	Interpretation	Location
1	67	18.9	CAD	Yes	Probable Dual Infarction	Anterior lateral wall
2	50			No	Probable myocarditis	Epicardial lateral wall
3	66	3	Non-CAD	No	Nonspecific	Basal and mid insertion point
4	60	3	Non-CAD	No	Nonspecific	Inferior insertion point mid and apical
5	50	1	Non-CAD	No	Nonspecific	Insertion point inferior mid/apical
6	51	1	Non-CAD	No	Nonspecific	Inferior insertion point

LGE; late gadolinium enhancement, CAD; coronary artery disease.

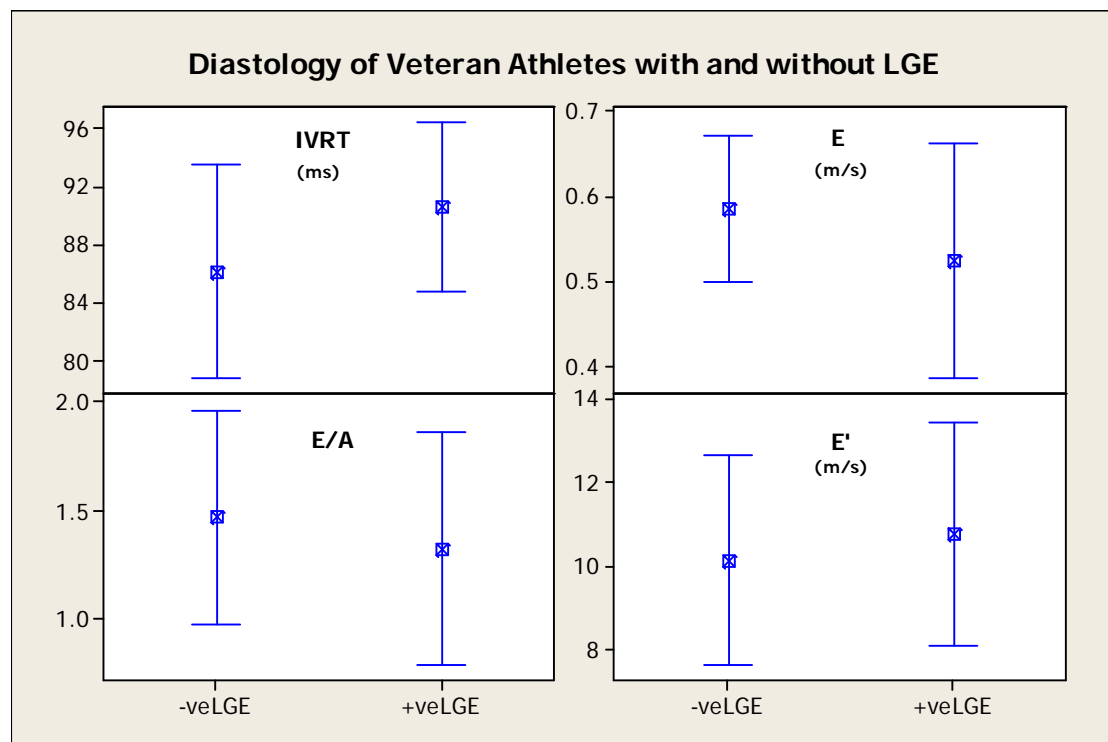


Figure 14: Diastolic function of veteran athletes presenting with and without LGE. IVRT, isovolumic relaxation time; E, peak early diastolic filling; E/A, ratio of E to A; E prime (or E'), tissue Doppler mitral annulus early diastolic E' wave velocity.

#### **6.7.4. Discussion**

The impact of lifelong ultra-endurance exercise on myocardial structure and function is poorly understood. The present study documented that lifelong veteran endurance athletes demonstrated significantly smaller LV and RV end-diastolic and end-systolic volumes, with maintenance of LV and RV systolic function and LV mass compared with young endurance athletes. Veteran athletes also demonstrate a significantly reduced LV diastolic function compared to young athletes consistent with previous published work. Furthermore, 6 (50%) of the veteran athletes examined using CMR demonstrated LGE indicative of myocardial fibrosis (4 veteran athletes with LGE of nonspecific cause, 1 probable previous myocarditis and 1 veteran athlete with LGE consistent with a previous silent myocardial infarction) compared to the absence of LGE in 17 young athletes.

