THE EFFECT OF PHYSICAL GROWTH, BIOLOGICAL MATURATION AND ETHNICITY ON CARDIAC PRE-PARTICIPATION SCREENING IN MALE PAEDIATRIC ATHLETES

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ABSTRACT

Cardiac screening of the paediatric athlete is now recommended by many international sporting governing bodies and aims to identify those at risk of sudden cardiac death/arrest (SCD/A) from an undiagnosed cardiac condition. Regular and sustained physical activity is associated with a number of electrophysiological, structural and functional cardiac adaptations, collectively referred to as the athlete's heart. In some cases, however, this may mimic the phenotypic expression of varying pathological conditions, often related to SCD/A. Clearly, this crossover complicates the differential diagnosis associated with cardiac screening. Ethnicity mediates cardiac adaptation within the adult athlete, yet little is known regarding the paediatric athlete, further complicating the distinction between physiological adaptation and cardiac pathology. The overarching aim of this thesis is to provide a comprehensive assessment of the competitive Arab and black paediatric athlete, using 12-lead-electrocardiogram (ECG) and transthoracic echocardiography.

Study 1 (Chapter 4), employed a systematic review with meta-analysis to describe the ECG and echocardiographic manifestations of the paediatric athlete's heart, and examine the impact of age, race, and sex on cardiac remodeling responses to competitive sport. Paediatric athletes demonstrated a greater prevalence of training-related and -unrelated ECG changes than non-athletes, with prevalence greater in black than white paediatric athletes. After accounting for chronological age, left ventricular (LV) structural parameters were larger among paediatric athletes than non-athletes, whilst posterior wall thickness during diastole was larger in black than white athletes. Paediatric athletes chronological age, and ethnicity are mediating factors on electrophysiological and LV structural

remodelling. Study 2 (Chapter 5), new international recommendations, outperformed both the Seattle and 2010 ESC criteria, reducing false positive rates while yielding a 'fair' (0.77, 95% CI 0.61 to 0.93) diagnostic accuracy for cardiac pathology that may predispose to SCD/A in a paediatric athlete. In clinical context, the 'chance' of detecting cardiac pathology within a paediatric male athlete with a positive ECG (+ve Likelihood Ratio=9.0) was 8.3%, whereas a negative ECG (−ve Likelihood Ratio=0.4) was 0.4%. In extension to these investigations, Study 3 (Chapter 6), employed 'biological' age (by radiological X-ray) assessment to T-wave inversion (TWI) interpretation on the paediatric athletes ECG. TWI confined to V_1–V_3 was predicted by black ethnicity and biological age <16 years, but not chronological age <16 years. Secondly, biological age outperformed chronological age criterion in the categorisation of 'physiological' to 'pathological' TWI in V_1-V_4, offering potential refinement to new international recommendations for interpretation in the male paediatric athlete ECGs. Study 4 (Chapter 7), using allometric modelling we present measures of cardiac chamber and aortic root morphology independent of body surface area, ethnicity, chronological, and biological age. We also presented chronological age independent LV and RV measures of function in male Arab and black paediatric athletes. This data may prove useful to the differential diagnosis in the paediatric athlete, with upper limits of physiological remodelling and lower limits of function defined by Z-scores to ease clinical interpretation. Furthermore, these data will allow for serial assessment relative to allometric growth in the paediatric athlete necessitating annual follow-up.

The empirical studies conducted within this thesis have furthered our understanding of the electrophysiological, structural and functional adaptations of the paediatric athlete's heart. It is hoped these works will aid cardiac screening within the paediatric athlete.

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CANDIDATE PUBLICATIONS

The contents of this thesis are the results of contributions from numerous people who I have worked alongside during the process and, therefore, a number of the chapters of the thesis have formed part of jointly authored peer reviewed publications.

Peer-Reviewed Journal Articles based on the work of this Thesis

Chapter 4 - **McClean, G**., Riding, N.R., Ardern, C.L., Farooq, A., Pieles, G.E., Watt, V., Adamuz, C., George, K.P., Oxborough, D. and Wilson, M.G., (2018) Electrical and structural adaptations of the paediatric athlete's heart: a systematic review with meta-analysis. British Journal of Sports Medicine, [online] 524, pp.230–230. Available at: http://bjsm.bmj.com/lookup/doi/10.1136/bjsports-2016-097052.

Chapter 5 – **McClean, G**., Riding, N.R., Pieles, G., Watt, V., Adamuz, C., Sharma, S., George, K.P., Oxborough, D. and Wilson, M.G., (2019) Diagnostic accuracy and Bayesian analysis of new international ECG recommendations in paediatric athletes. Heart, [online] 1052, pp.152–159. Available at: http://heart.bmj.com/lookup/doi/10.1136/heartjnl-2018-313466

Chapter 6 – **McClean, G**., Riding, N.R., Pieles, G., Sharma, S., Watt, V., Adamuz, C., Johnson, A., Tramullas, A., George, K.P., Oxborough, D. and Wilson, M.G., (2019) Prevalence and significance of T-wave inversion in Arab and Black paediatric athletes: Should anterior T-wave inversion interpretation be governed by biological or chronological age? European Journal of Preventive Cardiology, [online] 266, pp.641–652. Available at: http://journals.sagepub.com/doi/10.1177/2047487318811956.

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Conference Presentations

McClean G. How to interpret the ECG of paediatric athletes: can current recommendations be applied in paediatric athletes? *Anti-Doping Lab Qatar 6th Junior Symposium* 2018, Doha, Qatar.

McClean G. How to interpret the ECG of children practicing sports: can current recommendations be applied in pre-adolescent athletes? *EuroPrevent* 2018, Ljubljana, Slovenia.

Conference Abstracts

McClean G, Wilson MG, Pieles G, Watt V, Adamuz C, Shaw A, Riding N, George KP, Oxborough D, Prevalence of Major and Minor ARVC Criteria in Healthy Paediatric Arab and Black Athletes *EuroPrevent* 2018, Ljubljana, Slovenia.

McClean G, Riding NR, Ardern CL, Farooq A, Pieles G, Watt V, Adamuz C, George KP, George KP, Oxborough D, Wilson MG. Left Ventricular Morphology of the Paediatric Athletes Heart. *EuroPrevent* 2016, Nice, France.

ACRONYMS

2D	Two-Dimensional
A	Peak Late Mitral Diastolic Velocity
A'	Peak Late Diastolic Myocardial Velocity
AHA	American Heart Association
ARVC	Arrhythmogenic Right Ventricle Cardiomyopathy
ASE	American Society of Echocardiography
ATWI	Anterior T-Wave-Inversion
AUC	Area Under the Curve
BSA	Body Surface Area
CRBBB	Right Bundle Branch Block
CI	Confidence Interval
DEXA	Dual-Energy X-Ray Absorptiometry
DICOM	Digital Imaging and Communications in Medicine
DecT	Deceleration Time
E	Peak Early Mitral Diastolic Velocity
E'	Peak Early Diastolic Myocardial Velocity
ECG	Electrocardiogram
ESC	European Society of Cardiology
FA	Football Association
FIFA	Fédération Internationale De Football Association
FS	Fractional Shortening
HR	Heart Rate
IOC	International Olympic Committee
IRBBB	Incomplete Right Bundle Branch Block
IVSd	Intraventricular Wall Thickness During End-Diastole
Jt	J Termination
LA	Left Atria
LAD	Left Atrial Dimension
LBBB	Left Bundle Branch Block
LQTS	Long QT Syndrome
LR	Likelihood Ratio
LV Vol D	Left Ventricle Volume During End-Diastole
LV	Left Ventricle
LVEF	Left Ventricle Ejection Fraction
LVH	Left Ventricle Hypertrophy
LVIDd	Left Ventricle Internal Diameter During End-Diastole
LVIDs	Left Ventricle Internal Diameter During End-Systole
LVM	Left Ventricle Mass

M	Meters
M/S	Meters Per Second
Min	Minutes
Ml	Millilitres
Mm	Millimetres
MmHg	Millimetres of Mercury
Ms	Milliseconds
PE	Physical Examination
PRF	Pulse-Repetition Frequency
PRISMA	Preferred Reporting Items for Systematic Reviews And Meta-Analyses
PVCs	Premature Ventricular Contractions
PWTd	Posterior Wall Thickness During End-Diastole
Q	Cardiac Output
RA	Right Atria
RA_{area}	Right Atrial Area
RAD	Right Axis Deviation
$RA_{diammeter}$	RA Diameter
RAE	Right Atrial Enlargement
RFL	Rugby Football League
RFU	Rugby Football Union
ROC	Receiver Operator Curve
RSD	Regressed Standard Deviation
RV	Right Ventricle
RVD_1	Right Ventricle Basal Length
RVD_2	Right Ventricle Mid-Level Length
RVD_3	Right Ventricle Length
RVD_{area}	Right Ventricle Area During End-Diastole
RVS_{area}	Right Ventricle Area During End-Systole
RVESA	Right Ventricle End-Systolic Area
RVFAC	Right Ventricle Fractional Area Change
RVH	Right Ventricle Hypertrophy
$RVOT_1$	Right Ventricle Outflow Tract from a Proximal Level at a Parasternal Short-Axis Orientation
$RVOT_2$	Right Ventricle Outflow Tract from a Distal Level at a Parasternal Short-Axis Orientation
$RVOT_{PLAX}$	Right Ventricle Outflow Tract from a Parasternal Long-Axis Orientation
RWT	Relative Wall Thickness
S	Seconds
S'	Peak Systolic Myocardial Velocity
SCD/A	Sudden Cardiac Death/Arrest

SD	Standard Deviation
STE	Speckle Tracking Echocardiography
SV	Stroke Volume
TAPSE	Tricuspid Plane Systolic Excursion
TDI A'	Tissue Doppler Imaging During Late Diastole
TDI E'	Tissue Doppler Imaging Early Late Diastole
TDI S'	Tissue Doppler Imaging During Systole
TDI	Tissue Doppler Imaging
TWI	T-Wave-Inversion
UEFA	Union of European Football Associations
UK	United Kingdom
USA	United States of America

CHAPTER 1:

GENERAL INTRODUCTION

1.1 BACKGROUND

Sudden cardiac death (SCD) is a truly catastrophic, emotional event in the athlete; devastating for families of victims, peers, clubs and the sporting community as a whole. The cardiac arrest of Bolton professional football player Fabrice Muamba in March of 2012 aged 24 years is a testament of the intense public emotion such events create. However, SCD is not limited to the adult athlete, extending to the rising stars of tomorrow. The definition of a child playing sport is however ambiguous with various terms and age ranges (including, but not limited to children, adolescent, youth, scholar, pre-pubertal, peri-pubertal, high-school athlete, student-athlete), adopted within the scientific literature. Although the American Academy of Pediatrics recommends that paediatric healthcare services are delivered up until the age of 21 years (James, 1988), for the purposes of this thesis and in consideration of a UK governmental international comparison of selected service lines in seven health systems (UK Government, 2014) , the term paediatric is adopted and is concerned among only those ≤18 years old. Indeed SCD occurs in as many as 6.8 per 100,000 previously screened paediatric soccer players (Malhotra et al., 2018), higher than previously considered estimates of 2 per 100,000 (Harmon et al., 2014). Further, of all SCDs in athletes which occur in the UK, 22% occur in those aged under 18 years (Finocchiaro et al., 2016b). Accordingly, the European Society of Cardiology (ESC) (Corrado et al., 2005b) and the Association of European Paediatric Cardiology (Fritsch et al., 2017) recommend initiating cardiac screening at the onset of

competitive athletic activity, with the aim of identify underlying cardiac pathology predisposing to increased risk of sudden cardiac death/arrest (SCD/A), and, thereby reducing the incidence of such catastrophic events. The implementation of cardiac screening within the paediatric athlete is, however, regarded by some to be the 'impending dilemma' of sports cardiology (Léger et al., 2015).

An integral part of cardiac screening is the 12-lead-electrocardiogram (ECG). The 12-lead ECG is endorsed as a first-line screening tool, in addition to a physical examination and family history questionnaire by the European Heart Rhythm Association and the European Association of Preventative Cardiology (Mont et al., 2017). The performance of a 12-lead ECG within the paediatric athlete is, however, controversial (Friedman, 2014; Vetter, 2014), in view of a lack of international consensus with regards to undertaking such examinations. Regular and sustained athletic training is widely recognised to induce numerous electrophysiological changes (Drezner et al., 2013d), whilst ethnicity is universally recognised to impact upon the nature and magnitude of presentation (Papadakis *et al.*, 2012; Wilson *et al.*, 2012; Riding, Salah, *et al.*, 2014) in the adult athlete's heart. Comparatively, little is known regarding electrophysiological remodelling and the relative impact of ethnicity within the paediatric athlete. Furthermore, the paediatric ECG is different in appearance to the adults', changing during physical growth and maturation, making distinction between a marker of physiological adaptation and cardiac pathology more complex. Until recently, recommendations for ECG interpretation in athletes were constrained to the adult (Corrado et al., 2010; Drezner et al., 2013b, d, a; c), with only non-athlete derived paediatric reference values available (Davignon et

al., 1980; Rijnbeek et al., 2001; Molinari et al., 2016; Saarel et al., 2018a). It is, therefore, imperative that a greater understanding of the paediatric athletes ECG is obtained. This may offset the 'impending dilemma' of undertaking cardiac screening within the paediatric athlete across sports academies in North America, South America, Europe, Asia, and Australasia. It is hoped this will reduce the risk of false positive/negative diagnosis.

An echocardiogram overcomes many of the inherent limitations of the 12-lead-ECG as a screening tool for cardiac pathology that may predispose to an increased risk of SCD/A. Accordingly, some sporting organisations (Mont et al., 2017) advocate its use as a first-line screening tool to assess cardiac structure and function. Chronic training loads are recognised to induce bi-ventricular (Whyte *et al.*, 2004; Oxborough *et al.*, 2012; D'Andrea *et al.*, 2013; Utomi *et al.*, 2013) and bi-atrial (D'Ascenzi et al., 2014; McClean et al., 2015) physiological remodelling in the adult athlete, and, therefore, can be considered to be part of a 'whole-heart' athlete's heart phenomenon. The magnitude of which is understood to be underpinned by sporting discipline (Pluim et al., 2000; Utomi et al., 2013), training volume (Beaudry et al., 2016), ethnicity (Papadakis et al., 2012), body surface area (BSA) (Batterham et al., 1999), sex (Whyte *et al.*, 2004), and chronological age (Sharma et al., 2002; Makan et al., 2005a; Koch et al., 2014). Comparatively, little structural and functional data is available within the paediatric athlete population (Sharma *et al.*, 2002; Makan *et al.*, 2005b; Di Paolo *et al.*, 2012; Sheikh *et al.*, 2013; Calò *et al.*, 2015), with a lack of reference values available making the use of echocardiography in any differential diagnosis somewhat complex.

1.2 OVERARCHING AIM

The overarching aim of this thesis is to provide a comprehensive assessment of the competitive Arab and black paediatric athlete, using 12-lead-ECG and 2D echocardiography. This has direct implications and translation to pre-participation screening in these groups. The athletic heart phenotype in these paediatric athletes will also be considered relative to the impact of maturity status, chronological age, and ethnicity. To achieve this overarching aim, a literature review (Chapter 2) is first conducted, before a description of the general methods (Chapter 3) common to all original data collection contained within this thesis is provided. This section is then followed by four empirical studies (Chapters 4-7). The thesis concludes with a general discussion (Chapter 8), summarising the key findings from all of the studies, whilst providing consideration to future research.

CHAPTER 2:

LITERATURE REVIEW

2.1 WHAT IS A PAEDIATRIC ATHLETE?

The definition of a paediatric athlete is ambiguous. We are often asked, what is a paediatric and what differentiates a child playing in the playground with his peers to that of an athlete? The term used to describe this heterogenous population various significantly within the scientific literature as authors seek to accurately describe the population studied. As a consequence, a barrier is presented to the non-expert reader, whom wishes to relate the findings of various articles to their research or clinical practice. For the purposes of this Ph.D. thesis we will adopt the terminology, paediatric. Although the American Academy of Pediatrics recommends that paediatric healthcare services are delivered up until the age of 21 years (James, 1988), in consideration of a UK governmental international comparison of selected service lines in seven health systems (UK Government, 2014), the term paediatric is adopted and is concerned of only those ≤18 years old.

In reality, sports academies are the vehicle by which national governing bodies often develop talented sports stars of the future and, in recent decades, have undergone significant professionalisation to achieve this goal. Accordingly, coaches and practitioners attempt to develop paediatric athletes, chasing up to 10,000 accumulated hours of deliberate practice (Hambrick et al., 2014), utilising long-term athlete development

models (Bergeron et al., 2015; Lloyd et al., 2015a; b). In the case of the 'Elite Player Performance Plan', set by the UK football (soccer) academy system, formal registration commences at the chronological age of just 9 years (League, 2011). Since its establishment in 1998, the number of required contact hours for coaching has increased from 3760 (accumulated incrementally from chronological age 9 to 21 years) (League, 2011) to 8500 contact hours at the highest academy classification category. Whilst this process has perhaps been melodramatically compared to that of the Spartan military training of 'agoge' (Murray, 2017), in view of significant training volumes, and some paediatric athletes being separated from their families as they chase their dream (Weedon, 2012), this populations status as athletes is undisputed.

2.2 ROLE OF CARDIAC SCREENING IN PAEDIATRIC ATHLETES

Ultimately everyone wishes to reduce the incidence rate of SCD/A, but SCD/A is not a disease or medical condition, instead it is an outcome of a broad spectrum of diseases or conditions. The role, therefore, of cardiac screening within the paediatric athlete is to promote early detection of cardiac pathologies associated with SCD/A, which may reduce morbidity and mortality through individualised and evidence-based disease-specific management, but cannot be irrevocably ruled out (Cohen et al., 2012a; Johnson and Ackerman, 2012; Aziz et al., 2015; Maron and Zipes, 2015; Baggish et al., 2017).

The recommendation to undertake cardiac screening within paediatric athletes has often been framed as a binary 'all or none' response (Léger et al., 2015). In view of providing a

pragmatic approach and for the purposes of this review, we will first consider the rationale for cardiac screening in paediatric athletes, in line with the proposals of the American Medical Society for Sports Medicine (Figure 2.1). Consideration hereafter will be provided to the paediatric athlete's risk of SCD/A; cardiac conditions which may predispose to an increased risk of SCD/A; Association, National, and sporting requirements for cardiac screening in the paediatric athlete; the potential benefits and harm that may be caused by cardiac screening in this population; and the available resources, in this case, our current understanding of the paediatric athlete's heart by 12-lead ECG and echocardiographic assessment.

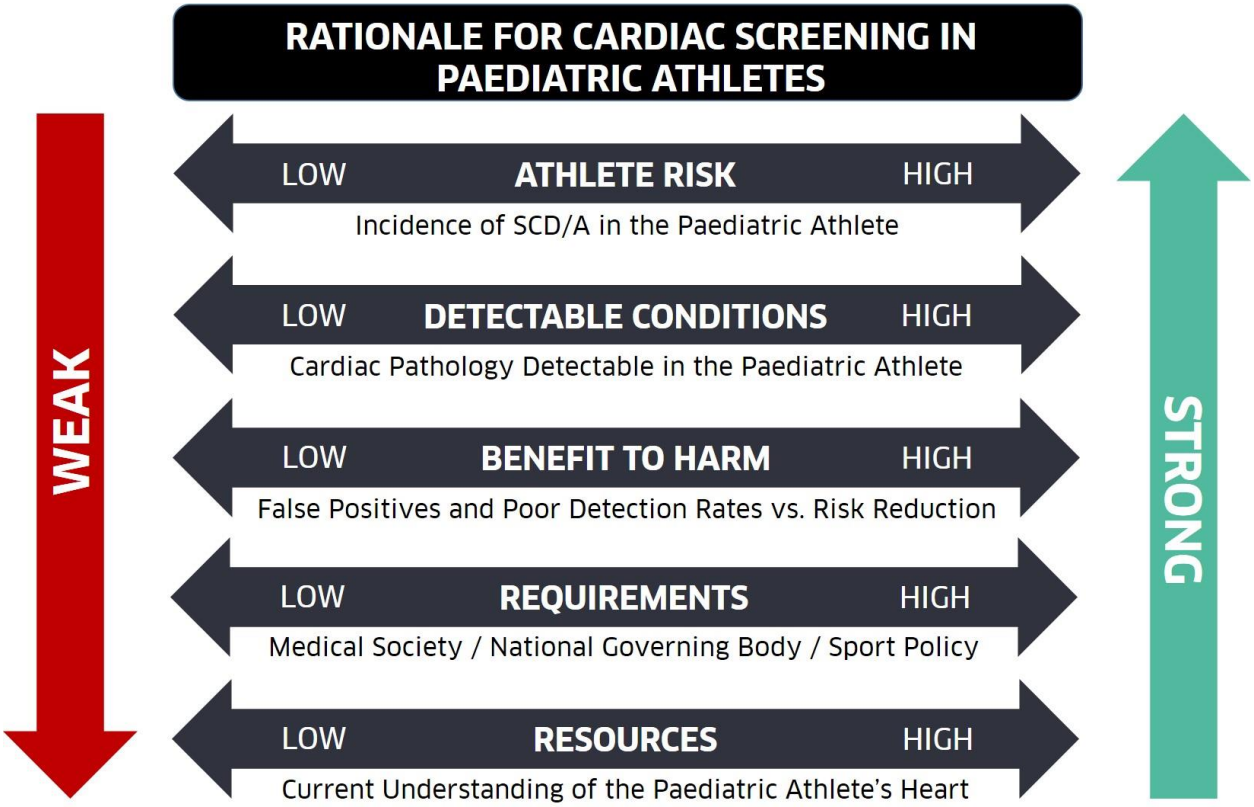

Figure 2. 1 Major considerations and strength of rationale for cardiac screening in the paediatric athlete, an adaptation of the American Medical Society for Sports Medicine proposed paradigm (Drezner et al., 2016).

2.2.1 RISK OF SCD/A TO THE PAEDIATRIC ATHLETE

Fatal cardiac events are believed to be uncommon (Maron et al., 2007; Roberts and Stovitz, 2013). The estimated incidence of SCD/A reported in the paediatric athlete, varies greatly, subject to the study methodology employed (Table 2.1). Specifically, comparison is made difficult in view of differences in reporting systems, the study population (sex, sporting discipline, ethnicity and the inclusion/exclusion of non-paediatric [≥18 years] athletes) (Corrado et al., 2003; Steinvil et al., 2011; Vetter et al., 2014; Bohm et al., 2016; Malhotra et al., 2018; Sweeting and Semsarian, 2018), the geographic area, , the variable definition of a competitive athlete, the exclusion of non-exertional events (Maron et al., 1998; Roberts and Stovitz, 2013), events occurring outside school (Maron et al., 1998; Drezner et al., 2009; Toresdahl et al., 2014) and SCA events (Maron et al., 1998, 2013; Roberts and Stovitz, 2013; Malhotra et al., 2018); with a survival rate dependent on the availability of an automated external defibrillator and emergency responders (Kovach and Berger, 2012; Drezner et al., 2013e, 2018). Accurate determination of incident rates of SCD/A within the paediatric athlete are further limited by retrospective study design (Maron et al., 1998, 2013; Roberts and Stovitz, 2013; Drezner et al., 2014; Toresdahl et al., 2014; Harmon et al., 2016), the use of only media reports (Steinvil et al., 2011; Drezner et al., 2014; Toresdahl et al., 2014; Harmon et al., 2016), and/or catastrophic insurance claims (Maron et al., 1998; Roberts and Stovitz, 2013), and the lack of longitudinal outcome data from those who have previously underwent cardiac pre-participation evaluation (Maron et al., 1998, 2013; Drezner et al., 2009, 2014; Roberts and Stovitz, 2013; Toresdahl et al., 2014; Harmon et al., 2016; Landry et al., 2017), until now (Malhotra et al., 2018). Ultimately, a true understanding of the relative risk of SCD/A within this population cannot be determined if the precise

number of events (numerator) and the population at risk (denominator) are not clearly defined.

Table 2. 1 Incidence Studies of Sudden Cardiac Arrest/Death in the Paediatric Athlete.

Article	Population	Age Range	Study Design	Case Identification	Denominator	Exertional deaths or all	SCD or all SCA/Ds?	Number of years	Annual Incidence
(Maron et al., 1998)	High School Athletes	16-17	Retrospective cohort	Insurance Claims	Minnesota State High School League	Exertional, only during the school-sponsored events	SCD	12	Overall, SCD: 1: 217,000 Male, SCD: 1: 129,000
(Drezner et al., 2009)	High School Athletes	14-18	Cross-sectional survey	Survey from 1710 High Schools with AEDs	Number of student athletes reported by schools	SCA/D occurring on campus	SCA + SCD	0.5	Overall, SCD: 1: 46,000 Overall, SCA/D: 1: 23,000
(Maron et al., 2013)	High School Athletes	12-18	Retrospective cohort	US Registry of Sudden Death in Athletes	Minnesota State High School League	All	SCD	26	Overall, SCD: 1: 150,000 Male, SCD: 1: 83,000
(Roberts and Stovitz, 2013)	High School Athletes	12-19	Retrospective cohort	Catastrophic insurance claims	Minnesota State High School League	Exertional, only during the school-sponsored events	SCD	19	Overall, SCD: 1: 417,000

(Drezner et al., 2014)	High School Athletes	14-18	Retrospective cohort	Media reports	National Federation of State High School Associations	All	SCA + SCD	10	Overall, SCD: 1:154,000 Overall, SCA/D: 1:71,000 Male: 1:37,000 Male, basketball: 1:21,000
(Toresdahl et al., 2014)	High School Athletes	14-18	Retrospective cohort	Media reports	Minnesota State High School League	All, cases occurring on the school campus	SCA + SCD	13	Overall, SCA/D: 1: 87,720 Male, SCD/D: 57,804
(Harmon et al., 2016)	High School Athletes	14-18	Retrospective cohort	Media reports	National Federation of State High School Associations	All	SCA + SCD	6	Overall, SCD: 1: 69,000 Overall, SCA/D: 1: 45,000 Male, SCA/D: 1:44,832 Male, Basketball SCA/D: 1:37087
(Landry et al., 2017)	Competitive Athletes	12-17	Prospective cohort	Rescu Epistry cardiac arrest database	Registered athletes with a sporting	All out-of-hospital cases	SCA	5	Overall, SCA: 1: 83,333

					organisation in Ontario				
(Malhotra et al., 2018)	Elite Adolescent Soccer Players	15-17	Prospective cohort	FA Voluntary Database, Health professional Survey, and Media Reports	Number of athletes screened	All	SCD	23	Male, SCD 1:14,706 White, SCD 1: 25,880 Black, SCD: 1: 3,708

AEDs, automated external defibrillator; FA, Football Association; SCD, sudden cardiac death; SCA, sudden cardiac arrest.

Mandatory reporting systems afford the most reliable results, although few exist (North Lincolnshire and Goole Hospitals NHS Foundation Trust, 2009). Accordingly, in the investigations of Roberts and Stovitz (2013) to determine the risk of SCD in Minnesota High School athletes, case identification was provided by catastrophic insurance claims only, over a 19-year period (1993 to 2012), yielding a low incidence rate; 1 in 417,000. Insurance claims exclude cases that occur during individual activity, unofficial practices or deaths which occur outside of sport. Upon revaluation of cases identified by the use of media reports over the last 10 years of the study period (2003 and 2012). Drezner *et al.,* (2014) identified 13 cases of SCA in Minnesota High School athletes (all in males), including 6 cases of SCD and 7 cases of SCA in student-athletes who survived. Of these 6 SCDs documented in media reports, only 1 would have been eligible for death benefits from an insurance claim. Accordingly, Drezner *et al.,* (2014) revealed the incidence of SCD to be 1 in 154,000, the incidence of SCD/A to be 1 in 71,000. If including only male athletes the incidence of SCD/A was 1 in 37,000 and if including only male basketball players, the incidence of SCD/A was 1 in 21,000. Such disparity clearly underscores the value of evaluating study design when considering the true risk of SCA/D to the male paediatric athlete.

The risk of SCD/A in the athlete has previously been described by the American Heart Association to be similar to that of a lightning strike fatality (Maron et al., 2014). Upon careful evaluation, using statistics from the National Oceanic and Atmospheric Administration (www.lightningsafety.noaa.gov/victims.htm), we understand that between 2008-2018, there were on average 27.4 lightning strike fatalities per year in the USA. In

view of an average population of 316,000,000 as per US Census Bureau data during this observational period, yields a lightning strike fatality incident rate of 1 in 11,532,849. Comparatively different to new findings from Malhotra *et al.,* (2018), employing a rigorous prospective study design, adopting case identification through the development of a voluntary report database, supplemented by sending surveys to healthcare professionals at each of the 92 Football Association-affiliated clubs, and by regular internet searches. Accordingly, Malhotra *et al.,* (2018), revealed the incident rate of SCD in the previously screened paediatric soccer player to be 1 in 14,794, constituting a 779.5-fold increased risk compared to a lightning strike fatality. If considering only the previously screened black male paediatric soccer player, the incidence of SCD was found to be 1 in 3,708, constituting a 3,708-fold increased risk. It, therefore, may be considered that a male paediatric athlete, is of substantially greater risk to SCD/A than a lightning strike fatality and of sufficient risk to warrant cardiac screening.

2.2.2 DETECTABLE CARDIAC CONDITIONS AND COMMON CAUSES OF SCD IN THE PAEDAITRIC ATHLETE

Cardiac pathology that may predispose to an increased risk of SCD/A, has been found to be present in as many as 1 in 100 or 1 in 265 paediatric athletes, who present for first-time cardiac evaluation (Grazioli et al., 2017; Malhotra et al., 2018). Such conditions often comprise of a variety of structural cardiovascular abnormalities (i.e., cardiomyopathies) and primary electrical diseases (i.e., channelopathies) that are often clinically silent and are unlikely to be suspected or detected on basis of spontaneous symptoms (Corrado et al., 2011), with fatal presentation often the first and only manifestation (Maron, 2003). In

the case of the previously screened paediatric soccer players in the UK, 12.5% may go undetected, with the first presentation being SCD, despite 12-lead ECG and echocardiogram assessment at a mean chronological age of 16 years (Malhotra et al., 2018). Recent investigations from the United Kingdom (UK), entailing detailed post-mortem examination, associated structural heart disease to 44% of SCDs among paediatric athletes (Finocchiaro et al., 2016b). Specifically, coronary artery abnormalities (11%), idiopathic left ventricular hypertrophy/fibrosis (10%), arrhythmogenic right ventricular cardiomyopathy (6%), hypertrophic cardiomyopathy (6%), myocarditis (2%) among other structural diseases (9%) (Finocchiaro et al., 2016b). Investigations were, however, limited to one tertiary referral hospital, were challenging cases with ambiguous autopsy findings are sent by local pathologists. It is, therefore, likely that a referral bias may have contributed to the significant proportion (56%) of cases, wherein no structural or myocardial disease was identifiable upon autopsy in the paediatric athlete; otherwise known as sudden arrhythmic death syndrome (SADS). Yet, a prevalence of SADS in 31% of USA collegiate athletes (Harmon et al., 2015a) and 23% of USA young military personnel (Eckart et al., 2006), together, with a prevalence rate 12% greater than that observed in athletes aged 18-35 years (Finocchiaro et al., 2016b), underscores the importance of the detection of such pathologies which fall under the umbrella diagnosis of SADS in the paediatric athlete. These cases include the inherited channelopathies of long QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia and Wolf-Parkinson-White syndrome (Asif and Harmon, 2017; Peterson et al., 2018; Sweeting and Semsarian, 2018).

2.2.3 THE HARMS AND BENEFITS OF UNDERTAKING CARDIAC SCREENING IN THE PAEDIATRIC ATHLETE

It has been proposed that cardiac pre-participation screening in athletes has 1) low potential to reduce deaths because of its '*poor detection rate and the uncertain effectiveness of the management of the diseases'* and 2) *'induces harm because of the high number of false positive test results leading to temporary or lifelong disqualification from competitive sports, psychological and financial harm, and medical follow-up and treatment with unknown benefit*.' These views were expressed by a health economist, in a *BMJ* report (Brabandt et al., 2016). Accordingly, it was subsequently recommended that '*as long as those at high risk of sudden death cannot reliably be identified and appropriately managed, young athletes should not be submitted to pre-participation screening'*.

2.2.3.1 Can cardiac screening identify cardiac pathology in the paediatric athlete?

In agreement with such recommendations, ~80% of athletes who suffer SCD/A (Finocchiaro et al., 2016b), and ~86% of paediatric athletes whom harbour a cardiac pathology that may predispose to SCD/A (Price *et al.*, 2014; Calò *et al.*, 2015; Grazioli *et al.*, 2017), have no documented warning symptoms by medical questionnaire and/or physical examination at the time of cardiac screening (Table 2.2). Conversely, ECG-inclusive cardiac screening, with interpretation led by either ESC 2010 recommendations or Seattle criteria, detects ~70% of cardiac pathologies that may predispose to SCD/A in the paediatric athlete (Price *et al.*, 2014; Calò *et al.*, 2015; Grazioli *et al.*, 2017), with a relatively small false positive rate (5.5%) (Table 2.2). It, therefore, seems reasonable to

suggest that paediatric athletes of predominantly white ethnicity at high risk of SCD/A can be readily identified by ECG-led cardiac screening. The impact of ECG-led cardiac screening in other populations of athletes such as male Arab and black paediatric athletes is unknown.

Table 2. 2 Sensitivity, Specificity, False Positive and Negative Rate Studies in the Paediatric Athlete.

Author	Country	Population	Chronological Age Range, Years	*N*	ECG Criteria	Sensitivity, %		Specificity, %		False Positive Rate, %		False Negative Rate, %	
						HQ + PE	ECG	HQ + PE	ECG	HQ + PE	ECG	HQ + PE	ECG
(Price *et al.*, 2014)	USA	Student athletes	14-18	2017	ESC 2010	40.0	100	85.3	97.2	14.7	2.8	60.0	0.0
(Calò et al., 2015)	Italy	Competitive Soccer Players	8-18	2261	ESC 2010	0.0	100	98.1	92.0	1.9	8.0	100	0.0
(Grazioli et al., 2017)	Spain	Competitive Athletes	12-18	1650	Seattle	6.3	56.3	94.9	96.6	5.1	3.4	93.8	43.8
Total			8-18	6083		13.6	68.2	92.9	94.5	7.1	5.5	86.4	31.8

ECG, 12-lead electrocardiogram; ESC 2010, European Society of Cardiology; HQ + PE, health questionnaire and physical examination

2.2.3.2 What are the benefits of undertaking cardiac screening in the paediatric athlete?

To ascertain the benefit of cardiac screening in the athlete, Van Brandet *et al.,* (2016), proposed that it be necessary to undertake a randomised controlled trial, subjecting only a selection of athletes to cardiac screening, leaving others to compete without any medical clearance. Whilst this may be considered an ethically improbable investigation, in view of the potential sinister outcome. We do, however, understand that mandatory screening has the potential to reduce incidence rates of SCD by up to 90% (Corrado et al., 2006). In criticism of such observations, Van Brandet *et al.,* (2016), correctly state that the incident rate of 3.6 in 100,000 observed before imposing mandatory cardiac screening was based on just 14 cases of SCD. Secondly, Van Brandet et al., (2016), note that the post mandatory cardiac screening rate of 0.4 in 100,000 is similar to that previously observed in the Minnesota high school athlete of 0.2 in 100,000 (Roberts and Stovitz, 2013). Finally, based on the conclusions of cardiac screening in Israel (Steinvil et al., 2011), it may be considered plausible that mandatory ECG screening of athletes has no apparent effect on their risk for cardiac arrest, and that the observed 90% reduction in the risk of SCD observed within the Veneto region of Italy (Corrado et al., 2006), is the result of simple sample variation and not cardiac screening when considering this evidence alone. However, one wonders if such a drop off was merely the result of simple sample variation, why did it take nearly 8 years before a drop off was observed? Secondly, it must be acknowledged that investigations detailing low incident rates in the USA high school athlete (Roberts and Stovitz, 2013), and that into the impact of cardiac screening within Israel (Steinvil et al., 2011), rely on case identification by media reports alone. A case identification tool understood to identify as low as 20% of SCD cases in athletes (Holst et

al., 2010). Finally, attention must be paid to the largest outcome study from cardiac screening in the paediatric (mean age 16.4±1.2 years) soccer player to date. Of the 42 athletes identified with cardiac pathology associated with SCD, almost 3 in 4 returned to play following corrective surgery and/or risk stratification (Malhotra et al., 2018), underscoring the truly positive impact of cardiac screening in the paediatric athlete.

2.2.3.3 What are the harms of undertaking cardiac screening in the paediatric athlete?

Van Brandet *et al.,* (2016) proposed that cardiac screening may induce anxiety and psychological harm. Propositions comparatively different to the perspectives expressed by the USA high-school athlete undergoing cardiac screening, wherein almost 3 in 4 wanted to learn if they had a cardiac abnormality prior to competition and among those with a false positive finding, no difference were observed in post screen anxiety (Asif et al., 2014). Furthermore, concerns were raised regarding a lack of treatment consensus in the asymptomatic individual. Specifically, consensus may lack owing to the potential risks and complications from such invasive procedures (Hamilton, 2016; Olde Nordkamp et al., 2016). Among paediatrics athletes diagnosed with long QT syndrome, individualised management, in-depth counselling, and treatment compliance has been associated with low cardiac event rates and no deaths in two independent cohorts of young athletes (Johnson and Ackerman, 2012; Aziz et al., 2015). Wolf-Parkinson-White syndrome, which accounts for ~62% of cardiac pathologies detected by cardiac screening in the paediatric (mean age 16.4±1.2 years) soccer player (Malhotra et al., 2018), is treatable by ablation, with paediatric specific consensus guidelines available, defining risk stratification and management strategies (Cohen et al., 2012a). Implantable cardioverter

defibrillators in paediatric patients are associated with complex challenges in terms of implantation and programming (Silka and Bar-Cohen, 2006). Indeed, follow-up is complicated by multiple device replacements, increasing the risk of infection, lead failure, and/or both appropriate and inappropriate shocks (Alexander et al., 2004; Korte et al., 2004; Ten Harkel et al., 2005). Despite such complications and concerns, implantable cardioverter-defibrillators have significantly improved survival rates in large hospital-based cohorts of paediatric and young adults with hypertrophic cardiomyopathy (Maron et al., 2016).

In further appeasement to the potential of 'temporary or lifelong disqualification from competitive sports, and financial harm' (Brabandt et al., 2016) cardiac screening in the paediatric athlete may induce. Recent calls have been made, for a shared decision making process with an ultimate goal of promoting safety without unnecessary risk aversion (Baggish et al., 2017) in addition to recent advancements in exercise training prescribed to hypertrophic cardiomyopathy patients (Dias et al., 2018; Saberi and Day, 2018) (Dias et al., 2018; To et al., 2018), allowing for a healthy and sustainable lifestyle free from cardiometabolic diseases, associated with physical inactivity. Calls which will further increase the benefit to harm ratio of cardiac screening in paediatric athletes. In fitting with such data, the most recent American Heart Association and American College of Cardiology recommendations stated that competitive sports may be allowed in selected athletes with an implantable cardioverter-defibrillator (Zipes et al., 2015).

2.2.4 MEDICAL SOCIETY, NATIONAL, AND SPORTING REQUIREMENTS FOR CARDIAC SCREENING IN THE PAEDIATRIC ATHLETE

On the basis of medical, ethical and legal justification, cardiac screening in the athlete is endorsed by the American College of Cardiology/American Heart Association (Maron et al., 2015) the ESC (Corrado et al., 2005a), and the Association of European Paediatric Cardiology (Fritsch et al., 2017). Whilst all respective organisations recommend the inclusion of a medical questionnaire, and physical examination, only the ESC and the Association of European Paediatric Cardiology recommend the inclusion of a 12-lead ECG (Corrado et al., 2005a). Yet, its implementation to paediatric athletes across Europe has sparked concern among investigators, described by some to be the impending dilemma of sports cardiology (Léger et al., 2015). Concerns expressed from the perspective that characteristics of the pre-pubertal ECG and of the phenotypical manifestation of SCD-related disease in children will result in less specific and less sensitive ECG-based screening programs. Accordingly, some recommended that cardiac screening within the paediatric athlete should be limited to a medical questionnaire, and physical examination only (Léger et al., 2015). This is despite the well documented significant limitations in the relative diagnostic capacity and cost-effectiveness of cardiac screening assessment without ECG (Harmon et al., 2015b).

In application, which paediatric athletes undertake cardiac screening, and by what examinations, greatly varies across Europe. Annual cardiac screening by physical examination, medical questionnaire and ECG is mandatory by law in Italy, and more recently now in Greece, for any individual wishing to partake in competitive sport including

paediatric athletes aged 8 years and above (Table 2.3). Comparatively, across the UK, Spain and France, cardiac screening recommendations are driven by national governing bodies, regional policy and national societies of cardiology (Table 2.3). Indeed in some countries, no cardiac screening of any sort is endorsed (Holst et al., 2010; Risgaard et al., 2016) .

Table 2. 3 European National Cardiac Screening Policies for the Paediatric Athlete.