#### **6.7.5. Diastolic function and the Veteran Athlete**

In line with the recognised age-related decline, veteran athletes have a depressed LV diastolic function compared with young athletes despite life-long physical activity (Nottin *et al.* 2004). Impairment of active and passive diastolic properties of the myocardium involves both muscular and interstitial components. Impaired  $\text{Ca}^{2+}$  uptake by the sarcoplasmic reticulum of the cardiomyocytes leads to slow and incomplete active ventricular relaxation (Nikitin *et al.* 2005), while expansion of the interstitium and alterations in collagen metabolism adversely affect the passive elastic properties of the myocardium (Villari *et al.* 1997). LV early diastolic filling rate progressively slows after the age of 20 years (Benjamin *et al.* 1992; Schulman *et al.* 1992; Swinne *et al.* 1992), with fibrotic changes within the LV myocardium or residual myofilament  $\text{Ca}^{2+}$  activation from the preceding systole the presumed

mechanisms for a reduced early diastolic LV filling rate. Despite the slowing of LV filling early in diastole, more filling occurs in late diastole, ultimately producing an exaggerated A wave (Lakatta and Levy 2003); likely due to a general increase in LV stiffness with ageing (Aronow 2001). At the sub-cellular level, ageing is associated with changes in excitation–contraction coupling mechanisms and diminished  $\beta$ -adrenergic contractile response (Lakatta 1993). At the cellular level, cardiac ageing is characterised by a significant reduction of cardiomyocyte number with hypertrophy of remaining cells and an increase in interstitial tissue (Olivetti *et al.* 1991). Data from the present study suggests that life-long endurance exercise does not halt the age-related reduction in diastolic function however; it may act to slow the rate of reduction.

#### **6.7.6. LGE in Veteran Athletes**

Gadolinium enhanced CMR provides a sensitive tool for detection of myocardial fibrosis. Of particular importance is the finding of LGE in 50% of our lifelong asymptomatic veteran athletes. Foci of fibrosis may act as an important nidus for re-entrant arrhythmia and cardiac diastolic dysfunction (Figure 14). The finding of insertion point fibrosis is a non-specific finding, albeit not present in the young athlete population studied despite matched ventricular volumes, wall thickness and mass. Excluding these individuals, significant LGE suggestive of a pathological event (myocarditis, myocardial infarction) was seen in 16% of our veteran athlete group (2/12).

A recent CMR study (Breuckmann *et al.* 2009) examining 102 healthy asymptomatic veteran male marathon runners reported an unexpectedly high prevalence of LGE

(12%), although not significantly different from control participants (4%,  $p = 0.07$ ). Sub-endocardial regions of LGE, typical of myocardial infarction (CAD) pattern, were distinguished from regions of a predominately, mid-myocardial patchy pattern of LGE (non-CAD pattern). The authors documented an adenosine perfusion defect in the same location as LGE in those veteran athletes presenting with a CAD pattern of LGE.

Whyte *et al.* (2007) proposed that in the absence of any other cause, life-long, repetitive bouts of arduous endurance exercise may result in fibrous replacement of the myocardium, resulting in a pathological substrate for the propagation of arrhythmias. This hypothesis is supported in studies of non-ischemic cardiomyopathy where myocardial damage leading to fibrosis has been implicated in myocardial re-entry leading to ventricular arrhythmias (Hsia and Marchlinski 2002). Furthermore, previous studies have supported the view that conduction system abnormalities and arrhythmias in athletes may be associated with myocardial damage (Bjornstad *et al.* 1993). Whyte *et al.* (2008) documented idiopathic interstitial myocardial fibrosis at post-mortem in the heart of an athlete that died suddenly during Marathon running. The deceased had been running for 20 years, having completed multiple marathons, with a personal best time of 2 h 30 min. At autopsy, the weight of the heart was 480 g (above that expected for a 75-kg male - upper limit of 431 g), with widespread replacement fibrosis particularly in the lateral and posterior ventricular walls as well as interstitial fibrosis in the inner layer of the myocardium. Pre-mortem, the athlete was healthy and free from cardiovascular disease, and there was no documented evidence of diseases associated with widespread myocardial fibrosis.

### 6.7.7. Causes of LGE

Changes to the myocardium with ageing are difficult to separate from diseases associated with ageing, i.e. hypertension (Lakhan and Harle 2008). An autopsy study of 230 non-cardiac patients demonstrated increased fibrosis and fat within the cardiac conduction system of elderly patients (Song *et al.* 1999), together with an age-related increase in right atrial fibrosis and a decrease in nerve plexus population (Burkauskiene *et al.* 2006). The causes of interstitial fibrosis are not well understood, however variable and dense interstitial fibrosis are observed in hypertrophic cardiomyopathy (O'Hanlon *et al.* 2007), dilated cardiomyopathy (Marijjanowski *et al.* 1995), non-infarcted myocardium from hearts with ischemic scars (Volders *et al.* 1993), dilated non-ischemic myocardium (Brooks *et al.* 2003) and systemic hypertension (Pardo-Mindan and Panizo 1993). An increased collagen content following sirius red FB3 staining of the myocardium is also observed in the presence of inflammatory and amyloid cells, and as a result of myocarditis. Wilson *et al.* (2002) suggested that myocardial ischemia secondary to intramyocardial small-vessel coronary artery disease and the increased oxygen requirements of a hypertrophied myocardium, may contribute to the development of myocardial fibrosis, LV dysfunction and atrial and ventricular arrhythmias. However, from a biochemical-mechanical standpoint, Lakhan and Harle (2008) noted that myocardial fibrosis that occurs with normal ageing may not be dependent upon the renin-angiotensin-aldosterone system or inflammatory mediators, as neither of these systems are activated in the healthy elderly patient. Even in the absence of overt hypertension, arterial vascular walls lose compliance with age, resulting in some degree of pressure overload with normal ageing. Whether this age-related pressure overload is severe enough to result in cardiac fibrosis is unknown. Recently, Trivax *et al.* (2010)

suggested that prolonged periods (>4h) of endurance exercise with sustained and elevated cardiac outputs, lead to increases in RA and RV wall tension, and in susceptible individuals, dilation of those chambers secondary to myocyte changes possibly due to slippage of myocytes within cardiac tissue. The loss of intercellular junction integrity may lead to chronic changes in activity of pericytes and myofibroblasts, participating in cardiac fibrosis.

#### **6.7.8. Correlation of LGE with Ultra-Endurance History**

Unlike Möhlenkamp et al. (2008) and Breuckmann et al. (2009), the present study did not observe a correlation between the presence of LGE and the number of marathons or ultra-endurance marathons (>50 miles per event) previously completed. It is worth distinguishing veteran athletes in the present study to those used by Möhlenkamp et al. and Breuckmann et al. Firstly, Möhlenkamp et al. state that their veteran athletes had run an average of 20 marathons (range 14 – 42) and had taken up marathon running 9 years prior to their study (range 7 – 16 years). This differs dramatically from the veteran athletes enlisted in the present investigation with an average of  $178 \pm 209$  marathons run (range 20 – 650) and a competitive endurance history of  $43 \pm 5.7$  years (range 35 – 52). Secondly, 51.9% (n = 56) of the veteran athletes used by Möhlenkamp et al. and Breuckmann et al. reported to be previous smokers, with a further 4.6% current smokers. In the present study, only 1 veteran athlete (not presenting with LGE) reported a previous smoking history of 15 years. This methodological distinction in participant recruitment is important, as LGE may be the sole result of CAD and associated endothelial dysfunction (Yared and Wood 2009). Considering Möhlenkamp et al. (2008) observed veteran athletes with LGE had

higher calcium scores than veteran athletes without LGE; the fact that over 50% of these veteran athletes previously smoked cannot be ignored.