Country	Medical/Sports Association	Target Athletic Population		Mandatory /Recommended	Primary Screening Methodology				Frequency	Funding
		Athlete Status	Chronological Age, Years		HQ + PE	ECG	Stress ECG	Echocardiogram		
Italy	Law	Competitive	8	Mandatory	✔	✔	✔		Annual	NHS
Greece	Law	Competitive	8	Mandatory	✔	✔			Annual	NHS
England	EIS	Competitive	14	Recommended	✔	✔			Biannual	Charity Funded
	FA/PFA	Elite and/or Academy Scholars	16	Recommended	✔	✔		✔	Repeat assessment at 18, 20 and 25 years-old	PFA
	British Cycling	Elite and/or Academy Scholars	14	Mandatory	✔	✔			Biannual	Research
	LTA	Competitive	14	Recommended	✔	✔			Biannual	LTA
	RFU/ Gallagher Premiership	Elite and/or Academy Scholars	16	Recommended	✔	✔			Biannual until 20-years-old.	Club and NGB
	RFL/Super League	Elite and/or Academy Scholars	15	Recommended	✔	✔			Annual	Club and NGB
France	French Society of Cardiology	Competitive	12	Recommended	✔	✔			Triannual until 20-years-old. Every 5 years until	Athletes

										35-years-old.	
Spain	Catalan Consensus	Competitive	12	Recommended	✔	✔				Biannual	Club and NGB

EFL, English Football League; EIS, English Institute of Sport; EPL, English Premier League; FA, Football Association; LTA, Lawn Tennis Association; M+PE, Health questionnaire and Physical Examination; NGB, National Governing Body; NHS, National Health System; PFA, Players Football Association; RFL, Rugby Football League; RFU, Rugby Football Union.

Protection of athlete health, however, is in some instances governed by major international sporting bodies, irrespective of national policy. The Union of European Football Associations (UEFA), mandate pre-tournament cardiac screening, inclusive of medical questionnaire, physical examination, ECG and echocardiographic assessment, for all athletes competing at the UEFA (Union of European Football Associations, 2017), Under-17 Championship. Furthermore, the International Triathlon Union mandate pre-competition cardiac screening, inclusive of medical questionnaire, physical examination, and ECG for all athletes competing in the Under-16 Junior category, and strongly recommend it to all athletes competing in sub-Junior categories. Whereas, the International Olympic Committee (IOC), simply recommend cardiac screening prior to competing in the Summer or Winter Youth Olympic Games (Mountjoy et al., 2015), recommending the adoption of a tailored health evaluation programme (Adami et al., 2018). In application, within adult athletes, it is understood that most countries (70%) performing at the 2016 Olympic Games, undertake annual cardiac screening of their athletes, with 85% implementing a personal and family history and 75% also employing a 12-lead-ECG (Pelliccia and Drezner, 2019). However, international implementation across paediatric athletes competing at the Youth Olympic Games is, unknown.

2.2.5 CURRENT KNOWLEDGE AND UNDERSTANDING OF THE PAEDIATRIC ATHLETE'S HEART

To be effective, a cardiac screening program within the paediatric athlete relies on clinicians knowledgeable in paediatric athlete-specific ECG interpretation and echocardiographic assessment. Our understanding of what electrophysiological (Sharma

et al., 1999; Bessem et al., 2015), structural, and functional cardiac adaptations (Sharma et al., 2002; Makan et al., 2005b) to expect when presented with a paediatric athlete of heterogeneous ethnicity, sporting discipline, maturity status, and chronological age, for cardiac screening however, is relatively limited in comparison to adults (Pluim et al., 2000; Utomi et al., 2013). Implementation of cardiac screening in the paediatric athlete, therefore, risks triggering high false-positive rates and false-negative findings, with the potential outcome fatal. We, therefore, turn the attention of this review to our current understanding of the paediatric athlete's 12-lead ECG and echocardiogram.

2.3 THE PAEDIATRIC ATHLETES ECG

Before consideration is provided to the impact of regular and sustained physical activity on the paediatric athlete's ECG, an understanding of the non-athlete's paediatric ECG is essential. This allows for accurate differentiation between what may be a product of chronological age (Papadakis et al., 2009; Calò et al., 2015; D'Ascenzi et al., 2018a), maturity status (Migliore et al., 2012; D'Ascenzi et al., 2017d), training (Brosnan et al., 2014b; D'Ascenzi et al., 2017d), or perhaps, the first and only sign of cardiac pathology (Wilson and Carre, 2015). Interpretation of the paediatric ECG is widely regarded to be challenging, leading to wide variability in interpretation. In one study, 53 experienced members of the Western Society of Paediatric Cardiology, presented with 18 ECGs; specifically, 10 indicative of cardiac pathology predisposing to SCD/A (1 with long QT syndrome; 4 with hypertrophic cardiomyopathy; 2 with Wolff–Parkinson–White syndrome; 1 with pulmonary arterial hypertension; 2 with myocarditis) and 8 indicative of a normal heart. Correct ECG interpretation varied by 34–98% (Hill et al., 2011).

Challenges in the interpretation of the paediatric ECG are largely attributable to a gradual transition of right (RV) to left ventricle (LV) dominance with increased chronological age. Specifically, progression to adulthood leads to decreased pulmonary pressure resistance and increased systemic blood pressure; contributing to a decreased RV mass dominance. LV dominance may be established by 6 months in the paediatric, reflected in an LV to RV weight ratio of 2:1 (Park and Guntheroth, Warren, 2006). Changes persist into early adulthood, reflected in a slow but progressive increase in LV mass until complete formation of ventricular mass, with an LV to RV weight ratio of 2.5:1 (Park and Guntheroth, Warren, 2006). In view of such challenges, investigators from Canada (Davignon et al., 1980), Netherlands (Rijnbeek et al., 2001), Italy (Molinari et al., 2016) and most recently the USA (Saarel et al., 2018a), have endeavoured to characterise the developmental changes presented on the paediatric ECG, leading to the establishment of an array of reference values, which account for sex, chronological age, and heart rate (HR), as a result of research backdating almost 40 years.

As a product of such research, it is understood that whilst HR demonstrates an inverse relationship with chronological age, PR, QRS, and QT intervals increase in duration (Park and Guntheroth, Warren, 2006), likely attributable to an increased vagal dominance. It is understood, that the QRS complex transitions from a large R wave amplitude (increased R-S-wave ratio) in V_1 and V_2, and a small R wave amplitude (decreased R-/S-wave ratio) in leads V_5 and V_6; reflecting rightward QRS axis, to a normal axis: R-wave amplitude decreases in leads V_1 and V_2 and increases in leads V_5 and V_6. Consequently, it is not

uncommon to observe incomplete right bundle branch block (IRBBB) and RV hypertrophy (RVH) on the paediatric ECG. Furthermore, paediatrics typically present thin chest walls, reflected in large voltages indicative of LV hypertrophy (LVH) on the ECG. Accordingly, LV voltage criteria (SV_1 + RV_5/V_6) within the paediatric non-athlete is governed by chronological age (upper limits: 8-12 years > 64 mm vs. 12-16 years > 48 mm) (Park and Guntheroth, Warren, 2006).

In correlation to a gradual transition of RV to LV dominance, repolarisation in the form of T-wave-inversion (TWI) reverses in polarity from being predominantly negative across leads V_1-V_5, to progressively positive from V_5-V_1, with growth and maturation (Davignon et al., 1980; Rijnbeek et al., 2001; Park and Guntheroth, Warren, 2006; Chan et al., 2008; Molinari et al., 2016; Saarel et al., 2018b). TWI confined to V_1-V_3 in the absence of other ECG abnormalities is therefore termed the 'Juvenile T wave pattern' in the paediatric with a chronological age <16 years, but occasionally presents in the paediatric ≥16 years (Drezner et al., 2017; Sharma et al., 2017b, 2018).

2.3.1 ELECTROPHYSIOLOGICAL ADAPTATIONS OF THE PAEDIATRIC ATHLETE

Preliminary findings in paediatric athletes indicate that regular and sustained physical activity is associated with a number of electrophysiological adaptations, akin to the adult athlete. Observations suggest that as many as 72% of paediatric athletes (Bessem et al., 2015) show "athletic" changes on ECG although this is a marginally lower than that reported (prevalence to that of 91.7%) in adult athletes (Wilson *et al.*, 2012). In

consideration of paediatric specific variations, Zdravkovic *et al*. (2017), proposed preadolescent athlete specific reference values to guide interpretation of R-R, PR, and QTc intervals in addition to P-, Q-, R-, S-, and T-wave voltages. Although applaudable, investigations were limited to 94 white male soccer players. Furthermore, the addition of such subtleties to ECG interpretation for a benign finding is likely to meet significant barriers before clinical acceptance, unless integrated into a computerised ECG interpretation system. Particularly in consideration of a less than perfect reproducibility rate for athlete ECG interpretation (Berte et al., 2015; Brosnan et al., 2015a). The reader is now directed to a number of key electrophysiological adaptations common to the paediatric athlete, before considering the impact of ethnicity.

2.3.1.1 Conduction System Findings

As observed in adult athletes, bradycardia (<60 bpm), in the absence of symptoms such as fatigue, dizziness, or syncope, with heart rates ≥30 bpm is a common manifestation in the paediatric athlete, resolved by the onset of physical activity. Prevalent in as many as 28% (Bessem et al., 2015), despite higher proposed cuts off within the non-athlete (chronological age < 10 years: 65 bpm), due to an immature heart. Traditionally, believed to be a result of high vagal tone, a recent theory based on investigations in rats and mice, implies that such adaptations may be attributed to a down-regulation of the funny channel, HCN4, and the corresponding funny current, I_f (Zicha et al., 2005; Milanesi et al., 2006; Yung-Hsin Yeh et al., 2009; El Khoury et al., 2013; D'Souza et al., 2014). First-degree AV block (PR interval >200 milliseconds) is regarded to be an electrophysiological adaptation to regular and sustained exercise. Although the prevalence in white athletes chronological

age <13 years (2%) (Bessem et al., 2015) is comparatively lower than observations in white adult athletes (12%) (Riding et al., 2014a), this observation is considered normal. Low prevalence rates are likely attributable to the dependence of PR length on both HR and chronological age within paediatric populations (Molinari et al., 2016). Furthermore, this observation in isolation has not been associated to cardiac pathology in the asymptomatic paediatric athlete (Wilson et al., 2008; Schmied et al., 2009; Migliore et al., 2012; Koch et al., 2014; Price et al., 2014a; Bessem et al., 2015; Calò et al., 2015; Grazioli et al., 2017). Mobitz type 1 second-degree atrioventricular block is regarded to be a benign finding in the asymptomatic paediatric athlete at rest, providing 1:1 conduction returns at the onset of exercise (Meytes et al., 1975; Zehender et al., 1990; Stein et al., 2002).

2.3.1.2 Incomplete Right Bundle Branch Block (IRBBB)

IRBBB is a common electrophysiological manifestation in the paediatric athlete's ECG, with presentation more common in athletes than chronologically age-matched non-athletes (29% vs. 11%, $p<0.0001$) (Sharma et al., 1999). Presentation is likely exaggerated in the athlete, due to an increased RV cavity size, to meet the physiological demands of high-intensity, dynamic activity. This postulation is supported, by observations of a concomitant increased presentation of right axis deviation in athletes compared to chronologically age-matched non-athletes (Sharma et al., 1999).

2.3.1.3 Left and Right Ventricular Hypertrophy

Isolated QRS Voltage criteria for LVH (Sokolow-Lyon criteria: SV_1 + RV_5 or RV_6 >35 mm (Sokolow and Lyon, 1949)) in isolation of ST-segment or T-wave repolarisation changes have been observed in a considerably lower prevalence of white paediatric (15%) (Bessem et al., 2015) than adult athletes (53%) (Riding et al., 2014a). Findings of relative surprise in the context that peadiatric non-athlete voltage criteria have considerably higher upper limits (upper limits: 8-12 years: 64 mm vs. 12-16 years: 48 mm) (Park and Guntheroth, Warren, 2006). This may in part be attributable to less accumulated hours of training at high-intensities i.e. training longevity (Beaudry et al., 2016). Comparatively, isolated QRS Voltage criteria for RVH has been found to be prevalent in as many as 12% of paediatric (14-18 years) athletes (Sharma et al., 1999), but in as few as 0.4% of paediatric soccer (football) players (14-19 years) (Somauroo et al., 2001), and 2% of adult endurance athletes (Brosnan et al., 2014b). This may be reflective of RV dominance, in the immature heart, which has not undergone complete formation of adult ventricular mass.

2.3.1.4 Early Repolarisation

Recognition of the electrical manifestation ‘early repolarisation’ backdates over 40 years (Kambara and Phillips, 1976). Its definition among investigators varies considerably, with prevalence rates varying between 2-31% among the healthy non-athlete population (Maury and Rollin, 2013). Accordingly, a consensus panel (Macfarlane et al., 2015) has provided a revised definition, which requires the peak of an end-QRS notch and/or the onset of an end-QRS slur, denoted *J termination* (Jt), to be determined when considering

the presentation of early repolarisation. Specifically, to be considered a marker of early repolarisation, necessitates Jt elevation (≥1mm), while ST-segment elevation is not a required criterion. It is considered benign in the paediatric athlete as it is present in as many as 16% (Bessem et al., 2015).

2.3.1.5 Juvenile T Wave Pattern

The significance of TWI on the athletes ECG has received substantial attention, with definitions of what constitutes 'normal' or 'abnormal' being revised in every edition of recommendations for ECG interpretation in athletes (Corrado et al., 2010; Drezner et al., 2013b, d, c; a, 2017; Sharma et al., 2017b, 2018). Of most significance to the paediatric athlete are the new international recommendations for ECG interpretation in athletes. Special consideration has been provided to the paediatric athlete, recognising the 'Juvenile T wave pattern' (chronological age <16 years with TWI in V_1-V_3) to be normal, not prompting further evaluation in the absence of symptoms, signs or a family history of cardiac disease.

As observed in the non-athlete, marked repolarisation in the form of anterior TWI (V_1-V_3), is dependent on chronological age. It is prevalent in as many as 32.2% 6-8 year-olds, but in as few as 3.3% 16-18-year-old white Italian competitive athletes (Attisani et al., 2011). Most recently, D'Ascenzi *et al.* (2018) confirmed the long-standing belief that negative T-wave polarity across the precordial leads reverses within increased chronological age in the paediatric athlete. Specifically, during a 4-year follow up period, anterior TWI (V_1-V_4)

normalised among 94% (D'Ascenzi et al., 2018a), although cross-sectional investigations detail that anterior TWI, typically normalises by chronological age 16 years in the white paediatric athlete (Papadakis et al., 2009).

2.3.1.5.1 Juvenile T Wave Pattern: Impact of maturity status

An arbitrary chronological age cut off for the interpretation of the 'Juvenile T Wave Pattern' of <16 years, lends easy clinical translation. We understand, however, that whilst chronological age is a linear factor, maturity status, which is believed to determine the presentation of TWI in V_1–V_3, owing to an incomplete formation of adult ventricular mass [14], is not linear. In extreme cases, this can vary by 6 years between two 9-year-old boys (Johnson et al., 2009). To overcome such barriers, previous investigators have considered maturity status, demonstrating incomplete pubertal development, not chronological age <14 years to predict presentation of TWI in V_1-V_3 (Migliore et al., 2012). Past work, however, has often used Tanner staging assessment to assess maturational status (Marshall and Tanner, 1970) but this is now regarded as inappropriate due to child protection concerns. Specifically, it requires assessment of the development of external genitalia (scrotum, penile and testicular development) and characterisation of the stages of pubic hair growth in male paediatrics (Marshall and Tanner, 1970). Furthermore, if self-assessment is adopted poor validity may be yielded (27%) (Schmitz, 2004). The utility of alternative measures such as the percentage of predicted mature (adult) height at the time of observation, which may provide an estimate of maturity status (Roche et al., 1983) could be explored. Care is warranted as, firstly, predicted mature (adult) height demonstrates only moderate concordance with classifications of maturity status, based

on skeletal (biological) age (Malina et al., 2007, 2012), and, secondly, necessitates historical height (stature) data of the athlete to rule out sudden growth spurts. Accordingly, during the first-time assessment of the paediatric athlete with TWI V_1-V_3, in the absence of other ECG findings considered to be abnormal as per new international recommendations for ECG interpretation in athletes, assessment of predicted mature (adult) height is improbable, offering little clinical insight. Skeletal (biological) age assessment by radiological hand–wrist X-ray examination, recognised by the IOC as the 'gold standard' estimate of maturity status (Engebretsen et al., 2010), may be more appropriate but requires exploration and drives rationale for empirical investigation in Chapter 6.

2.3.1.5.2 Juvenile T Wave Pattern: Assessment of the preceding Jt and/or ST Segment

Investigations in white and black adult athletes demonstrate that detailed assessment of the Jt and/or ST-segment amplitude preceding TWI in V_1-V_4 can accurately discriminate physiological adaptation from cardiomyopathy, independent of ethnicity (Calore et al., 2016). The utility of such an assessment, however, does not appear to extend to 2227 white male paediatric athletes (D'Ascenzi et al., 2018a). D'Ascenzi *et al*. (2018) detailed TWI limited to V_1-V_3 in 7.5%, and TWI limited to V_1-V_2 in 3.2%, of which an isoelectric ST-segment preceded TWI in 36%, and 82%, respectively. Similar investigations are yet to be extended to the male Arab and black paediatric athlete, and thus drive rationale for exploration within chapter 6.

2.3.2 IMPACT OF ETHNICITY ON ELECTROPHYSIOLOGICAL ADAPATIONS IN THE PAEDIATRIC ATHLETE

Increasing globalisation has provided athletes of various ethnicities and nationalities the opportunity to compete at the very highest level. This is exemplified by the proportion of British Premier League players from black, Asian and minority ethnic groups competing this season (2018/19), which has doubled since its inception in 1992. Observations such as this extend to the paediatric athlete. During the Buenos Aires, 2018 Youth Summer Olympic Games, Argentina, athletes from over 28 West Asian and North African nations (countries of predominantly Arab ethnicity), and 79 Afro-Caribbean nations (countries of predominantly black ethnicity) competed, winning 56 and 38 medals, respectively. In view of calls for a tailored pre-participation health evaluation in athletes competing at the Youth Olympic Games, inclusive of ECG and echocardiographic assessment (Adami et al., 2018), it is apparent, that paediatric athletes presenting for such screening are heterogeneous in ethnicity. The impact of ethnicity on electrophysiological adaptations to regular and sustained exercise in adult athletes is now globally understood (Magalski *et al.*, 2008a; Papadakis *et al.*, 2011; Kervio *et al.*, 2012; Wilson *et al.*, 2012; Riding, Salah, *et al.*, 2014; Riding, Sheikh, *et al.*, 2014; Waase *et al.*, 2018). It is, therefore, imperative to determine its' relative impact on the paediatric athletes ECG to minimise the risk of false-positive diagnosis, resulting in unnecessary further evaluation or a false-negative diagnosis, with the potential outcome fatal.

2.3.2.1 Impact of Black Ethnicity

Black paediatric athletes represent one of the highest at-risk athlete populations to SCD/A, with the incidence of SCD as high as 1 in 3,708, in previously screened black paediatric soccer players in the UK (Malhotra et al., 2018). Consequently, the distinction between paediatric athlete's heart and cardiac pathology associated with SCD is especially important for this population. This importance is heightened in the context that presented with a black paediatric athlete from Africa, wherein healthcare infrastructure and knowledge base are relatively poor, this may represent their first healthcare assessment of any kind (Schmied et al., 2009).

Investigations detailing repolarisation abnormalities in a black population backdates to 1946 (Littmann, 1946; Powell, 1959; Somers and Rankin, 1962; WG et al., 1964; Seriki and Smith, 1966). Over the past two decades, black ethnicity has emerged as an important determinant of electrophysiological adaptations in the adult athlete (Papadakis et al., 2011). Data from adult black athletes demonstrate an almost 5-fold increase in the early repolarisation (63.2% vs. 26.5%, $p<0.001$), and 12-fold increase in the prevalence of TWI in V_1-V_4 (12.7% vs. 1.9%, $p<0.001$) (Papadakis et al., 2011). Consistent with such investigations, an increased prevalence of ECG abnormalities appears to extend to the paediatric athlete (Schmied *et al.*, 2009; Di Paolo *et al.*, 2012; Sheikh *et al.*, 2013; Pelà *et al.*, 2014). Specifically, the black paediatric athletes ECG is typically characterised by a QRS voltage (R5 + S1, mean = 48 mm, maximum = 94 mm), and of relatively short duration (mean = 90 mm, minimum = 74 mm) (Di Paolo *et al.*, 2012). In comparisons of black and white paediatric athletes, a 2-fold increased prevalence of early repolarisation

(34.7% vs. 21.1%, p <0.001), a 7-fold increased prevalence of anterior TWI (V_1-V_4) (14.3% vs. 2.5%, p <0.001) and a 32-fold increased prevalence of deeply inverted TWI (≥2 mm) (6.7% vs. 0.2%, p <0.001) have been observed (Sheikh et al., 2013).

TWI may represent the first and only sign of cardiac pathology predisposing to SCD/A without phenotypic manifestation on secondary investigation (Wilson *et al.*, 2012). Furthermore, isolated anterior TWI is a recognised repolarisation abnormality, present in as many as 80% of patients with arrhythmogenic right ventricular cardiomyopathy (Steriotis et al., 2009; Marcus et al., 2010; Migliore et al., 2012; Bhonsale et al., 2013) and 2-4% of hypertrophic cardiomyopathy patients (Gersh et al., 2011). These cardiomyopathies collectively account for 12% of SCDs in paediatric athletes in the UK (Finocchiaro, *et al.*, 2016). Differentiation of this relatively common observation, from one indicative of pathology, is essential to minimise the risk and consequences of erroneous diagnosis.

Anterior TWI within black paediatric athletes has been demonstrated to persist and progress during long-term follow-up among those who continue to exercise into adulthood, in the absence of phenotypic expression of cardiomyopathy (Sheikh et al., 2013). TWI is preceded by Jt elevation and/or convex (domed) ST-segment elevation in up to 12% of adult and paediatric black athletes (Di Paolo et al., 2012a; Sheikh et al., 2013; Riding et al., 2019) (Papadakis *et al.*, 2011; Di Paolo *et al.*, 2012; Sheikh *et al.*, 2013). Furthermore, such marked repolarisation appears to resolve with as little as 8

weeks of detraining (Sheikh et al., 2013). In consideration of such observations, it is now globally recognised that Jt elevation and convex ('domed') ST-segment elevation preceding TWI in leads V_1-V_4, is a 'classic' presentation of early repolarisation in both the adult and paediatric black athlete. This is considered a normal variant which does not require secondary investigation, in the absence of other clinical or ECG features of cardiomyopathy (Drezner et al., 2017; Sharma et al., 2017b, 2018).

2.3.2.1 Impact of Arab Ethnicity

The relative risk of SCD in the Arab paediatric athlete remains to be determined, however, it is understood from previous investigations in adult Arab athletes (Riding *et al.*, 2014), that the 'chance' of detecting a cardiac pathology predisposing to an increased risk of SCD/A, is 3 times greater than in white athletes (Corrado *et al.*, 1998; Basavarajaiah *et al.*, 2008). Although the reasons for this observation are incompletely understood, it may be postulated that the rapid economic growth and subsequent improvements in healthcare services that this geographical location has and is undergoing may impact.

Similar to observations in white and black athletes, regular and sustained exercise is reflected on the adult Arab athlete's ECG; first noted among 800 Arab athletes, originating from 7 Gulf States and 6 Middle-Eastern Countries in 2011 (Wilson *et al.*, 2012). Characterised by a prolongation of the PR interval, in addition to an increased prevalence of sinus bradycardia, repolarisation changes, atrial enlargement and ventricular hypertrophy in comparison to non-athletes (Wilson *et al.*, 2012). Albeit, to smaller

magnitude than observed in black adult athletes (Magalski et al., 2008b; Rawlins et al., 2010; Papadakis et al., 2011; Waase et al., 2018), but to a similar extent as the white adult athlete (Pelliccia *et al.*, 2007, 2008; Sheikh *et al.*, 2014). The chance of an abnormal finding appears to be similar among both white and Arab adult athletes (5.8% vs. 7.9%), occurring less frequently than those observed in the black adult athlete (18%) (Wilson *et al.*, 2012). Accordingly, it has been concluded that modern recommendations for ECG interpretation in athletes (Corrado et al., 2010), are appropriate for application in the Arab adult athlete. Our understanding of the Arab adult athletes' heart in the preceding 6 years has undergone remarkable growth (Wilson *et al.*, 2012; Riding *et al.*, 2012, 2013; Allison *et al.*, 2014; Riding *et al.*, 2014; Riding, *et al.*, 2014; Schnell *et al.*, 2014), both confirming and extending understandings from initial investigations (Wilson *et al.*, 2012). An understanding of the paediatric Arab athlete's ECG is unavailable, potentially risking false-positive diagnosis and unnecessary disqualification or a false-negative with the potential outcome fatal, in the rising stars of tomorrow. This provides significant rationale for empirical studies, conducted within Chapters 5 and 6 of this thesis.

2.3.3 ECG INTERPRETATION GUIDELINES THROUGH THE AGES

Running in parallel to investigations of the athletes' ECG, which backdate to 1972 (Von Lutterotti, 1972), has been the dissemination of recommendations/criteria for ECG interpretation in athletes (Corrado *et al.*, 1998; Corrado *et al.*, 2005; Corrado *et al.*, 2010; Drezner, *et al.*, 2013; Drezner, *et al.*, 2013a, 2013b; Drezner, *et al.*, 2013; Drezner *et al.*, 2017; Sharma, *et al.*, 2017; Sharma *et al.*, 2018). Guidelines have acted as road signs, marking gaps in our knowledge that need to be filled with new research, or acted as a

framework to compare back against as new ideas have been pitched in view of refinement (Gati *et al.*, 2013; Zaidi, *et al.*, 2013; Sheikh *et al.*, 2014; Riding, *et al.*, 2014). A process likened to that of sharpening the lead of a pencil (La Gerche and Calkins, 2016), as investigators have continuously sought to create recommendations/criteria, which account for athletes of any sporting discipline (Brosnan *et al.*, 2014; Waase *et al.*, 2018), ethnicity (Kervio et al., 2013; Sheikh et al., 2013; Riding et al., 2014a; Waase et al., 2018), chronological age (Sharma et al., 1999; Migliore et al., 2012; Bessem et al., 2015; Calò et al., 2015) and sex (Mandic et al., 2010; Rawlins et al., 2010). The ultimate goal is to develop a set of recommendations for ECG interpretation in athletes which provide 100% sensitivity (the probability of testing positive given the presence of a cardiac condition), and specificity (the probability of testing negative in the absence of a cardiac condition), respectively. Thus providing a false positive (the probability of testing positive in the absence of a cardiac condition) and false negative (the probability of testing positive in the presence of a cardiac condition) rate of 0%, respectively. Whilst unlikely to be ever achieved the closer the recommendations get the better.

2.3.3.1 European Society of Cardiology 2005 Recommendations

In 1998, Corrado *et al.* (1998), published the first recommendations for ECG interpretation in athletes to detect occult structural diseases, derived from over 20 years of experience from mandatory cardiac screening in Italy that significantly reduced the incidence rate of SCD (Pelliccia and Maron, 1995). Specifically, this intervention reduced the incidence of hypertrophic cardiomyopathy-related SCD to lower levels than in the USA (Burke et al., 1991), and prevented death in all 22 athletes detected with hypertrophic cardiomyopathy,

during a mean follow-up period of 8 years (Corrado et al., 1998). It was apparent that the application of such recommendations was effective in detecting and preventing death from hypertrophic cardiomyopathy in a predominantly white athletic population and therefore served as a framework for the 2005 European Society of Cardiology criteria for ECG interpretation in athletes (Corrado *et al.*, 2005). Criteria were mostly derived from abnormal findings in the general population. Perhaps, most significantly it regarded isolated voltage criteria for LVH to be abnormal (Table 2.4), warranting further evaluation before clearance to play may be permitted. Accordingly, false-positive rates were exceedingly high and, therefore, considered unacceptable. This was despite a capacity to detect all cardiac pathology that may predispose to an increased risk of SCD/A, including a negative predictive value of 99.8% for hypertrophic cardiomyopathy (Baggish, 2010).

Table 2. 4 2005 European Society of Cardiology Recommendations for Interpretation of 12-Lead Electrocardiogram in the Athlete (Corrado et al., 2005b).

Abnormal ECG Finding	Definition
LAE	P wave ≥40 ms in duration and ≥1 mm in depth in lead V_1
RAE	P wave ≥2.5 mm in leads II, III or V_1.
LAD	−30° to −90°.
RAD	>120°
Increased Voltage	Any one of the following: - R/S wave ≥20 mm in a standard lead - S in leads V_1/V_2 ≥30 mm - R in leads V_5/V_6 ≥30 mm
Pathological T waves	T-Wave flattening or inversion in ≥2 leads.
ST segment depression	ST depression in ≥2 leads
Pathological Q waves	Q/R ratio of ≥0.25 or ≥40 ms in duration or QS pattern in ≥2 leads.
Complete LBBB	QRS duration >120 ms
Complete RBBB	QRS duration >120 ms
	R or R' wave ≥ 5 mm in lead V_1 and R:S ratio ≥1
Ventricular pre-excitation	PR interval <120 ms with/without evidence of a delta wave (slurred upstroke in the QRS complex)
Prolonged QT interval	QTc ≥440 ms
Profound sinus bradycardia	<40 beats per minute and increasing to <100 beats per minute during limited exercise testing
1° AV block	PR ≥210 ms, not shortening with hyperventilation or limited exercise testing
Mobitz type II 2° AV block	Intermittently non-conducted P waves with a fixed PR interval.
3° AV block	Complete AV block, characterised by more P waves than QRS complexes, with a the ventricular rhythm.
Atrial tachyarrhythmias	Supraventricular tachycardia, atrial fibrillation, atrial flutter.
Premature ventricular contractions	≥2 premature ventricular contractions per 10 s tracing.

AV; atrioventricular; LAD, left axis deviation; LAE, left atrial enlargement; LBBB, left bundle branch block; min, minutes; ms, milliseconds; RAD, right axis deviation; RAE, right atrial enlargement; RBBB, right bundle branch block; S, seconds.

2.3.3.2 European Society of Cardiology 2010 Recommendations

In 2010, a European task force led by Domenic Corrado of Italy, recognised the impact of electrophysiological remodelling to regular and sustained exercise, contributing to the phenomenon of an athletes ECG. Accordingly, a set of 'Group 1: common and training-related ECG changes' and 'Group 2: uncommon and training-unrelated ECG changes' were defined (Corrado et al., 2010), based on observations in a primarily white athletic population (Table 2.5). Whilst the data was of individuals entering competitive sport for the first time, the criteria were designed for application in the competitive athlete chronologically aged 12-35 years.

The categorisation of 'uncommon and training-unrelated ECG changes' was based on observations that these patterns constituted fewer than 5% of all abnormal ECG patterns (Corrado et al., 2010). No consideration was provided to ethnicity, in addition to the duration and intensity of exercise training undertaken. It may, therefore, be considered relatively unsurprising that such criteria were associated with an unacceptable number of false positives (Brosnan, *et al.*, 2014; Sheikh *et al.*, 2014; Riding, *et al.*, 2014). Specifically, 1) all TWIs were considered abnormal (≥1 mm in depth in ≥2 contiguous leads; excluding leads aVR and V_1) irrespective of ethnicity; 2) upper limits of Long QT syndrome (QTc ≥440 milliseconds) and lower limits of short QT syndrome (In children, QT<310 milliseconds; QTc <380 milliseconds) were identical to those used for a sedentary population; 3) ventricular pre-excitation was defined by the presence of only a short PR interval (<120 ms) with/without evidence of a delta wave (slurred upstroke in the QRS complex); and finally, 4) although designed for application in the athlete

chronologically aged 12 years, little consideration was provided to paediatric specific ECG patterns.

Table 2. 5 2010 European Society of Cardiology Recommendations for Interpretation of 12-Lead Electrocardiogram in the Athlete (Corrado et al., 2010).

Group 1: Common and training-related ECG changes	
Normal ECG finding	**Definition**
Sinus bradycardia	<60 beats.min^{-1}.
1˚ AV block	PR interval 200-400 ms, with each P-wave followed by a QRS complex and a regular R–R interval.
Mobitz type I (Wenckebach) 2˚ AV block	A progressive lengthening of the PR interval from beat to beat until there is a non-conducted P-wave with no QRS complex observed. Confirmed by the first PR interval after the dropped beat being shorter than the last conducted PR interval before the dropped beat.
Incomplete RBBB	Right bundle branch block (RBBB) morphology (rSR' pattern in lead V_1 and wide terminal qRS pattern in leads I and V_6), with a QRS duration ≤120 ms.
Isolated QRS voltage criteria for LVH	Isolated Sokolow–Lyon index voltage criteria for left ventricular hypertrophy (SV_1 + RV_5/RV_6 >35 mm).
Early repolarisation	Elevation of the QRS–ST junction (J-point) ≥1 mm from baseline, associated with notching or slurring of the terminal QRS complex.
Group 2: Uncommon and training-unrelated ECG changes	
LAE	P wave ≥40 ms in duration and ≥1 mm in depth in lead V_1
RAE	P wave ≥2.5 mm in leads II, III or V_1.
LAD	−30° to −90°.
left anterior hemiblock	- QRS axis –45° and –60° - qR pattern in leads I and aVL - rS pattern in leads II, III, and aVF
RAD	>120°
left posterior hemiblock	- QRS axis 90° to 180° - The presence of a qR complex in lead III and a rS complex in lead I. - Absence of RAE and RVH.
Right ventricular hypertrophy (RVH)	RV_1 + SV_5 or SV_6 >11 mm
T-wave inversion	≥1 mm in depth in ≥2 contiguous leads; excluding leads aVR and V_1
ST segment depression	≥0.5 mm in depth, relative to the isoelectric line between the end of the T wave and the beginning of the P wave, in ≥2 contiguous leads.
Pathological Q waves	>0.4 mm in depth in any lead; excluding III, aVR

Complete LBBB	Left bundle branch block with QRS duration >120 ms
Complete RBBB	Right bundle branch block with QRS duration >120 ms
Non-specific intraventricular conduction disturbance.	QRS duration >110 ms, not satisfying criteria for either LBBB or RBBB
Ventricular pre-excitation	PR interval <120 ms with/without evidence of a delta wave (slurred upstroke in the QRS complex)
Long- QT interval	QTc ≥440 ms
Short-QT interval	In children: - QT <310 ms - QTc <380 ms
Brugada-like early repolarisation	Elevation of the QRS–ST junction (J-point) ≥2 mm from baseline, and downsloping ST-segment elevation ('J-wave') of either 'coved' (negative T-wave) or 'saddle-back' (positive T-wave) morphology in V_1–V_2/V_3
Profound sinus bradycardia	<30 beats per minute or sinus pauses ≥3 s.
Mobitz type II 2° AV block	Intermittently non-conducted P waves with a fixed PR interval.
3° AV block	Complete AV block characterised by AV dissociation with more P-waves than QRS complexes.
Atrial tachyarrhythmias	Supraventricular tachycardia, atrial fibrillation, atrial flutter.
Premature ventricular contractions	≥2 premature ventricular contractions per 10 s tracing.
Ventricular arrhythmias	Couplets, triplets and non-sustained ventricular tachycardia.

AV; atrioventricular; LAD, left axis deviation; LAE, left atrial enlargement; LBBB, left bundle branch block; LVH, left ventricular hypertrophy; min, minutes; ms, milliseconds; RAD, right axis deviation; RAE, right atrial enlargement; RBBB, right bundle branch block; RVH, right ventricular hypertrophy; S, seconds.

2.3.3.3 The Seattle Criteria

In 2012, the American Medical Society for Sports Medicine co-sponsored by the Fédération Internationale de Football Association (FIFA), Medical Assessment and Research Centre held a 'Summit on Electrocardiogram Interpretation in Athletes' in Seattle, Washington. The aim of the meeting was to 'update' the ESC 2010 recommendations (Table 2.6) using data to support the classification of normal and abnormal ECG patterns.

In addition to the common training-related findings originally listed in the ESC 2010 recommendations, the Seattle criteria also included ethnicity-specific ECG changes. TWI in leads V_1-V_4 when preceded by J-point elevation and convex ST-segment elevation, was regarded to be normal. Based on observations from 904 black athletes presenting for cardiac screening, wherein, more than two-thirds exhibited ST-segment elevation and 12.7% presented TWI in leads V_1-V_4 (Papadakis et al., 2011). Secondly, less conservative cut-offs for an abnormal QT interval were imposed by the Seattle criteria, revising both the upper (≥470 milliseconds) and lower (≤320 milliseconds) limits of QT interval length, for classification of long and short QT syndrome respectively. Upper limits were revised in consideration that 0.4% of elite athletes presented a QT interval of 460–570 ms (Basavarajaiah et al., 2007). Whilst lower limits were reduced in light of data from over 18,000 asymptomatic individuals (Dhutia et al., 2015). Finally, consideration of ventricular pre-excitation criteria was revised to necessitate the observation of a delta wave (slurred upstroke in the QRS complex) in addition to a short PR interval (<120 ms). In application, such revisions reduced the proportion of athletes triggered for further evaluation by ECG

from 26% to 5.7% in 1417 high school, collegiate and professional athletes in the USA (Pickham et al., 2014).

Table 2. 6 Seattle Criteria for Interpretation of 12-lead Electrocardiogram in the Athlete (Drezner et al., 2013a).

Normal ECG findings in athletes	
Normal ECG finding	**Definition**
Sinus bradycardia	<60 beats.min^{-1}.
Sinus arrhythmia	R-R interval which decreases slightly during inspiration and increases slightly during expiration
Ectopic atrial rhythm	P waves are present but are of a different morphology compared to the sinus P wave, typically negative in leads II, III and aVF.
Junctional escape rhythm	P waves hidden by the QRS complex.
First-degree AV block	PR interval 200-400 ms, with each P-wave followed by a QRS complex and a regular R–R interval.
Mobitz type I (Wenckebach) second-degree AV block	A progressive lengthening of the PR interval from beat to beat until there is a non-conducted P-wave with no QRS complex observed. Confirmed by the first PR interval after the dropped beat being shorter than the last conducted PR interval before the dropped beat.
Incomplete RBBB	Right bundle branch block (RBBB) morphology (rSR' pattern in lead V_1 and wide terminal qRS pattern in leads I and V_6), with a QRS duration ≤120 ms.
Isolated QRS voltage criteria for LVH	Isolated Sokolow–Lyon index voltage criteria for left ventricular hypertrophy (SV_1 + RV_5/RV_6 >35 mm).
Early repolarisation	ST elevation and/or a J wave (distinct notch) or slur on the downslope of the R wave.
Black repolarisation variant	Elevated ST segment with upward convexity ('dome' shaped), followed by T wave inversion confined to V_1–V_4
Abnormal ECG findings in athletes	
Abnormal ECG finding	**Abnormal ECG finding**
LAE	P wave >120 ms in leads I or II and P wave ≥40 ms in duration and ≥1 mm in depth in lead V_1
RAE	P wave ≥2.5 mm in leads II, III or V_1.
LAD	−30° to −90°.
RVH pattern	RVH (RV1 + SV5 or SV6 >11 mm) and RAD (>120°)
T wave inversion	≥1 mm in depth in ≥2 contiguous leads; excludes leads aVR, III and V_1 and black athlete repolarisation variant

ST segment depression	≥0.5 mm in depth, relative to the isoelectric line between the end of the T wave and the beginning of the P wave, in ≥2 contiguous leads.
Pathological Q waves	>3 mm in depth or >40 ms in duration in ≥2 leads; excluding III and aVR
Complete LBBB	QRS ≥120 ms, predominantly negative QRS complex in lead V_1 (QS or rS), and upright monophasic R wave in leads I and V_6
Complete RBBB	rSR' pattern in lead V1 and wide terminal qRS pattern in leads I , Avl and V6 and a QRS duration ≥120 ms.
Intraventricular conduction delay	Any QRS duration ≥140 ms
Ventricular pre-excitation	PR interval <120 ms with a delta wave (slurred upstroke in the QRS complex) and wide QRS (≥120 ms).
Long- QT interval	QTc ≥470 ms
Short-QT interval	QTc ≤320 ms
Brugada-like ECG pattern	Elevation of the QRS–ST junction (J-point) ≥2 mm from baseline, and downsloping ST-segment elevation ('J-wave') of either 'coved' (negative T-wave) or 'saddle-back' (positive T-wave) morphology in V_1–V_3
Profound sinus bradycardia	<30 beats per minute or sinus pauses ≥3 s.
Mobitz type II 2° AV block	Intermittently non-conducted P waves with a fixed PR interval.
3° AV block	Complete AV block characterised AV dissociation with more P-waves than QRS complexes. .
Atrial tachyarrhythmias	Supraventricular tachycardia, atrial fibrillation, atrial flutter.
Premature ventricular contractions	≥2 premature ventricular contractions per 10 s tracing.
Ventricular arrhythmias	Couplets, triplets and non-sustained ventricular tachycardia.

AV; atrioventricular; LAD, left axis deviation; LAE, left atrial enlargement; LBBB, left bundle branch block; LVH, left ventricular hypertrophy; min, minutes; ms, milliseconds; RAD, right axis deviation; RAE, right atrial enlargement; RBBB, right bundle branch block; RVH, right ventricular hypertrophy; S, seconds.

2.3.3.4 International Recommendations for Electrocardiographic Interpretation in Athletes

In 2016, an international panel of experts from over 10 countries met again in Seattle, Washington, under the chair of Jonathan Drezner, with the goal of creating interpretation recommendations that were applicable in athletes chronological aged 12-35 years (Table 2.8 and Figure 2.2). In view of providing maximal international impact and worldwide compliance, such recommendations were co-published in the Journal of American College of Cardiology (Sharma, *et al.*, 2017), the European Heart Journal (Sharma et al., 2018), and the British Journal of Sports Medicine (Drezner et al., 2017), and endorsed by 15 professional sports medicine societies.