#### **6.7.9. Myocarditis: A substrate for Arrhythmia and Fibrosis**

Whilst numerous authors have examined myocarditis and its role within sudden cardiac death (Andersson *et al.* 2001; Durakovic *et al.* 2005; Chimenti *et al.* 2006; Basso *et al.* 2007; Durakovic *et al.* 2008), few have examined the link between myocarditis, fibrotic infiltrate and life-long endurance exercise in veteran athletes (Andersson *et al.* 2001). Our group recently observed myocardial fibrosis in a lifelong male endurance athlete, presenting with symptoms of chest discomfort, dyspnoea and loss of competitive running performance (Study Nine). The patient kept an accurate diary documenting 43 years of continuous daily running (totalling over 148,000 miles), and importantly, noted several periods of intensive endurance activity whilst suffering with flu like symptoms. CMR demonstrated no regional wall motion abnormality together with normal RV and LV volumes and wall thicknesses; however, LGE indicated myocardial scarring in the basal and lateral wall as a result of previous myocarditis. It would seem logical for the veteran athletes in the present study to experience episodes of 'flu like' illness on more than one occasion throughout a 43 year competitive endurance career. Treatment is often difficult for endurance athletes to comprehend, as initial treatment for athletes with myocarditis should be complete absence from all physical activity for at least 6 months. Athletes should only resume training when ventricular function and cardiac dimensions return to normal and the clinically relevant arrhythmias disappear (Chimenti *et al.* 2006; Babu-Narayan *et al.* 2007).

## **6.8. Role of Cardiac Biomarkers with Ultra-Endurance Exercise**

The release of cardiac troponins (cTnT and cTnI) following prolonged exercise has been extensively documented, but the aetiology and clinical significance of post-exercise troponin release is yet to be elucidated (Koller 2003; George *et al.* 2005; Shave *et al.* 2005; Neilan *et al.* 2006; Neilan *et al.* 2006; Shave *et al.* 2007; Michielsen *et al.* 2008; Scharhag *et al.* 2008). Recently, our group reported a lack of association between troponin release and diastolic dysfunction following a marathon, suggesting that they are distinctly separate phenomena (Wilson *et al.* 2009). Shave *et al.* suggested that post-exercise release of troponin may represent either necrosis of cardiac myocytes leading to irreversible damage, or may be a transient and reversible change in membrane permeability of the myocyte (Shave *et al.* 2007). The mechanisms for troponin release may come from the unbound pool found in the cardiomyocyte cytoplasm and may reflect a physiologic as opposed to a pathologic process (Dawson *et al.* 2008). It appears unlikely that the minor elevations in biomarkers of cardiac damage observed following prolonged endurance exercise indicate myocardial necrosis of sufficient magnitude to cause LV dysfunction. It is tempting to suggest that elevated cardiac troponins represent reversible cardiomyocyte membrane damage that may reflect part of a remodelling process however; further study is required to elucidate the mechanism(s) and clinical significance (Middleton *et al.* 2008). Myocardial inflammation has been suggested as a potential mechanism for the release of troponin and NTproBNP following a marathon; however recent studies have documented that serum markers of myocardial cell damage post ultra-endurance exercise are not associated with CMR detectable levels of myocardial oedema, inflammation or scarring, suggesting lower degrees of

myocardial damage than in patients with acute myocardial infarction, inspite of similar levels of troponin elevation (O'Hanlon *et al.* 2009; Wilson *et al.* 2009; Trivax *et al.* 2010).

### **6.8.1. Conclusion**

Lifelong veteran endurance athletes demonstrate a significantly smaller LV and RV end-diastolic and end-systolic volumes, with maintenance of LV and RV systolic function and LV mass compared with young endurance athletes. Veteran athletes also demonstrate a significantly reduced LV diastolic function compared to young athletes consistent with previous published work. Furthermore, 6 (50%) of the veteran athletes examined using CMR demonstrated LGE indicative of myocardial fibrosis compared to the absence of LGE in 17 young athletes; with prevalence of LGE in veteran athletes not correlating to the number of competitive marathons or ultra-endurance marathons (>50 miles) completed.

In conclusion, Study ten reports that there is limited evidence at present demonstrating that cardiovascular re-modelling following life-long endurance exercise leads to long-term disease progression, cardiovascular disability or sudden cardiac death. However, the unexpected high prevalence of LGE (50%) in life-long veteran athletes insinuates that the veteran athlete may not be as healthy as believed. Future studies employing large cohorts of veteran athletes are warranted to enhance our understanding of the impact of long-term endurance exercise on cardiac structure and function; particularly in those veteran athletes currently experiencing cardiac arrhythmia. These studies will add to the relatively small body of knowledge providing important information regarding the differentiation of physiologic and

pathologic cardiovascular re-modelling and in the identification and management of cardiovascular pathology in veteran endurance athletes.