Of significance was the introduction of the 'traffic-light' ECG system. Accordingly, the asymptomatic athlete with no significant family history presenting 'normal ECG findings' in isolation of other ECG abnormalities, should be given the 'green' light to play without further evaluation. Athletes presenting 'borderline ECG findings', should be given the 'amber' light as a note of caution, but ultimately awarded the 'green' light to play without further diagnostic investigation, should these findings be observed in isolation or with a 'green' light ECG pattern. But a 'red' light should be awarded when 2 or more borderline ECG findings are present. In the case of a 'red' light, athletes are required to undergo further diagnostic investigation.

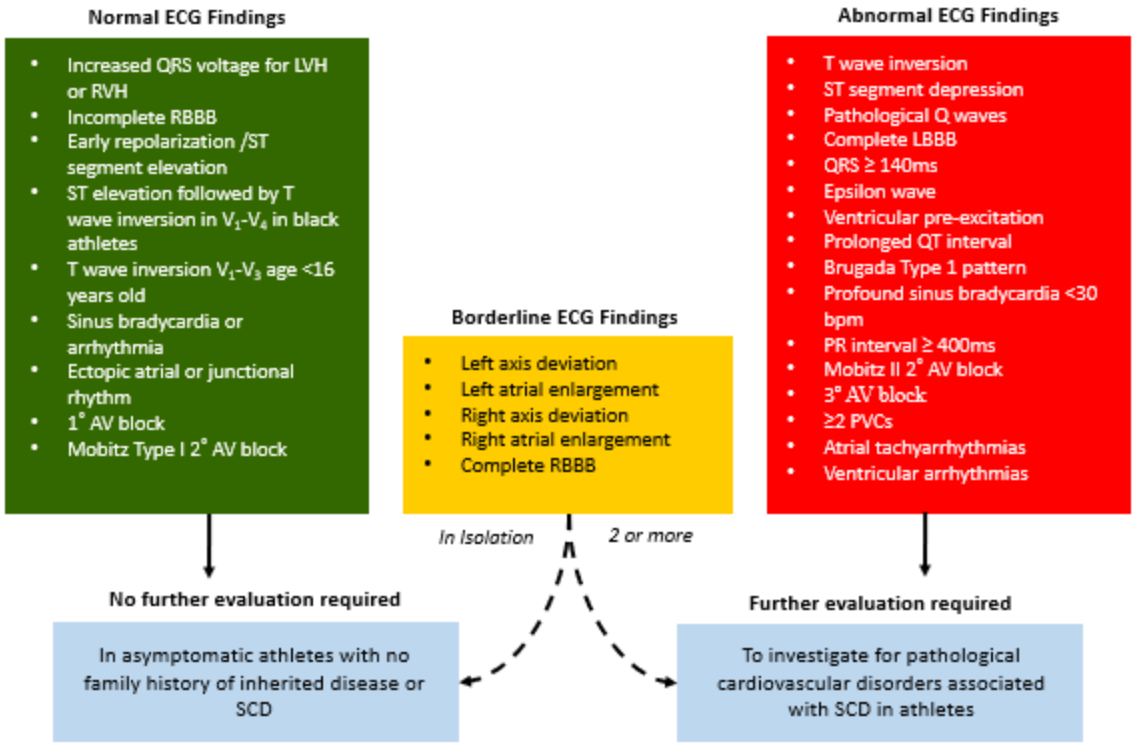

Figure 2. 2. New international recommendations for electrocardiographic interpretation in athletes aged 12-35 years (Drezner et al., 2017; Sharma et al., 2017b, 2018).

Key: AV, atrioventricular; ECG, electrocardiography; LBBB, left bundle branch block; LVH, left ventricular hypertrophy; PVCs, premature ventricular contractions; RBBB, right bundle branch block; RVH, right ventricular hypertrophy; SCD, sudden cardiac death.

Consensus to move the previously considered ‘abnormal’ ECG findings of axis deviation and atrial enlargement into the category of ‘borderline’ ECG findings conceives from the calls for re-appraisal by Gati et al., (2013). Specifically, Gati et al., (2013), identified isolated axis deviation and atrial enlargement to constitute 42% of all abnormal findings in 2533 athletes aged 14-35 years. Furthermore, in athletes whom presented axis deviation and/or atrial enlargement in isolation to other ECG abnormal findings, no

evidence of cardiomyopathy was detected, with a similar prevalence congenital/minor valvular defects detected in comparison to athletes who presented a normal ECG. A re-appraisal validated by the 'refined' criteria (Riding et al., 2014b; Sheikh et al., 2014b), found to significantly reduce the number of false-positive ECGs in Arab, Black and white adult athletes while maintaining 100% sensitivity for serious cardiac pathologies. Finally, RBBB was added to the category of 'borderline' ECG findings, although it must be noted, evidence for whether RBBB is pathological in the long term is lacking (Kim and Baggish, 2015). A single study of 510 US athletes showed that athletes with RBBB had larger LV dimensions, a reduced ejection fraction but a preserved fractional area change. Among all athletes presenting RBBB in isolation, no evidence of cardiomyopathy was detected (Kim et al., 2011). Unlike RBBB, left bundle branch block (LBBB) is found in <1000 athletes (Lakdawala et al., 2011; Kim and Baggish, 2015) and therefore should be considered abnormal, requiring further diagnostic investigation.

New international recommendations for ECG interpretation in athletes contained revisions beyond the introduction of a 'traffic-light' system. Of most significance to cardiac screening in the paediatric athlete, was the recognition of the 'Juvenile T Wave Pattern' (TWI in the anterior leads (V_1-V_3) in athletes <16 years of age) to be normal and should not prompt further evaluation in the absence of symptoms, signs or a family history of cardiac disease (Table 2.7). In application, new international recommendations for ECG interpretation in athletes have been found to trigger further evaluation for the exclusion of confirmation of cardiac pathology in only 1 in 33 athletes presenting for first time cardiac screening (Dhutia et al., 2017); findings of significance in light of a 86% and 50% reduction

in the number of positive ECGs compared with the 2010 ESC recommendations (Corrado et al., 2010) and Seattle criteria (Drezner et al., 2013a, c; d; b), respectively. Investigations were, however, limited to a primarily white adult athletic population, and, therefore, it is unknown if such significant improvements will extend to the comparatively different population of Arab and black paediatric athlete examined within this thesis. Furthermore, although the 12-lead-ECG interpreted as per new international recommendations detected all 15 cases of cardiac pathology (i.e., 100% sensitivity), an echocardiogram assessment was reserved to only those with an abnormal physical examination, health questionnaire, and 12-lead-ECG, precluding the assessment of a false-negative. The limitations of such investigations are clear when consideration is provided to recent outcome data from cardiac screening in the paediatric soccer player (Malhotra et al., 2018). Investigations revealed that 6 players proceeded to die from previously undetected cardiac pathology, despite a normal physical examination, medical questionnaire, ECG and echocardiographic assessment at the chronological age of 16 years (Malhotra et al., 2018). In consideration of the cardiac screening programmes implemented across North America, South America, Europe, Asia, and Australasia, it is, therefore, necessary to determine the efficacy of new international recommendations. This requires investigation among only those screened by health questionnaire, physical examination, 12-lead ECG, and finally an echocardiographic assessment, irrespective of the preceding clinical findings, serving as rationale for empirical studies conducted within chapter 5 and 6 of this thesis. Such investigations will allow for the assessment of false-negative and false-positive rates, in extension to the number of athletes triggered for further evaluation as per the investigations of Dhutia *et al.* (2017). Providing a robust investigation into the

clinical appropriateness of new international recommendations to ECG interpretation in the paediatric Arab and black male athlete.

Table 2. 7 New International Recommendations for Electrocardiographic Interpretation in Athletes (Drezner et al., 2017; Sharma et al., 2017b, 2018).

Normal ECG findings in athletes

These ECG findings were considered to reflect physiological adaptations to regular and sustained exercise, not warranting further evaluation in the absence of other ECG features suggestive of cardiomyopathy

Normal ECG finding	Definition
Sinus bradycardia	≥30 beats.min^{-1}.
Sinus arrhythmia	Slight heart rate variation with respiration: rate increases during inspiration and decreases during expiration.
Ectopic atrial rhythm ('low atrial rhythm')	P-waves are present but with a different morphology to the sinus P-wave, typically observed with a heart rate ≤100 beats.min^{-1}.
Junctional escape rhythm	The QRS rate is typically less than 100 beats.min^{-1}, with a narrow QRS complex (<120 ms), unless the baseline QRS has a bundle branch block.
1˚ AV block	PR interval 200-400 ms, with each P-wave followed by a QRS complex and a regular R–R interval.
Mobitz type I (Wenckebach) 2˚ AV block	A progressive lengthening of the PR interval from beat to beat until there is a non-conducted P-wave with no QRS complex observed. Confirmed by the first PR interval after the dropped beat being shorter than the last conducted PR interval before the dropped beat.
Incomplete RBBB	Right bundle branch block (RBBB) morphology (rSR' pattern in lead V_1 and wide terminal qRS pattern in leads I and V_6), with a QRS duration ≤120 ms.
QRS voltage criteria for LVH and RVH	Isolated Sokolow–Lyon index voltage criteria for left (SV_1 + RV_5/RV_6 >35 mm) or right ventricular hypertrophy (RV_1 + SV_5 or SV_6 >1.1 mm).
Early repolarisation	- *Jt elevation*, measured at the end of the QRS complex (the onset of the ST-segment) with reference to the onset of the QRS complex (isoelectric line) and was considered elevated if Jt were ≥0.1mm. - *ST elevation*, measured 100ms after Jt, and was considered elevated if amplitude were greater than amplitude at Jt.

	- *End-QRS notching or slurring*, on the downslope of a prominent R-wave. A notch was considered present only when entirely above the baseline. Whilst a slur was considered present only when onset above the baseline.
Beningn anterior TWI	- *Juvenile T wave pattern*, TWI in V_1-V_3 in athletes with a chronological age <16 years - *Black athlete repolarisation variant*, J-point elevation and/or convex ST segment elevation followed by TWI in V_2-V_4 - *Biphasic T wave pattern*, biphasic TWI in V_3 only

Borderline ECG findings in athletes

These ECG findings in isolation were regarded to be normal and thus not warranting further evaluation, but the presence of two or more were considered abnormal and thus warranting further evaluation.

Borderline ECG Finding	Definition
Left axis deviation	−30° to −90°.
Left atrial enlargement	P wave of >120 ms in leads I or II with a negative P wave ≥1 mm in depth and ≥40 ms in duration in lead V_1.
Right axis deviation	>120°.
Right atrial enlargement	P wave ≥2.5 mm in II, III or aVF.
Complete right bundle branch block	rSR' pattern in lead V_1 and wide terminal qRS pattern in leads I and V_6 and a QRS duration ≥120 ms.

Abnormal ECG findings in athletes

These ECG findings may suggest the presence of pathological cardiovascular disease and require further diagnostic investigation.

Abnormal ECG Finding	Definition
T wave inversion	≥1 mm in depth in ≥2 contiguous leads; excludes leads aVR, III and V_1, Juvenile T wave pattern, Black athlete repolarisation variant and biphasic TWI in lead V_3 only.
ST segment depression	≥0.5 mm in depth, relative to the isoelectric line between the end of the T wave and the beginning of the P wave, in ≥2 contiguous leads.
Pathological Q waves	Q/R ratio of ≥0.25 or ≥40 ms in duration in ≥2 leads; excluding III and aVR.
Complete left bundle branch block	QRS ≥120 ms, with a predominantly negative QRS complex in lead V_1 (QS or rS) and upright notched/slurred R wave in leads I and V_6.

Profound non-specific intraventricular conduction delay	Any QRS duration ≥140 ms.
Epsilon wave	Distinct low amplitude signal (small positive deflection or notch) between the end of the QRS complex and onset of the TWI in leads V_1-V_3.
Ventricular pre-excitation	PR interval <120 ms with a delta wave (slurred upstroke in the QRS complex) and wide QRS (≥120 ms).
Prolonged QT interval	QTc ≥470 ms (male). QTc ≥480 ms (female). QTc ≥500 ms (marked QT prolongation).
Brugada type 1 pattern	Coved pattern: initial ST elevation ≥2 mm (high take-off) with downsloping ST segment elevation followed by TWI in ≥1 leads in V_1-V_3.
Profound sinus bradycardia	<30 beats per minute or sinus pauses ≥3 s.
Profound 1° AV block	≥400 ms.
Mobitz type II 2° AV block	Intermittently non-conducted P waves with a fixed PR interval.
3° AV block	Complete AV block characterised by AV dissociation with more P-waves than QRS complexes.
Atrial tachyarrhythmias	Supraventricular tachycardia, atrial fibrillation, atrial flutter.
Premature ventricular contractions	≥2 premature ventricular contractions per 10 s tracing. OR ≥1 premature ventricular contractions per 10 s tracing in the high dynamic athlete.
Ventricular arrhythmias	Couplets, triplets and non-sustained ventricular tachycardia.

AV; atrioventricular; ms; milliseconds; LVH, left ventricle hypertrophy; RVH, right ventricle hypertrophy; S, seconds; TWI, T wave inversion.

2.3.4 INTERPRETATION OF DIAGNOSTIC TESTS: TRUTH TABLES VS. RECIEVER OPERATOR CURVE AND BAYES ANALYSIS

Interpretation of an ECG provides a binary outcome (positive/negative). If we wish to examine the diagnostic utility of the ECG, against a 'gold-standard' test (in most cases an echocardiogram), with also provides a binary outcome (no pathology/cardiac pathology), in most cases, a two-by-two table analysis (Sheikh *et al.*, 2014; Riding, Sheikh, *et al.*, 2014), is the obvious and most commonly applied statistical examination. In some cases, however, this may make for difficult interpretation. Let us say ECG interpretation recommendations 'A', yields a sensitivity (the probability of testing positive in the presence of cardiac pathology) of 80% and a specificity (the probability of testing negative in the absence of cardiac pathology) of 65%, whereas ECG interpretation recommendations 'B', yields a sensitivity and specificity of 70%. For the clinician screening athletes, deciding which criteria to use is confusing. In the interest of providing a cost-effective cardiac screening program, the clinician may decide to apply recommendations 'A' in their practice, triggering the lowest number of false positives. Comparatively, in the interest of detecting all cardiac pathology that may cause SCD/A, the clinician may decide to apply recommendations 'B'.

An alternative approach comes in the form of receiver operator curve (ROC) analysis, a statistical approach employed in the 1940s to measure how well a sonar 'signal' (e.g. from an enemy submarine) could be detected from 'noise' (a school of fish) (McNicol, 2005). ROC analysis is advantageous as it allows us to plot sensitivity against specificity,

to compare several recommendations for ECG interpretation simultaneously under the sum ‘area under the curve’ (AUC) and visually in a ROC space. In application, a ROC curve lying across the diagonal line reflects the performance of a diagnostic test with a 50/50 chance of correct diagnosis (Figure 2.3). An ideal test would have a point in the upper left corner of the graph, indicative of a sensitivity and specificity of 100% (Figure 2.3). This is, however, unlikely to be achieved and, therefore, an understanding of what a positive or negative test may mean is precluded. Specifically, we understand that a positive ECG does not always equate to cardiac pathology, in the same manner, we understand that a negative ECG does not always equate to the absence of cardiac pathology.

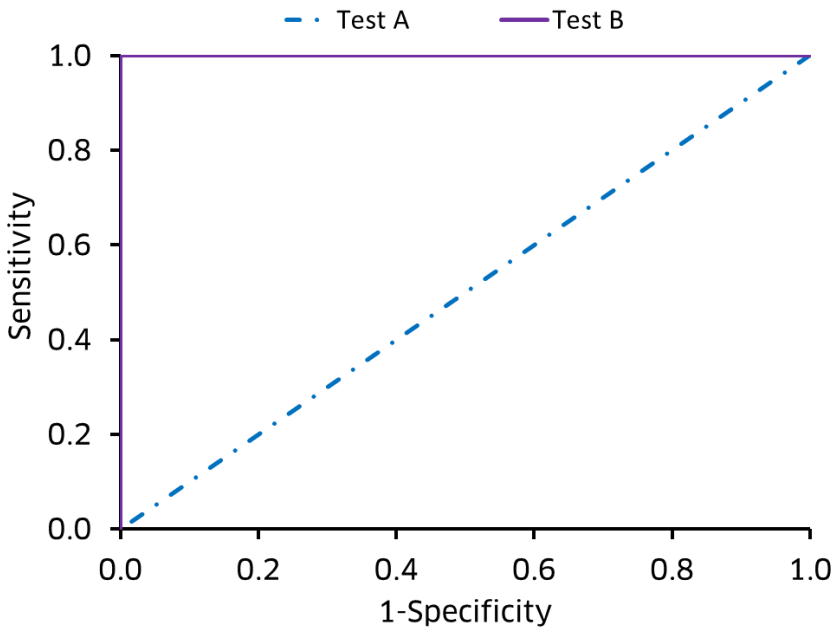

Figure 2. 3 Receiver operating curves according to test A, illustrative of an area under the curve of 0.50 (0.24 - 0.76) and test B illustrative of an area under the curve of 1.00 (1.00 - 1.00).

Likelihood ratios provide an alternative means of summarising diagnostic accuracy that may prove more clinically relevant if employed using Bayes analysis. Subject to the screening recommendations of the sports medical society or national governing body, an echocardiogram may be reserved for only those with an abnormal finding as per physical examination, health questionnaire or ECG. It is, therefore, impossible for the attending clinician to determine if this was a false-negative. With such information, the clinician may have chosen to apply different interpretation criteria. Bayesian analysis allows for the quantification of 'chance' of having a cardiac pathology following ECG interpretation, based on the *pre*-test and *post*-test odds (Whiteley, 2016), providing a relatable statistic to the clinician. To the best of the author's knowledge, no investigations comparing recommendations for ECG interpretation in athletes, have employed such statistical methodology. Application in Chapters 5 and 6 will ensure that the empirical studies 2 and 3, are interpreted in appropriate clinical context.

2.4 THE PAEDIATRIC ECHOCARDIOGARM

An echocardiogram assessment represents one of the most widely used non-invasive imaging tools for assessing cardiac structure and function. Like any diagnostic investigation, its relative effectiveness is subject to the establishment of a set of accurate and extensive reference values.

2.4.1 NON-ATHLETES' PAEDIATRIC CARDIAC STRUCTURE

We understand that paediatric years are associated with a number of physiological changes, namely rapid physical and sexual development. The process of heart growth is characterised by a near 200-fold increase in LV end-diastolic volume, from premature infants to young adulthood (Gutgesell and Rembold, 1990). Secondly, characterised by a gradual transition of RV to LV dominance with increased chronological age, a process that only stops when complete formation of ventricular mass has been obtained (Park and Guntheroth, Warren, 2006). Collectively such changes make for a complex cardiac structural assessment. This is further complicated by the impact of sex (Pelliccia *et al.*, 1996; Whyte *et al.*, 2004; Sheikh *et al.*, 2013; Kinoshita, Katsukawa and Yamazaki, 2015; Finocchiaro, Dhutia, *et al.*, 2016), ethnicity (Basavarajaiah, Boraita, *et al.*, 2008; Di Paolo *et al.*, 2012; Sheikh *et al.*, 2013; Pelà *et al.*, 2014; Riding, Salah, *et al.*, 2014) and both the type and magnitude of physical training (Agrebi et al., 2015; Beaudry et al., 2016; Oxborough et al., 2016). Aside from abnormal hemodynamics, body size represents the most powerful determinant of cardiac size in the paediatric non-athlete (Gutgesell and Rembold, 1990; de Simone et al., 1995). Accordingly, unlike investigations in adult echocardiography (Antonio. Pelliccia *et al.*, 1991; Whyte *et al.*, 2004; Sun *et al.*, 2007; Basavarajaiah, Boraita, *et al.*, 2008; Basavarajaiah, Wilson, *et al.*, 2008), which often ignore its relative impact, clear recognition is paid in paediatric echocardiography (Cantinotti and Lopez, 2013; Cantinotti et al., 2014; Koestenberger et al., 2014; Dallaire et al., 2015; Lopez et al., 2017; Cavarretta et al., 2018; Krysztofiak et al., 2018). Indeed, as per the recommendations for quantification by the American Society of Echocardiography (ASE) Pediatric and Congenital Heart Disease Council (Lopez et al.,

2010a), when normative data are available, measurements of cardiac size should be expressed as Z-scores using the Haycock formula (Haycock et al., 1978) to calculate BSA

2.4.2 CARDIAC STRUCTURAL ADAPTATIONS OF THE PAEDIATRIC ATHLETE

The onset of dynamic exercise is characterised by an increase in both HR and stroke volume (SV), and, therefore, cardiac output (Q), to meet the oxygen delivery demands of the activity (Whyte, 2006). At a cardiac chamber level, this is characterised by a sustained elevation in preload, which increases incrementally with exercise intensity until an approximate point of anaerobic threshold, from which point ventricular volumes reduce slightly (La Gerche et al., 2015); supporting the delivery of oxygenated blood to the respective working muscles (Whyte, 2006). Subsequently, this places a repetitive volumetric challenge and wall stress upon both ventricles (La Gerche et al., 2011, 2015) and both atria (Gabrielli et al., 2016). It, therefore, stands to reason that a paediatric athlete training ≥8 hours a week (Brownlee et al., 2018), and thus regular inducing volumetric challenges and wall stress upon both ventricles, and both atria, will likely have a comparatively different cardiac morphology to the paediatric non-athlete. Consequently, it is likely that normative ranges derived from a non-athletic population will be inappropriate for application in the paediatric athlete, triggering a high number of false positives.

Secondly, we understand that maximal oxygen uptake (VO_{2max}); the gold-standard measurement of cardiopulmonary fitness (Taylor et al., 1955), to have a direct association

to previous training history (training intensity * training volume) (Bjerring et al., 2018). By definition VO_{2max} ($Q^*a\text{-}vO_{2\ difference}$) (Ekblom et al., 1968) is a product of the hearts capacity to deliver oxygenated blood to the working muscles. Accordingly, a strong correlation between VO_{2max} and cardiac size exists (La Gerche et al., 2012; Bjerring et al., 2018). It, therefore, stands to reason that cumulative time in which the heart is exposed to high hemodynamic stress is likely to correlate with cardiac size (Bjerring et al., 2018). If we consider the training age of the paediatric athlete vs. the adult athlete, it is likely that the paediatric athlete's heart will be comparatively smaller. It would, therefore, seem improbable that reference values derived from the adult athlete, could be applied to the paediatric athlete, before consideration is even given to the relative impact of BSA, maturation and, therefore, the incomplete formation of the adult heart. To be an effective diagnostic test, an echocardiographic assessment in the paediatric athlete, therefore, necessitates paediatric athlete specific normative ranges.

2.4.2.1 The Left Ventricle

Increased LV cavity, wall thickness, and mass are established manifestations of the adult athlete's heart (Pluim et al., 2000; Utomi et al., 2013), adaptations that have been reported to extend to the paediatric athlete chronologically aged 9 years and above (Ayabakan et al., 2006). This refutes notions that adaptations to regular and sustained high-intensity exercise training may be blunted in the pre-pubertal athlete (Rowland et al., 1994, 1998; George et al., 2005), owing to low testosterone levels (Schaible et al., 1984). Specifically, observations comparing 720 elite adolescent athletes to 250 sex, and BSA matched non-athletes, found athletes presented on average an LV wall thickness ~13% larger and an

LV cavity diameter ~6% larger (Sharma et al., 2002). In some cases, such remodelling has been found to overlap with phenotypic expressions of dilated cardiomyopathy, hypertrophic cardiomyopathy, and idiopathic left ventricular hypertrophy (Sharma et al., 2002; Makan et al., 2005b). Collectively, these pathologies account for 62% of SCDs in previously screened male paediatric soccer players in the UK (Malhotra et al., 2018). It, therefore, appears prudent to clearly define the upper limits of left ventricular remodelling within this population to aid the diagnostic utility of the paediatric athlete echocardiogram assessment.

Until recently, investigations defining upper limits of normality within the paediatric athlete, have focussed on the impact of chronological age. Providing chronological age-specific upper limits, derived from two standard deviations (SD) (97.5 percentile) above the mean observed in non-athletes (14-18 years) (Sharma et al., 2002; Makan et al., 2005b) and athletes (10-11, 12-13, and 14-15 years) (Koch et al., 2014). Both studies paid no regard to the impact of BSA and are limited to athletes of white ethnicity. Most recently, however, Cavarretta *et al.* (2018), provided reference values in white Italian paediatric (chronological age 8-18 years) soccer players, which account for both chronological age and BSA, whilst allowing for the calculation of Z-scores in accordance to the recommendations of the ASE Pediatric and Congenital Heart Disease Council (Lopez et al., 2010b). Cavarretta *et al.* (2018), therefore, provide a new tool to the echocardiographic assessment of the paediatric athlete, which may ease clinical interpretation. Validation, however, is required in a population of heterogeneous ethnicity

and sporting discipline, reflective of real-world cardiac screening in the paediatric athlete, and thus drives rationale for exploration within Chapter 7 of this thesis.

2.4.2.2 The Right Ventricle

It is now globally understood that individuals engaging in high-intensity (>70% VO_{2max}) exercise of significant volume (hours of training) demonstrate physiological cardiac remodelling that extends beyond the LV (Utomi et al., 2013; D'Ascenzi et al., 2017a). Cardiac chamber enlargement and to a smaller extent increased wall thickness (eccentric hypertrophy), are established manifestations of physiological RV remodelling in the adult athlete's heart (Oxborough et al., 2012; Zaidi et al., 2013a; Aengevaeren et al., 2018; Qasem et al., 2018b; a). More recently, such observations have been found to extend beyond the adult athlete, presenting, albeit to a smaller magnitude, in the male scholar (chronological age 15-18 years) soccer player, that in some cases overlap with the phenotypic expression of arrhythmogenic RV cardiomyopathy (ARVC) (Popple et al., 2018). Findings of concern, in light of recent evidence that ARVC was responsible for 33.3% of sudden cardiac deaths, not detected by ECG and echocardiography assessment owing to a false-negative in paediatric soccer players in the UK (Malhotra et al., 2018). This may, in part, be a consequence of the age penetrance of phenotype expression, with death occurring 7.9 and 9.7 years post initial screening, respectively, or due to the lack of normal ranges of RV structure in paediatric athletes.

During exercise, increases in pulmonary artery systolic pressure are proportionally greater than increases in systemic pressure observed in the LV (La Gerche et al., 2011). This is characterised by an increased mean pulmonary arterial pressure, exceeding 30 mmHg (Bevegard et al., 1963; Groves et al., 1987), occurring in parallel to increases in Q, exceeding 20 Litres/minute in adult athletes (Argiento et al., 2010; La Gerche et al., 2010). Responses to exercise which induce a disproportionately greater wall stress in the RV to LV during exercise (La Gerche et al., 2011), likely acting as acute stimuli for chronic adaptation (Oxborough et al., 2014a). Such differing responses to exercise, may in part, explain observations of a disproportionate increase in RV to LV size observed in some adult athletes (La Gerche et al., 2011; Oxborough et al., 2012).

To guide RV assessment within the paediatric athlete, normative values derived from a non-athlete paediatric population (Daubeney *et al.*, 1999; Pettersen *et al.*, 2008; Cantinotti *et al.*, 2014), an endurance adult athletic population (Oxborough et al., 2012), a predominantly adult (8.3% chronological age >18 years) ARVC population (Marcus et al., 2010), and a white male scholar (chronological age 15-18 years) soccer population are available (Popple et al., 2018). Yet guidelines, which account for heterogeneous sporting disciplines, ethnicities and the full chronological and biological age range (11-18 years) of the paediatric athlete, are currently not available. This represents a true diagnostic challenge when presented with RV cardiac chamber enlargement and increased wall thickness in the male paediatric athlete of non-white ethnicity playing a different sport than football. Accordingly, this drives the rationale for exploration within Arab and black paediatric athletes of heterogeneous sporting discipline within Chapter 7 of this thesis.

2.4.2.3 The Atria

Akin to the LV and RV, regular and sustained exercise induces repetitive volumetric challenges upon the left (LA) and right (RA) atria. Challenges underlined by the respective role of the atria in the cardiac cycle. First serving as a 'reservoir' during ventricular systole, secondly, maintaining passive filling during early diastole, acting as a 'conduit', and finally acting as a 'booster' pump during late diastole (Ogawa et al., 2009). It is, therefore, of little surprise; bi-atrial enlargement is an established manifestation of the 'whole-heart' adult athletes heart phenomenon (D'Ascenzi *et al.*, 2015; McClean *et al.*, 2015). Atrial enlargement may be an indicator of underlying pathology, secondary to raised ventricular filling pressures in conditions such as hypertrophic cardiomyopathy (Harris et al., 2006) and may act as a precursor for the development of atrial fibrillation, should sporting activity continue later in life (Andersen et al., 2013). Furthermore, RA enlargement can provide relevant indications for the diagnosis and follow-up in cases of pulmonary hypertension (Kassem et al., 2013; Bartelds et al., 2014; Redington and Friedberg, 2014). It is, therefore, important to ensure atrial enlargement in the paediatric athlete is physiological in nature.

Investigations of Pelliccia *et al.* (2005) detailing LA enlargement within 1777 competitive adult athletes, backdate nearly 15 years, observing 18% to have a 'mildly' dilated LA anteroposterior diameter (LAD) (≥40 mm) and 2% to present 'marked' LA dilatation (≥45 mm). Observations which extend to the paediatric athlete, with LAD equivocally demonstrated to be larger in paediatric athletes than non-athletes, a disparity of

increasing magnitude with increased chronological age (Medved et al., 1986; Rowland et al., 1987; Ozer et al., 1994; Obert et al., 1998; George et al., 2001; Hoogsteen et al., 2003; Makan et al., 2005b; Zdravkovic et al., 2010; Koch et al., 2014; Agrebi et al., 2015), likely attributable to increased cumulative hours of training (Beaudry et al., 2016). The LA, however, is a non-symmetrically shaped three-dimensional structure, and, therefore, linear assessment of dimension, fails to account for non-symmetrical enlargement, which is often the case during LA remodelling (Lester et al., 1999; Vyas et al., 2011). It is, therefore, necessary to build upon investigations which assess LA size and remodelling within the paediatric athlete by measurement of LA volume (Ayabakan et al., 2006), as per the recommendations of the ASE (Lang et al., 2015). An assessment technique which accounts for alterations in LA chamber size in all directions. Finally, although it may be possible to infer reference values for measurement of LAD from the 13 articles (Medved, Fabecic-Sabadi and Medved, 1985; Rowland *et al.*, 1987, 1994; Ozer *et al.*, 1994; Obert *et al.*, 1998; George *et al.*, 2001; Hoogsteen *et al.*, 2003; Makan *et al.*, 2005b; Zdravkovic *et al.*, 2010; Di Paolo *et al.*, 2012; Sheikh *et al.*, 2013; Koch *et al.*, 2014; Agrebi *et al.*, 2015; Beaudry *et al.*, 2016) which detail its size in the male paediatric athlete, only 5 pay regard to BSA (Obert et al., 1998; George et al., 2001; Hoogsteen et al., 2003; Zdravkovic et al., 2010; Agrebi et al., 2015), often employing ratiometric indexing *(y/x*), which as will be discussed in detail later in this review, has obvious limitations.

In parallel to observations in adult athletes, bi-atrial adaptation in association to cumulative hours of training has been demonstrated in the paediatric athlete (Ascenzi et al., 2016). Data, however, are limited to three empirical investigations (Triposkiadis et al.,

2002; Ascenzi et al., 2016; Bjerring et al., 2018), upon a total sample of 158 athletes, with RA minor axis dimension detailed in none. Furthermore, whilst all paid regard to the impact of BSA in the maturing athlete, ratiometric *(y/x*) indexing was employed in all. Owing to our limited understanding of bi-atria physiological remodelling within the paediatric athlete, together with the clinical utility of atria assessment to enable early detection of an inherited cardiomyopathy which may predispose to SCD/A (Harris et al., 2006). It is, therefore, necessary to accurately define the upper limits of LA and RA size within a large cohort of paediatric athletes, of heterogeneous chronological age and BSA, so that it's association to allometric growth may be accurately defined. Thus, driving rationale for investigations conducted within Chapter 7 of this thesis.

2.4.2.4 The Aorta

Increased aortic dimension is an established manifestation of the adult athletes' heart (Kinoshita et al., 2000; Babaee Bigi and Aslani, 2007; Pelliccia et al., 2010; Iskandar and Thompson, 2013; Boraita et al., 2016). Conflicting evidence exists pertaining to the modality of exercise which induces greatest cavity enlargement, some indicating static (>50% maximal voluntary contraction) (Babaee Bigi and Aslani, 2007), and others dynamic (>70%VO_{2max}) (Iskandar and Thompson, 2013; Boraita et al., 2016). It is also apparent that aortic root dimension, measured at the Sinus of Valsalva, is positively correlated to both BSA and height (Riding et al., 2012; Oxborough et al., 2014b; Boraita et al., 2016). Irrespective of sport played (Babaee Bigi and Aslani, 2007; Iskandar and Thompson, 2013; Boraita et al., 2016), or in cases of extreme anthropometry (Riding et

al., 2012; Engel et al., 2016), investigations to exclude Marfan syndrome are warranted in the adult athlete presenting dimensions greater than 40 mm (Pelliccia et al., 2010).

Observations of aortic root (at the Sinus of Valsalva) enlargement in response to regular and sustained training, extend to the paediatric athlete (Ozer et al., 1994; Zdravkovic et al., 2010; Sheikh et al., 2013). Likely a result of the increase in elastic fibres in the ascending part of the Sinus of Valsalva, in contrast to other sections of the aortic root, namely, the sinotubular junction, which has a greater presence of collagen type I, with greater tensile strength. A clear disparity is evident between aortic root size in the paediatric athlete and upper limits derived from a non-athletic paediatric population (Cavarretta et al., 2018), necessitating the application of paediatric athlete specific upper limits. Yet, such upper limits are derived from only the white soccer player, and therefore the impact of ethnicity or sport played is not accounted for, and thus drives rationale for exploration within Chapter 7 of this thesis.

2.4.3 NON-ATHLETES PAEDIATRIC CARDIAC FUNCTION

Research attention has been paid to the assessment of systolic and diastolic function in paediatric populations over the past 30 years (Moskowitz et al., 1990; Frommelt et al., 1992; Hershenson et al., 2010). Historically, standard paediatric echocardiographic assessment has assumed normal LV ejection fraction (LVEF) [(stroke volume/end-diastolic volume) *100] equals normal systolic function and that abnormal LVEF equals abnormal function (Lang et al., 2006). As illustrated in the case of a pathological

hypertensive patient, diagnosed with heart failure, but with a normal EF (MacIver and Townsend, 2008), this assumption may not always hold true. Pulsed wave Doppler allows for the quantification of peak flow velocities in early (E) and late (A) diastolic phases non-invasively (Nishimura et al., 1989), allowing for calculation of the E/A ratio, providing an overview of diastolic function. Doppler, however, is understood to be significantly altered by preload and changes in LA pressure (Stoddard et al., 1989; Sohn et al., 1997; O'Leary et al., 1998); challenges of particular significance to paediatric echocardiographic assessment, in view of changes induced during physical growth and maturation (Sohn et al., 1997).

Doppler may also be applied to the assessment of myocardial walls to determine the velocity of tissue movement (Oxborough, 2008), known as Tissue Doppler Imaging (TDI). Specifically, placement of the Doppler sample volume in the ventricular walls (LV: mitral annulus at the inferoseptal and the lateral wall; RV: tricuspid annulus at the lateral wall) throughout the cardiac cycle, allows for the assessment of segmental specific early (E') and late (A') diastolic and systolic (S') function. Furthermore, a combination of E and E' (E/E') acts as a useful surrogate for assessment of LA pressure, correlating with capillary wedge pressure (Nagueh Sherif F et al., 1997; Sohn et al., 1997). In contrast to observations within cardiac size, a negative relationship of pulse wave Doppler and TDI to increased body size (Cui and Roberson, 2006; Roberson and Cui, 2007; Roberson et al., 2007; Cui et al., 2008), chronological age (Harada et al., 1995; Eidem et al., 2003; Roberson and Cui, 2007; Cui et al., 2008), and HR (Roberson and Cui, 2007; Cui et al., 2008) exists. How this may relate to the paediatric athlete, coinciding with structural

remodelling as a result of repetitive volumetric challenges from regular and sustained training, will now be reviewed.

2.4.4 CARDIAC FUNCTIONAL ADAPTATIONS IN THE PAEDIATRIC ATHLETE

In the male paediatric athlete, regular and sustained exercise may be associated with an ~8% improvement in maximal Q when indexed to BSA (Unnithan et al., 2018), largely explained by an ~7% improvement in SV, when indexed to BSA (Unnithan et al., 2018), as maximal HR does not increase with training (Whyte et al., 2008). It, therefore, may be considered probable that cardiac systolic and diastolic function may be comparatively different between the paediatric athlete and non-athlete at rest.

2.4.4.1 Systolic Functional Adaptations in the Paediatric Athlete

At rest, the paediatric echocardiogram is typically characterised by a 'reduced' LVEF, observed to be as low as 50% (Vasiliauskas *et al.*, 2006; Di Paolo *et al.*, 2012; Calò *et al.*, 2015). These observations are often explained by the presence of an enlarged LV, with a diminished need for vigorous contraction to maintain sufficient SV at rest. Unnithan *et al*. (2018) observed similar indexed TDI S' velocities, in a small cohort of paediatric soccer players (n=22) and non-athletes (n=15). It may be postulated that this index is less-load dependent than LVEF, and may act as a better discriminator from physiology to pathology in the paediatric athlete. Before clinical utility may be considered, the applicability of normative values derived from a non-athlete population (Dallaire et al., 2015) requires validation in a large cohort of paediatric athletes of heterogeneous sporting

discipline and ethnicity, driving rationale for application within empirical investigations conducted in Chapter 7.

2.4.4.2 Diastolic Adaptations in the Paediatric Athlete

Diastole in the LV and RV includes active relaxation and chamber compliance, allowing for (re)filling prior to the next ejection period. In a closed loop system, the importance of optimal diastolic filling, allowing for appropriate SV and therefore Q generation is well understood. Assessment of diastolic function is complex because Doppler parameters are not directly related to overall volume and are dependent on atrial and LV pressures (George et al., 2010). It is, therefore, relatively unsurprising that observations of increased peak E (early diastole) and decreased peak A (late diastole) filling velocities in paediatric athletes compared to non-athletes are equivocal (Ozer et al., 1994; Makan et al., 2005b; Ayabakan et al., 2006; Bartkevičienė, 2015). The E/A ratio is, however, more commonly reported as an index of diastolic function. As a consequence of the equivocal changes in peak E and A filling velocities observed, most investigators have reported resting E/A ratio to be either unchanged (Ozer et al., 1994; Makan et al., 2005b; Ayabakan et al., 2006; Sheikh et al., 2013), or slightly increased (Bartkevičienė, 2015; Csajági et al., 2015) in paediatric athletes to non-athletes.

TDI parameters have been proposed to be relatively less load-dependent, than Doppler (Hershenson et al., 2010). A prospective 2-month endurance training study supports this premise, observing diastolic function (Septal and Lateral, E' and A') to be not altered in

9-11-year-old children (Obert et al., 2009). These observations have most recently been replicated when adjusting for cardiac size, namely LV length, in comparisons between elite paediatric soccer players and non-athletes (Unnithan et al., 2018). Investigations in the paediatric athlete are, however, restricted by inadequate sample sizes to confirm these outcomes. Secondly, although athlete-specific lower limits for indication of impaired function have most recently been defined (Finocchiaro et al., 2018) The myocardial velocities assessed (Septal and Lateral E'), varied significantly by chronological age; necessitating the need for future investigations to determine chronological age-specific thresholds. Furthermore, it is currently unknown if thresholds derived from non-athletes which account for chronological age in the paediatric (Eidem et al., 2003; Dallaire et al., 2015) are appropriate for application in the paediatric athlete. This serves to drive the application of non-athlete thresholds, and if necessary, define paediatric athlete-specific thresholds for parameters of diastolic function by Doppler, and TDI assessment in Chapter 7 of this thesis.

2.4.5 IMPACT OF ETHNICITY ON STRUCTURAL AND FUNCTIONAL ADAPTATIONS IN THE PAEDIATRIC ATHLETE'S HEART

2.4.5.1 The Left Ventricle

Consistent with observations in adults (Basavarajaiah et al., 2008a; Riding et al., 2014a), ethnic-specific LV remodelling appears to be prevalent in the paediatric athlete (Di Paolo *et al.*, 2012; Sheikh *et al.*, 2013; Pelà *et al.*, 2014). With comparison of data in black paediatric (Di Paolo *et al.*, 2012; Sheikh *et al.*, 2013; Pelà *et al.*, 2014) vs. adult data (Basavarajaiah et al., 2008a; Papadakis et al., 2011; Riding et al., 2014a), indicative of a

moderate increase in cardiac dimensions in association with increased body size and cumulative hours of training (Beaudry et al., 2016), from paediatric years to adulthood. Specifically, the black paediatric athlete may develop significant LVH (>12 mm), observed to be as large as 15 mm (Sheikh et al., 2013). Indeed, prevalence of LVH (>12 mm) is approximately 17-fold higher in the black than white paediatric athletes (7.1% vs. 0.4%) (Figure 2.4). Furthermore, in the investigations of Sheikh *et al.* (2013), almost 25% of black athletes who presented LVH (>12 mm), were chronologically aged < 16 years old. It is, therefore, of little surprise, upper limits of posterior and septal wall thickness (Di Paolo *et al.*, 2012; Sheikh *et al.*, 2013; Pelà *et al.*, 2014; Calò *et al.*, 2015) are significantly greater in black than white paediatric male athletes (Table 2.8). In the context that during paediatric years, hypertrophic cardiomyopathy can rapidly emerge (Maron et al., 1986), it is apparent ethnic-specific upper limits must be considered during careful evaluation of LVH in the paediatric athlete. Data pertaining to LV remodelling in the paediatric athlete are limited to athletes of white and black ethnicity. In view of the previously detailed increased prevalence of paediatric Arab athlete's competing at the highest level, namely the Youth Olympic Games, together with an understanding that Arab ethnicity significantly affects cardiac remodelling in the adult athlete's heart (Riding et al., 2014a), future work is required to establish upper limits of normality within this unique population. This drives rationale for empirical investigations within Chapter 7 of this thesis to define ethnic-specific normative reference values in the paediatric athlete, which then may serve to reduce the prevalence of SCD in a young athlete population.

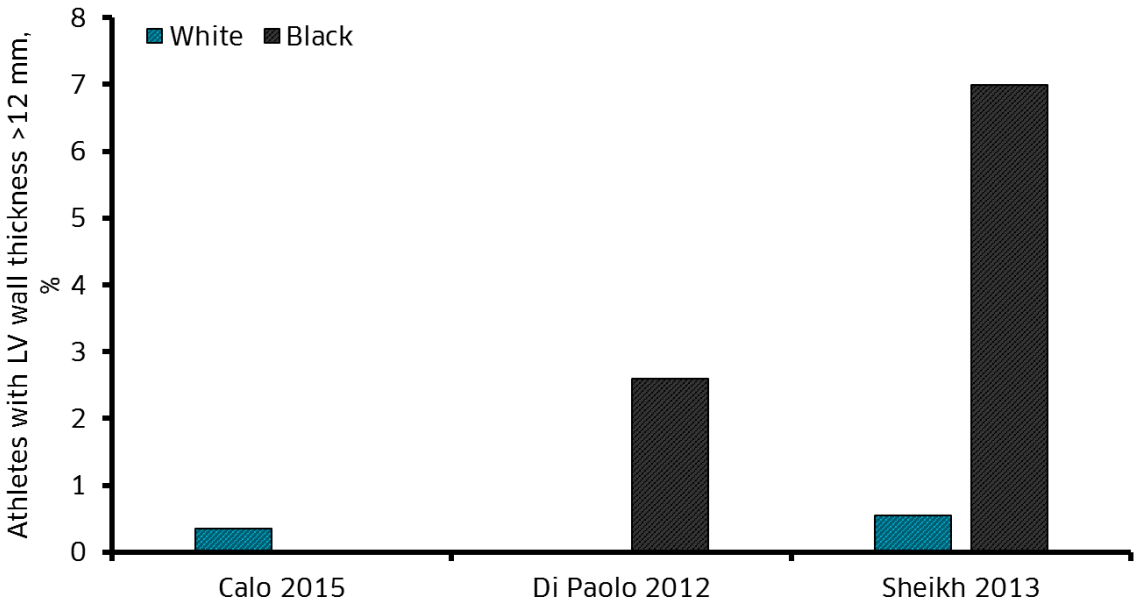

Figure 2. 4 Ethnic-related differences of left ventricular hypertrophy in male paediatric athletes. The bars represent the percentage of athletes showing left ventricular wall thickness >12mm on echocardiography in white and black male paediatric athletes, respectively**.**

Table 2. 8 Upper Limits of Normal Left Ventricular End-Diastolic Diameters and Wall Thickness in Male White and Black Paediatric Athletes.

Study	Ethnicity	Chronological Age		LVIDd, mm		IVSd, mm		PWTd, mm	
		Mean ± SD	Range, Years	Mean ± SD	Upper Limit, Mean + 2SD	Mean ± SD	Upper Limit, Mean + 2SD	Mean ± SD	Upper Limit, Mean + 2SD
(Calò et al., 2015)	white	12.4 ± 2.6	8-18	46.3 ± 5.0	56.3	7.2 ± 1.3	9.8	7.2 ± 1.1	9.4
(Di Paolo *et al.*, 2012)	white	16.5 ± 1.1	14-18	51.9 ± 2.6	57.1	9.2 ± 1.0	11.2	9.0 ± 0.8	10.6
(Pelà et al., 2014)	white	13.9 ± 1.6	11-17	47.2 ± 4.5	56.2	8.5 ± 1.2	10.9	8.1 ± 1.2	10.5
(Sheikh et al., 2013)	white	16.4 ± 1.3	14-18	51.0 ± 5.1	61.2	-	-	-	-
(Di Paolo *et al.*, 2012)	black	15.9 ± 0.7	14-18	51.0 ± 3.6	58.2	9.7 ± 1.3	12.3	9.6 ± 1.4	12.4
(Pelà et al., 2014)	black	14.3 ± 1.8	11-17	45.8 ± 3.8	53.4	9.8 ± 1.7	13.2	10.0 ± 1.8	13.6
(Sheikh et al., 2013)	black	16.4 ± 1.3	14-18	51.4 ± 5.0	61.4	-	-	-	-

IVSD, Intraventricular wall thickness during end-diastole ;LVIDd, Left ventricle internal diameter during end-diastole; PWTd, Posterior wall thickness during end-diastole

Global systolic and diastolic measures of cardiac function appear not to be mediated by ethnicity, within the adult (Basavarajaiah et al., 2008a; Riding et al., 2014a) or paediatric (Di Paolo *et al.*, 2012; Sheikh *et al.*, 2013) athlete. There are no LV TDI or STE data examining ethnic-specific adaptation in the paediatric athlete, and this requires further work to allow for appropriate interpretation of standard and advanced echocardiographic assessment.

2.4.5.2 The Right Ventricle

The importance of evaluating the relative impact of ethnicity on RV remodelling in the paediatric athlete is undisputed, when consideration is provided to: 1) prevalence of anterior (V_1-V_3) TWI is not uncommon in the black paediatric athlete, thus creating considerable overlap in the differential diagnosis of ARVC (Zaidi et al., 2013a) and 2) black paediatric athletes are among the highest at-risk population to SCD/A (Malhotra et al., 2018). Until 2013, the relative impact of ethnicity on physiological RV remodelling remained to be investigated. As per Zaidi *et al.,* (2013) ethnic-specific remodelling appears not to extend to the RV. Although cavity enlargement may be smaller in magnitude in black than white athletes (RV outflow tract from a parasternal long-axis orientation [$RVOT_{PLAX}$]: 28.8 ± 4.6 vs. 30.4 ± 4.6 mm; RVOT at a proximal level [$RVOT_1$]: 30.9 ± 5.5 vs. 32.8 ± 5.3 mm; RVOT at a distal level [$RVOT_2$]: 22.9 ± 3.7 vs. 24.3 ± 4.3 mm; and longitudinal RV dimension [RVD_3]: 86.6 ± 9.5 vs. 89.8 ± 9.6 mm; all $P < 0.001$), differences in cavity enlargement were considered non-clinically significant. Furthermore, irrespective of ethnicity, RVOT dilatation, mimicking phenotypic features of ARVC (Zaidi et al., 2013a), are observed in a significant proportion of adult black and white athletes

($RVOT_{PLAX}$ ≥32 mm was seen in 28% of black and 41% of white athletes; $RVOT_1$ ≥36 mm was seen in 22% of black and 29% of white athletes). However, in the context of cardiac screening, concomitant 'major' ECG and 'major' structural criteria for ARVC (Zaidi et al., 2013a) is more commonly met by black than white athletes (3.0% vs. 0.3%, P <0.01) (Zaidi et al., 2013a), creating a considerable diagnostic challenge in this ethnic population.

Investigations detailing the relative impact of ethnicity on RV remodelling are, however, limited to the adult athlete of black and white ethnicity (Oxborough et al., 2012; Zaidi et al., 2013a). This creates a further diagnostic challenge in the context that normative ranges on RV remodelling in the Arab athlete are unavailable, and phenotypic features of arrhythmogenic RV cardiomyopathy, appear to extend to the scholar (15-18 years) athlete (Popple et al., 2018). It is, therefore, prudent, that ethnic-specific upper limits are established in the paediatric athlete.

2.4.5.3 The Atria

The relative impact of ethnicity on bi-atrial enlargement within the adult athlete remains equivocal (Basavarajaiah et al., 2008a; Rawlins et al., 2010; Papadakis et al., 2011). Whilst empirical investigations in adults from the UK and France (Basavarajaiah et al., 2008a; Rawlins et al., 2010; Papadakis et al., 2011), reveal black athletes to present larger LAD than white athletes (35.4 ± 4.5 vs. 34.7 ± 4.7 mm, p<0.001). Investigations from Qatar (Riding et al., 2014a), detail LAD to be not dissimilar in black and white

athletes, but smaller in Arab than both black (33.4 ± 3.9 vs. 34.4 ± 3.7 mm, $p<0.05$) and white (33.4 ± 3.9 vs. 34.4 ± 3.8 mm, $p<0.05$) athletes (Riding et al., 2014a). Although the clinical and/or physiological reasoning for such disparity in findings is poorly understood, it must be taken into consideration that assessment was limited to LAD. As previously detailed within this review, this is a relatively limited measure of LA size, failing to account for the LA non-symmetrically shaped three-dimensional structure. To date, observations within paediatric athletes, remain consistent to those from adults in the UK and France (Riding et al., 2014a). Specifically, black paediatric athletes appear to present larger LAD (34.7 ± 4.7 vs. 33.8 ± 4.5 mm, $p<0.001$) than white athletes (Sheikh et al., 2013). An understanding of the relative impact of ethnicity in male paediatric athletes is, however, limited to assessment of the LA by LAD within black and white athletes only. To obtain a true understanding of LA ethnic-specific physiological remodelling, therefore, requires an extension of investigations to other ethnicities, namely the Arab paediatric athlete, in consideration of equivocal findings within adults (Basavarajaiah et al., 2008a; Rawlins et al., 2010; Papadakis et al., 2011). Secondly additional assessment of LA size, by LA volume, to account for the three-dimensional structure of this chamber is required. Observations within adult athletes indicate RA size to be not dissimilar in size between white and black athletes, but smaller in Arab athletes (Zaidi et al., 2013a; Riding et al., 2014a). Exploration of the impact of ethnicity to physiological RA remodelling within the paediatric athlete, however, has yet to explored. It is therefore necessary to establish appropriate ethnic-specific upper limits of atria physiological remodelling, within the paediatric athlete, which then may serve to reduce the prevalence of SCD in a young

athlete population. Thus serving as further rationale for empirical investigations conducted in Chapter 7 of this thesis.

2.4.6 NORMALISATION OF CARDIAC STRUCTURAL VARIBLES IN THE PAEDIATRIC ATHLETE

Cardiac enlargement of the paediatric athlete's heart is significantly impacted by differences in anthropometrics (George et al., 2001), chronological age (Vasiliauskas et al., 2006; Koch et al., 2014) and maturity status (Valente-Dos-Santos et al., 2013). It is, therefore, improbable to make meaningful inter- and intragroup comparisons without appropriate normalisation. Accordingly, a significant volume of the paediatric athlete's heart literature has sought to normalise, using the simple ratiometric approach (Shi and Selig, 2005; Di Paolo *et al.*, 2012; Koch *et al.*, 2014; Calò *et al.*, 2015), whereby a cardiac measure is indexed to a body size parameter (y/x). Y/X assumes a constant linear and proportional relationship between the cardiac length, area, and volume to BSA, and, therefore, observation of Tanners 'special circumstance' (Tanner, 1949). A circumstance that is rarely satisfied for any physiological data and relies on the contradiction of the theory of geometric similarity. To address such concerns, Mawad *et al.* (2013) proposed that appropriate normalisation of cardiac data must include: 1) careful selection of the optimal normalising variable; 2) determination of the best mathematical predictor of cardiac size, and; 3) assessment for the elimination of nonconstant variance (heteroscedasticity) of measures of cardiac size.

2.4.6.1 Normalising Variable

Chronological age, height, body mass and BSA, represent the most commonly utilised parameters for normalisation because of their ease of access. More recently, the efficacy of free fat mass as a normalising variable has become apparent (Whalley et al., 2004; Valente-dos-Santos et al., 2014; Giraldeau et al., 2015). Estimation of free fat mass is achievable by skinfold calipers, and Dual-energy X-ray absorptiometry (DEXA). DEXA is considered the gold-standard by many, owing to its two different x-ray intensities allowing for differentiation of lean and fat body mass, and has been commonly used in the literature because of its greater accuracy compared with skinfold caliper measurements. This may allow for the accurate establishment of free fat mass –independent values, providing a better platform for comparison (D'Ascenzi *et al.*, 2015). Although considered optimal, practical issues are apparent if undertaking nationwide cardiac screening, limiting its use to the hospital setting. Secondly, use of BSA, will generate acceptable body-size independent values and only necessitates a stadiometer. Accordingly, normalisation by BSA is often utilised, as it appears to be a superior parameter of somatic growth in paediatrics than height or weight alone (Hanséus et al., 1988; Sluysmans and Colan, 2005), often computed by the formula of Du bois and Du bois (1916) within the athlete's heart (Sharma *et al.*, 1999, 2002; Hoogsteen *et al.*, 2003; Makan *et al.*, 2005b; Papadakis *et al.*, 2009; Di Paolo *et al.*, 2012; Sheikh *et al.*, 2013; Koch *et al.*, 2014; Pelà *et al.*, 2014; Pela *et al.*, 2015). The formula of Du bois and Du bois (1916) , however, is derived from only 9 individuals and no children, often underestimating BSA as a result (Sluysmans and Colan, 2005). As per theoretical and empirical consideration of Sluysmans and Colan

(2005), and the recommendations of ASE Pediatric and Congenital Heart Disease Council (Lopez et al., 2010b), the Haycock (1978) formula, should instead be used.

2.4.6.2 Normalising Formula

Determination of the best mathematical predictor of mean cardiac size has received significant attention in non-athlete paediatric echocardiography (Mawad et al., 2013). Although increasingly adopted in adult athlete investigations (Oxborough et al., 2012; Utomi et al., 2014; Rothwell et al., 2018; Riding et al., 2019), considerations are scant within the paediatric athlete (George et al., 2001; Cavarretta et al., 2018; Popple et al., 2018). The allometric model ($y = a * chronological\ age^{b} * BSA^{c}$) adopted by Cavarretta *et al.* (2018), allowed for the determination of cardiac variable, chronological age, and BSA specific geometric relationships. Such investigations, however, employed logarithmic transformations of cardiac size, chronological age, and BSA. Although a statically sound approach to account for the effects of nonconstant variance (heteroscedasticity), such analysis does not conform to biological plausibility. Specifically, mathematical logarithmic transformations are artificial, often introducing distortion of the data, and obeys statistical models that behave very differently than those in the arithmetic scale (Packard and Boardman, 2008).

2.4.6.3 Heteroscedasticity

Measurements of cardiac size within the paediatric non-athlete commonly manifest a standard deviation that increases progressively with increasing body size and/or

chronological age (Colan, 2013). In other words, the presence of non-constant variance (heteroscedasticity), is highly likely for a measure of cardiac size in the paediatric athlete. Such considerations may seem trivial, but if not considered, for a measurement of Intraventricular Wall Thickness During End-Diastole (IVSd) to be outside the predicted upper limits, the difference between the mean and the measured value would be the same for two individuals of very differing body size. Let us say athlete A has a BSA of 1.0, as per Pettersen *et al.* (2008), he is predicted to have an IVSd of 5.9 mm, whereas athlete B with a BSA of 1.7, is predicted to have an IVSd of 7.7 mm. If heteroscedasticity is not accounted for, we would assume that the difference between the predicted mean and the upper limit would be the same for both athletes. This would seem counterintuitive, when a 23.4% change in predicted size has occurred. The potential clinical error would be a measurement obtained at a BSA of 1.0 that should be considered abnormal, will be considered normal if assuming a constant variance. Evaluation for the presence of heteroscedasticity is therefore necessary, and can be determined by the presence of a statistically significant slope between the absolute residual values and the dependent variable; indicative that heteroscedasticity is likely present (Mawad et al., 2013). Although Cavarretta *et al.* (2018), adopt logarithmic transformation to account for heteroscedasticity, residual analysis is not presented.

2.4.6.4 Z-Scores

Interpretation of the paediatric athlete's echocardiogram has typically adopted the practice seen in the adult's athlete's heart, directed by the establishment of cut offs, derived from 2 SD upward from the population mean. Alternatively, upper limits of

normality may be expressed as Z-scores or centiles, as recently provided by Cavarretta *et al.* (2018). Allowing for an easy understanding of how far the respective measure is from the predicted mean, removing the requirement for the clinician to recall chronological and/or BSA specific normal ranges for a variety of measures. In practice, a measurement 2 SDs above the mean (the 97.7th percentile) has a Z-score of 2, whereas a measurement that is 2 SDs below the mean (the 2.3rd percentile) has a Z-score of -2. Application of Z-scores is of further benefit during longitudinal follow-up of the paediatric athlete who presents cardiac enlargement falling within the 'grey zone' of differential diagnosis of physiological remodelling and cardiac pathology. An increase of RVD_3 disproportionate to normal increases associated with growth is succinctly indicated by an increased Z-score, as per Cantinotti *et al*. (2014). Z-scores derived from the paediatric non-athlete, altering the clinician (Table 2.9).

Table 2. 9 Increasing Z-score over time of the Right Ventricle Length, Suggesting Pathological Enlargement.

Chronological age, years	Height, cm	Weight, kg	RVD_3, mm	Z-Score
11	140	36	65.9	+1.9
12	145	40	68.7	+2.0
13	150	43	74.1	+2.5
14	160	48	79.7	+2.8
15	170	55	87.9	+3.3

Cm, centimetres; IVSd, intraventricular wall thickness during end-diastole; kg, kilograms; mm, millimetres.

Z-scores have obvious clinical utility during the assessment of the paediatric athlete. Until now, calculation of Z-scores has often required the attending clinician to manually calculate the respective Z-score. Clinical migration has now become feasible with the implementation of electronic reporting, allowing for the calculation to be embedded in software or made publically available via websites designed to be usable on devices of any size, ranging from small smartphones to laptops/desktop computers. Future investigations detailing normative ranges within the paediatric athlete's heart should consider such electronic advancements for maximal clinical impact, driving the establishment of athlete-specific Z-scores within Chapter 7 of this thesis.

2.5 CONCLUSION

It is apparent from this review that a small proportion of male paediatric athletes are at risk of SCD/A due to the presence of undetected hereditary or congenital cardiac disease. This has led to the implementation of cardiac screening across academies in in North America, South America, Europe, Asia, and Australasia. Chronic high-intensity exercise induces a number electrophysiological (Sharma et al., 1999; Bessem et al., 2015), structural (Sharma et al., 2002; Makan et al., 2005b), and functional (Sharma et al., 2002; Makan et al., 2005b), cardiac adaptations in the paediatric athlete, akin to the adult athlete (Pluim et al., 2000; Utomi et al., 2013). Significant variations exist in the magnitude and type of adaptations observed in the maturing athlete, compared to the fully developed adult athlete, modulated by significant variability in maturity status (Migliore et al., 2012) and changes in BSA (George et al., 2001). It, therefore, may be considered inappropriate

to regard the paediatric athlete as a mini adult, blindly applying recommendations derived from the adult athlete to the detection of cardiac pathology in the paediatric athlete.

The relative impact of ethnicity (Papadakis et al., 2012) upon the manifestations of the adult athlete's heart have been determined with appropriate systematic reviews. As alluded to within this review, data for paediatric athletes is limited to empirical investigations, with the determination of the impact of ethnicity and chronological age limited by inadequate sample sizes. It, therefore, appears prudent to objectively determine the relative impacts of chronological age and ethnicity to electrophysiological, structural and functional adaptations of the paediatric athlete by the adoption of a systematic review with meta-analysis (level 1 evidence), therefore setting the 'scene' in chapter 4, before embarking upon study investigations, in chapters 5-7 of this thesis.

ECG-led cardiac screening has demonstrated optimal diagnostic capacity and cost-effectiveness within the adult athlete (Harmon et al., 2015b), improving with every revision of recommendations for ECG interpretation in athletes (Sheikh *et al.*, 2014; Riding, Sheikh, *et al.*, 2014). New international recommendations for ECG interpretation in athletes have been demonstrated to significantly reduce positive ECG rates compared with the ESC 2010, Seattle and Refined criteria, whilst detecting all cardiac pathology that may predispose to SCD/A in athletes with positive screening evaluations (Dhutia et al., 2017). Investigations to date, however, were limited to adult athletes of predominantly white ethnicity, with an inability to calculate sensitivity and specificity because secondary

evaluations were limited to athletes with positive screening evaluations. In view of the significant impact of ethnicity, together with the increased implementation of cardiac screening in academies across in North America, South America, Europe, Asia, and Australasia, it is necessary to validate such recommendations by calculation of diagnostic accuracy in chapter 5, before clinical application may be considered appropriate in the paediatric athlete.

New international recommendations for ECG interpretation in athletes consider anterior TWI (V_1-V_3) in athletes chronologically aged < 16 years, to be a 'Juvenile T Wave Pattern', that should not prompt further evaluation in the absence of symptoms, signs or a family history of cardiac disease (Drezner et al., 2017; Sharma et al., 2017b, 2018); largely based on observations in white athletes (Papadakis et al., 2009; Migliore et al., 2012). Whilst chronological age is linear, maturity status may vary in extreme cases by 6 years between two 9-year-old boys (Johnson et al., 2009). Accordingly, investigators have indicated maturity status to be a more appropriate discriminator of the 'Juvenile T Wave Pattern' to one indicative of cardiac pathology (Migliore et al., 2012). To date most work has used Tanner staging assessment (Marshall and Tanner, 1970; D'Ascenzi et al., 2017d), regarded by many to be an unnecessary invasion of personal privacy and thus a child protection concern. Alternatively, skeletal age (biological age) assessment by radiological hand–wrist X-ray examination is recognised by the IOC as the 'gold standard' estimate of maturity status (Engebretsen et al., 2010), with trivial radiation exposure (Blake, 1998; Huda and Gkanatsios, 1998) will be employed in chapter 6.

Not all cardiac screening programs (mandated or otherwise) within the paediatric athlete include an echocardiographic assessment as a primary screening examination. It is, therefore, difficult for the attending clinician to determine the respective diagnostic accuracy of an ECG test. Alternatively, Bayesian analysis permits quantification of 'chance' of cardiac pathology, when presented with an abnormal or normal ECG, governed by a respective recommendation for interpretation, thereby better informing the attending clinician's decision making on appropriate cardiology work up. Appropriate considerations of these analysis and interpretation issues will be made in chapters 5 and 6.

An effective echocardiogram is crucial to the efficacy of any cardiac screening program that mandates its use as a first-line screening tool, or reserves it, to act as a second-line screening tool. As indicated in this review, the complexity of a paediatric echocardiogram assessment in a maturing heart is further challenged by physiological remodelling induced from regular and sustained high-intensity exercise, with magnitude significantly impacted by both ethnicity and body habitus. Although preliminary left heart structural data are available in the white paediatric soccer player (Cavarretta et al., 2018), normative right heart structural data and functional data pertaining to both sides of the heart are scant, largely limited to Doppler assessment. Furthermore, although immaturity has been a largely cited reason to expect a blunted cardiac structural adaptation owing to regular and sustained exercise in the paediatric athlete, only one empirical investigation (Valente-Dos-Santos et al., 2013) has considered maturity status to the determination of LV size in the paediatric athlete. To be effective, and thereby reduce the risk of false negative /

positive diagnoses there is a requirement for appropriate reference values to be generated within the Arab and black male paediatric athlete within chapter 7.

2.5 HYPOTHESIS

Study 1 - H1: Owing to regular and sustained training, paediatric athletes will demonstrate a number of electrophysiological, structural and functional adaptations when compared to non-athletes.

Study 1 - H2: Electrophysiological, structural and functional adaptations will be dependent on the chronological age, sex, and ethnicity of the paediatric athlete.

Study 2 - H3: New international recommendations for ECG interpretation in athletes will be appropriate for application in paediatric athletes, outperforming the previous ESC 2010 recommendations and Seattle criteria, irrespective of ethnicity and chronological age.

Study 3 - H4: Detailed assessment of the preceding Jt and/or ST-segment preceding TWI in V_1-V_4, irrespective of ethnicity and chronological age will significantly aid the detection of cardiac pathology in the paediatric athlete

Study 3 - H5: The prevalence and significance of TWI in V_1-V_3 (the juvenile T wave pattern) will be determined by ‘biological’ not ‘chronological’ age, irrespective of ethnicity within the paediatric athlete.

Study 4 - H6: Cardiac growth within the paediatric athlete will conform to the allometric relationship of body size to cardiac growth but will importantly differ by ethnicity.

CHAPTER 3:

GENERAL METHODS

The following pages describe methods common to original data collection in studies 2-4 (chapters 5-7) contained within this thesis. The general methods are discussed in detail according to the setting, health questionnaire and physical examination, 12-lead ECG, transthoracic echocardiogram and skeletal age assessments, supported with further investigations to confirm or exclude cardiac pathology. These assessments are employed across studies. When specific studies utilise methods unique to a data set these are described in the relevant chapter.

3.1 ETHICS

Ethics approval was provided by Anti-Doping Laboratory Qatar (IRB #E2013000003 and #E20140000012) for studies 2-5 within this thesis, with all parents or guardians providing informed consent (Appendix 1 for ethics approval documentation).

3.2 SETTING

All examinations were undertaken at Aspetar Sports Medicine Hospital and the Aspire Academy Sports Medicine Centre, Qatar, Doha, an accredited FIFA Medical Centre of excellence. In the state of Qatar, every athlete who is registered with the Qatar Olympic Committee must undergo cardiac pre-participation screening. Accordingly, athlete status was defined as: ‘an individual *who participates in an organised team or individual sport*

that requires regular competition against others as a central component, places a high premium on excellence and achievement, and requires some form of systematic (and usually intense) training' (Maron and Zipes, 2005) with ≥6 h/week structured exercise considered as a minimum requirement. The state of Qatar, located in Western Asia, has a population with heterogeneous ethnicity, with athletes from over 49 countries, presenting for cardiac pre-participation evaluation. For the purposes of this thesis, investigations were limited to male athletes, chronologically aged 10-18 years, and of Arab and black ethnicity. Ethnicity was self-determined by the athlete (or guardian) in accordance with the definitions offset by the UK government's statistical service (Harmonised concepts and questions for social data sources, GSS Harmonised Principle: Ethnic group).

3.3 HEALTH QUESTIONAIRE

Athletes completed a health questionnaire regarding family history of cardiovascular disease and personal symptoms, as directed by the IOC derived Lausanne recommendations (Bille et al., 2006), the European Society of Cardiology (Corrado et al., 2005b), the Association of European Paediatric Cardiology (Fritsch et al., 2017) and the FIFA pre-competition medical assessment in collaboration with an Arabic, French and/or English-speaking nurse (Appendix 2).

3.4 PHYSICAL EXAMINATION

A physical examination consisted of anthropometric (height, cm and body mass, kg [Seca, Germany]) assessment, allowing for the determination of BSA calculated in accordance to the equation of Haycock $(0.024265 * (wieght^{0.3964} * height^{0.5378})$ (Haycock et al., 1978). Systemic blood pressure was determined from the left brachial using an automated device (Carescap VC150 GE Healthcare, USA) with systolic and diastolic blood pressure being documented as the mean of two consecutive measurements. It is therefore possible, coarction of the aorta may have been missed. Finally, precordial auscultation in both supine and standing positions, as well as assessment for any physical characteristics of underlying congenital or syndromal disorder, were undertaken by a sports medicine physician. Abnormal findings triggering further investigation included a blood pressure >140/90 mmHg on three consecutive occasions, radio-femoral delay, stigmata of Marfan Syndrome or a pathological murmur including widely split-second heart sound or a third/fourth heart sound.

3.5 RESTING 12-LEAD ELECTROCARDIOGRAM

A 12-lead ECG was performed on all athletes after a period of 5-minutes rest in the supine position using a commercially available system (GE Mac 5500 New York, USA), calibrated to a paper speed of 25 mm/s and amplification of 0.1 mV/mm. Electrode placement was undertaken utilising standardised guidelines from the American Heart Association (AHA) by a team of cardiac nurses and physiologists (Mason et al., 2007) Specifically, six electrodes were placed on the chest: V_1 and V_2 were placed close to the sternum in the fourth intercostal space. V_4 was placed in the fifth intercostal space at the

midclavicular line, with V_3 placed on a line midway between V_2 and V_4. On the horizontal plane set by V_4, not curving along the interspace, V_5 was placed on the anterior axillary fold (if ambiguous, midway between V_4 and V_6) and V_6 on the midaxillary line (Figure 3.1). Four-limb lead electrodes were placed on the shoulders and iliac crest, owing to prior standardised protocol, which may have caused an increased prevalence of axis deviation.

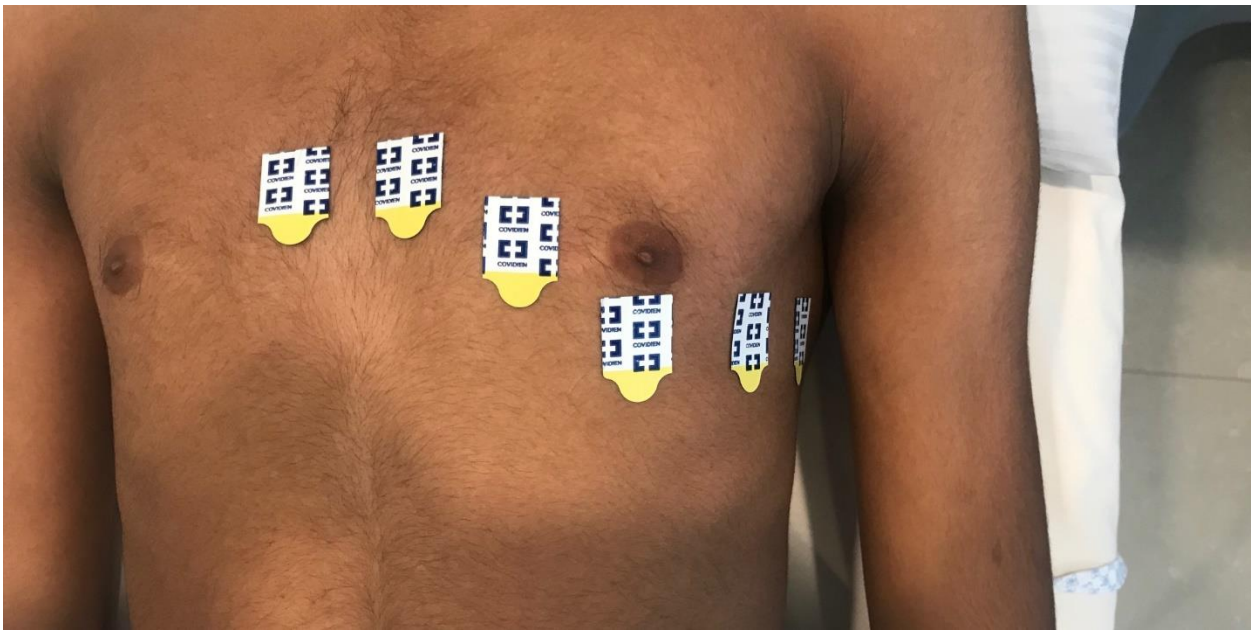

Figure 3. 1 Precordial electrode placement (V_1-V_6).

All ECGs were retrospectively interpreted by a single physiologist while blinded to pathology. P-, Q-, R-, S-, and T-wave voltages and ST-segments were measured in each lead (P-wave only I, II, aVF and V_1) using a millimeter (mm) ruler as described elsewhere (Friedmann, 1971). Confirmation of the computer-derived QRS duration, PR and QTc interval, with QTc assessment and calculation undertaken in accordance to the six principles of Postema *et al.* (2008).

First, the formula of Bazett (1997) ($QTc=QT/\sqrt{RR}$), by examination of lead II and/or V_5, with QTc assessment.

Second, in the athlete who presented with a HR <50 bpm, the ECG was repeated after some mild aerobic activity (10 squats) to obtain a HR (60–90 bpm), overcoming loss of accuracy to the formula of Bazett to slow HR.

Third, upon observation of sinus arrhythmia (beat-to-beat variation in RR interval), an average of 3 QT and RR intervals were taken, divided by the square root of the shortest RR interval, thus avoiding gross overestimation (Johnson and Ackerman, 2010).

Fourth, during manual confirmation, the end of the T wave was carefully identified, using the rhythm strip (lead II and/or V_5), was the best delineation of the T wave could be observed.

Fifth, during manual confirmation, the ‘Teach-the-Tangent’ (also known as ‘avoid the tail’) method were applied for measurement of the QT interval. Specifically, a straight line was drawn on the downslope of the T wave to the point of intersection with the isoelectric line, allowing for discrimination of the U wave, thus preventing inflantation of the QT/QTc.

Sixth, careful examination of the morphology of the T wave in the lateral precordial leads, for a notch, indicative of possible Long QT Syndrome, irrespective of QT prolongation

Finally, all ECGs were interpreted by application of new international recommendations for ECG interpretation in athletes (Drezner et al., 2017; Sharma et al., 2017b, 2018) and regarded to be normal, borderline, or abnormal accordingly (Figure 3.2, and Table 3.1).

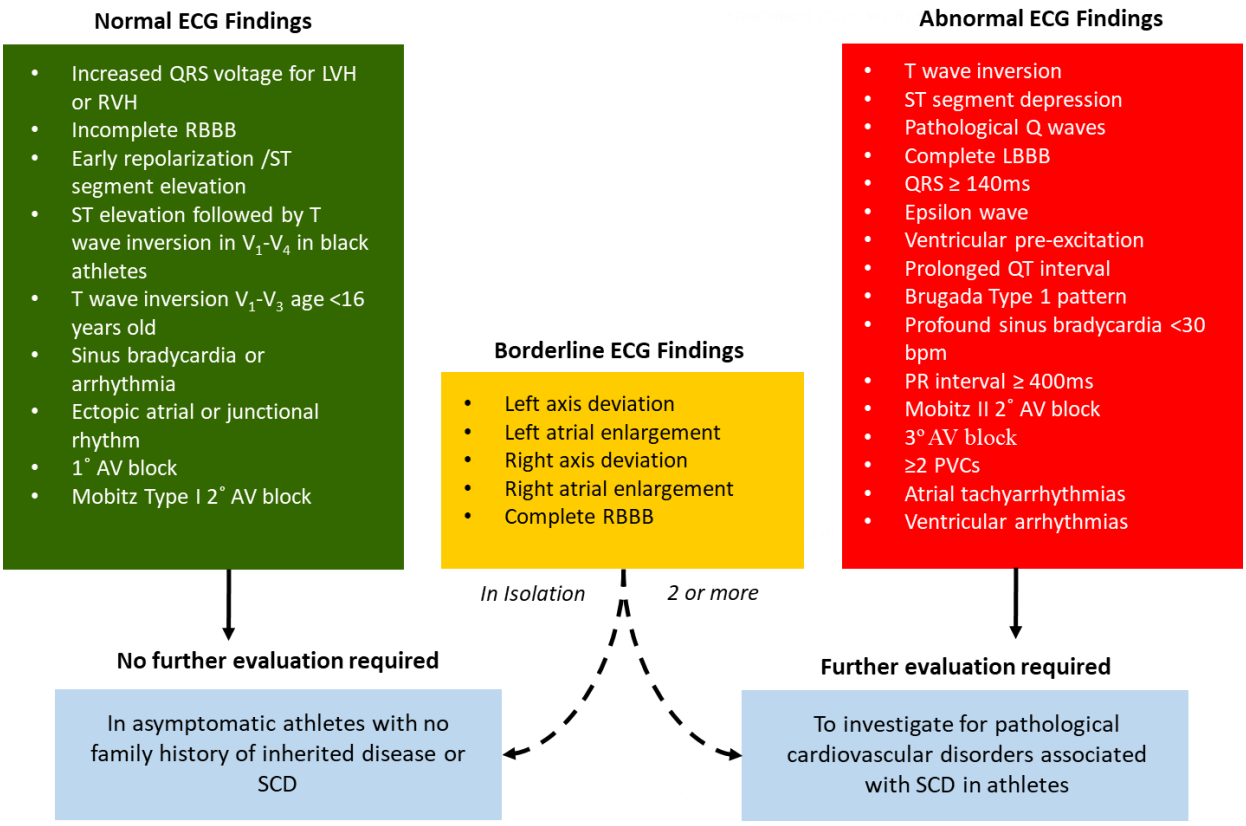

Figure 3. 2 New international recommendations for electrocardiographic interpretation in athletes aged 12-35 years (Drezner et al., 2017; Sharma et al., 2017b, 2018).

Key: AV, atrioventricular; ECG, electrocardiography; LBBB, left bundle branch block; LVH, left ventricular hypertrophy; PVCs, premature ventricular contractions; RBBB, right bundle branch block; RVH, right ventricular hypertrophy; SCD, sudden cardiac death.

Table 3. 1 New International Recommendations for Electrocardiographic Interpretation in Athletes.

Normal ECG findings in athletes

These ECG findings were considered to reflect physiological adaptations to regular and sustained exercise, not warranting further evaluation in the absence of other ECG features suggestive of cardiomyopathy

Normal ECG finding	Definition
Sinus bradycardia	≥30 beats.min^{-1}.
Sinus arrhythmia	Slight heart rate variation with respiration: rate increases during inspiration and decreases during expiration.
Ectopic atrial rhythm ('low atrial rhythm')	P-waves are present but with a different morphology to the sinus P-wave, typically observed with a heart rate ≤100 beats.min^{-1}.
Junctional escape rhythm	The QRS rate is typically less than 100 beats.min^{-1}, with a narrow QRS complex (<120 ms), unless the baseline QRS has a bundle branch block.
1˚ AV block	PR interval 200-400 ms, with each P-wave followed by a QRS complex and a regular R–R interval.
Mobitz type I (Wenckebach) 2˚ AV block	A progressive lengthening of the PR interval from beat to beat until there is a non-conducted P-wave with no QRS complex observed. Confirmed by the first PR interval after

	the dropped beat being shorter than the last conducted PR interval before the dropped beat.
Incomplete RBBB	Right bundle branch block (RBBB) morphology (rSR' pattern in lead V_1 and wide terminal qRS pattern in leads I and V_6), with a QRS duration ≤120 ms.
QRS voltage criteria for LVH and RVH	Isolated Sokolow–Lyon index voltage criteria for left (SV_1 + RV_5/RV_6 >35 mm) or right ventricular hypertrophy (RV_1 + SV_5 or SV_6 >1.1 mm).
Early repolarisation	- *Jt elevation*, measured at the end of the QRS complex (the onset of the ST-segment) with reference to the onset of the QRS complex (isoelectric line) and was considered elevated if Jt were ≥0.1mm. - *ST elevation*, measured 100ms after Jt, and was considered elevated if amplitude were greater than amplitude at Jt. - *End-QRS notching or slurring*, on the downslope of a prominent R-wave. A notch was considered present only when entirely above the baseline. Whilst a slur was considered present only when onset above the baseline.
Benign anterior TWI	- *Juvenile T wave pattern*, TWI in V_1-V_3 in athletes with a chronological age <16 years

	- *Black athlete repolarisation variant*, J-point elevation and/or convex ST segment elevation followed by TWI in V_2-V_4 - *Biphasic T wave pattern*, biphasic TWI in V_3 only

Borderline ECG findings in athletes

These ECG findings in isolation were regarded to be normal and thus not warranting further evaluation, but the presence of two or more were considered abnormal and thus warranting further evaluation.

Borderline ECG Finding	**Definition**
Left axis deviation	−30° to −90°.
Left atrial enlargement	P wave of >120 ms in leads I or II with a negative P wave ≥1 mm in depth and ≥40 ms in duration in lead V_1.
Right axis deviation	>120°.
Right atrial enlargement	P wave ≥2.5 mm in II, III or aVF.
Complete right bundle branch block	rSR' pattern in lead V_1 and wide terminal qRS pattern in leads I and V_6 and a QRS duration ≥120 ms.

Abnormal ECG findings in athletes

These ECG findings may suggest the presence of pathological cardiovascular disease and require further diagnostic investigation.

Abnormal ECG Finding	Definition
T wave inversion	≥1 mm in depth in ≥2 contiguous leads; excludes leads aVR, III and V_1, Juvenile T wave pattern, Black athlete repolarisation variant and biphasic TWI in lead V_3 only.
ST segment depression	≥0.5 mm in depth, relative to the isoelectric line between the end of the T wave and the beginning of the P wave, in ≥2 contiguous leads.
Pathological Q waves	Q/R ratio of ≥0.25 or ≥40 ms in duration in ≥2 leads; excluding III and aVR.
Complete left bundle branch block	QRS ≥120 ms, with a predominantly negative QRS complex in lead V_1 (QS or rS) and upright notched/slurred R wave in leads I and V_6.
Profound non-specific intraventricular conduction delay	Any QRS duration ≥140 ms.
Epsilon wave	Distinct low amplitude signal (small positive deflection or notch) between the end of the QRS complex and onset of the TWI in leads V_1-V_3.

Ventricular pre-excitation	PR interval <120 ms with a delta wave (slurred upstroke in the QRS complex) and wide QRS (≥120 ms).
Prolonged QT interval	QTc ≥470 ms (male). QTc ≥480 ms (female). QTc ≥500 ms (marked QT prolongation).
Brugada type 1 pattern	Coved pattern: initial ST elevation ≥2 mm (high take-off) with downsloping ST segment elevation followed by TWI in ≥1 leads in V_1-V_3.
Profound sinus bradycardia	<30 beats per minute or sinus pauses ≥3 s.
Profound 1° AV block	≥400 ms.
Mobitz type II 2° AV block	Intermittently non-conducted P waves with a fixed PR interval.
3° AV block	Complete AV block, characterised by more P waves than QRS complexes.
Atrial tachyarrhythmias	Supraventricular tachycardia, atrial fibrillation, atrial flutter.
Premature ventricular contractions	≥2 premature ventricular contractions per 10 s tracing. OR ≥1 premature ventricular contractions per 10 s tracing in the high dynamic athlete.
Ventricular arrhythmias	Couplets, triplets and non-sustained ventricular tachycardia.