### **6.8.2. Limitations**

Like many studies of this type, the numbers of veteran athletes are small and the findings may not necessarily be applicable to larger populations. We concede the lack of an age- matched control population for veteran athletes. Study ten does not apply to women and may not be representative for veteran athletes, as we cannot exclude recruitment bias. Lastly, the spatial resolution of the CMR technique may also be insufficient to image small focal areas of myocardial inflammation or scarring caused by subclinical myocyte damage.

## **6.9. PART TWO CONCLUSIONS**

Over the past few decades, prolonged endurance events, such as marathon running have become more popular. In 2001, nearly 480,000 runners completed a marathon in the United States alone, with a shift toward older participants. Strenuous endurance activities, such as marathon running, may even lead to an increased risk of acute cardiac events, although the occurrence of coronary events during marathons is rare. In spite of such risks, the central and peripheral cardiovascular benefits of regular physical exercise on the health of the general public have been well documented. Much of this work has focused on endurance exercise of moderate intensity, duration and frequency. In contrast, there is a burgeoning debate surrounding the cardiovascular benefits of endurance and ultra-endurance exercise. With a growing population of veteran endurance athletes regularly participating in endurance training

and competition there is an emerging requirement to establish the impact of such exercise on the cardiovascular system.

With this in mind, Study 7 set out to provide a systematic review of the cardiac and vascular structure and function of the veteran athlete and examined whether the aetiology of these exercise induced changes are physiologic or pathologic in nature. In summary, Study 7 found that whilst  $\dot{V} O_{2\max}$  declines with age regardless of activity status, the higher absolute cardio-respiratory capacities in veteran endurance athletes compared to age-matched controls are well documented. Exercise training may be associated with enhanced LV diastolic function and also have normal intrinsic global LV systolic function. Exercise training into old age may maintain ventricular compliance that, during exercise, could explain an augmented SV and thus elevate  $VO_{2\max}$  in veteran athletes when compared to age matched sedentary individuals. Regular aerobic exercise is associated with enhanced arterial compliance in ageing larger arteries; it also helps prevent the attenuation of the age-related endothelial dysfunction in conduit and resistance arteries. Furthermore, physical activity is also associated with an elevated cerebral blood flow, meaning that individuals with a higher cardiorespiratory fitness have a 17% higher cerebral blood flow than those who are sedentary of the same age. Veteran athletes may also have an enhanced systemic arterial endothelial function, reduced large artery stiffness and a reduced risk of atherosclerosis.

Structurally, Study 7 found that evidence was a little more controversial. Recently, Pelliccia et al. (2010) concluded that intensive endurance conditioning over many years in Olympic athletes was not associated with inappropriate LV remodelling or

dysfunction or with adverse clinical events, onset of symptoms, or new diagnosis of cardiomyopathies. However, Naylor et al. (2005) reported a reduction in diastolic function following short-term cessation of training in elite athletes that was normalised on return to training raising the possibility that diastolic function may be normal in athletes who exhibit ventricular hypertrophy in the presence of a training stimulus, whereas the absence of an ongoing training stimulus may be associated with decreased diastolic function in subjects who exhibit ventricular hypertrophy. Furthermore, detraining in athletes has been associated with only partial reversal of LV enlargement and that the E/A ratio was lower after athletic retirement, transforming a physiological entity into a pathological phenomena.

ECG changes are common in athletes with up to 40% demonstrating minor changes. However, in veteran athletes there has been an increase in the prevalence of supraventricular, complex ventricular and profound bradyarrhythmias in endurance-trained veteran athletes. Idiopathic ventricular arrhythmias have also been identified in athletes, which, by definition, originate in hearts without structural abnormalities. Some authors have noted that ventricular arrhythmias are sensitive to deconditioning in athletes with and without structural heart disease, and are thus a benign extension of the athlete's heart entity. Whilst others have noted that endurance athletes with arrhythmias have a high prevalence of right ventricular structural and/or arrhythmic involvement, providing further evidence for the development and/or progression of the underlying arrhythmogenic substrate with high-intensity life-long endurance activity.