AV; atrioventricular; ms; milliseconds; LVH, left ventricle hypertrophy; RVH, right ventricle hypertrophy; S, seconds; TWI, T wave inversion.

3.6 TRANSTHORACIC ECHOCARDIOGRAM

A transthoracic echocardiogram involves the insonation of the cardiac chambers from the anterior surface of the patient's chest. All echocardiographic examinations were performed with the athlete in the left lateral decubitas position using commercially available ultrasound systems (IE33, Philips Medical, USA and Artida, Cannon Medical Systems, Japan), with multi-frequency-phased array transducers (1.7–4 MHz with harmonic imaging). HR was acquired from the 3-lead ECG inherent to the ultrasound system. To provide standardisation and ensure quality, a systematic approach was adopted to image acquisition, with images optimised to maximise spatial and temporal resolution utilising small movements of the transducer, including tilting and rotation, alongside optimisation of the equipment settings through adjustment of gain, focal zones, depth, sector width, scale and sweep speed. A minimum of three cardiac cycles were acquired for offline analysis, undertaken by an accredited healthcare professional (Oxborough, 2008). Specifically, a complete 2-dimensional (2D), M-mode, Doppler, and TDI echocardiographic examination was obtained for the ventricular and atrial chambers, allowing for assessment of dimensions, function and hemodynamics. In addition, careful assessment of the aortic root allowed for the identification of the origins of the left and right coronary arteries. All images were acquired in accordance with the ASE (Rudski et al., 2010a; Lang et al., 2015) and the ASE Paediatric and Congenital Heart Disease Council (Lopez et al., 2010a). Images were stored as a raw digital imaging and communications in medicine (DICOM) format and exported to the offline workstations of QLab (Philips Medical, USA) and UltraExtend (Cannon Medical Systems, Japan) for subsequent analysis. For the purposes of this thesis, the techniques provide

morphological and functional information pertaining to the LV, RV, LA, RA, and the aortic root. The following sections provide detailed methods for acquisition and quantification of all chambers.

3.6.1 LEFT VENTRICLE

The LV was first assessed from the parasternal long axis (PLAX) orientation (Figure 3.3), with the placement of the transducer on the third or fourth intercostal spaces against the left sternal border, and the index point of the transducer directed towards the athlete's right shoulder.

The PLAX orientation, allowed for 2D linear measurements of LV Internal Cavity Diameter, Intraventricular Septal wall thickness and Posterior Wall Thickness, at end-diastole (LVIDd, IVSd, and PWTd), defined as the frame in the cardiac cycle in which LV dimension was at its largest, and end-systole (LVIDs, IVSs, and PWTs), defined as the frame in the cardiac cycle in which the LV dimension was at its smallest, respectively. Allowing for subsequent calculation of LV mass by the cube formula $(0.8 * 1.04 * (IVSd + LVIDd + PWTd)^3 - LVIDd^3) + 0.6)$ (Lang et al., 2015).

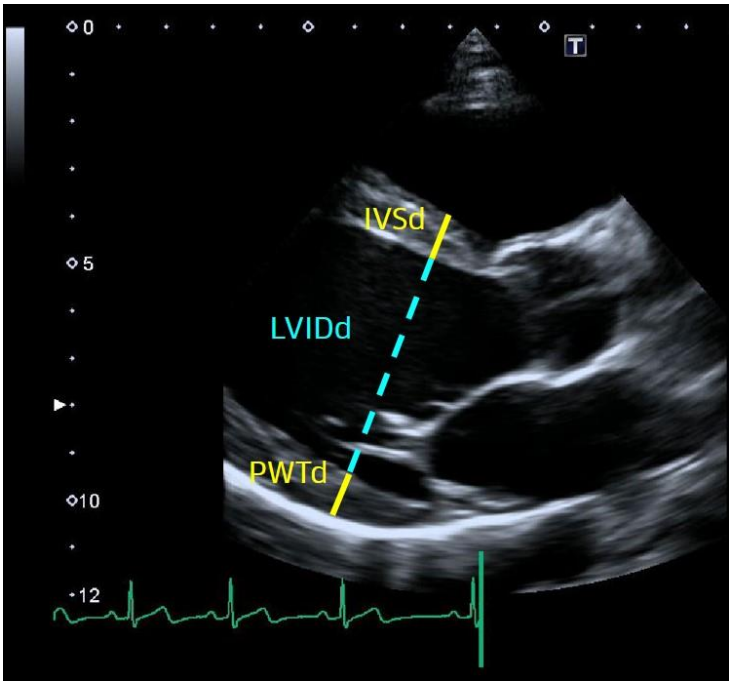

Figure 3. 3 LVIDd, Left Ventricular Internal Diameter during diastole; IVSd, Intraventricular Septum wall thickness during diastole; and PWTd, Posterior Wall Thickness during diastole from a parasternal long-axis orientation during diastole.

To assess LV volumes, 2D echocardiography images were acquired from the standard apical four-chamber and two-chamber orientations using the Simpson's biplane methodology, as recommended by the ASE, the ASE Pediatric and the Congenital Heart Disease Council (Lopez et al., 2010b; Lang et al., 2015) To allow for the acquisition of an apical four-chamber view, athletes were moved to a slightly more supine position, with the transducer placed over the apex of the heart, (approximately between the sixth and seventh rib spaces in the mid-axilla and moved between ribs, more medially or more laterally depending on anatomy) and the index directed to the athletes left shoulder.

Whilst in the same position, acquisition of the apical two-chamber view was sought by rotation of the transducer (approximately 90º) counter-clockwise, with placement maintained in the same rib space of the apical four-chamber view, for an accurate orthogonal cut (Figure 3.4).

Assessment of LV volume was obtained by tracing the endocardial border, at end-diastole (end diastolic volume [EDV]) and end-systole (end systolic volume [ESV]). Volume was calculated as the sum of the volume of all the disks using equation ($Volume = \pi / 4(\mathrm{h}) \sum (\mathrm{D1})\,(\mathrm{D2})$) where h is the height of each disk and D1 and D2 are the orthogonal minor and major axis of each disk. Subsequently, allowing for the estimation of systolic function by calculation of LVEF ($(\mathrm{EF})\,(\%) = (\mathrm{EDV} - \mathrm{ESV} / \mathrm{EDV})$) (Pombo et al., 1971).

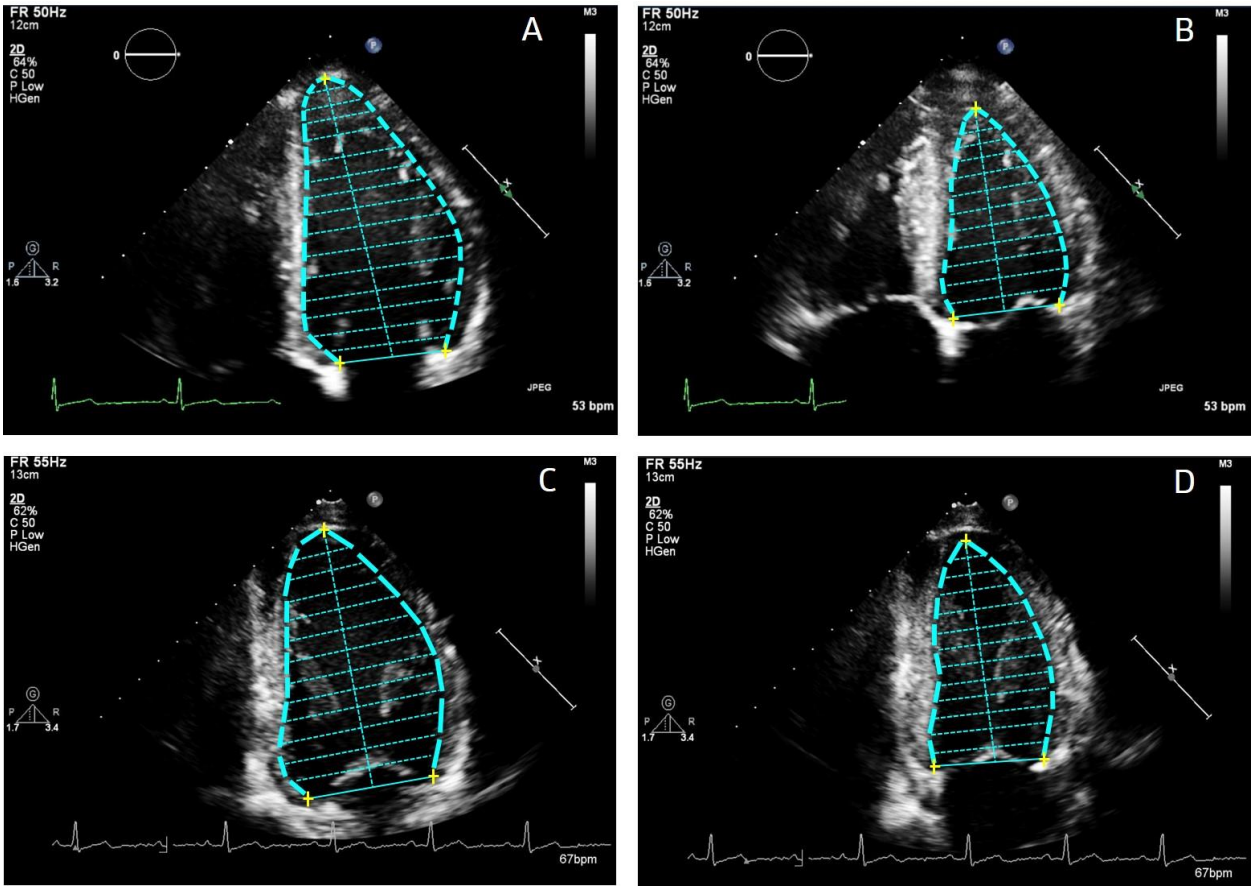

Figure 3. 4 LVEDV, Left ventricle end diastolic volume (A and C); and LVESV, LV end systolic volume (B and D) from a focused apical four-chamber and an apical two-chamber orientation.

Evaluation of global LV diastolic function, was assessed using standard pulsed wave Doppler from the apical four-chamber view, by placement of a 4-mm sample volume at the tips of the mitral leaflets in diastole, parallel to mitral inflow, to obtain peak early diastolic (E) and late diastolic (A) flow velocities, allowing for calculation of the ratio E/A (Garcia et al., 1998) (Figure 3.5), whilst also allowing for assessment of deceleration time of the E wave (DceT).

Further evaluation of LV diastolic and systolic longitudinal function was assessed via TDI by placement of a Pulsed Wave sample volume of 2 mm axial length (Waggoner and Bierig, 2001) within the mitral annulus at the inferoseptal (medial) and the lateral wall, allowing for peak myocardial tissue velocities in systole (S'), early diastole (E'), and late diastole (A') (Figure 3.5). Specifically, this technique allowed for interrogation of myocardial movement instead of blood flow, achieved by bypassing the high-pass filter, reducing the pulse-repetition frequency (PRF) and reducing the overall amplitude of the returning Doppler signals (Sutherland et al., 1999), whilst gains were set to minimal values to obtain the best signal-to-noise ratio. E/E' was subsequently derived from peak early diastole (E) flow, divided by an average of the septal (E') and lateral (E') myocardial velocities.

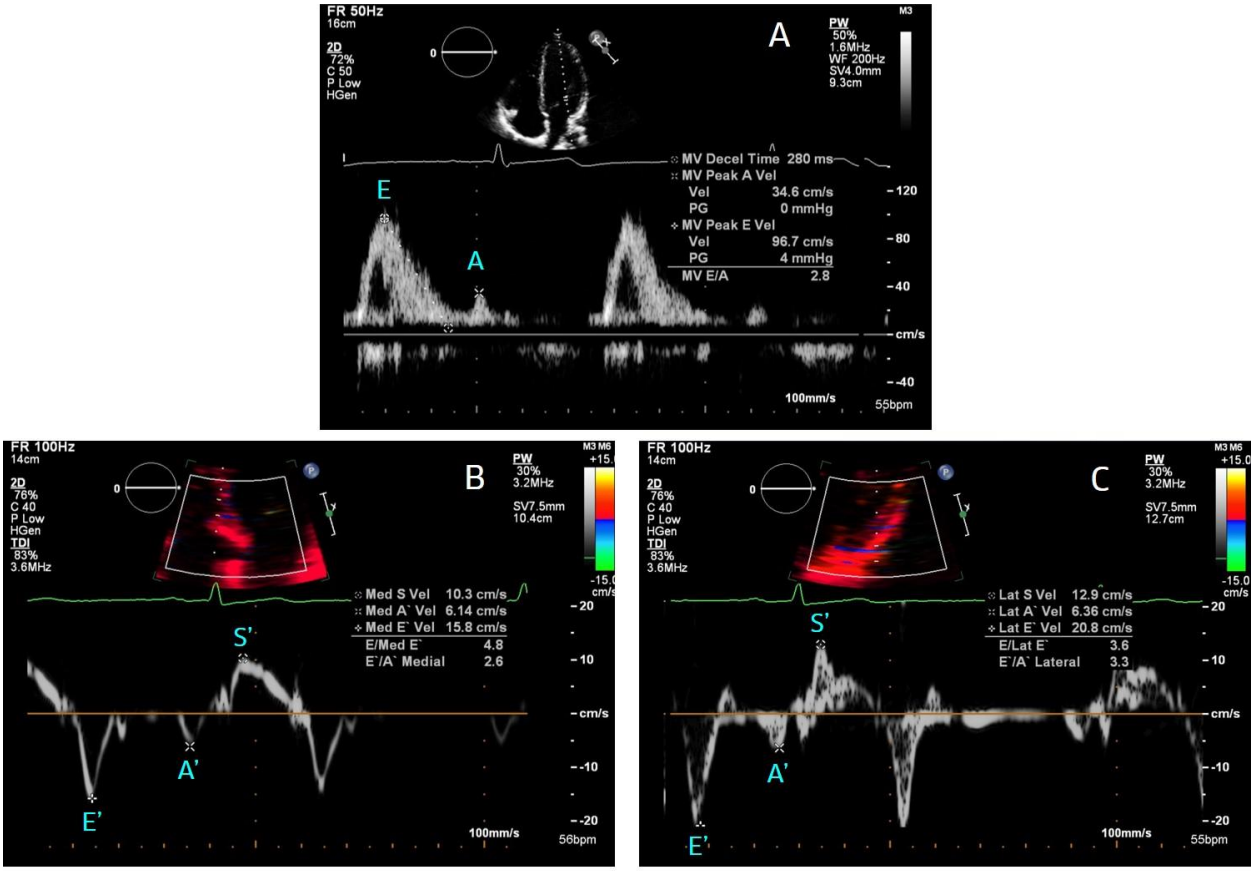

Figure 3. 5 Transmitral Doppler flow (A), Tissue Doppler Imaging of the Septal (B) and Lateral (C) wall, measurements from an apical four-chamber orientation.

Key: E, early diastolic; and A, late diastolic flow velocity; E', peak early diastole; A', peak late diastole; and S', peak systole myocardial tissue velocities

3.6.2 RIGHT VENTRICLE

To provide a comprehensive assessment of RV structure, a range of measurements were utilised for the purposes of this thesis. Specifically, the RV Outflow Tract (RVOT) diameter was first assessed in the PLAX view ($RVOT_{PLAX}$), with the measurement made during end-diastole, at the proximal level from the RV anterior wall to the aortic wall, perpendicular

to the interventricular septum, (Figure 3.6). The RVOT was also assessed from the parasternal short axis orientation (transducer rotated clockwise (approximately 90º), to allow for a true short axis of the ventricle to be seen). Subsequently, the RVOT was assessed at the proximal ($RVOT_1$) and distal ($RVOT_2$) levels with measurements made from the RV anterior wall to the anterior aortic wall (Figure 3.6).

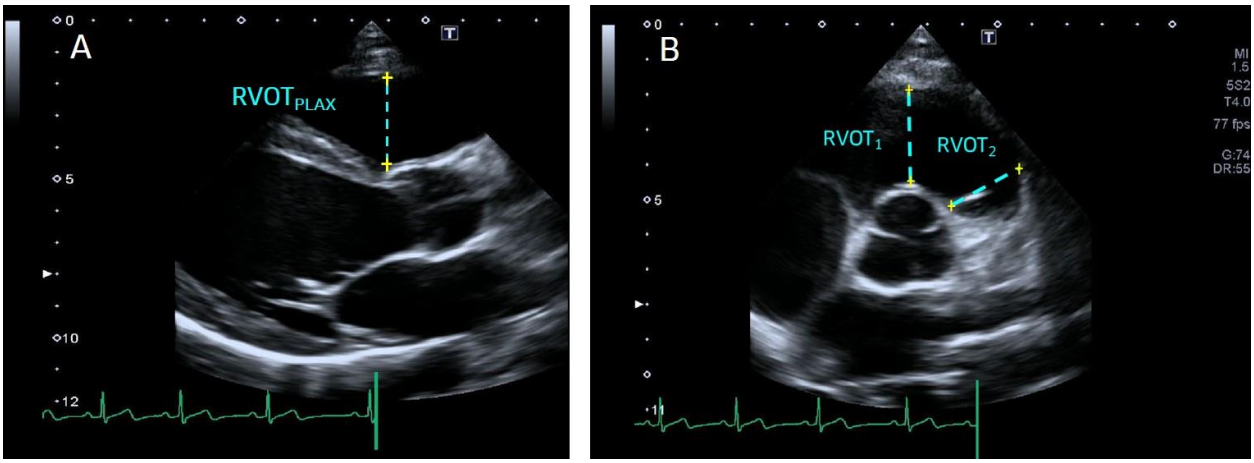

Figure 3. 6 Right ventricular outflow tract dimension ($RVOT_{PLAX}$) in a parasternal long-axis orientation (A) and $RVOT_1$ and $RVOT_2$, proximal and distal right ventricular outflow tract dimensions, respectively, in a parasternal short-axis orientation (B).

Assessment of the RV inflow was made using an RV focused apical four-chamber view, achieved by lateral movement of the transducer, allowing for the ultrasound beam to capture the widest part of the RV, whilst ensuring the aortic root remained closed. Subsequently, linear RV inflow dimensions were made from the widest point at the basal level (RVD_1), at the mid-level (RVD_2) and finally length was measured from the apex to tricuspid annulus (RVD_3) (Figure 3.7). Further measurements from this view, allowed for the determination of RV area, obtained by tracing the endocardial border, from the

annulus, along the lateral wall to the apex, and then back to the annulus, along the interventricular septum, at end diastole (RV end-diastolic area [EDA]), and at end-systole (RV end-systolic area [ESA]) (Figure 3.7). Subsequently, allowing for calculation of RV systolic function by RV fractional area change $((\mathrm{RVFAC})\,(\%) = (\mathrm{RVEDA} - \mathrm{RVESA}/\ \mathrm{RVEDA}) * 100)$ (Lai et al., 2008).

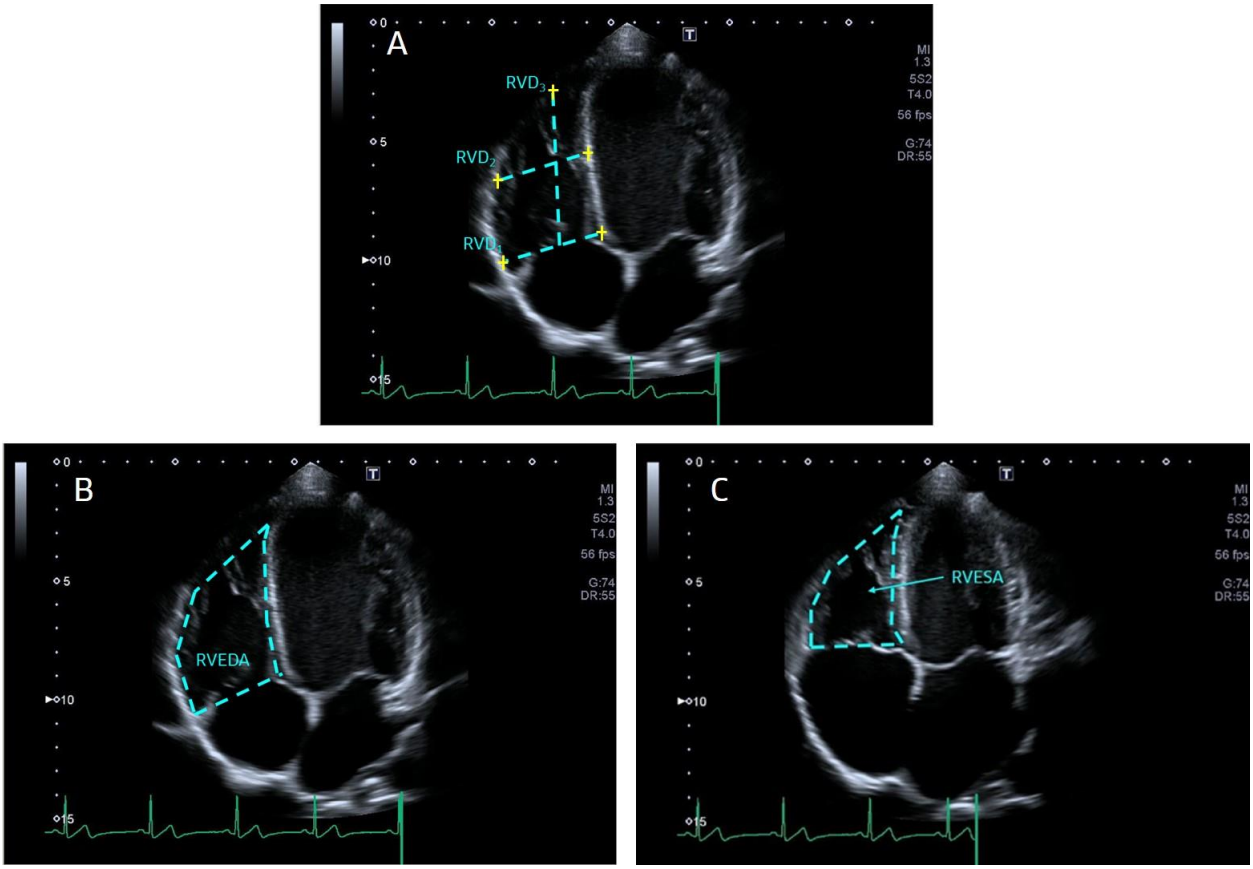

Figure 3. 7 Right ventricular inflow dimensions of basal level (1), mid-level (2), and length (3), during end diastole (A); RVEDA, right ventricular end diastolic area (B); and RVESA, right ventricular end systolic area (C); from a modified apical four chamber orientation, respectively.

Utilising a conventional apical four-chamber orientation application of M-mode echocardiography with the cursor positioned through the lateral aspect of the tricuspid valve annulus, allowed for measurement of the distance of systolic excursion of the RV annular segment along its longitudinal plane, Tricuspid Plane Systolic Excursion (TAPSE). Further evaluation of RV diastolic and systolic longitudinal function was assessed via TDI by placement of a 2 mm Pulsed Wave sample volume within the tricuspid annulus at the RV lateral wall allowing for peak myocardial tissue velocities in systole (S'), early diastole (E'), and late diastole (A'), (Figure 3.8). Due to the inability to obtain an adequate tricuspid regurgitant Doppler signal in a sufficient number of participants, and the relatively poor accuracy for deriving pulmonary artery pressures (Roberts and Forfia, 2011), the probability of pulmonary hypertension was determined on a multifactorial assessment of echocardiographic signs as defined by the European Society of Cardiology and the European Respiratory Society guidelines (Galiè et al., 2016).

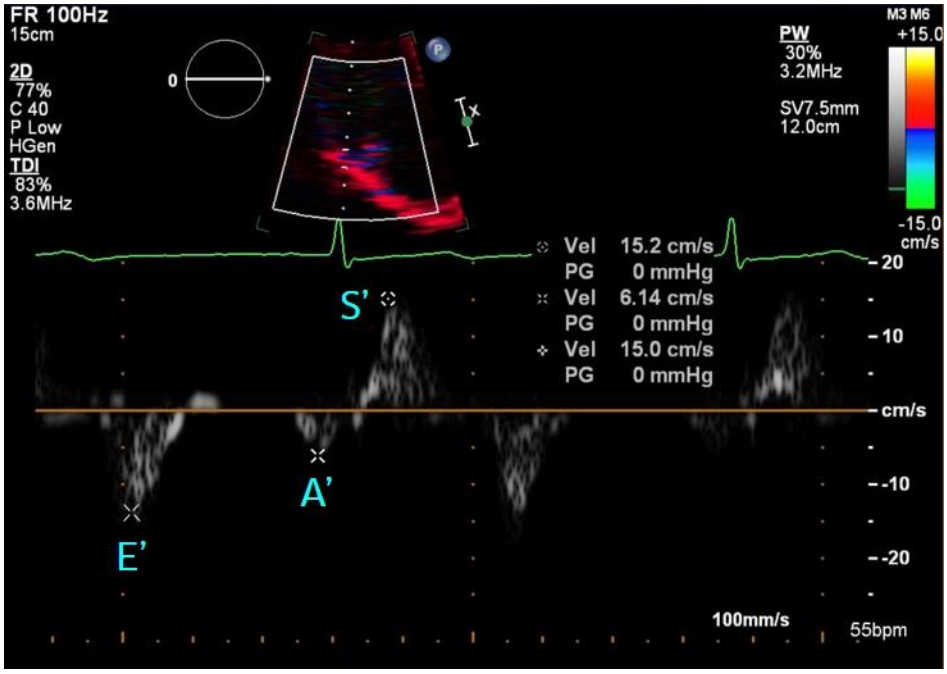

Figure 3. 8 Right Ventricle Tissue Doppler Imaging measurements from an apical four-chamber orientation.

Key: S', peak systole; E', peak early diastole; and A', peak late diastole myocardial tissue velocities

3.6.3 LEFT AND RIGHT ATRIA

The LA was first measured linearly, from the PLAX orientation, at the frame immediately prior to mitral valve opening (end ventricular systole), LA anteroposterior diameter (Figure 3.9). Specifically, 2D measurements were made from the posterior aortic wall to the posterior left atrium wall. LA volume was assessed using both the apical four and two-chamber views, with the application of the previously described biplane Simpson's method, in accordance to the ASE, the ASE Echocardiography Pediatric and the Congenital Heart Disease Council recommendations (Lopez et al., 2010b; Lang et al., 2015). LA volume was measured at end ventricular systole by tracing the endocardial border, with careful exclusion of the pulmonary veins and the LA appendage (Figure 3.9).

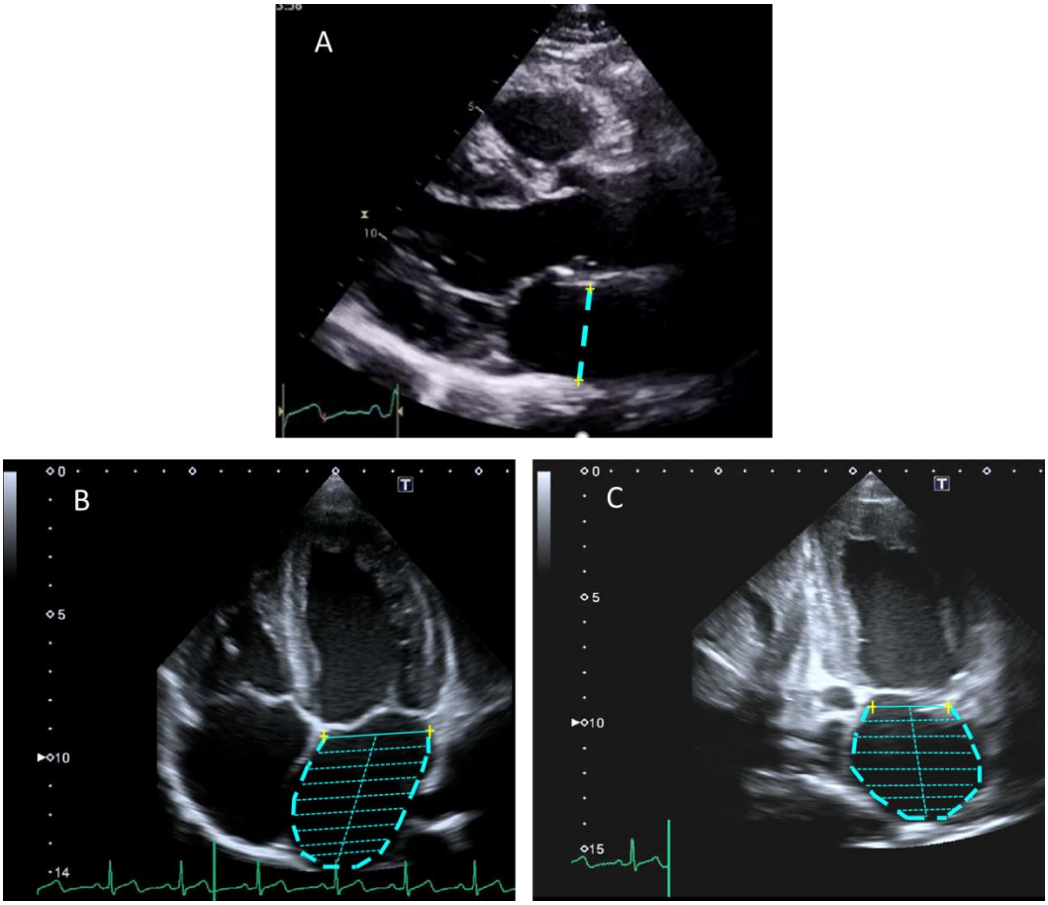

Figure 3. 9 Left atrial anteroposterior diameter during end-ventricular systole, from a parasternal long-axis orientation (A) and left atrial volume during end-ventricular systole, from an apical four-chamber (B) and two-chamber (C) orientation.

Assessment of right atrial (RA) size was acquired in the apical four-chamber orientation only. Firstly, RA_{area} was measured at the frame immediately prior to tricuspid valve opening (end ventricular systole) by tracing the endocardial border, with careful exclusion of the inferior vena cava, superior vena cava and RA appendage (Figure 3.10). Secondly, RA (minor axis) dimension was measured linearly from the mid-level of the RA free wall to the interatrial septum, perpendicular to the long axis (Figure 3.10).

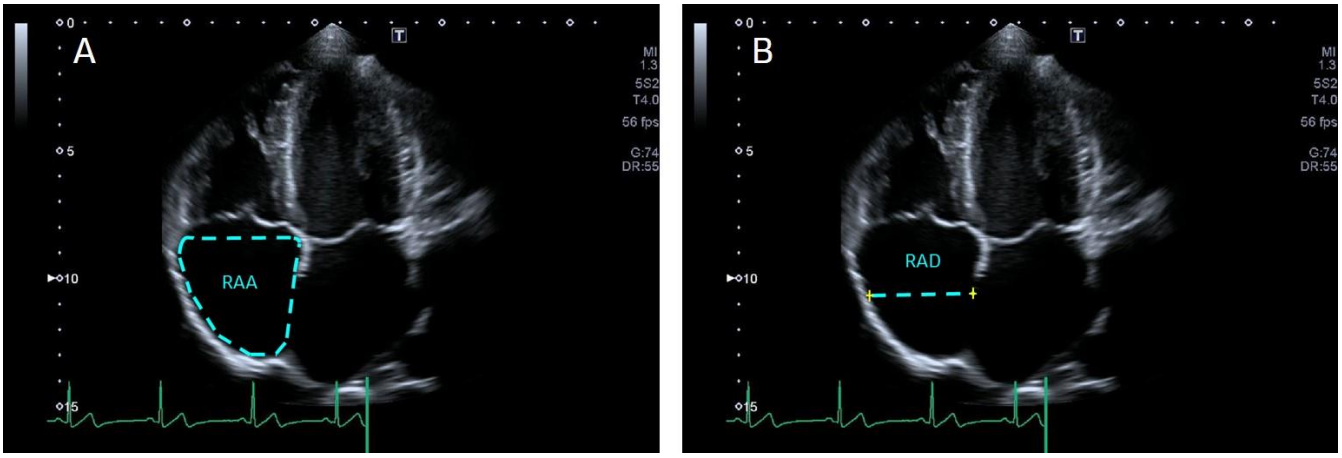

Figure 3. 10 Right atrial area (A) and right atrial diameter (minor axis) (B) during end-ventricular systole, from an apical four-chamber orientation**.**

3.6.4 AORTIC ROOT

Acquisition of aortic root diameter was made from the PLAX orientation. Measurement at the Sinus of Valsalva level was made during end-diastole (defined as the onset of the QRS complex on the ECG) by application of the 'inner edge' method (defined as blood pool/intima border of the anterior aortic wall to the same border on the posterior aortic wall) (Figure 3.11).

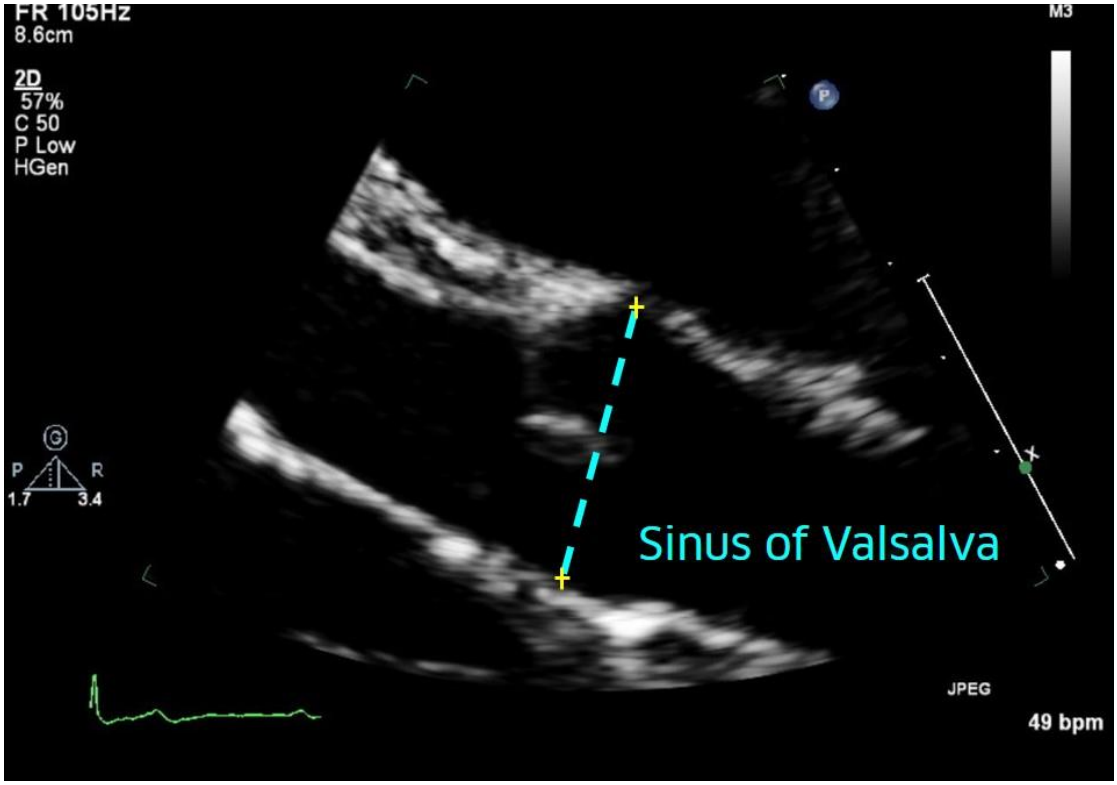

Figure 3. 11 Aortic root diameter, measured at the Sinus of Valsalva, from a parasternal long axis orientation.

3.6 BIOLOGICAL AGE ASSESSMENT

Assessment of biological age was determined by estimation of skeletal age from a single posterior–anterior radiogram of the left hand-wrist, thus minimizing radiation. Radiation exposure was considered almost negligible (0.00017 millisieverts); corresponding to 1 hour of background radiation from major cities in the UK (Blake, 1998; Huda and Gkanatsios, 1998). For the purposes of investigations conducted within this thesis, films were rated in accordance to the Fels method for estimation of skeletal age (Roche et al., 1988), by a single examiner with a previously demonstrated intra-class correlation

coefficient of 0.998 (Johnson et al., 2009). The protocol assigns grades to specific maturity indicators for the radius, ulna, carpals, and metacarpals and phalanges of the first (I), third (III), and fifth (IV) rays and utilises ratios of linear measurements of the widths of the epiphysis and metaphysis of the long bones (Figure 3.12). Presence (ossification) or absence of the pisiform and adductor sesamoid was also noted.

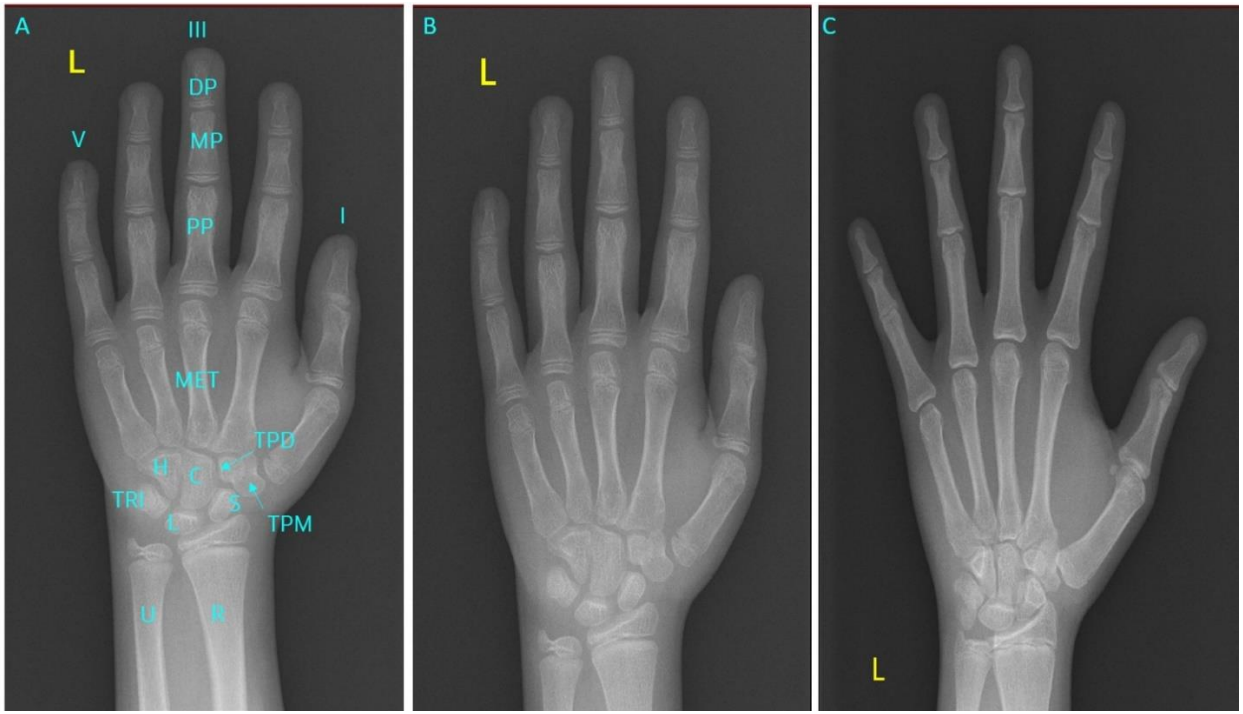

Figure 3. 12 Plain posterior–anterior radiogram of the left hand-wrist, with relevant measures indicated in athlete (A). Athlete (B) and (C) have a chronological age of 12 years. Athlete (B) has a biological age of 12.4 years and athlete (C) has a biological age of 17.2 years, as per Fels methodology.

Key: C, Capitate; DP, Distal Phalanx; H, Hamate; L, Lunate; MET, metacarpals; MP, Medial Phalanx; Proximal Phalanx; R, Radius; S, Scaphoid; TPD, Trapezoid; TPM, Trapezium; TRI, Triquet

3.7 FURTHER INVESTIGATIONS

Athletes presenting with a personal or family history of cardiovascular disease, an abnormal physical examination, ECG or echocardiographic abnormalities suggestive of underlying cardiac pathology were invited for further evaluation to exclude or confirm cardiac pathology. Those who declined to attend were excluded from the relevant studies, owing to the inability to exclude or confirm cardiac pathology. The methods for additional investigations to exclude underlying cardiac disease are summarised below.

3.7.1 AMBULATORY ECG/ BLOOD PRESSURE MONITORING

A 24-h ECG recording was undertaken using a DigiTrk XT (Philips, USA) for cardiac arrhythmia evaluation with Zymed Holter software 1810 (Philips, USA) used for offline analysis. All reports were undertaken by an appropriate healthcare professional adhering to the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Zipes et al., 2006). In order to assess 24-h blood pressure monitoring an A-PULSE CASPro Health (STATS, USA) was used. Athletes were encouraged to continue day-to-day activities, including exercise, during Holter monitoring. All reports were undertaken by an appropriate healthcare professional adhering to the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee of the Council on Cardiovascular Disease in the Young and the Council for High Blood Pressure Research (Zipes et al., 2006).

3.7.2 EXERCISE TESTING

A maximal exercise test by ergometer (SRM, Germany), using an individualised ramp protocol to define initial resistance (watts), increasing by 25 watts per minute to achieve a test duration of 8-12 minutes, allowing for optimal assessment of VO_{2max} (Myers and Froelicher, 2017). Throughout the test, continuous ECG monitoring was conducted in addition to ventilation volume and expired gas assessment using a MasterScreen ^{TM} CPX metabolic cart (CareFusion, USA). The exercise test was undertaken in accordance with the recommendations of the American Heart Association Council on Cardiovascular Disease in the Young, Committee on Atherosclerosis, Hypertension, and Obesity in Youth (Paridon et al., 2006), adhering to required methods for undertaking, terminating and reporting. Specific attention was paid to cardiac symptoms, ischaemic changes, attenuated blood pressure response, or arrhythmias.

3.7.3 CARDIAC MAGNETIC RESONANCE IMAGING

Cardiac magnetic resonance imaging was performed using a MAGNETOM Espree 1.5T (Siemens, Germany). Balanced steady-state free-precession sequences were used to obtain breath-hold cine images in three long-axis planes, followed by a contiguous stack of short-axis slices from the atrioventricular ring to the apex, ranging from 11-15 slices subject to heart size, as per the report of the American College of Cardiology Foundation Task Force (Hundley et al., 2010). Preliminary findings indicative of cardiac pathology directed the acquisition of disease-specific images as per the report of the American College of Cardiology Foundation Task Force (Hundley et al., 2010). If late gadolinium enhancement was required, images were acquired after ~6 minutes when resting HR

was <60 bpm, and after ~3 minutes when resting HR was ≥60 bpm, post administration of~0.5 ml/kilograms intravenous gadolinium contrast agent.

LV and RV volumes, mass, and function were quantified using a semi-automated threshold-based technique. All volume and mass measurements were indexed to BSA. Wall motion was analysed based on the 16-segment American Heart Association/American College of Cardiology model (Cerqueira, 2002). Late enhancement was defined as an area of high signal intensity on a background of adequately nulled myocardium present in two orthogonal phase-encoding directions (Hundley et al., 2010).

3.7.4 COMPUTED TOMOGRAPHY SCAN

Athletes with suspected coronary artery abnormalities underwent Computed Tomography cardiac angiogram investigation, using multidectector tomography with ECG gating. This facilitates a multidimensional display of the coronary arteries and their relation to the adjacent structures (Attili et al., 2013). These procedures were undertaken externally at the Heart Hospital (Hamad Medical Corporation).

3.7.5 ELECTROPHYSIOLOGY STUDY AND FOLLOW-UP

Athletes presenting with Wolf-Parkinson White pattern on ECG not confirmed by non-invasive testing, underwent electrophysiology study and ablation. These procedures were

undertaken externally at the Heart Hospital (Hamad Medical Corporation) according to standard protocols (Pappone et al., 2004).

CHAPTER 4:

ELECTRICAL AND STRUCTURAL ADAPTATIONS OF THE PAEDIATRIC ATHLETE'S HEART: A SYSTEMATIC REVIEW WITH META-ANALYSIS

McClean, G., Riding, N.R., Ardern, C.L., Farooq, A., Pieles, G.E., Watt, V., Adamuz, C., George, K.P., Oxborough, D. and Wilson, M.G., (2018) Electrical and structural adaptations of the paediatric athlete's heart: a systematic review with meta-analysis. British Journal of Sports Medicine, [online] 524, pp.230–230. Available at: http://bjsm.bmj.com/lookup/doi/10.1136/bjsports-2016-097052.

4.1 INTRODUCTION

Regular and sustained intensive physical activity is associated with a number of electrophysiological (Drezner et al., 2013d), structural and functional cardiac adaptations (Pluim et al., 2000); collectively referred to as the 'Athlete's Heart'. It is also well documented that ethnicity and sex significantly impact these manifestations of the adult athlete's heart (Pelliccia *et al.*, 1996; Sheikh *et al.*, 2014). Whilst previous systematic reviews and meta-analyses have detailed the adult athlete's heart phenotype (Pluim et al., 2000; Utomi et al., 2013), with some accounting for ethnicity and sex (Whyte *et al.*, 2004; Papadakis *et al.*, 2012), data from paediatric (6-18 years) athletic populations is limited to original research; often restricted by inadequate sample sizes and heterogeneity to assess the impact of age, ethnicity and sex in tangent.

Sports academies are increasingly used by clubs and governing bodies alike to develop and nurture talented sports stars of the future. Consequently, there is increasing competitiveness, professionalism and training demands placed upon the paediatric athlete during the maturational period. The IOC, amongst others, has called for more diligence to safeguard the physiological development of the paediatric athlete (Bergeron et al., 2015; Mountjoy and Bergeron, 2015; Mountjoy et al., 2015). Performing a pre-participation cardiac screening within paediatric populations is controversial due to a lack of international consensus with regards to when, how, and who should undertake such examinations (Friedman, 2014; Vetter, 2014). Whilst data from the USA indicate that paediatric black athletes are particularly susceptible to SCD (Harmon et al., 2016) , there is a general lack of understanding as to which factors (e.g., physical growth, ethnicity and sex) have the potential to increase the likelihood of generating a false-positive diagnosis and unnecessary disqualification from competitive sport. Consequently, the distinction between paediatric athlete's heart and cardiac pathology associated with SCD is especially important for this population.

Therefore, the primary aim of this systematic review and meta-analysis was to describe the ECG, structural and functional manifestations of the paediatric athlete's heart compared to that of age-matched non-athletes. The secondary aims were to determine the impact of an athlete's chronological age, ethnicity, and sex on cardiac remodelling responses to intensive competitive sport.

4.2 METHODS

This review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009).

4.2.1 LITERATURE SEARCHING

A systematic search was conducted using six electronic databases; (1) MEDLINE, (2) PubMed, (3) EMBASE, (4) Web of Science, (5) CINAHL, and (6) SPORTDISCUS. Databases were searched from inception, to May 2016. Search terms were mapped to relevant MeSH terms or subject headings under four concepts:

1) 'Paediatric'
2) 'Athlete',
3) 'Electrocardiography', 'Echocardiography', 'Magnetic Resonance Imaging'
4) 'European Society of Cardiology Criteria', 'Seattle Criteria', 'Ventricle', 'Atrium' and 'Septum'.

Terms within each concept were combined with the Boolean operator 'OR', then concepts were combined with the 'AND' operator to, produce the search strategy (Table 4.1) To supplement the electronic database searching, we hand searched reference lists of eligible articles, ePublication lists of key journals, and undertook citation tracking using Google Scholar (Table 4.2). All identified articles were imported into Endnote X4 for application of selection criteria (Thomson Reuters, California, USA).

Table 4. 1 Full Search Strategy as applied to the MEDLINE Electronic Database.

#	Query	Results
1	Adolescent/ or Child/ or Paediatrics/	2340649
2	(Girl* OR Boy* OR Junior* OR Juvenile* OR Teen* OR Paediatric* OR Prepubescent OR Pubescent OR Peri Pubertal).ti,ab,kw.	316474
3	Athlete/	4416
4	(Athlete* or Players).ti,ab,kw.	52511
5	Electrocardiography/	169256
6	(Electrocardiogram* or 12 Lead Electrocardiogram* or ECG* or 12 Lead ECG* or EKG* or 12 Lead EKG*).ti,ab,kw.	81490
7	Echocardiography, Doppler/ or Echocardiography, Doppler, Color/ or Echocardiography/ or Echocardiography, Transesophageal/ or Echocardiography, Doppler, Pulsed/	103453
8	(Echocardiogram* or Speckle Tracking or STE Resolution or 2D STE or 2DSTE or Speckle or STE).ti,ab,kw.	21310
9	Magnetic Resonance Imaging/	304307
10	(MRI* or CMRI*).ti,ab,kw.	162605
11	Ultrasonography/ or Ultrasonography, Doppler/ or Blood Flow Velocity/	52496
12	Ultrasound.ti,ab,kw.	167633
13	Ventricular Function/ or Hypertrophy, Right Ventricular/ or Ventricular Function, Left/ or Ventricular Function, Right/ or Ventricular Septum/ or Hypertrophy, Left Ventricular/ or Ventricular Remodeling/ or Myocardial Contraction/ or Heart Atria/	130852
14	(Ventric* or Atria* or Atrium or Septum).ti,ab,kw.	443254
15	Arteries/ or Brachial Artery/ or Radial Artery/ or Carotid Artery/ or Femoral Artery/ or Popliteal Artery/ or Vasodilation/ or Vasoconstriction/ or Vascular Resistance/ or Muscle Smooth, Vascular/ or Endothelium, Vascular/ or Arterioles/	282428

16	(Artery Structure or Artery Function or Arteriolar or Conduit Artery or Resistance Artery or Arterial Size or Arterial Wall Thickness or Intima Media Wall Thickness or Arterial Remodeling or Lumen Dimension or Vascular Function or FMD or Flow Mediated Dilation or Flow Mediated Dilatation or Shear Stress or Shear Pattern or Shear Rate).ti,ab,kw.	36920
17	(Heart rate or HR or PR Interval or QT Interval or QTc or QRS Duration or QRS or LVH or RVH or Sokolow or Cornell or Pediatric Specific or Romhilt Estes or Early Repolarization or ER or ST Elevation or J Point Elevation or J Wave* or ST Segment Elevation or QRS Slurring or Incomplete Right Bundle Branch Block or Incomplete RBBB or Incomplete Left Bundle Branch Block or Incomplete LBBB or T Wave Inversion or TWI or First Degree Atrio Ventricular Block or 1st Degree AV Block or Q Wave* or LAE or RAE or Left Atrial Enlargement or Right Atrial Enlargement or Bradycardia or Arrhythmia or Ectopic Atrial Rhythm or Junctional Rhythm or Mobitz Type I or Mobitz I or Wenckebach or Second Degree AV Block or 2nd Degree AV Block or Premature Ventricular Contraction* or PVC* or ESC Criteria or European Society of Cardiology Recommendation or Seattle Criteria or Refined Criteria or ECG Criteria).ti,ab,kw.	417843
18	OR/1-2	2470231
19	OR/3-4	53440
20	OR/5-12	842415
21	OR/13-17	1096521
22	AND/18-21	433

Table 4. 2 ePublication Lists of Key Journals Hand Searched to Supplement Electronic Database Searching.

#	Journal	Yield
1	Journal of the American College of Cardiology	0
2	Circulation	0
3	Circulation: Arrhythmia and Electrophysiology	0
4	Circulation: Cardiovascular Imaging	0
5	European Heart Journal	0
6	European Heart Journal: Cardiovascular Imaging	0
7	American Heart Journal	0
8	Chest	0
9	Heart	0
10	British Journal of Sports Medicine	1
11	Nature Cardiology	0
12	The New England Journal of Medicine	0
13	European Journal of Preventive Cardiology	0
14	Journal of Electrocardiology	0
15	Journal of the American Society of Echocardiography	2
16	Scandinavian Journal of Sports Medicine	2
17	Europace	1
18	European Journal of Applied Physiology	2
19	Pediatric Exercise Science	0
20	Pediatric Cardiology	1
21	Cardiology in the Young	1
22	Pediatrics	0
23	European Journal of Pediatrics	1
24	American Journal of Hypertension	1
25	The Journal of Physiology	0

26	Journal of Applied Physiology	0
Total		12

4.2.2 SELECTION CRITERIA

Titles and abstracts of potentially eligible articles were independently screened by two authors (GMC and NRR) against the selection criteria. For articles where it was not immediately clear from the title and/or abstract whether they should be included, we obtained the full text for independent screening. Discrepancies were resolved via consensus discussion, with a third reviewer (MGW) consulted if consensus could not be reached.

Inclusion criteria were: 1) data reported for male and/or female competitive athletes, with or without comparison to non-athletes, 2) all participants were aged 6-18 years old at the time of assessment, and 3) an original research article published in English language. We defined a competitive athlete as:

> *"One who participates in an organised team or individual sport that requires regular competition against others as a central component, places a high premium on excellence and achievement, and requires some form of systematic (and usually intense) training"* (Maron and Zipes, 2005).

Participants not meeting this definition were classified as non-athletes. Articles were limited to English-language owing to translation costs. Articles that did not document athlete age range were excluded because of the risk of including athletes >18 years. If ECG and/or echocardiographic outcome data were not reported, or if professional guidelines for data acquisition were not observed or cited, articles were also excluded.

4.2.3 RISK OF BIAS ASSESSMENT

We developed a 15-item risk of bias assessment checklist (Table 4.3), comprising items from Downs & Black's 'Assessment of Methodological Quality of Randomised and Non-Randomised Studies' checklist (Downs and Black, 1998), and a previously published athletes heart meta-analysis checklist (Utomi et al., 2013). The purpose was to identify articles of low methodological quality that could bias results (van Tulder et al., 2009); with articles achieving ≤ 50% of total possible appraisal score, excluded from quantitative synthesis. Two reviewers (GMC & NRR) independently assessed all included articles. Discrepancies were resolved via consensus discussion and consistency was measured using an interclass correlation coefficient ($ICC_{2,1}$).

Table 4. 3 15-Item Risk of Bias Assessment Checklist			
#	Risk of bias assessment item	Yes	No/Unclear
1	Sufficient power to detect clinically important effect where probability for difference being due to chance < 5% (*answer yes if sample size calculated and adequate to detect clinically important effect*)		
2	Are the inclusion and exclusion criteria clearly stated?		
	Test-control		
3	Are activity levels for the control group reported?		
4	Are the control group matched for age?		
5	If groups are unmatched, have statistical differences been controlled for? *(Answer yes if groups matched for age)*		
	Test-athletes		
6	Are athletes of competitive status? *"One who participates in an organised team or individual sport that requires regular competition against others as a central component places a high premium on excellence and achievement, and requires some form of systematic (and usually intense) training"*		
7	Are training details available? (*years, volume, duration/intensity*)		
	Data acquisition		
8	Is there detailed information to allow replication? *(Answer yes if professional guidelines cited)*		
9	Are the observer(s) stated?		
10	Are more than one observer used? If so is interobserver variability stated?		

	Measurement technique		
11	Are professional guidelines observed/cited		
	Reporting Data		
12	Is an explanation for missing data given? *(Score yes if none missing)*		
13	Is data clearly and accurately presented? (*Simple outcome data, including denominators and numerators, should be reported for all major findings*)		
14	Estimates of random variability in data provided for main outcomes? (*e.g. interquartile range, standard error, standard deviation, confidence intervals*)		
15	Are anthropometrics reported? (Height and weight or BSA (with formula presented))		
	Total Score		

Items 1,2,14 were selected from Downs & Black's Assessment of Methodological Quality of Randomised and Non-Randomised Studies checklist (Downs and Black, 1998).

Items 3-5,7,10-13 were selected from a previously published athletes heart meta-analysis checklist (Utomi et al., 2013).

Items 6,9,15 were written specifically for the purposes of this review

4.2.4 DATA EXTRACTION

All ECG and echocardiographic data were extracted by one reviewer (GMC) using a predefined extraction form and reviewed by a second reviewer (NRR), with discrepancies resolved by consensus (Table 4.4). Data extraction included the calculated mean (±SD) for continuous data and *n* for dichotomous data. If insufficient data were reported, corresponding authors were contacted to request additional data.

Table 4. 4 Variables Extracted for Analysis

Primary Variables	ECG	Characteristics	Group 1: common and training-related ECG changes	Group 2: uncommon and training-unrelated ECG changes
		Heart rate, bpm	Sinus bradycardia (≥30 bpm)	T-wave inversion
		PR interval, ms	Sinus arrhythmia	ST-segment depression
		QRS duration, ms	1st degree AV block (PR interval>200 ms)	Pathological Q waves
		QTc duration, ms	Morbitz type 1 (Wenckeback) 2nd degree AV block	Left atrial enlargement
		QRS axis, degree	Incomplete RBBB (QRS duration, 120 ms)	Left axis deviation
		S V1 + R V5/6, mm	Early repolarisation (ST elevation, J-point elevation, J waves, notching or terminal QRS slurring)	Right axis deviation
			Isolated QRS voltage criteria for LVH (Sokolow-Lyon)	Complete LBBB or RBBB
				Long QT interval
				Ventricular pre-excitation
				Brugada-like early repolarization

Echocardiography parameters	Structure	Function
	LV end-diastolic internal diameter, mm	Ejection fraction, %
	LV end-systolic internal diameter, mm	Fractional shortening, %
	Interventricular septal wall thickness, mm	Stoke volume, ml
	Posterior wall thickness, mm	Cardiac output, lpm
	Maximal wall thickness, mm	E wave (m/s)
	Relative wall thickness.	A wave (m/s)
	LV end-diastolic volume, ml	E/A
	LV end-systolic volume, ml	
	LV mass, grams	
	Aortic root (Sinus of Valsalva), mm	
	Left atrial diameter, mm	
	RV outflow tract dimension (parasternal), mm	
	RV outflow tract dimension (proximal), mm	
	RV outflow tract dimension (distal), mm	
	RV basal dimension, mm	

		RV mid-ventricular dimension
		RV longitudinal dimension
		RV free wall thickness, mm
		RV end-diastolic area, cm^2
Secondary Variables	Contextual Factors	
		Age range
		Sex
		Ethnicity
		Height, cm
		Weight, kg
		BSA
		Sport
		Training Hours/Week, hours
		Training Years, years

Bpm: beats per minute; ms: milliseconds; mm; millimeters; cm; centimeters; LBBB: left bundle branch block; RBBB: right bundle branch block; LVH: left ventricle hypertrophy; LV: left ventricle; RV: right ventricle; m/s: meters per second; kg: kilograms; BSA: body surface area.

4.2.5 DATA MANAGEMENT

4.2.5.1 Demographics

BSA (Du Bois, D. and Du Bois, 1989) was extracted or manually calculated from the height and body mass reported in individual articles.

4.2.5.2 ECG

The 2010 European Society of Cardiology (ESC) recommendations for interpretation of the 12-lead ECG in athletes were applied, dividing ECG patterns into Group 1 training-related and Group 2 training un-related patterns accordingly (Corrado et al., 2010).TWI was classified if ≥1mm and in ≥2 contiguous leads, localised as follows: anterior leads (V_1–V_3), extended anterior leads (V_1–V_4), inferior leads (Leads II–aVF), lateral leads (V_5–V_6/I–aVL) and infero-lateral leads (Leads II–aVF/V_5–V_6/I–aVL). Deep TWI was defined as a negative T wave ≥2 mm in ≥2 contiguous leads, (excluding leads III and aVR). ECG classification of LVH was made according to the Sokolow–Lyon criteria (Sokolow and Lyon, 1949). Early repolarisation was defined as ST segment elevation (≥0.1 mV) and/or J point elevation manifested either as QRS slurring or notching, in ≥2 contiguous leads (Miyazaki et al., 2010).

4.2.5.3 Echocardiography

Two-dimensional echocardiography data, where the ASE paediatric guidelines were followed, were extracted (Lai et al., 2006; Lopez et al., 2010b). On the basis of previous publications within the paediatric athlete's heart, participants with an LV wall thickness

>12 mm were considered to have LVH (Sharma et al., 2002). LV mass was calculated according to the formula of Devereux (1986). Relative left ventricular wall thickness (RWT) was calculated and expressed as a fraction: [PWTd + IVSd)/LVIDd]. If IVSd was not reported, it was considered equal to PWTd (Pluim et al., 2000).

4.2.6 DATA SYNTHESIS

Data were analysed using StatsDirect (Altrincham, UK) and Stata V.12 (Stata Corp, College Station, Texas, USA). Demographic data were analysed using arithmetic means. Pooled dichotomous data were analysed using random-effects proportion meta-analyses (as we expected significant statistical heterogeneity) and presented as odds ratios (ORs) or risk ratios (RRs) as appropriate. We only pooled data for variables with a minimum of 3 articles reporting on the variable. Pooled continuous data were presented as standardised mean differences (i.e. effect size). The magnitude of pooled standardised mean differences were interpreted according to Cohen's guidelines; with small medium and large effects interpreted as ≥20%, ≥50% and ≥80% respectively (Cohen, 1988). A p-value of <0.05 was used to denote statistical significance.

Random-effects meta-regression (Kendall's non-parametric statistic) was utilised to explore and account for the impact of the covariates; age, ethnicity (black vs. white) and sex (Male vs. Female) upon ECG and echocardiographic variables. Random-effects meta-regression analysis was deemed inappropriate when <10 articles were available for synthesis (Thompson and Baxter-Jones, 2002).

Sub-analysis was used to explain the effect of the covariates; age (<14 years vs. ≥14 years), ethnicity (black vs. white), sex and where possible, the interaction of age (<14 years vs. ≥14 years) was explored within ethnicity and sex. With regards to maturational age, 14 years was set according to the attainment of selected development landmarks in boys (Mean age of peak height velocity = 14; Peak weight velocity = 14.3; Peak leg length velocity = 14.4; 90% of adult stature = 13.9; 95% of adult stature = 14.9; Genital stage IV = 14.6; and Pubic hair stage IV = 15.1) (Bielicki et al., 1984) and the onset of menarche within females (13.2 years) (Wellens et al., 1990).

Data were combined as per Cochrane guidelines (Higgins, 2008). If data were reported for the same participants in more than one article, the data were extracted from the article with the largest cohort size (with corresponding author's confirmation). If an article reported multiple follow-ups, data were extracted from the latest visit (i.e. longest follow-up). When standard deviation (SD) was not reported, it was imputed from the average SD (Higgins, 2008), only utilising articles containing ≥30 participants. To ensure results were not subsequently biased, sensitivity analysis was conducted omitting imputed SD data. Statistical heterogeneity was examined using the I^2 index (Higgins et al., 2003).

4.3 RESULTS

4.3.1 LITERATURE SEARCH

The literature search identified 2030 potentially eligible articles, of which 972 were duplicates. After application of the selection criteria, 43 articles remained for qualitative analysis and 40 remained for quantitative analysis (Figure 4.1).

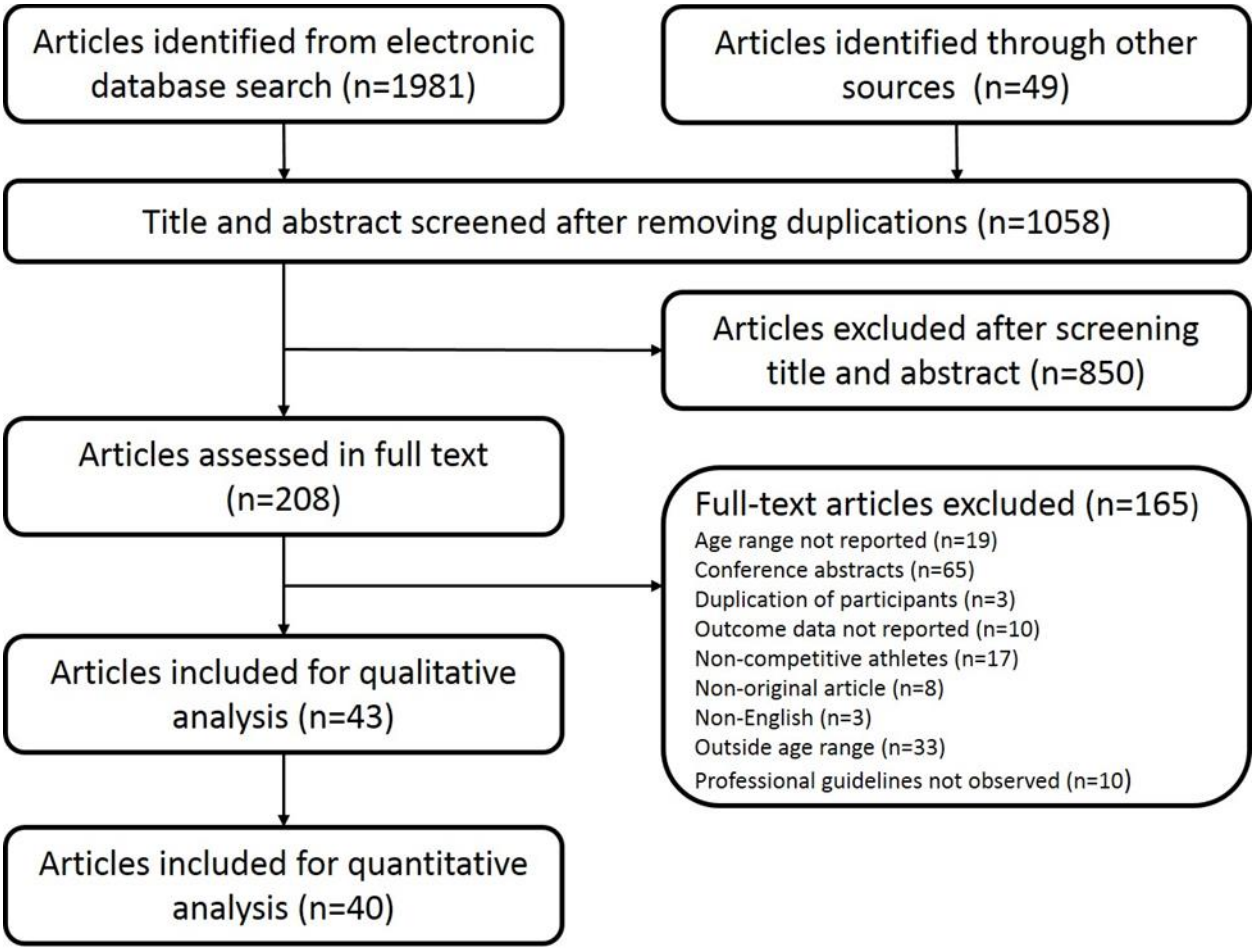

Figure 4. 1 Flow diagram for search results and study selection.

4.3.2 RISK OF BIAS ASSESSMENT

There was substantial agreement (71% 95% CI (49-84)) (Viera and Garrett, 2005) between the reviewers for the risk of bias assessment (Table 4.5). Most frequently,

discrepancies occurred when assessing ‘professional guidelines’ and ‘missing data’ (77% 95% CI 61-68)). Risk of bias scores ranged from 4 to 13 out of a maximum possible score of 15. No articles reported ‘power analysis’ or ‘intra-observer reliability’, with non-athlete ‘activity levels’ poorly described in 44%. Three articles were excluded (Morales, 1992; Dinu et al., 2010; Attisani et al., 2011) from quantitative synthesis due to low methodological quality.

Table 4. 5 Risk of Bias Assessment

Article	Criterion 1 Power analysis	Criterion 2 Selection criteria	Criterion 3 Non-athlete activity levels	Criterion 4 Control age matched	Criterion 5 Statistical differences accounted for	Criterion 6 Competitive athletes	Criterion 7 Athlete training details	Criterion 8 Detailed data acquisition
(Agrebi et al., 2015)		✓				✓	✓	
(Attisani et al., 2011)		✓				✓		
(Ayabakan et al., 2006)		✓	✓	✓	✓	✓	✓	✓
(Bartkevičienė, 2015)		✓	✓	✓	✓	✓	✓	✓
(Bessem et al., 2015)		✓				✓		✓
(Calò et al., 2015)		✓				✓	✓	✓
(Csajági et al., 2015)		✓	✓	✓	✓	✓	✓	✓
(Di Paolo *et al.*, 2012)		✓				✓	✓	✓
(Dinu et al., 2010)			✓	✓	✓	✓		
(Hauser et al., 2013)		✓				✓	✓	✓
(Hoogsteen et al., 2003)		✓				✓	✓	✓

Article	Criterion 1 Power analysis	Criterion 2 Selection criteria	Criterion 3 Non-athlete activity levels	Criterion 4 Control age matched	Criterion 5 Statistical differences accounted for	Criterion 6 Competitive athletes	Criterion 7 Athlete training details	Criterion 8 Detailed data acquisition
(Kinoshita et al., 2015)		✓				✓	✓	✓
(Koch et al., 2014)		✓				✓	✓	✓
(Konopka et al., 2015)		✓				✓	✓	✓
(Madeira et al., 2008)		✓				✓	✓	✓
(Makan et al., 2005b)		✓	✓	✓	✓	✓	✓	✓
(Medved et al., 1986)		✓	✓	✓	✓	✓	✓	✓
(Meško et al., 1993)		✓	✓	✓	✓	✓	✓	✓
(Migliore et al., 2012)		✓				✓		✓
(Morales, 1992)		✓				✓		✓
(Obert et al., 1998)		✓	✓	✓	✓	✓	✓	✓
(Ozer et al., 1994)		✓	✓	✓	✓	✓	✓	✓

	Criterion 1	Criterion 2	Criterion 3	Criterion 4	Criterion 5	Criterion 6	Criterion 7	Criterion 8
Article	Power analysis	Selection criteria	Non-athlete activity levels	Control age matched	Statistical differences accounted for	Competitive athletes	Athlete training details	Detailed data acquisition
(Papadakis et al., 2009)		✓	✓	✓	✓	✓	✓	✓
(Pavlik et al., 2001)		✓			✓	✓	✓	✓
(Pelà et al., 2014)		✓				✓	✓	✓
(Pela et al., 2015)		✓				✓	✓	✓
(Petridis et al., 2004)		✓		✓	✓	✓	✓	✓
(Rowland et al., 1987)		✓	✓	✓	✓	✓	✓	✓
(Rowland et al., 1994)		✓		✓	✓	✓	✓	✓
(Rowland et al., 1997)		✓				✓	✓	✓
(Rowland et al., 2000)		✓	✓	✓	✓	✓	✓	✓
(Schmied et al., 2009)		✓				✓		✓
(Sharma et al., 1999)		✓	✓	✓	✓	✓	✓	✓
(Sharma et al., 2002)		✓	✓	✓	✓	✓	✓	✓

	Criterion 1	Criterion 2	Criterion 3	Criterion 4	Criterion 5	Criterion 6	Criterion 7	Criterion 8
Article	Power analysis	Selection criteria	Non-athlete activity levels	Control age matched	Statistical differences accounted for	Competitive athletes	Athlete training details	Detailed data acquisition
(Sheikh et al., 2013)		✓	✓	✓	✓	✓		✓
(Shi and Selig, 2005)		✓	✓	✓	✓	✓	✓	✓
(Stoner, 1997)		✓	✓	✓	✓	✓	✓	✓
(Sundberg and Elovainio, 1982)		✓			✓	✓	✓	✓
(Telford et al., 1988)		✓	✓	✓	✓	✓	✓	✓
(Valente-Dos-Santos et al., 2013)		✓				✓	✓	✓
(Vasiliauskas et al., 2006)		✓				✓	✓	✓
(Yildirim et al., 2016)		✓	✓	✓	✓	✓	✓	✓
(Zdravkovic et al., 2010)		✓	✓	✓	✓	✓	✓	✓
No. of articles fulfilling each criterion (% of total included studies)	0 (0%)	42 (98%)	19 (44%)	23 (53%)	24 (56%)	42 (100%)	36 (84%)	40 (93%)

Proportions of agreement	100% (90-100)	88% (74-96)	84% (69-93)	91% (77-97)	86% (71-94)	91% (77-97)	91% (77-97)	95% (83-99)

✓ = *criterion fulfilled,* Blank = *criterion not fulfilled*.

Article	Criterion 9 Observer(s) stated	Criterion 10 Interobserver reliability	Criterion 11 Professional guidelines	Criterion 12 Missing data	Criterion 13 Data presentation	Criterion 14 Random variability	Criterion 15 Anthropometrics	Total
(Agrebi et al., 2015)			Y	✓	✓	✓	✓	8
(Attisani et al., 2011)				✓	✓			4
(Ayabakan et al., 2006)	✓		✓	✓	✓	✓	✓	13
(Bartkevičienė, 2015)			✓	✓	✓	✓	✓	12
(Bessem et al., 2015)	✓		✓	✓	✓	✓	✓	9
(Calò et al., 2015)	✓		✓	✓	✓	✓	✓	10
(Csajági et al., 2015)	✓		✓	✓	✓	✓	✓	13
(Di Paolo *et al.*, 2012)			✓	✓	✓	✓	✓	9
(Dinu et al., 2010)					✓	✓	✓	7
(Hauser et al., 2013)	✓		✓	✓	✓		✓	9

	Criterion 9	Criterion 10	Criterion 11	Criterion 12	Criterion 13	Criterion 14	Criterion 15	Total
Article	Observer(s) stated	Interobserver reliability	Professional guidelines	Missing data	Data presentation	Random variability	Anthropometrics	
(Hoogsteen et al., 2003)	✓		✓		✓	✓	✓	9
(Kinoshita et al., 2015)	✓		✓	✓	✓	✓	✓	10
(Koch et al., 2014)	✓		✓	✓	✓	✓	✓	10
(Konopka et al., 2015)			✓	✓	✓	✓	✓	9
(Madeira et al., 2008)	✓		✓	✓	✓	✓	✓	10
(Makan et al., 2005b)	✓		✓	✓	✓	✓	✓	13
(Medved et al., 1986)			✓	✓	✓	✓		11
(Meško et al., 1993)			✓	✓	✓	✓	✓	12
(Migliore et al., 2012)	✓		✓	✓	✓	✓		8

	Criterion 9	Criterion 10	Criterion 11	Criterion 12	Criterion 13	Criterion 14	Criterion 15	Total
Article	Observer(s) stated	Interobserver reliability	Professional guidelines	Missing data	Data presentation	Random variability	Anthropometrics	
(Morales, 1992)			✓				✓	5
(Obert et al., 1998)	✓		✓	✓	✓	✓	✓	13
(Ozer et al., 1994)	✓		✓	✓	✓	✓		12
(Papadakis et al., 2009)	✓		✓	✓	✓	✓	✓	13
(Pavlik et al., 2001)	✓		✓	✓	✓	✓		10
(Pelà et al., 2014)	✓		✓	✓	✓	✓	✓	10
(Pela et al., 2015)	✓		✓	✓	✓	✓	✓	10
(Petridis et al., 2004)			✓	✓	✓	✓	✓	11
(Rowland et al., 1987)	✓		✓	✓	✓	✓		12
(Rowland et al., 1994)	✓		✓	✓	✓	✓	✓	12

Article	Criterion 9	Criterion 10	Criterion 11	Criterion 12	Criterion 13	Criterion 14	Criterion 15	Total
	Observer(s) stated	Interobserver reliability	Professional guidelines	Missing data	Data presentation	Random variability	Anthropometrics	
(Rowland et al., 1997)			✓	✓	✓	✓	✓	9
(Rowland et al., 2000)			✓	✓	✓	✓	✓	12
(Schmied et al., 2009)	✓		✓	✓	✓	✓	✓	9
(Sharma et al., 1999)			✓	✓	✓	✓	✓	12
(Sharma et al., 2002)	✓		✓	✓	✓	✓	✓	13
(Sheikh et al., 2013)	✓		✓	✓	✓	✓	✓	12
(Shi and Selig, 2005)			✓	✓	✓	✓	✓	12
(Stoner, 1997)			✓	✓	✓	✓	✓	12
(Sundberg and Elovainio, 1982)	✓			✓	✓	✓	✓	11
(Telford et al., 1988)			✓	✓	✓	✓	✓	12

	Criterion 9	Criterion 10	Criterion 11	Criterion 12	Criterion 13	Criterion 14	Criterion 15	Total
Article	Observer(s) stated	Interobserver reliability	Professional guidelines	Missing data	Data presentation	Random variability	Anthropometrics	
(Valente-Dos-Santos et al., 2013)	✓		✓	✓	✓	✓	✓	10
(Vasiliauskas et al., 2006)	✓		✓	✓	✓	✓	✓	10
(Yildirim et al., 2016)			✓	✓	✓	✓	✓	12
(Zdravkovic et al., 2010)	✓		✓	✓	✓	✓	✓	13
No. of articles fulfilling each criterion (% of total included studies)	26 (60%)	0 (0%)	40 (93%)	40 (93%)	43 (98%)	40 (93%)	37 (86%)	452 (70%)
Proportions of agreement	81% (66-91)	100% (90-100)	77% (61-88)	77% (61-88)	84% (69-93)	93% (80-98)	88% (74-96)	70% (47-83)

Y = criterion fulfilled, N = criterion not fulfilled

4.3.3 DEMOGRAPHIC DATA

Data from 14,278 athletes (mean age 13.8 ± 1.3 years [range: 6-18]) and 1,668 non-athletes (mean age 12.6 ± 0.6 years [7-18]) were extracted from 43 articles. There were no differences in age or BSA between paediatric athletes and non-athletes. Athletes competed in 30 different sports, with football (soccer) predominating (33%). There were more males and whites, but proportionately distributed among both athletes and non-athletes. In 2 articles, sex was not reported (Medved et al., 1986; Dinu et al., 2010). In 23 articles, ethnicity was not documented (Sundberg and Elovainio, 1982; Medved et al., 1986; Rowland et al., 1987, 1994, 1997, 2000; Telford et al., 1988; Morales, 1992; Meško et al., 1993; Ozer et al., 1994; Obert et al., 1998; Hoogsteen et al., 2003; Shi and Selig, 2005; Madeira et al., 2008; Dinu et al., 2010; Attisani et al., 2011; Valente-Dos-Santos et al., 2013; Hauser et al., 2013; Pelà et al., 2014; Koch et al., 2014; Menafoglio et al., 2014; Bartkevičienė, 2015; Pela et al., 2015; Yildirim et al., 2016) and in 29 articles maturational status was not reported (Sundberg and Elovainio, 1982; Medved, Fabecic-Sabadi and Medved, 1986; Rowland *et al.*, 1987; Morales, 1992; Meško *et al.*, 1993; Rowland *et al.*, 1994; Ozer *et al.*, 1994; Stoner, 1997; Obert *et al.*, 1998; Sharma *et al.*, 2002; Hoogsteen *et al.*, 2003; Petridis *et al.*, 2004; Shi and Selig, 2005; Vasiliauskas *et al.*, 2006; Madeira *et al.*, 2008; Schmied *et al.*, 2009; Zdravkovic *et al.*, 2010; Dinu *et al.*, 2010; Attisani *et al.*, 2011; Di Paolo *et al.*, 2012; Sheikh *et al.*, 2013; Hauser *et al.*, 2013; Pelà *et al.*, 2014; Koch *et al.*, 2014; Agrebi *et al.*, 2015; Konopka *et al.*, 2015; Pela *et al.*, 2015; Bartkevičienė, 2015; Bessem, de Bruijn and Nieuwland, 2015; Kinoshita, Katsukawa and Yamazaki, 2015; Yildirim *et al.*, 2016) (Table 4.6)

Table 4. 6 Article Characteristics

Author, year	Athletes						Non-Athletes					Outcome data	
	n	Chronological age Mean (range)	Biological age	Ethnicity (W:B:O)	Sex (M:F)	Sport	*n*	Chronological age Mean (range)	Biological age	Ethnicity (C:B:O)	Sex (M:F)	ECG	ECHO
(Agrebi et al., 2015)	24	13.9 (11-17)	NR	0:0:24	24:0	Handball						✓	✓
(Attisani et al., 2011)	1865	13.7 (6-18)	NR	NR	1865:0	Soccer/Gymnastics						✓	
(Ayabakan et al., 2006)	22	11.0 (9-12)	Prepubertal	22:0:0	22:0	Swimming	21	10.7 (9-12)	Prepubertal	21:0:0	21:0		✓
(Bartkevičienė, 2015)	167	14.8 (12-17)	NR	NR	167:0								✓
(Bessem et al., 2015)	193	14 (10-19)	NR	134:29:30	193:0	Soccer						✓	
(Calò et al., 2015)	2261	12.4 (8-18)	Peripubertal	2261:0:0	2261:0	Soccer						✓	✓
(Csajági et al., 2015)	18	13.7 (13-15)	Mid pubertal	18:0:0	8:7	Swimming	15	13.8 (13-15)	Mid pubertal	15:0:0	8:7		✓
(Di Paolo *et al.*, 2012)	216	16.1 (14-18)	NR	63:153:0	216:0	Soccer						✓	✓
(Dinu et al., 2010)	40	12.7 (10-17)	NR	NR	NS	Athletics							✓
(Hauser et al., 2013)	26	12.6 (7-17)	NR	NR	18:8	Triathlon							✓
(Hoogsteen et al., 2003)	66	17.5 (17-18)	NR	NR	66:0	Cycling							✓
(Kinoshita et al., 2015)	34	16.5 (16-17)	NR	0:0:34	0:34	Middle / long-distance runners							✓

Author, year	Athletes						Non-Athletes					Outcome data	
	n	Chronological age Mean (range)	Biological age	Ethnicity (W:B:O)	Sex (M:F)	Sport	*n*	Chronological age Mean (range)	Biological age	Ethnicity (C:B:O)	Sex (M:F)	ECG	ECHO
(Koch et al., 2014)	343	13 (10-15)	NR	NS	189:154	High school athletes						✓	✓
(Konopka et al., 2015)	78	14.3 (12-17)	NR	78:0:0	64:14	Soccer, Tennis, Rowing.							✓
(Madeira et al., 2008)	21	15.9 (15-16)	NR	NR	21:0	Soccer; Swimming							✓
(Makan et al., 2005b)	900	15.7 (14-18)	Post pubertal	882:0:18	693:207	10 sporting disciplines (*Invasion games/ racket/ endurance/combat*)	250	15.5 (14-18)	Post pubertal	NR	177:48		✓
(Medved et al., 1986)	72	10 (8-14)	NR	NR	NR	Swimming	72	10 (8-14)	NR	NR	NS		✓
(Meško et al., 1993)	23	14.5 (14-15)	NR	NR	23:0	Hockey	17	14.5 (14-15)	NR	NR	17:0		✓
(Migliore et al., 2012)	2765	13.9 (8-18)	Peri pubertal	2765:0:0	1914:851	18 sporting disciplines (*Invasion games/ gymnastics/winter sports/horse-riding/racket/ endurance/combat*)						✓	
(Morales, 1992)	9	16.2 (14-17)	NR	NR	9:0	Basketball							✓
(Obert et al., 1998)	10	10.7 (10-11)	Pre pubertal	NR	4:6	Swimming	11	10.9 (10-11)	Prepubertal	NR	4:7		✓
(Ozer et al., 1994)	82	11.2 (7-14)	NR	NR	41:41	Swimming	41	10.8 (7-15)	NS	NR	22:19		✓

Author, year	Athletes						Non-Athletes					Outcome data	
	n	Chronological age Mean (range)	Biological age	Ethnicity (W:B:O)	Sex (M:F)	Sport	*n*	Chronological age Mean (range)	Biological age	Ethnicity (C:B:O)	Sex (M:F)	ECG	**ECHO**
(Papadakis et al., 2009)	1710	16 (14-18)	Post-pubertal	1642:0:0	1414:291	15 sporting disciplines (Invasion games/ racket/ endurance/combat)	400	16 (14-18)	Post pubertal	385:0:0	330:70	✓	
(Pavlik et al., 2001)	165	14.7 (10-18)	NR	165:0:0	165:0	7 sporting disciplines (*Endurance/invasion games/weightlifting*)	22	14.7 (10-18)	NR	22:0:0	22:0		✓
(Pelà et al., 2014)	138	14.3 (11-17)	NR	96:42:0	138:0	Soccer						✓	✓
(Pela et al., 2015)	206	13.8 (11-17)	NR	206:0:0	158:48	Soccer						✓	✓
(Petridis et al., 2004)	137	16.6 (15-18)	NR	NS	137:0	Swimming							✓
(Rowland et al., 1987)	14	11 (8-14)	Prepubertal	NR	14:0	Swimming	19	10.4 (8 -13)	Prepubertal	NR	19:0	✓	✓
(Rowland et al., 1994)	10	12.2 (11-13)	Prepubertal	NR	10:0	Middle distance runners	18	11.3 (10–14)	Pre pubertal	NR	18:0	✓	✓
(Rowland et al., 1997)	9	12.2 (9-15)	Early pubertal	NR	9:0	Cyclists							✓
(Rowland et al., 2000)	8	11.9 (10-13)	Early pubertal	NS	8:0	Cyclists & Triathletes	39	12.2 (10-13)	Early pubertal	NR	39:0		✓
(Schmied et al., 2009)	155	16.4 (14-17)	NR	0:155:0	155:0	Soccer						✓	✓
(Sharma et al., 1999)	1000	15.7 (14-18)	Post-pubertal	998:8:4	730:180	9 Sporting disciplines (*Invasion games/ racket/ endurance/combat*)	300	15.6 (14-18)	Post pubertal	293:0:7	210:90	✓	
(Sharma et al., 2002)	720	15.7 (14-18)	NR	706:14:0	540:180	10 Sporting disciplines (*Invasion games/ racket/ endurance/combat*)							✓

	Athletes											Outcome data	
Author, year	*n*	Chronological age Mean (range)	Biological age	Ethnicity (W:B:O)	Sex (M:F)	Sport	*n*	Chronological age Mean (range)	Biological age	Ethnicity (C:B:O)	Sex (M:F)	ECG	ECHO
(Sheikh et al., 2013)	1232	16.4 (14-18)	NR	903:329:0	980:252	Swimming/Athletics	134	15.3 (14–18)	NR	0:134:0	88:46	✓	✓
(Shi and Selig, 2005)	13	15.3 (14-16)	NR	NR	13:0	Gymnastics/Swimmers							✓
(Stoner, 1997)	37	9.9 (7-11)	NR	NR	0:37	Athletics	22	9.1 (7-11)	NR	NR	0:22		✓
(Sundberg and Elovainio, 1982)	59	13.7 (10-17)	NR	NR	59:0	Athletics	81	13.9 (10-17)	NR	NR	81:0	✓	
(Telford et al., 1988)	85	11.9 (11-12)	Pre-mid pubertal	NR	48:37	Hockey	106	12.3 (12-13)	Pre-mid pubertal	NR	60:46		✓
(Valente-Dos-Santos et al., 2013)	73	15.4 (15-17)	Skeletal age 16.4	NR	73:0	Basketball							✓
(Vasiliauskas et al., 2006)	62	13.6 (8-17)	NR	62:0:0	62:0	Soccer							✓
(Yildirim et al., 2016)	140	14.3 (10-18)	NR	NS	107:33	Basketball, Soccer, Swimmers.	31	14.1 (10-18)	NR	NR	21:10	✓	✓
(Zdravkovic et al., 2010)	94	12.9 (12-14)	NR	94:0:0	94:0	Soccer	47	12.9 (12-14)	NR	47:0:0	47:0		✓

Abbreviations: W, White; B, Black; O, Other; M, Male; F, Female; NR, Not reported; ✓, Yes; Blank, No.