Consequently, Study 8 set out to examine the impact of an acute bout of ultra-endurance exercise upon cardiac structure and function. A large body of research has suggested that acute bouts of ultra-endurance exercise result in a depression in indices of global left ventricular (LV) diastolic and systolic function and the unrelated appearance of elevations in serum markers of cardiac myocyte damage often above acute myocardial infarction cut-off levels. Despite such conclusions, this is still a controversial research area with many aspects of these phenomenon equivocal, lacking data or poorly understood. Thus, Study 8 examined 17 male participants (mean  $\pm$  SD (range): age  $33.5 \pm 6.5$  years (46–26 years), body mass  $80 \pm 9.2$  kg (100–63 kg), height  $1.81 \pm 0.06$  m (1.93–1.70 m)) using cardiac magnetic resonance (CMR) and echocardiography before and after a marathon to investigate the relationship between systolic function and diastolic function against biomarkers of cardiac damage.

Study 8 results demonstrated that cardiac biomarkers suggestive of myocyte damage are elevated after a marathon, but these elevations are not associated with any detectable myocardial damage or acute changes in left or right ventricular function. cTnI and NTproBNP were significantly elevated immediately post-marathon completion, with cTnI was further elevated at 6 hours post-Marathon in 15 of the 17 runners. Whilst NTproBNP remained significantly elevated above baseline values it was falling at 6 hours post-Marathon. In conclusion, evidence from Study 8 found that biomarkers of myocardial cell damage following an acute bout of prolonged exercise are not associated with either systolic or diastolic functional measures, and do not seem to be associated with any detectable myocardial inflammation, oedema,

or scarring using either gold standard techniques of gadolinium enhanced CMR or echocardiography respectively.

Recently, using cardiac magnetic resonance, Breuckmann et al. (2009) examined 102 healthy asymptomatic veteran male marathon runners and reported an ominously high prevalence of late gadolinium enhancement (12% - indicative of myocardial fibrosis), although not significantly different from control participants. The presence of idiopathic interstitial fibrosis could act as a pathological substrate in the development of fatal arrhythmias resulting in SCD, with the cause(s) and consequence(s) of the myocardial fibrosis in veteran athletes unknown. Whilst numerous authors have examined myocarditis and its role within SCD, few have examined the link between myocarditis, fibrotic infiltrate and life-long endurance exercise in veteran athletes. Study 9 documented myocardial fibrosis in a lifelong male endurance athlete, presenting with symptoms of chest discomfort, dyspnoea and loss of competitive running performance. The patient kept an accurate diary documenting 43 years of continuous daily running (totalling over 148,000 miles), and importantly, noted several periods of intensive endurance activity whilst suffering with flu like symptoms. CMR demonstrated no regional wall motion abnormality together with normal RV and LV volumes and wall thicknesses; however, LGE indicated myocardial scarring in the basal and lateral wall as a result of previous myocarditis. Acute myocarditis is typically a viral or post-viral process that may result in the acute onset of left ventricular systolic dysfunction. The presence of idiopathic interstitial fibrosis could act as a pathological substrate in the development of fatal arrhythmias resulting in sudden cardiac death. Importantly, it is not the density of fibrosis that

dictates the arrhythmia potential rather the position of fibrosis, i.e. near the conduction system and the architecture of fibrosis.

The lack of association between troponin rise with cardiac symptoms, ECG abnormalities or sustained deterioration in cardiac function in the short term (Study 8), have led some investigators to conclude that the phenomenon may reflect a regulatory physiological adaptive process facilitating compensatory cardiac hypertrophy to cope with the haemodynamic burden of prolonged intensive exercise. However, care is warranted for the interpretation of short term, acute impact studies upon a career of lifelong physical endurance activity. Consequently, the impact of multiple episodes of prolonged exercise, as experienced by highly trained veteran endurance athlete is not fully understood. Study 10 set out to examine the cardiac structure and function of a unique cohort of documented life-long, competitive endurance veteran athletes (> 50 years, mean  $\pm$  SD marathons  $178 \pm 209$  (range 20 – 650)).