4.3.4 DATA MANAGEMENT

Within the 40 articles that were quantitatively synthesised; two articles reported overlapping data from a group of 155 athletes (Schmied *et al.*, 2009; Di Paolo *et al.*, 2012), two articles reported overlapping data from a cohort of 158 athletes (Pelà et al., 2014; Pela et al., 2015) and two articles reported overlapping data from a cohort of 900 athletes (Sharma et al., 2002; Makan et al., 2005b). Four articles presented multiple follow-up data (Meško et al., 1993; Stoner, 1997; Csajági et al., 2015; Kinoshita et al., 2015). Adjustments were made, to account for this in the meta-analysis (Table 4.7-4.9)

Table 4. 7 Articles with Overlapping Electrocardiographic Data

First Author	Overlapping participants	Number of participants included
(Di Paolo *et al.*, 2012)	Athlete (males, black; n=154)	155/155
(Schmied et al., 2009)	Athlete (males, black; n=155)	
(Pela et al., 2015)	Athlete (males, white; n=158)	158/158
(Pelà et al., 2014)	Athlete (males, white; n=96)	

Table 4. 8 Articles with Overlapping Echocardiographic Data

First Author	Overlapping participants	Number of participants included
(Di Paolo *et al.*, 2012)	Athletes (males, black; n=154)	155/155
(Schmied et al., 2009)	Athletes (males, black; n=155)	
(Makan et al., 2005b)	Athletes (males, 98% white; n=693) Athletes (females, 98% white; n=207)	900/900
(Sharma et al., 2002)	Athletes (males, 98% white; n=540) Athletes (females, 98% white; n=180)	
(Pela et al., 2015)	Athletes (male, white; n=158)	158/158
(Pelà et al., 2014)	Athletes (male, white; n=96)	

Table 4. 9 Articles Reporting Repeat Echocardiographic Measurements (Within The Same Article)

First Author	Follow-up	Participants	Number of participants included
(Csajági et al., 2015)	Six repeat assessments: • Start • Endurance • Race 1 • Detraining • Endurance • Race2	Athletes (male; n =8; female; n=7, white)	15/15
(Meško et al., 1993)	Four repeat assessments: • Year 1 • Year 2 • Year 3 • Year 4	Athletes (male; n=23) Non-athletes (males; n=17)	40/40
(Stoner, 1997)	Two assessments: • Pre-onset of training • 1 Year post onset of training	Athletes (male; n=37) Non-athletes (male; n=20)	57/57
(Kinoshita et al., 2015)	Five repeat assessments: • Baseline • 0.5 Years post • 1 Year post • 1.5 Years post • 2 Years post • 2.5 Years post • 3 Years post	Athletes (females, East Asian; n=51)	34/51

4.3.5 ELECTROCARDIOGRAPHIC CHARACTERISTICS

4.3.5.1 Paediatric Athlete vs. Paediatric Non-Athlete

Paediatric athletes had a significantly longer PR interval, and a significantly greater frequency of sinus bradycardia, 1st ºAV block, IRBBB, voltage criteria for LVH and early repolarisation when compared to paediatric non-athletes (Table 4.10). The prevalence of TWI ≥1mm was similar between athletes and non-athletes (6.7% vs. 5.9%). However, athletes were 12.7 times more likely to have deep TWI ≥2 mm in ≥2 contiguous leads (except leads III and aVR) than non-athletes (4.7% vs. 0.3%). Athletes were 1.4 times more likely to have anterior TWI (6.5% vs. 5.7%) and 1.5 times more likely to have extended anterior TWI (1.4% vs. 0.9%) than non-athletes. Whilst inferior (0.9%) and lateral (0.2%) TWI was present among athletes, these were not observed in non-athletes. Other training un-related ECG patterns suggestive of underlining cardiac pathology including ST segment depression, abnormal Q waves, complete bundle branch blocks and abnormal QTc measurements were rarely observed in athletes (≤0.6%) and were not observed in non-athletes.

Table 4. 10 ECG Characteristics of Paediatric Athletes and Paediatric Non-Athletes

Characteristics	Athletes	Non-Athletes	% Difference
PR interval, ms	148 (142 – 154)*	139 (136- 141)	6.1%
	[10; 5671] {98%}	[4; 737] {41%}	
QRS duration, ms	86 (84 -88)	83 (79 -86)	4%
	[11; 6938] {97%}	[6; 952] {97%}	
QTc duration, ms	396 (391-400)	386 (375 - 398)	3%
	[11; 7018] {97%}	[6; 902] {97%}	
QRS axis*, degrees	70 (63.1 - 76.1)	70 (67.9 - 73.0)	0%
	[8; 5476] {99%}	[4; 779] {60%}	
Group 1 ECG patterns			Odds Ratio
Sinus bradycardia,	37.4 (17.6 – 59.7)**	19.2 (16.6 21.90)	2.5 (2.1 - 3.0)
%	[11; 9745] {99%}	[3; 834] {0%}	
Sinus arrhythmia, %	45.8 (35.7 -56.0)		
	[3; 2898] {95.9%}		
1st ºAV block, %	2.2 (0.8 - 4.2)**	0.4 (0.1 - 1.1)	4.6 (1.7 - 12.4)
	[8; 9488] {97%}	[3; 834] {26%}	
2nd ºAV block	0.2 (0.1 - 0.4)		
(Morbitz Type I), %	[3; 2898} {0%}		
Incomplete RBBB,	25.8 (18.2 - 33.7)**	7.8 (4.2 - 12.4)	4.3 (3.5 – 5.6)
%	[10; 9736] {97%}	[3; 834] {78%}	
LVH, %	35.2 (26.0 - 45.0)**	24.1 (20.3 - 28.1)	1.7 (1.5 - 2.0)
	[11; 9745] {98%}	[3; 834] {41%}	
Early	37.1 (25.6 -49.2)**	29.2 (17.2 – 43.0)	1.4 (1.2 -1.7)
Repolarisation, %	[10; 9736] {99.3%}	[3; 834] {93.9%}	
Group 2 ECG patterns			Risk Ratio
TWI (≥1mm), %	6.7 (4.7 - 8.9)	5.9 (2.2 – 11.2)	1.1 (0.8 – 1.5)
	[7; 9372] {93.3%}	[3; 834] {86.7%}	
Deep TWI (≥2mm),	4.7 (2.3 - 8.1)**	0.3 (0.04 - 1.8)	12.7 (3.1 – 50.7)
%	[7; 6514] {95.9%}	[2; 534] {60.3%}	

Anterior, %	6.5 (2.9 - 11.3) [7; 9372] {98.4%}	5.7 (2.2 - 10.6) [3; 834] {84.9%}	1.2 (0.9 – 1.5)
Extended Anterior, %	1.4 (0.2 - 3.5) [4; 5391] {95.8%}	0.9 (0.2 - 2.2) [2; 534] {24.1%}	1.5 (0.6 – 3.6)
Inferior, %	1.0 (0.3 - 2) [5; 7446] {93%}	0.0 [3; 834]	NC
Lateral, %	0.3 (0.05 - 0.6) [5; 7446] {80%}	0.0 [3; 834]	NC
Infero-lateral, %	2.0 (1.0 – 3.3) [8; 9256] {93%}	0.0 [3; 834]	NC
ST-segment depression, %	0.03 (0.003 - 0.08) [6; 7615] {0%}	0.0 [3; 834]	NC
Abnormal Q waves, %	0.1 (0.03 - 0.2) [10; 9902] {25%}	0.0 [3; 834]	NC
LAE, %	3.5 (0.4 - 9.5) [8; 5804] {98%}		
RAE, %	5.9 (0.9 - 14.8) [4; 2575] {98%}		
LAD, %	0.4 (0.1 - 0.9) [6; 5683] {75%}		
RAD, %	3.7 (0.1 -11.8) [5; 4352] {98%}		
RVH, %	9.8 (7.0 -13.0) [3; 2420] {81%}		
Ventricular pre-excitation, %	0.6 (0.2 - 1.1) [6; 7422] {79%}		
Complete RBBB (%)	0.5 (0.3 - 0.7) [8; 9715] {55%}	0.0 [3; 834]	NC
Complete LBBB, %	0.1 (0.008 - 0.3)	0.0	NC

	[7; 9499] {81%]	[3; 834]	
Long QT interval, %	0.6 (0.1 - 1.3) [9; 10247] {57%}	0.0 [3; 834]	NC
Short QT interval, %	0.4 (0.02 - 1.1) [4; 4108] {81%}	0.0 [3; 834]	NC
Brugada-like Early Repolarisation, %	0.2 (0.03- 0.4) [5; 7079] {0%}		

Data are presented mean or percentage (95%CI) [number of articles; number of participants]
{heterogeneity}
*p ≤0.05 Significantly greater or more prevalent in athletes than non-athletes
** p ≤0.001 Significantly greater or more prevalent in athletes than non-athletes
NC: Non-Computable
Abbreviations: AV, atrioventricular; RBBB: right bundle branch block; LVH: left ventricular hypertrophy; TWI: T-wave inversion; Anterior: V_1–V_3; Extended Anterior: V_1–V_4; Inferior: Leads II-aVF; Lateral: V_4-V_6/I-aVL; Infero-lateral: Leads II-aVF/V_4-V_6/I-aVL; LAE: left atrial enlargement; RAE: right atrial enlargement; LAD: left axis deviation; RAD: right axis deviation; LBBB: left bundle branch block

4.2.5.2 Impact of paediatric athlete age

Paediatric athletes ≥14 years had a significantly longer QRS duration, and a significantly greater frequency of sinus bradycardia and voltage criteria for LVH than athletes <14 years (Table 4.11). Athletes ≥14 years were 1.3 times more likely to have TWI than athletes <14 years (6.9% vs 5.4%). Athletes <14 years were 1.2 times more likely to have anterior TWI than athletes ≥14 years (6.7% vs. 5.4%). Athletes ≥14 years were 3.1 times more likely to have extended anterior TWI (1.7% vs. 0.5%), and 15.8 times more likely to have inferolateral TWI (2.5% vs. 0.1%) than athletes <14 years.

Table 4. 11 ECG Characteristics of Paediatric Athletes: Impact of Age

Characteristics	≥14 years	<14 years	% Difference
PR interval, ms	151 (140 - 162) [4; 1985] {99%}	142 (137 - 147) [4; 89] {58%}	6%
QRS duration, ms	92 (91 - 93)* [4; 1991] {59%}	74 (70 - 82) [3; 77] {88%}	9%
QTc duration, ms	377 (354 - 400) [5; 4205] {99%}	394 (375 - 412) [3; 77] {6%}	-5%
QRS axis*, degree	76 (73 - 78) [4; 2816] {89%}	74.7 (61.4 - 88.0) [2; 63] {75%}	2%
Group 1 ECG patterns			Odds Ratio
Sinus bradycardia, %)	61.3 (46.3 - 75.3)** [5; 4205] {98%}	18.8 (12.1 - 26.7) [2; 109] {0%}	6.6 (4.1-10.7)
LVH, %)	48.0 (36.4 - 59.5)** [5; 4205] {98%}	20.7 (9.3 – 35.1) [2; 109] {30%}	3.4 (2.2 -5.5)
Group 2 ECG patterns			Risk Ratio
TWI (≥1mm), %	6.9 (3.7 - 10.9** [6; 5051] {96%}	5.4 (0.2 - 16.9) [2; 1272] {92%}	1.3 (1.0-1.7)
Anterior, %	5.4 (1.4 - 11.8) [7; 6575] {98%}	6.7 (4.4 – 9.4)† [3; 2516] {78%}	1.2 (1.0 - 1.5)
Extended Anterior, %	1.7 (0.4 – 4.0)* [4; 3823] {94%}	0.5 (0.1 - 3.0) [2; 1257] {68%}	3.1 (1.4 – 6.6)
Infero-lateral, %)	2.5 (1.0 - 4.6)** [5; 3710] {89%}	0.1 (0.01 - 0.4) [2; 1272] {0%}	15.8 (3.9 – 63.9)

Data are presented mean or percentage (95%CI) [number of articles; number of participants]
{heterogeneity}
*p ≤0.01 Significantly greater or more prevalent in athletes ≥14 years than in athletes <14 years

** p ≤0.001 Significantly greater or more prevalent in athletes ≥14 years than in athletes <14 years

† ≤0.05 Significantly greater or more prevalent in athletes <14 years than in athletes ≥14 years

NC: Non-Computable

Abbreviations: LVH: left ventricular hypertrophy; TWI: T-wave inversion; Anterior: V_1–V_3; Extended Anterior: V_1–V_4; Infero-lateral: Leads II-aVF/V_4-V_6/I-aVL.

4.2.5.3 Impact of paediatric athlete ethnicity

Black paediatric athletes had a significantly greater frequency of sinus bradycardia, 1ºAV block, IRBBB, voltage criteria for LVH and early repolarisation compared to white athletes (Table 4.12). Black athletes were 4 times more likely to have TWIs (23.4% vs. 5.9%) and 2.6 times more likely to have deep TWIs (10.6 vs. 4.2%), than white athletes. Further, black athletes were 2.9 times more likely to have anterior TWI (12.2% vs. 4.2%), 36 times more likely to have extended anterior TWI (10.8% vs. 0.3%) and 6.5 times more likely to have inferolateral TWI (8.2% vs. 1.3%) than white athletes. Finally, black athletes were 5 times more likely to have abnormal Q waves (0.5% vs. 0.1%) and 2.9 times more likely to have LAE (5.7% vs. 2.0%) when compared to white athletes.

Table 4. 12 ECG Characteristics of Paediatric Athletes: Impact of Ethnicity

Characteristics	Black (10-18 years)	White (8-18 years)	% Difference
PR interval, ms	161 (146 -177) [2; 196] {91.6%}	141 (135 to 148) [3; 2529] {95%}	12%
QRS duration, ms	86 (82 - 90)** [3; 525] {94.9%}	92 (88 - 95) [4; 3232] {98.3%}	-7%
QTc duration, ms	394 (387 - 401) [3; 525] {95%}	398 (392 - 403) [4; 3232] {98.4%}	-1%
Group 1 ECG patterns			Odds Ratio
Sinus bradycardia, %	38.2 (18.6 - 60.1)*** [3; 525] {95%}	29.3 (10.9 - 52.2) [5; 6197] {99%}	1.5 (1.3 - 1.8)
1st ºAV block, %	11.4 (6.9 - 16.9)*** [2; 483] {65%}	1.1 (0.25 - 2.5) [4; 5991] {92%}	11.6 (8.0 – 17.0)
Incomplete RBBB, %	22.1 (13.1 - 32.7) [3; 525] {83%}	21.1 (15.0 - 27.9) [5; 6197] {97%}	1.1 (0.9 - 1.3)
LVH, %	60.3 (11.0 - 98.3)*** [3; 525] {99%}	28.1 (20.2 - 36.7) [5; 6197] {97%}	3.9 (3.3 - 4.7)
Early Repolarisation, %	74.3 (41.0 - 96.6)*** [3; 525] {98%}	31.0 (17.4 - 46.5) [5; 6197] {99%}	6.4 (5.2 – 7.9)
Group 2 ECG patterns			Risk Ratio
TWI (≥1mm), %	23.4 (19.8 – 27.1)*** [3; 512] {69%}	5.9 (5.3 - 6.6) [5; 5263] {71%}	4.0 (3.3 – 4.8)
Deep TWI (≥2mm), %	10.6 (5.5 -17.2)*** [3; 525] {73%}	4.2 (0.7 - 10.4) [4; 3936] {97%}	2.6 (1.9 – 3.4)
Anterior, %	12.2 (8.2 -16.9)*** [3; 512] {43%}	4.2 (3.0 - 5.6) [4; 6063] {25%}	2.9 (2.2 – 3.8)
Anterior Extended, %	10.8 (7.8 -14.2)*** [2; 358] {0%}	0.3 (0.03 - 0.8) [3; 3298] {66%}	36 (18 – 71)

Infero-lateral, %	8.2 (6.0 - 10.7)*** [3; 512] {95%}	1.3 (0.3 - 3.1) [4; 6063] {0%}	6.5 (4.5 – 9.3)
Abnormal Q waves, %	0.5 (0.0 - 2.0)* [3; 526] {52%}	0.1 (0.04 - 0.3) [4; 6135] {19%}	5.0 (1.3 - 19.3)
LAE, %	5.7 (1.2 - 1.3)*** [4; 680] {91%}	2.0 (0.02 - 7.0) [4; 3936] {97%}	2.9 (2.0 - 4.2)
LAD, %	0.8 (0.0 - 3.1) [2; 484] {70%}	0.7 (0.4 - 0.9) [2; 3668] {0%}	1.3 (0.4 - 3.6)
Complete RBBB, %	0.3 (0.02 - 1.1) [2; 483] {0%}	0.3 (0.2 -0.6) [4; 5991] {46%}	1.2 (0.3 – 5.0)
Long QT, %	1.1 (0.03 - 3.7) [3; 638] {79%}	0.1 (0.0 - 0.2) [4; 5991] {0%}	16.4 (4.8 – 56.0)

Data are presented mean or percentage (95%CI) [number of articles; number of participants] {heterogeneity}

*p ≤0.05 Significantly greater or more prevalent in black than white athletes

**p ≤0.01 Significantly greater or more prevalent in black than white athletes

*** p ≤0.001 Significantly greater or more prevalent in black than white athletes

Abbreviations: LVH: left ventricular hypertrophy; TWI: T-wave inversion; Anterior: V_1–V_3; Extended Anterior: V_1–V_4; Infero-lateral: Leads II-aVF/V_4-V_6/I-aVL.

4.2.6 ECHOCARDIOGRAPHIC PATTERNS

4.2.6.1 Paediatric athletes vs paediatric non-athletes

Athletes had a significantly greater LVIDd (+8.2%), LVID during systole (LVIDs) (+14.2%), IVSd (+12.9%), PWTd (+12.2%), relative wall thickness (RWT), (+5.6%) LV mass (LVM) (+27.6%), and left atrial diameter (LAD) (+12.3%) than non-athletes (Table 4.13). One percent of athletes (95% CI 0.3 - 2.3, 5 articles; n=4460) had LVH (LV wall thickness >12 mm). LVH was not observed in non-athletes. There were no significant differences in

cardiac functional parameters between athletes and non-athletes. Using imputed SDs did not influence the results.

Table 4. 13 Echocardiographic Patterns of Paediatric Athletes and Paediatric Non-Athletes

Parameter	Athletes	Non-Athletes	% Difference
LVIDd, mm	47.3 (46.2 - 48.3)*** [33; 6681] {99%}	43.4 (41.7 - 45.1) [18; 1042] {98%}	8.2
LVIDs, mm	29.6 (28.4 - 30.8)*** [19; 3354] {98%}	25.4 (24.8 - 26.0) [7; 177] {64%}	14.2
IVSd, mm	8.5 (8.2 - 8.8)*** [28; 5083] {99%}	7.4 (7.1 - 7.8) [16; 804] {98%}	12.9
PWTd, mm	8.2 (7.8 - 8.6)** [29; 5168] {99%}	7.2 (6.6 - 7.8) [17; 908] {92%}	12.2
RWT	0.36 (0.34 - 0.37)*** [29; 6315] {99%}	0.34 (0.33 - 0.35) [16; 804] {99%}	5.6
LVM, g	135.7 (122.2 - 149.1)*** [29; 5086] {99%}	98.2 (84.6 - 111.8) [17; 908] {99%}	27.6
LVEDV, ml	106.8 (91.8 - 121.8) [6; 494] {98.3%}		
LVESV, ml	38.3 (35.1 - 41.6) [5; 457] {86%}		
Aortic Root, mm	26.3 (24.9 - 27.8)* [10; 3055] {99%}	23.5 (20.9 - 26.0) [6; 563] {99%}	10.6
LAD, mm	30.2 (28.7 - 31.7)* [13; 5324] {99%}	26.5 (24.5 - 28.6) [8; 587] {97%}	12.3
EF, %	65.6 (61.1 - 70.1) [11; 3150] {99%}	70.9 (63.8 - 77.9) [4; 130] {99%}	-8.1
FS, %	37.2 (35.5 - 38.9) [14; 1829] {98%}	36.9 (34.7 - 39.1) [11; 666] {96%}	0.8
E Wave, m/s	0.88 (0.81 - 0.96) [10; 1915] {0%}	0.91 (0.86 - 0.96) [4; 480] {93%}	-3.4

A Wave, m/s	0.46 (0.43 - 0.49) [10; 1915] {98%}	0.49 (0.46 - 0.52) [4; 480] {84%}	-6.5
E/A ratio	2.1 (2.0 - 2.2) [14; 3634] {96%}	1.9 (1.8 - 2.1) [8; 672] {93%}	9.5
DceT, ms	133 (108 - 157) [4; 201] {97%}		
IVRT, ms	60 (39 - 82) [3; 168] {99%}		

Data are mean (95% CI), [number of studies; number of participants] {heterogeneity}

*p ≤0.05 Significantly greater in athletes than non-athletes

**p ≤0.01 Significantly greater in athletes than non-athletes

*** p ≤0.001 Significantly greater in athletes than non-athletes

LVIDd, left ventricular cavity diameter in end-diastole; LVIDs, left ventricular cavity diameter in end-systole; IVSd, interventricular septum thickness in end-diastole; PWTd, posterior wall thickness in end-diastole; RWT, relative wall thickness; LVM, left ventricular mass; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LAD, left atrial diameter; EF, ejection fraction; FS, fractional shortening; DceT, Deceleration time; IVRT, interventricular septum relaxation time

4.2.6.2 Impact of age: paediatric athletes vs paediatric non-athletes

Age was a positive predictor of LVIDd, IVSd, PWTd, RWT and LVM in athletes and non-athletes (P≤0.001). After accounting for age, athletes had greater LVIDd, IVSd, RWT and LVM (P≤0.05) than non-athletes.

4.2.6.3 Impact of paediatric athlete age

Paediatric athletes ≥14 years had a significantly greater LVIDd (+13.5%), LVIDs (+15.9%), IVSd (+15.2%), PWTd (+21.3%), LVM (+38.7%), Aortic Root (+14.2%), and

LAD (+15.6%) than athletes <14 years (Table 4.14). With the exception of E/A ratio (+13.6% greater in athlete's ≥14 years) there were no statistical differences with regards to LV function.

Table 4. 14 Echocardiographic Patterns of Paediatric Athletes: Impact of Age

Parameter	≥14 years	<14 years	% Difference
LVIDd, mm	51.2 (50.6 - 51.9)** [14; 2856] {93%}	44.3 (43.3 - 45.3) [14; 872] {94%}	13.5
LVIDs, mm	32.8 (30.8 - 34.7)** [5; 288] {97%}	27.6 (25.9 - 29.2) [8; 363] {98%}	15.9
IVSd, mm	9.2 (8.8 - 9.6)** [12; 1366] {97%}	7.8 (7.5 - 8.0) [13; 787 {96%}	15.2
PWTd, mm	8.9 (8.5 - 9.3)** [12; 1378] {98%}	7 (6.6 - 7.3) [14; 872] {0%}	21.3
RWT	0.36 (0.33 - 0.39) [12; 2857] {99%}	0.35 (0.33 - 0.36) [13; 787] {96%}	2.8
LVM, g	167 (153.5 - 180.4)** [12; 1378] {96%}	102.3 (91.8 - 112.8) [14; 872] {87%}	38.7
Aortic Root, mm	28.9 (27.3 - 30.4)** [5; 2396] {98%}	24.8 (23.7 - 25.8) [6 2420] {97%}	14.2
LAD, mm	33.3 (32.0 - 34.5)** [6; 2462] {95%}	28.1 (27.0 - 29.2) [8; 601] {93%}	15.6
EF (%)	63.7 (59.1 - 68.2) [4; 285] {99%}	67.5 (55.2 - 79.8) [4; 217] {99%}	-6.0
FS (%)	35.8 (33.0 - 38.7) [3; 1052] {98%}	38.1 (37.0 - 39.2) [6; 226] {56%}	-6.4
E Wave (m/s)	0.86 (0.83 - 0.90) [6; 1264] {92%}	0.72 (0.56 - 0.88) [8; 884] {99%}	16.3
A Wave (m/s)	0.43 (0.39 - 0.46) [6; 1264] {95.3%}		
E/A ratio	2.2 (2.1 - 2.3)* [9; 2710] {92%}	1.9 (1.9 – 2.0) [5; 530] {77%}	13.6

Data are mean (95% CI), [number of studies; number of participants] {heterogeneity}

*p ≤0.05 Significantly greater in athletes ≥14 years than in athletes <14 years

** p ≤0.001 Significantly greater in athletes ≥14 years than in athletes <14 years

LVIDd, left ventricular cavity diameter in end-diastole; LVIDs, left ventricular cavity diameter in end-systole; IVSd, interventricular septum thickness in end-diastole; PWTd, posterior wall thickness in end-diastole; RWT, relative wall thickness; LVM, left ventricular mass; LAD, left atrial diameter; EF, ejection fraction; FS, fractional shortening.

4.2.6.4 Impact of paediatric athlete ethnicity

Black athletes had a significantly greater PWTd (+12.4%) and LAD (+13.4%) than white athletes (Table 4.15). Prevalence of LVH (LV wall thickness >12 mm) was 17.1 times greater among black [2 articles, n=319] than white athletes [3 articles, n=3318] (7.1% vs. 0.4%).

Table 4. 15 Echocardiographic Patterns of Paediatric Athletes: Impact of Ethnicity

Parameter	Black (12-18 years)	White (8-18 years)	% Diff
LVIDd, mm	49.5 (47.0 - 51.9) [3; 525] {97%}	48.2 (46.3 – 50.0) [10; 3919] {99%}	2.6
IVSd, mm	9.7 (9.5 - 9.9) [2; 196] {0%}	8.7 (8.0 - 9.3) [9; 3016] {99%}	10.3
PWTd, mm	9.7 (9.4 - 10.1)* [2; 196] {44%}	8.5 (7.9 - 9.0) [9; 3016] {99%}	12.4
RWT	0.39 (0.38 - 0.40) [4; 680] {90%}	0.36 (0.34 - 0.38) [10; 3919] {99%}	7.7
LVM, g	169.4 (143 - 195.9) [2; 196] {95%}	148.2 (129.0 -167.4) [9; 3016] {99%}	12.5
Aortic Root, mm	29.7 (28.9 - 30.5) [3; 638] {90%}	26.9 (24.1 - 29.7) [4; 1137] {99%}	9.4
LAD, mm	35.4 (34.6 - 36.1)** [3; 638] {81%}	30.5 (27.0 – 34.0) [4; 3320] {99%}	13.4
E/A	2.1 (1.9 - 2.3) [2; 483] {88%}	2.1(1.9 - 2.3) [5; 1207] {93%}	0.0

Data are mean (95% CI), [number of studies; number of participants]

*p ≤0.05 Significantly greater in black than white athletes

**p ≤0.01 Significantly greater in black than white athletes

LVIDd, left ventricular cavity diameter in end-diastole; IVSd, interventricular septum thickness in end-diastole; PWTd, posterior wall thickness in end-diastole; RWT, relative wall thickness; LVM, left ventricular mass; LAD, left atrial diameter.

4.2.6.5 Impact of paediatric athlete sex

Male athletes had a significantly larger IVSd (+9.2%) than female athletes (Table 4.16). Prevalence of LVH was 2.6 times greater among male [5 articles; n=4028) than female athletes [2 articles; n=432] (1.2% vs. 0.4%).

Table 4. 16 Echocardiographic Patterns of Paediatric Athletes: Impact of Sex

Parameter	Male (8-18 years)	Female (10-18 years)	% Diff
LVIDd, mm	47.8 (46.5 - 49.2) [21; 4294] {99%}	45.3 (43.5 - 47.1) [6; 479] {98%}	5.2
LVIDs, mm	30.2 (28.5 - 31.8) [12; 2879] {99%}	28.5 (25.2 - 31.9) [3; 92] {98%}	5.6
IVSd, mm	8.7 (8.3 - 9.1)* [19; 4066] {99%}	7.9 (7.5 - 8.4) [6; 452] {96%}	9.2
PWTd, mm	8.4 (7.8 - 8.9) [19; 4066] {99%}	7.8 (6.9 - 8.7) [6; 452] {99%}	7.1
RWT	0.36 (0.34 - 0.38) [19; 4066] {99%}	0.34 (0.33 0.36) [6; 452] {95%}	5.6
LVM, g	137.5 (115.3 - 159.6) [14; 3482] {99%}	129.5 (99.8 - 159.2) [5; 298] {98%}	5.8
EDV, ml	114.3 (108.0 - 120.7) [5; 409] {86%}	82.2 (69.0 - 95.4) [2; 85] {94%}	28

Data are mean (95% CI), [number of studies; number of participants]

*p ≤0.05 Significantly greater in Male than Female athletes

LVIDd, left ventricular cavity diameter in end-diastole; LVIDs, left ventricular cavity diameter in end-sytsole; IVSd, interventricular septum thickness in end-diastole; PWTd, posterior wall thickness in end-diastole; RLVWT, relative left ventricular wall thickness; LVM, left ventricular mass; LVEDV, left ventricular end-diastolic volume.

4.4 DISCUSSION

In the first systematic review and meta-analysis investigating the ECG, structural and functional manifestations of the paediatric athlete's heart, we found that 1) Paediatric athletes had a greater prevalence of training-related and training unrelated ECG changes than non-athletes, 2) Whilst the overall prevalence of TWI remained similar, the distribution and magnitude differed; 3) Paediatric athletes had larger echocardiographic derived LV dimensions than non-athletes, even after accounting for age; 4) Paediatric black athletes had increased levels of training and training unrelated ECG findings (particularly TWI); and finally 5) Paediatric black athletes had a greater prevalence of echocardiographic derived indices of LVH compared to white athletes.

4.4.1 ECG CHARACTERITICS OF THE PAEDIATRIC ATHLETE

This study confirms that regular and prolonged physical training is associated with a high prevalence of bradycardia, repolarisation changes, atrial enlargement and ventricular hypertrophy in paediatric athletes (Sharma et al., 1999). However, the magnitude, prevalence and distribution of such changes are dependent on the chronological age of the paediatric athlete. Similar to adult athletes, ethnicity impacted ECG remodelling in the paediatric athlete (Papadakis et al., 2011). Black paediatric athletes had significantly more training-related changes, anterior, extended anterior, inferolateral and deep TWIs, in addition to Q waves and LAE compared to white athletes (Papadakis et al., 2012).

4.4.2 T WAVE INVERSION IN THE PAEDIATRIC ATHLETE: IMPACT OF AGE AND ETHNICITY

Inverted T-waves may represent the only sign of an inherited heart muscle disease even in the absence of any other features or before structural changes in the heart can be detected (Sheikh et al., 2013). Yet, until complete formation of adult ventricular mass, T wave inversions may persist across leads V_1-V_3 within the paediatric population, owing to right ventricular dominance (Molinari et al., 2016). Our findings on over 9000 paediatric athletes and over 800 paediatric non-athletes, support this notion, with a relatively high, but similar prevalence of anterior TWI (V_1-V_3) observed in both athletes and non-athletes (6.5% vs. 5.7%) respectively; suggesting this is a maturational trait largely not resultant upon athletic training. The slightly higher prevalence of anterior TWI in athletes vs. non-athletes also suggests that regular exercise may exacerbate or prolong the presence of juvenile TWI. Nevertheless, paediatric athletes were 12.7-times more likely to present with deep TWI (≥2mm) than non-athletes. Deep TWI (≥2mm) in the precordial leads are a major concern as these ECG alterations are a recognised manifestation of hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy (Drezner et al., 2013b).

TWIs are uncommon among adult white athletes. Conversely, African/Afro–Caribbean black athletes have a higher prevalence of TWI, as well as more striking repolarisation changes and magnitude of voltage criteria for LVH than white athletes of similar age and size participating in identical sports (Basavarajaiah et al., 2008a; Magalski et al., 2008b). Similar to their adult counterparts (Papadakis et al., 2011), we found that black paediatric

athletes are 4 times more likely to exhibit any TWI and 36 times more likely to exhibit extended anterior TWI (V_1-V_4) than white paediatric athletes (Sheikh et al., 2013); this likely represents an ethnic response to physiological adaptation to exercise rather than an effect of ethnicity alone, exuberated by right ventricular dominance during pubertal years.

4.4.3 WHEN IS ANTERIOR T-WAVE INVERSION NORMAL?

Recently updated international consensus standards for 12-lead ECG interpretations in athletes (Drezner et al., 2017; Sharma et al., 2017a) recommends that TWI ≥ 1 mm in depth in two contiguous anterior leads (V_2-V_4) is abnormal (with the exception of TWI confined to leads V_1-V_4 in black athletes and leads V_1-V_3 in all athletes aged <16 years) and should prompt further evaluation for underlying structural heart disease. Our data support this recommendation, demonstrating a significantly reduced prevalence of anterior TWI (V_1-V_3) in athlete's ≥14 years, likely as a consequence of maturation, wherein incomplete formation of ventricular mass is present, with TWI presentation likely owing to the displacement of the right ventricle towards the left axilla (Brosnan et al., 2015b). Based on current evidence, TWI in the anterior leads (V_1-V_3) in paediatric athletes <14 years of age (or pre-pubertal athletes) should not prompt further evaluation in the absence of symptoms, signs or a family history of cardiac disease.

Our data also support the observation that like their adult counterparts, paediatric black athletes were 3 times more likely to have anterior TWI (V_1-V_3) and 36 times more likely to

have extended anterior TWI (V_1-V_4) when compared to paediatric white athletes. In adult black athletes, it is recognised that anterior TWI is a normal variant when preceded by J-point elevation and convex ST segment elevation (Calore et al., 2016), unlike in arrhythmogenic right ventricular cardiomyopathy where the J-point and/or ST segment is usually isoelectric or depressed prior to TWI. Appreciating the J-point and preceding ST segment may help differentiate between physiological adaptation and cardiomyopathy in athletes with anterior TWI affecting leads V_3 and/or V_4 and may prove to be especially useful in athletes of mixed ethnicity. A recent study compared black and white healthy athletes against hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy patients, all of whom had anterior TWI. Within athletes, the combination of J-point elevation ≥1mm and TWI confined to leads V_1-V_4 excluded hypertrophic cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy with 100% negative predictive value, regardless of ethnicity (Calore et al., 2016). Conversely, anterior TWI associated with minimal or absent J-point elevation (<1 mm) may reflect a cardiomyopathy. Such detailed investigations have yet to be extended to the paediatric athletic population.

4.4.4 INFERIOR AND/OR LATERAL TWI WARRANTS INVESTIGATION

We were surprised by the high prevalence of inferolateral TWI in both black (8.5%) and white (1.3%) paediatric athletes. It is unlikely that all such athletes harbour a sinister cardiomyopathy and may represent a racial variant in black athletes. Indeed, two cases of hypertrophic cardiomyopathy were detected in 1 white male athlete, aged 15 years presenting lateral TWI (Migliore et al., 2012), and 1 white male athlete, aged 13 years

presenting inferolateral TWI (Calò et al., 2015). However, owing to inconsistent methodological design imposed across articles included for meta-analysis, with long-term follow up reported only by Sheikh et al., (2013), diagnostic yield is not reported. Despite this, lateral lead TWI should be viewed with caution. We recently investigated 155 athletes presenting with pathological TWI with clinical examination, ECG, echocardiography, exercise testing, 24h Holter ECG and cardiac magnetic resonance (Schnell et al., 2014). Cardiac disease was established in 44.5% of athletes (81% hypertrophic cardiomyopathy). Inferior and/or lateral TWI were the most commonly observed ECG abnormalities (83.9%) and were largely isolated findings without other ECG abnormalities (43.2%). In our experience, regardless of an increased frequency after 14-years and a higher prevalence in adolescent black athletes, inferolateral TWI should be considered pathological in all cases until proven otherwise. While exclusion from competitive sport is not warranted in the asymptomatic paediatric athlete without a family history of SCD and normal secondary examinations, annual follow-up is essential to ascertain possible disease expression.

4.4.5 LEFT VENTRICULAR MORPHOLOGHY OF THE PAEDIATRIC ATHLETE

While most adult athletes have left ventricular structural changes that are considered physiological, there are a small proportion who develop pronounced morphological changes that overlap with phenotypic expressions of cardiac pathology associated with SCD. Several groups have produced algorithms to aid in this differentiation (Rudski et al., 2010a; Caselli et al., 2014; Sheikh et al., 2015). Data for these algorithms primarily derives from five large echocardiographic studies (Pelliccia *et al.*, 1991; Whyte *et al.*,

2004; Sun *et al.*, 2007; Basavarajaiah, Boraita, *et al.*, 2008; Basavarajaiah, Wilson, *et al.*, 2008) examining 5053 elite, predominately male adult athletes; 134 (2.7%) had a maximal wall thickness ≥12 mm (of which 27 (0.5%) athletes had a maximum wall thickness of ≥13 mm). In absolute terms and regardless of an athlete's BSA, the upper limit of physiological hypertrophy for adult male athletes is considered ≥13 mm for maximal wall thickness and ≥65 mm for LVIDd.