Twelve lifelong veteran male endurance athletes (mean  $\pm$  SD [range] age:  $56.3 \pm 6.2$  yr [50-67]) and 17 body-size matched young male endurance athletes ( $31.0 \pm 4.5$  years [26-40]) without significant co-morbidities underwent 2D, M-mode, Doppler and tissue Doppler echocardiographic investigations and CMR to assess cardiac morphology and function as well as CMR with late gadolinium enhancement (LGE) to assess myocardial fibrosis. Study 10 documented that diastolic function was reduced in the lifelong veteran athletes ( $p < 0.05$ ) compared to young athletes (E/A:  $1.41 \pm 0.48$  vs.  $1.72 \pm 0.44$  and E':  $10.4 \pm 2.4$  vs.  $12.8 \pm 3.7$  respectively). Lifelong veteran athletes had smaller LV and RV end-diastolic and end-systolic volumes

( $p < 0.05$ ) but maintained LV and RV systolic function. In 6 (50%) of the veteran athletes LGE of CMR indicated the presence of myocardial fibrosis (4 veteran athletes with LGE of nonspecific cause, 1 probable previous myocarditis and 1 probable previous silent myocardial infarction). There was no LGE in the young athletes. Importantly, the prevalence of LGE in veteran athletes was not associated with the number of competitive marathons or ultra-endurance marathons (>50 miles) completed, veteran athletes age, LV and RV end-diastolic volumes or LV mass ( $p > 0.05$ ).

In conclusion, Study 10 found that lifelong veteran endurance athletes demonstrated significantly reduced diastolic function and smaller LV and RV end-diastolic and end-systolic volumes, with maintenance of LV and RV systolic function and LV mass compared with young endurance athletes. Furthermore, an unexpectedly high prevalence of myocardial fibrosis (50%) was observed in healthy, asymptomatic life-long veteran male athletes. Thus, Study 10 reports that there is limited evidence at present demonstrating that cardiovascular re-modelling following lifelong endurance exercise leads to long-term disease progression, cardiovascular disability or SCD. However, the unexpected high prevalence of LGE (50%) in life-long veteran athletes insinuates that the lifelong veteran athlete may not be as healthy as once believed.

## **CHAPTER SEVEN**

### **7. Thesis Conclusions and Directions for Future Studies**

Ever since Henschen et al. (1889) first described the cardiac adaptations to intensive physical activity over a century ago, the question of whether the pronounced cardiac morphological and functional changes observed in athletes represent a benign physiological adaptation or along a continuum of pathology remains controversial. An important distinction in exercise related sudden cardiac death is made on the basis of age. Sudden cardiac deaths (SCD) in older athletes (>35 years) are predominately caused by atherosclerotic coronary artery disease. In contrast, most SCD in young athletes (<35 years of age) are associated with inherited or congenital cardiac pathologies.

Prevention of SCD in young athletes remains one of the most hotly debated topics in sports medicine. A large number of SCD in young athletes occurs in the absence of structural cardiac abnormalities, often classified in coroner's reports as 'death by natural causes'. The implementation of pre-participation cardiovascular screening in young athletes has received substantial support as structural cardiac diseases i.e. cardiomyopathies and electrical diseases i.e. Long QT, are detectable during life with appropriate screening methods. The importance of timely identification by the screening of asymptomatic athletes is illustrated by the real possibility of preventing SCD by lifestyle modification; including: sporting disqualification, prophylactic treatment or implantation of a cardiac-defibrillator.

The screening debate, however, is centred on the inclusion (or not) of a resting 12-lead electrocardiogram in addition to a medical history and physical examination

during the preparticipation screening. This ultimately places the sports medicine physicians in a difficult situation regarding best practice and begs the question, “What is the most appropriate protocol to screen athletes for underlying inherited cardiovascular disease?” This thesis can conclude that the ECG is simple, efficient, safe, non-invasive, accurate, validated and inexpensive. The findings of study 2 are supported by the British Journal of Sports Medicine and the International Olympic Committee (IOC) ‘special interest’ issue on SCD in athletes. Study 2 provides additional information that supports the ESC protocol for pre-participation screening, moving the current debate away from the American Heart Association’s policy of screening without a 12-Lead ECG (Study 2 has received 2 editorials, 2 journal responses and has been cited a further 17 times to date). In conclusion, the present data should allow healthcare and sport governing bodies to support the 12-Lead ECG screening protocol in all young athletes (<35 years).

At times, however, debate over the best practice screening strategy has stalled because of a continuing disagreement on the incidence of SCD in young athletes, the prevalence of SCD diseases in elite athletes, and the continued fear of disqualifying athletes based upon a false positive diagnosis. To address the prevalence of SCD diseases in elite athletes and the false positive issue, Studies 3 and 4 document the cardiovascular structure, function and electrical activity in a range of athletes of different ages and ethnicity. These 2 studies provide the worlds 2<sup>nd</sup> largest screening population to date, outside of the ‘Italian Experience’ for the prevalence of hypertrophic cardiomyopathy and Long QT syndrome. Study 3 disputes the widely accepted HCM prevalence figure of 1 in 500. Consequently, Study 3’s observed lack of diagnosed individuals with HCM in an extremely large cohort of UK elite athletes

has resulted in 15 citations to date, whilst Study 4 was subject to an editor's open choice article in the European Heart Journal, receiving 2 journal responses and was cited a further 7 times. At the time of publication, Study 6 examined the largest cohort (n = 300) of nationally ranked UK black male athletes. For the first time, Study 6 demonstrated that Black athletes exhibit greater LV wall thicknesses compared with white athletes. A minority of black athlete's exhibit LVH  $\geq 15$  mm; proposing that in the absence of cardiac symptoms or a family history of HCM, an LV wall thickness  $\geq 15$  mm in black athletes may represent physiologic LVH when the LV cavity is enlarged and diastolic indexes are normal. This is especially important when dealing with conditions that cause sudden cardiac death, when the established upper limits of LVH have been previously published at 16mm in Caucasian athletes. Consequently, Study 6 was subject to an editorial in the Journal of the American College of Cardiology and has been cited a further 20 times. In conclusion, the six studies in part one of this thesis discuss non-invasive strategies and document outcome data that are useful in distinguishing the benign physiological consequences of systematic athletic training from pathology with the potential for SCD across a variety of athletic populations.

Part two of this thesis considers the impact of acute and longitudinal ultra-endurance physical activity upon the cardiovascular structure and function of young and veteran athletes. Several case series and studies have reported an increased prevalence of supraventricular and complex ventricular in endurance-trained veteran athletes. Furthermore, when compared to age-matched sedentary controls, a higher prevalence of sub-clinical cardiac disease has been reported in veteran athletes that may increase risks of an exercise induced cardiac event. On the basis of this descriptive data and

autopsy some authors have speculated that, in the absence of any other cause, life-long repetitive bouts of arduous endurance exercise may result in fibrous replacement of the myocardium, resulting in a pathological substrate for the development of arrhythmias.

Only limited case evidence exists for exercise-induced myocardial fibrosis in lifelong endurance veteran athletes. Due to this speculation, Part two of this thesis set out to establish the impact of such ultra-endurance exercise on the cardiovascular system following an acute bout of physical activity (a Marathon) and after a lifelong career in endurance events (> 50 years of age, mean  $\pm$  SD marathons  $178 \pm 209$  (range 20 – 650)). Study 8 failed to identify any features of myocardial ischaemia or inflammation post-Marathon and failed to demonstrate any correlation between troponin concentration and the magnitude of cardiac dysfunction following after a marathon. Study 10 did however; document an unexpectedly high prevalence of myocardial fibrosis (50%) in healthy, asymptomatic life-long veteran male athletes. Whether this myocardial fibrosis reflects ageing, lifelong intense endurance training, sub-clinical cardiovascular disease or the interaction of these factors in some individuals cannot be determined from available data.

In conclusion, the veteran athlete may not be as healthy as once believed with many established areas lacking conclusive evidence to support the benefits of a life-long career in high intensive endurance exercise. Future studies employing large cohorts of veteran athletes, employing modern techniques such as cardiac magnetic resonance, are warranted to enhance our understanding of the impact of long-term endurance exercise on cardiovascular structure and function. Importantly, the systematic and

longitudinal follow up of veteran athletes (both male and female) who are currently experiencing arrhythmia is paramount. These studies will add to the relatively small body of knowledge providing important information regarding the differentiation of physiologic and pathologic cardiovascular re-modelling and in the identification and management of cardiovascular pathology in veteran endurance athletes.

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## Appendix 1

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## Appendix 2

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### **Appendix 3**

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#### **Appendix 4**

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## Appendix 5

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## Appendix 6

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## **Appendix 7**

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## Appendix 8

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## Appendix 9

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## **Appendix 10**

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