Despite undergoing significant changes in anthropometry during maturation paediatric athletes have significantly larger cardiac diameters, wall thicknesses and LV mass than non-athletes even after adjusting for age. From 4460 paediatric athletes analysed, just 1.1% presented with a maximal wall thickness ≥12 mm; although a maximal wall thickness of 15mm was documented in one study. A pooled mean LVIDd of 47mm (<14 years: 44.2mm vs. ≥ 14 years: 51.1 mm) is similar to upper limits previously observed among paediatric hypertrophic cardiomyopathy patients (48mm) (Maron et al., 1999). Thus, such adult upper limit criteria may not be applicable to the paediatric athlete. Regardless of ethnicity, values above these should be viewed with suspicion in paediatric athletes, particularly if the athlete also presents with cardiac symptoms, a family history of SCD and/or an abnormal ECG. Given the widely recognised impact of chronological age and somatic growth upon paediatric echocardiographic variables, it is our suggestion that Z-scores (which account for the effects of body size and chronological age) are instead used for differential diagnosis when normative data are available (Daubeney *et al.*, 1999; Kampmann *et al.*, 2000; Zilberman, Khoury and Kimball, 2005), as previously suggested within paediatric specific echocardiographic guidelines (Lopez et al., 2010b).

4.4.6 IMPACT OF CHRONOLOGICAL AGE ON LV REMODELLING

Cardiac enlargement increased with chronological age, as demonstrated by our meta-regression as well as by others (George et al., 2001), and helps to explain the heterogeneity observed within this dataset. After accounting for age (using meta-regression), paediatric athletes had greater LV morphology than paediatric non-athletes, demonstrating the potent stimulus exercise has upon cardiac structure. These changes appeared to be exaggerated during the pubertal growth stage, suggesting a potential role of hormonal factors in cardiac remodelling (Cavasin et al., 2003). We recognise that whilst chronologic age is a linear factor, growth and maturation are not (Malina et al., 2004), and thus maturational status for children of the same chronological age can differ dramatically (Cox, 1997; Mirwald et al., 2002). Yet, assessment of maturational status was conducted among only 14 of the 43 (33%) articles included for qualitative synthesis and relied largely on assessment by Tanner Scale (79%), regarded to be inappropriate by many due to obvious child protection concerns. In our experience, clinical interpretation of pre-participation cardiac screening data should be governed by skeletal (biological) age rather than chronological age. According to the IOC consensus statement on youth athletic development (Engebretsen et al., 2010), skeletal (biological) age is the most useful estimate of maturity status and can be used from childhood into late adolescence. However, this can only be confirmed by radiological hand-wrist imaging. Since this is not widely available in most cardiological units, alternative simple measures such as percentage of predicted mature (adult) height at the time of observation may provide an estimate of maturity status (Roche et al., 1983). However

care is warranted, as 1) predicted mature (adult) height only demonstrates moderate concordance with classifications of maturity status, based on skeletal age (Malina et al., 2007, 2012), and 2) historical height data of the patient is required to rule out sudden growth spurts.

4.4.6 IMPACT OF ETHNICITY ON LV REMODELLING

Data from the USA indicate that paediatric black athletes are particularly susceptible to SCD (Harmon et al., 2016), and therefore, the distinction between athlete's heart and cardiac pathology is of particular relevance in this group. Consistent with previous observations in adults (Basavarajaiah et al., 2008a; Rawlins et al., 2010; Kervio et al., 2013), we found that paediatric black athletes had increased LVH in response to chronic training loads compared to white athletes. This change is consistent with a concentric remodelling pattern. Furthermore, the likelihood of LVH was 17.1 times greater among black when compared to white athletes. We speculate that these ethnic-specific manifestations of the athlete's heart are the result of hemodynamic influences; specifically greater peripheral vascular resistance and a smaller nocturnal decline in BP (Heffernan et al., 2008; DeLoach et al., 2012).

4.4.7 IMPACT OF SEX ON LV REMODELLING

The last three decades have witnessed an exponential rise in the number of females participating in high-level competitive sport (International Olympipc Comittee, 2016). Consistent with observations among adults (Pelliccia et al., 1996), we found a reduced LVH response to chronic training loads in female athletes compared to males. This might

be due to hormonal differences and lower testosterone concentrations (McGill Jr and Sheridan, 1981). However, the relative differences of sex across maturational years has yet to be fully elucidated among paediatric athletes. Females reach complete pubertal development at an earlier chronological age and thus we may expect such relative differences between female and male athletes to be smaller during the early stages of pubertal development.

4.4.8 LIMITATIONS

A high statistical heterogeneity (I^2) was observed; this may be because it was not possible to stratify data according to biological age, ethnicity or sex due to inconsistent methodology and designs implemented within the observational studies included. Because of this, a random-effects meta-analysis model was adopted to provide a more conservative pooled estimate. Activity levels of our non-athlete cohort are unknown and thus they may not actually be sedentary, however, in all cases, participants did not meet classification criteria for a competitive athlete.

Whilst we utilised the 2010 ESC recommendations for interpretation of the 12-lead ECG (Corrado et al., 2010), at the time of publication, it was not intended to be used in athletes ≤12 years old. We recently observed that the 2014 ‘Refined Criteria’ for ECG interpretation in athletes outperformed both the 2013 Seattle Criteria and the 2010 ESC recommendations, by significantly reducing the number of false-positive ECGs in Arab, black and white adult athletes while maintaining 100% sensitivity for serious cardiac

pathologies (Riding et al., 2014b). Again, however, all three ECG criteria are only applicable for adult athletes and not paediatric athletes. Thus, for paediatric pre-participation cardiac screening, the attending cardiologist or sports medicine physician is left with the conundrum of which criteria should be used for ECG interpretation. Recently published International consensus standards for ECG interpretation in athletes (Sharma et al., 2017a) do account for age and ethnicity respectively. TWI in the anterior leads (V_1-V_3) in adolescent athletes <16 years of age (or pre-pubertal athletes) and black adult athletes with J-point elevation and convex ST segment elevation followed by TWI in V_2-V_4, would now not prompt further evaluation in the absence of symptoms, signs or a family history of cardiac disease. But in most non-black athletes age ≥ 16 years, anterior TWI beyond lead V_2 would prompt further evaluation given the potential overlap with arrhythmogenic right ventricular cardiomyopathy.

Finally, echocardiographic data were largely limited to LV structural variables, owing to insufficient data available for synthesis. Such limitations highlight the importance of further research in the paediatric athlete extending to other chambers of the heart, and beyond load dependent measurements of cardiac function (EF or fractional shortening) towards Tissue Doppler imaging and myocardial speckle tracking.

4.4.9 CONCLUSION

Similar to adult athletes, paediatric athletes had a greater prevalence of training related and training unrelated ECG changes than non-athletes. Significant cardiac remodelling in

paediatric athlete occurs both before and during their ‘maturational years’; with ethnicity and sex significantly impacting upon the pattern of remodelling observed. The results demonstrate the importance of adjusting for age when assessing LV morphology in paediatric athletes, whilst consideration for an athletes’ ethnicity and sex is further required when differentiating between physiological and pathological cardiac remodelling.

CHAPTER 5:

DIAGNOSTIC ACCURACY AND BAYESIAN ANALYSIS OF NEW INTERNATIONAL ECG RECOMMENDATIONS IN PAEDIATRIC ATHLETES

McClean, G., Riding, N.R., Pieles, G., Watt, V., Adamuz, C., Sharma, S., George, K.P., Oxborough, D. and Wilson, M.G., (2019) Diagnostic accuracy and Bayesian analysis of new international ECG recommendations in paediatric athletes. Heart, [online] 1052, pp.152–159. Available at: http://heart.bmj.com/lookup/doi/10.1136/heartjnl-2018-313466.

5.1 INTRODUCTION

Studies based on high school populations in the United States reveal that paediatric athletes (14-18 years) are 3.6-times more likely to experience a sudden cardiac arrest than their non-athletic peers (Toresdahl et al., 2014). In the UK, 22% of all sudden cardiac deaths occur in athletes aged under 18 years (Finocchiaro et al., 2016b). The ESC (Corrado et al., 2005b) and the Association of European Paediatric Cardiology (Fritsch et al., 2017), recommend initiating 12-Lead electrocardiography (ECG) screening to coincide with the onset of competitive athletic activity. Screening aims to identify

underlying cardiac pathology predisposing to sudden cardiac arrest/death (SCA/D), and thereby reduce the incidence of such catastrophic events.

Until recently clinicians undertaking ECG screening in athletes applied interpretation criteria that were applicable only to adults (Corrado et al., 2010; Drezner et al., 2013a). In chapter 3, we observed a high but similar prevalence of anterior (V_1-V_3) T-wave inversion (TWI) in ≥9000 paediatric athletes and ≥800 paediatric non-athletes (6.5% vs 5.7%), suggesting that this repolarization pattern is maturational and not abnormal within the paediatric athlete. New ECG interpretation recommendations now account for athletes aged ≤16 years, with particular focus on individuals displaying anterior (V_1-V_3) TWI (often called juvenile T-wave pattern) (Drezner et al., 2017; Sharma et al., 2017b, 2018). Whilst these new recommendations have been shown to significantly reduce the number of abnormal ECGs compared to previous ECG criteria [2010 ESC recommendations (Corrado et al., 2010) and Seattle criteria (Drezner et al., 2013a)], this result was observed in a primarily white adult athletic population (Dhutia et al., 2017).

The past few decades have observed an exponential increase in the number of Arab and black athletes excelling in international competitive sport, with ethnicity now universally recognized as an important determinant of the electrical manifestations of an athlete's heart (Riding et al., 2014a). Sports academies throughout in North America, South America, Europe, Asia, and Australasia who undertake ECG screening in paediatric athletes of Arab and black ethnicity require knowledge of the clinical appropriateness of these new ECG recommendations to distinguish physiological cardiac adaptations from

cardiac pathology predisposing to SCA/D. A second conundrum relates to ensuring that ECG screening results are interpreted in context, especially when there is no 'gold standard' test to identify cardiac pathology. Bayesian analysis allows for the quantification of 'chance' of having a disease as per examination methodology (in this case, ECG interpretation recommendations), based upon *pre-* and *post-test odds* (Whiteley, 2016).

Accordingly, the aim of this study was to establish the diagnostic accuracy of new international ECG interpretation recommendations for athletes against the Seattle criteria and 2010 ESC recommendations in a large cohort of Arab and black male paediatric athletes using ROC analysis. Clinical context was calculated using Bayesian analysis.

5.2 METHODS

5.2.1 ETHICAL APPROVAL

Ethics approval was provided by Anti-Doping Laboratory Qatar (IRB #E2013000003 and #E20140000012), with all parents or guardians providing informed consent, as detailed in chapter 3.

5.2.2 PARTICIPANTS

Between 2009 and 2017, 876 Arab and 428 black male paediatric athletes registered with the Qatar Olympic Committee [exercising ≥6 hours/week, aged 11-18 years] presented at our institution for ECG screening. No athlete had been previously screened. Ethnicity was self-determined by the athlete (or guardian) in accordance with definitions offset by the UK government's statistical service (Harmonised concepts and questions for social

data sources, GSS Harmonised Principle: Ethnic group). Based on 2-year chronological age categories, athletes were distributed as per Table 5.1. Whilst we acknowledge ECG interpretation criteria were developed for application in athletes aged 12-35 years (Drezner et al., 2017; Sharma et al., 2017b, 2018), a minority of athletes <12 years presented at the request of the Qatar Olympic Committee.

5.2.3 PRELIMINARY INVESTIGATIONS

5.2.3.1 Health questionnaire and physical examination

Athletes completed a health questionnaire regarding family history of cardiovascular disease and personal symptoms, together with anthropometric (height and body mass; BSA (Haycock et al., 1978)) and left brachial artery blood pressure assessment in collaboration with an Arabic, French, and/or English-speaking nurse. To ensure accurate medical history was taken, primary guardians were present where appropriate. Precordial auscultation in supine and standing positions, and assessment for any physical characteristics of underlying congenital or syndromal disorder were undertaken by a sports medicine physician.

5.2.3.2 Resting 12-lead ECG

ECG was recorded with standard 12-lead positions using a GE Mac 5500 (New York, USA), as described elsewhere (Riding et al., 2014b). All 1304 ECGs were retrospectively interpreted by GMC applying the 2010 ESC recommendations (Corrado et al., 2010), the Seattle Criteria (Drezner et al., 2013a), and the new international recommendations

(Figure 5.1) (Drezner et al., 2017; Sharma et al., 2017b, 2018). At the time of ECG interpretation, GMC was blinded to all pathological conditions that were subsequently diagnosed.

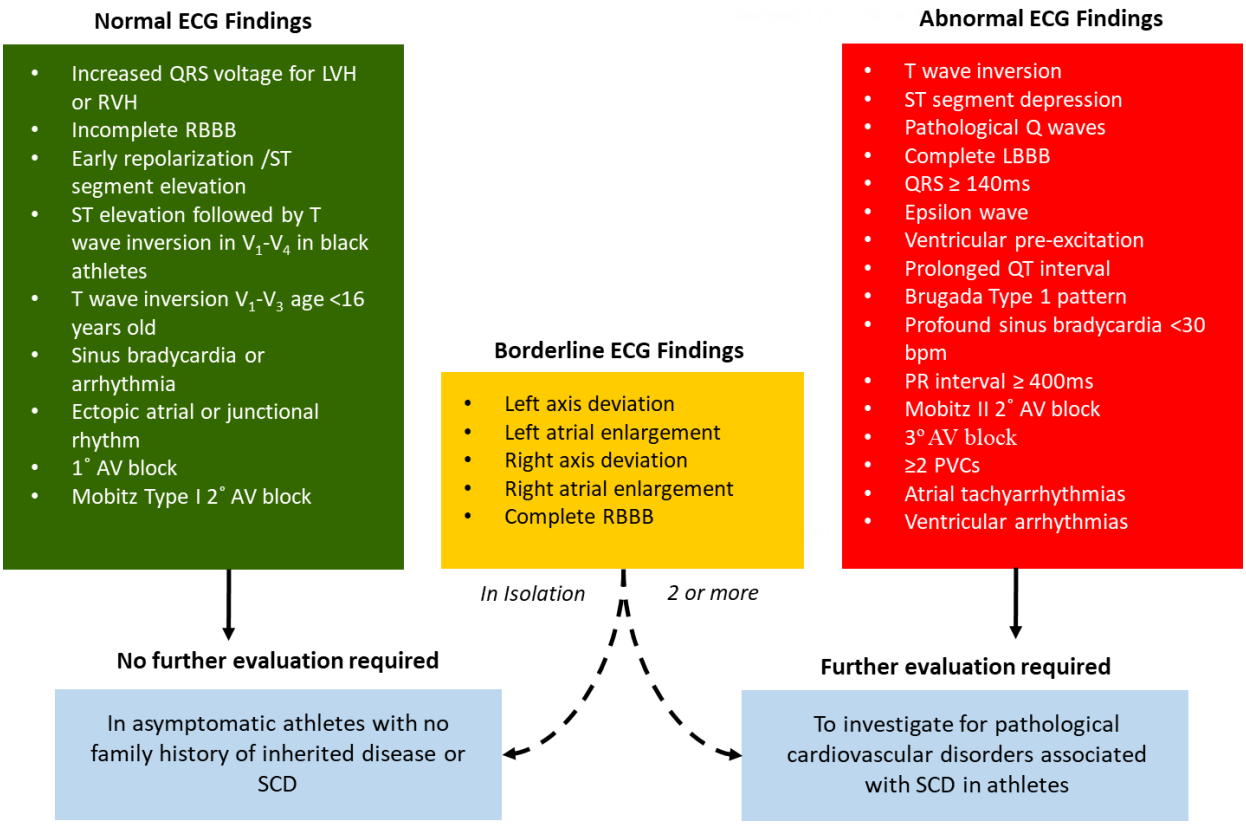

Figure 5. 1 New international recommendations for electrocardiographic interpretation in athletes aged 12-35 years (Drezner et al., 2017; Sharma et al., 2017b, 2018).

Key: AV; atrioventricular LBBB; left bundle branch block; LVH, left ventricular hypertrophy; ms; milliseconds; PVCs, premature ventricular contractions; RBBB; right bundle branch block; RVH; right ventricular hypertrophy.

5.2.3.3 Echocardiography

2D transthoracic echocardiographic examination was performed using a IE33, (Philips, USA) and Artida (Toshiba Medical Systems, Japan) ultrasound systems. Standard views were obtained and analysed for left and right ventricular wall thickness, cavity dimension measurements, as well as the identification of the origins of the left and right coronary arteries in accordance with current guidelines (Lopez et al., 2010b; Lang et al., 2015).

5.2.4 FURTHER EVALUATION

Athletes presenting with an abnormal health questionnaire, physical examination, ECG or echocardiographic examination suggestive of underlying cardiovascular pathology were invited for further evaluation. Subsequent examinations included (but were not limited to) 24h ECG or ambulatory blood pressure monitoring, maximal cardiopulmonary exercise stress testing, electrophysiology study, computerized tomography and cardiac magnetic resonance imaging including contrast studies. Diagnosis of disease was established and managed in accordance to established guidelines (Jenni, 2001; Brothers et al., 2009; Marcus et al., 2010; Cohen et al., 2012b; Elliott et al., 2014; Flynn et al., 2014; Friedrich et al., 2014; Nishimura et al., 2014).

5.2.5 STATISTICAL ANALYSIS

Data were expressed as mean (± SD) or percentages as appropriate and analysed with SPSS software (Version 21.0, Chicago, IL). Continuous variables were tested for normality using the Shapiro-Wilk test. Comparisons between groups were performed

using a student *t*-test for continuous variables by ethnicity (Arab vs. black), and χ2 test or Fisher's exact tests for categorical variables by ethnicity (Arab vs. black) and age, both within and between ECG interpretation criteria. A p value <0.05 was considered significant.

ROC analysis was used to describe the sensitivity and specificity of the 3 ECG interpretation criteria to identify cardiac pathology that may predispose to SCA/D in sports (Finocchiaro et al., 2016b). Echocardiography was used as the gold-standard test for the detection or exclusion of cardiac pathology that may predispose to SCA/D in sports. AUC represents diagnostic accuracy in differentiating athletes with cardiac pathology; interpreted as excellent (>0.90), good (0.80-0.90), fair (0.70-0.80), poor (0.60-0.70), or fail (<0.60) (Mehdi and Ahmadi, 2011). False positives were calculated from the specificity and sensitivity values of the 3 ECG interpretation criteria. Bayesian analysis was used to calculate the positive (+Likelihood Ratio [LR]) and negative likelihood ratios (-LR) from the specificity and sensitivity values of the ECG interpretation criteria, allowing estimation of the chance of cardiac pathology after application of the 3 ECG interpretation criteria. Specifically, the base prevalence rate was determined from the *pre-test odds*, and the +LR and –LR was used to compute the *post-test odds* (Whiteley, 2016).

5.2.6 INTER-INTRA OBSERVER VARIABILITY IN ECG INTERPRETATION

Inter- and intra-observer reproducibility for ECG interpretation using the new international recommendations, Seattle Criteria and ESC 2010 recommendations were assessed

using Cohen κ coefficient between two physiologists (GMC, NRR). Data were interpreted as poor (<0.20), fair (0.20-0.40), moderate (0.41-0.60), good (0.61-0.80) and very good (>0.80) (Altman, 1999). A power calculation using R package CIBinary determined that 361 athletes were sufficient to detect a 'good' reliability (0.75 95% CI (0.60-0.85) when prevalence of abnormalities was 5.9%. Type 1 error (to falsely infer the existence of something that is not there) was 5% and power was set 0.80 (also known as Type II error, to falsely infer the absence of something that is present). Inter- and intra-observer reliability was therefore conducted on 400 consecutive independent athletes. Inter-observer reliability for categorizing an ECG as abnormal was very good for ESC 2010 recommendations (k=0.85; 95% CI 0.71-0.99), very good for Seattle criteria (k=0.90; 95% CI 0.86-0.94), and very good for new international recommendations (k=0.90; 95% CI 0.88-0.92). Intra-observer reliability was very good for ESC 2010 recommendations (k=0.95; 95% CI 0.91-0.99), very good for Seattle criteria (k=0.91; 95% CI 0.78-1.00), and very good for new international recommendations (k=0.91; 95% CI 0.78-1.00).

5.3 RESULTS

5.3.1 DEMOGRAPHICS

Arab athletes descended from West-Asia [836; 80.3%], Africa [171; 19.5%], and Europe [2; 0.2%]. Black athletes descended from Africa [275; 64.2%], West-Asia [139; 32.5%], Central America [7; 1.6%], South America [5; 1.2%], and Europe [2; 0.5%]. Athletes participated in 33 different sports with football (50%) dominating. Mean chronological age (15.9 ± 2.0 vs. 15.2 ± 1.9 years, p<0.001) was significantly greater in Arab than black athletes, whilst BSA (1.7 ± 0.3 vs 1.7 ± 0.3 m^2, p=0.68) was not different (Table 5.1).

Table 5. 1 Anthropometric Data of Paediatric Athletes

Age group, years	Group	*n*	%	Height, cm	Body mass, kg	BSA, m^2
11-12	Total	117	9.0	152.8 ± 9.4	45.2 ± 11.0	1.38 ± 0.20
	Arab	91		151.1 ± 8.5	44.3 ± 9.5	1.36 ± 0.17
	Black	26		158.5 ± 10.4**	48.5 ± 15.1	1.45 ± 0.26†
13-14	Total	410	31.4	167.9 ± 9.5	58.3 ± 13.8	1.6 ± 0.23
	Arab	204		166.6 ± 9.7	58.1 ± 15.9	1.63 ± 0.25
	Black	206		169.2 ± 9.1*	58.6 ± 11.5	1.66 ± 0.19
15-16	Total	351	26.9	174.9 ± 9.6	67.3 ± 16.4	1.80 ± 0.25
	Arab	261		174.1 ± 8.6	66.7 ± 16.6	1.79 ± 0.25
	Black	90		177.2 ± 11.8**	69.0 ± 15.9	1.83 ± 0.25
17-18	Total	426	32.7	177.2 ± 8.6	70.5 ± 14.3	1.86 ± 0.22
	Arab	320		176.7 ± 8.0	70.4 ± 14.0	1.86 ± 0.12
	Black	106		178.6 ± 10.3	70.8 ± 15.2	1.87 ± 0.23

Values are mean ± standard deviation.

* p≤0.01, significantly more prevalent or greater in black than Arab athletes

*** p≤0.001, significantly more prevalent or greater in black than Arab athletes

† p≤0.01, significantly more prevalent or greater in Arab than black athletes

BSA, Body surface area.

5.3.2 HEALTH QUESTIONAIRE AND PHYSICAL EXAMINATION

Overall, 242 (18.6%; 20.2% Arab and 15.2% black) athletes revealed cardiovascular abnormalities identified by health questionnaire and/or physical examination. Specifically, 216 (16.6%; 18.3% Arab and 13.1% black) athletes self-reported cardiovascular medical issues; syncope (1.7% Arab vs. 0.5% black), arrhythmia (0.8% Arab vs. 0.9% black), chest pain/tightness (6.1% Arab vs. 5.1% black), palpitations (3.9% Arab vs. 2.6% black), and Family history of cardiomyopathy (0.6% Arab vs. 0.5% black), congenital heart disease (4.6% Arab vs. 1.8% black), and unexplained premature SCD (1.8% Arab vs. 4.7% black).

31 (2.4%; 2.1% Arab and 3.0% black) athletes demonstrated an abnormal physical examination. Specifically, cardiac murmur (1.9% Arab vs. 1.6% black), elevated blood pressure ≥140/90 mm Hg (0.1% Arab vs. 1.2% black) and stigmata of Marfan syndrome (0.08% Arab vs. 0.2% black).

5.3.3 ECG PATTERNS BETWEEN ETHNICITY USING NEW INTERNATIONAL RECOMMENDATIONS

5.3.3.1 Normal and borderline ECG findings

Normal ECG findings were significantly more frequent in black than arab athletes (93.0% vs. 88.7%; p≤0.001) (Figure 5.2). TWI in V_1-V_3 was observed in 69 (16.1%) black athletes compared to 56 (6.4%) Arab athletes aged <16 years old (p<0.0001). Borderline ECG findings, either in isolation or in association with a recognized training-related ECG

finding, were significantly more frequent in black than Arab athletes (11.0% vs. 7.4%; $p<0.05$), with an increased prevalence of isolated right atrial enlargement (8.9% vs. 5.1%; $p<0.01$).

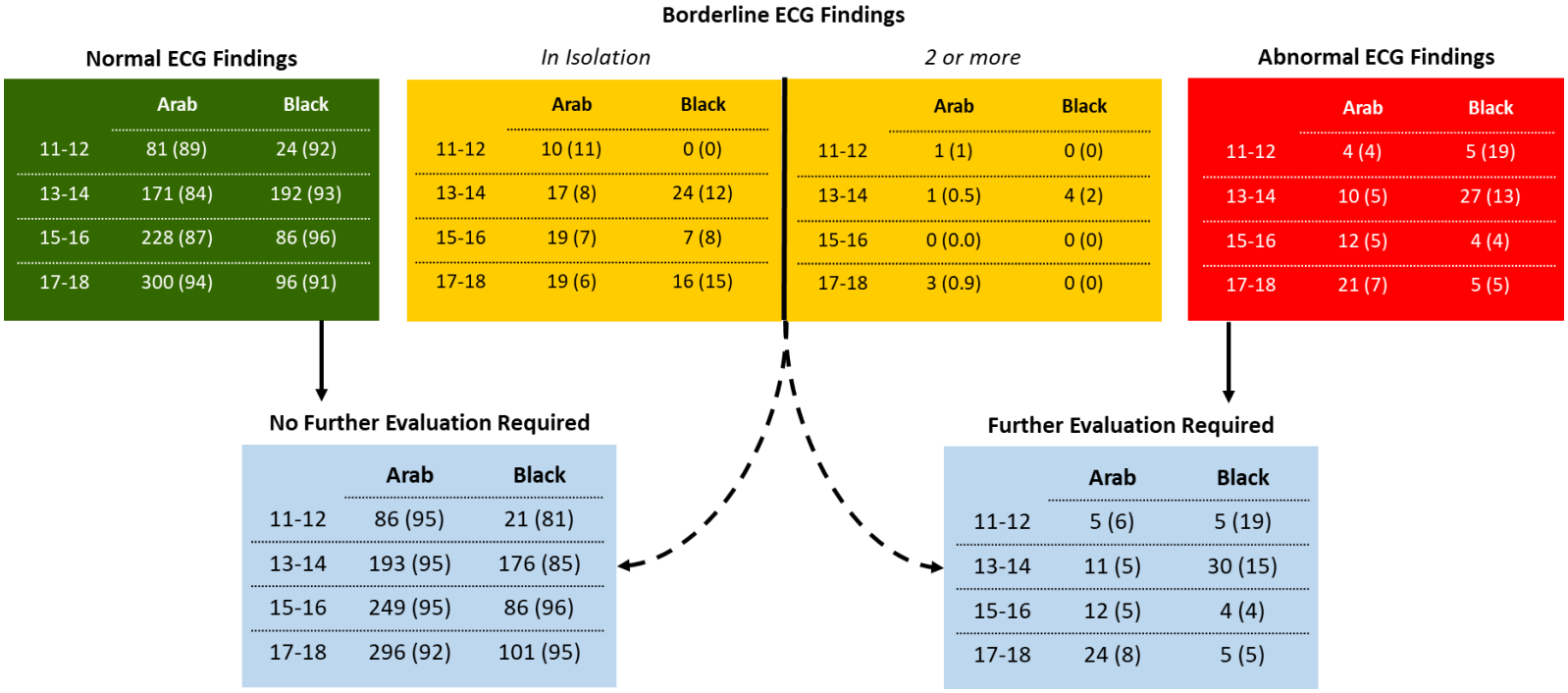

Figure 5. 2 Prevalence of normal, borderline and abnormal ECG findings by chronological age group for Arab and black paediatric athletes according to new international recommendations.

Key: Data are presented as n (%)

5.3.3.2 Abnormal ECGs findings

Abnormal ECGs that required further evaluation were more frequent in black than Arab athletes (10.5% vs. 6.1%; P<0.01). Specifically, abnormal TWIs were significantly more frequent in black than Arab athletes (7.0% vs. 2.1%, p<0.001); with an increased prevalence of both anterior (2.6% vs, 1.0%; P<0.05), and lateral (3.3% vs. 1.4%; p<0.05) TWI. Black athletes demonstrated a greater prevalence of pathological Q waves than Arab athletes (4.4% vs. 1.6%; p<0.01). Other abnormal ECG findings were rarely observed in paediatric athletes (≤1.3%), with no statistical difference observed between ethnicity.

5.3.4 IDENTIFICATION OF CARDIAC PATHOLOGY

Thirteen (1.0%, 95% CI 0.5-1.7) athletes were diagnosed with pathology that may predispose to SCA/D [8 (0.9%, 95% CI 0.4-1.8) Arab and 5 (1.2%, 95% CI 0.4-2.7) black] (Table 5.2). Of these 13, 6 (46.2%) demonstrated an abnormal health questionnaire and/or physical examination, 10 (76.9%) an abnormal ECG according to ESC 2010 recommendations, and 8 (61.5%) an abnormal ECG according to both the Seattle Criteria and the new international recommendations.

Table 5. 2 Characteristics of Athletes Diagnosed with Cardiac Pathology that may Predispose to Sudden Cardiac Death in Sports.

Pathology	Age	Ethnicity	Sport	HQ + PE Abnormality	ECG Abnormality	ESC 2010	Seattle	International	Diagnostics	Risk Stratification
Anomalous origin of left coronary artery	15	Arab	Football	Nil	Short PR interval	+	-	-	Echo, CMRI, CT	EST, Holter
ARVC	18	Black	Football	Family history of cardiomyopathy	TWI V_2-V_6	+	+	+	Echo, CMRI	EST, Holter
Aneurysm with aortic root dilatation (Z score 4)	12	Arab	Football	Nil	Nil	-	-	-	Echo, CMRI, CT	Gene Test
Aortic coarctation with aortic root dilatation (moderate [Valsalva Sinus – Z Score 3.06] to mild [ascending aorta – Z score 2.98]), BAV and moderate PR	18	Arab	Football	Murmur	Nil	-	-	-	Echo, CMRI, Angiogram	EST

HCM	13	Black	Football	Nil	TWI AVL, V_2-V_5 Q waves II, III, AVF, V_5, V_6	+	+	+	Echo, CMRI	EST, Holter, Gene Test
LVNC	13	Black	Football	Nil	TWI II, III, AVF, V_1-V_6 Q waves II, III, AVF, V_4 -V_6	+	+	+	Echo, CMRI	EST, Holter, Gene Test
MVP with severe MR, necessitating surgical repair	18	Black	800m runner	Murmur Chest Pain	Nil	-	-	-	Echo	-
Myocarditis, with anterolateral, lateral and inferolateral mid-wall fibrosis at basal level.	14	Arab	Football	Nil	TWI V_1-V_3	+	+	-	Echo, CMRI	EST, Holter

Myocarditis, with anterolateral, lateral and inferolateral mid-wall fibrosis at basal and mid ventricular level.	13	Arab	Golf	Family history of cardiomyopathy	TWI AVL, V_1 V_4-V_5	+	+	+	Echo, CMRI	EST, Holter
Myocarditis, with anterolateral and lateral mid-wall fibrosis at basal level.	16	Arab	Football	Syncope	TWI III, AVF, V_1, V_4-V_6	+	+	+	Echo, CMRI	EST, Holter
SVT with re-entry	14	Arab	Football	Nil	Short PR interval PVCs	+	+	+	Echo, CMRI	EST, Holter, EPS
WPW	13	Arab	Swimmer	Nil	Short PR interval Delta Wave Wide QRS	+	+	+	Echo	EST, Holter, EPS
WPW	13	Black	Football	Family history of SCA/D	Short PR interval Delta Wave Wide QRS	+	+	+	Echo, CMRI	EPS

	TWI AVL, V_1-V_4

ARVC; arrhythmogenic right ventricular cardiomyopathy; BAV; bicuspid aortic valve; CMRI; Cardiac Magnetic Resonance Imaging; ECG; 12-lead electrocardiogram; EST; Exercise Stress Testing; HQ + PE = history questionnaire and physical examination; HCM; hypertrophic cardiomyopathy; LVNC, left ventricular non-compaction; MVP; Mitral Valve Prolapse; MR; mitral regurgitation; PR; pulmonary regurgitation; SCA/D, sudden cardiac death; SVT, supraventricular tachycardia; TWI, T-wave inversion; WPW; Wolf-Parkinson-White syndrome.

5.3.5 FALSE POSITIVE RATES PER CRITERIA

The false positive rate for pathology that may predispose to SCA/D was 41.0% for the 2010 ESC recommendations, 21.8% for the Seattle criteria, and 6.8% for the new international recommendations (specifically, 5.5% and 9.5% for Arab and black athletes).

5.3.5 SPECIFIC FALSE POSITIVES PER CRITERIA

Ventricular pre-excitation was a false positive in 7.0% of athletes as per 2010 ESC recommendations (short PR interval with/without evidence of delta wave, measured in Lead II, V_3, or V_5) compared to zero cases using the Seattle criteria and new international recommendations (PR interval <120 ms with a delta wave (slurred upstroke in the QRS complex) and wide QRS [≥120 ms]). Reclassifying axis deviation, atrial enlargement and complete right bundle branch block (CRBBB) to be normal when observed in isolation or in association with a recognized training-related ECG finding, reduced false positive rates from 11.8% and 11.2% using the 2010 ESC recommendations and Seattle criteria, respectively, to 0.7% using the new international recommendations (Figure 5.3-5.5). The false positive rate for anterior TWI was 12.8% for 2010 ESC recommendations, 3.0% for Seattle criteria and 1.2% for new international recommendations.

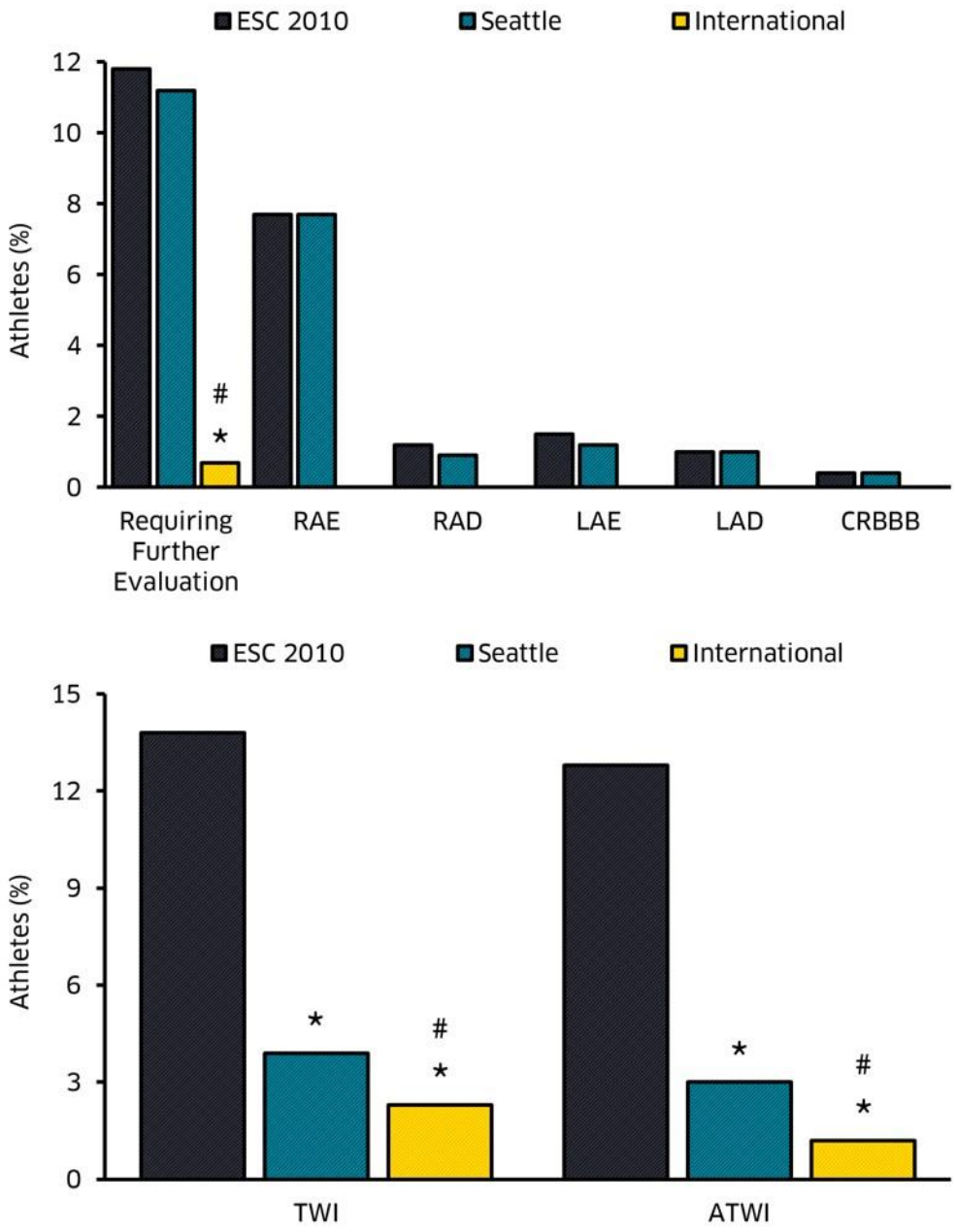

Figure 5. 3 Bar chart shows specific ECG false positives rates with reference to the 3 ECG interpretation criteria.

Key: ATWI, anterior T-wave-inversion; CRBBB, Complete right bundle branch block; LAD, left axis deviation; LAE, left atrial enlargement; RAD, right axis deviation RAE, right atrial enlargement.

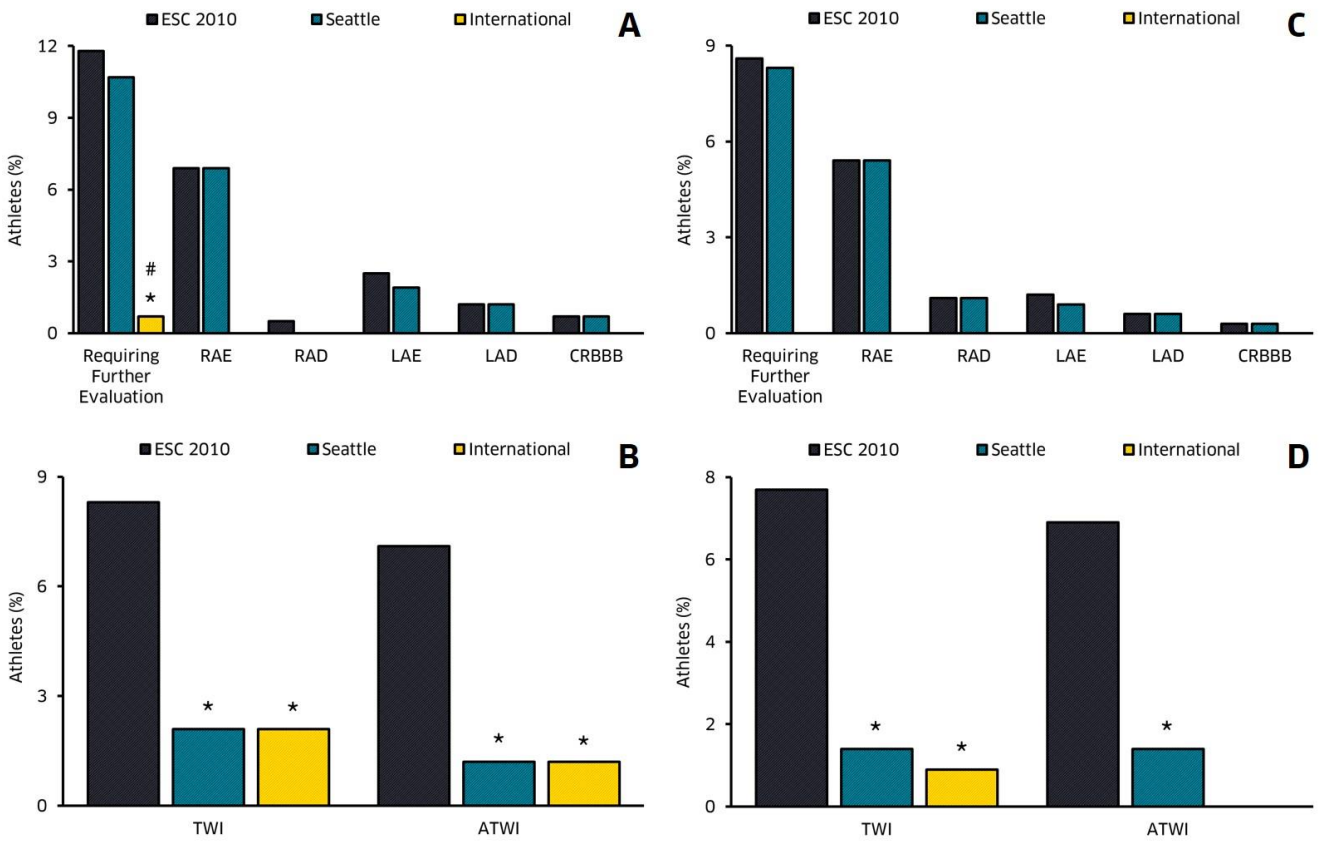

Figure 5. 4 Bar chart shows specific ECG false positives rates with reference to 3 ECG interpretation criteria, within athletes aged 17-18 years (A and B) and aged 15-16 years (C and D).

Key: ATWI, anterior T-wave-inversion; CRBBB, Complete right bundle branch block; LAD, left axis deviation; LAE, left atrial enlargement; RAD, right axis deviation RAE, right atrial enlargement.

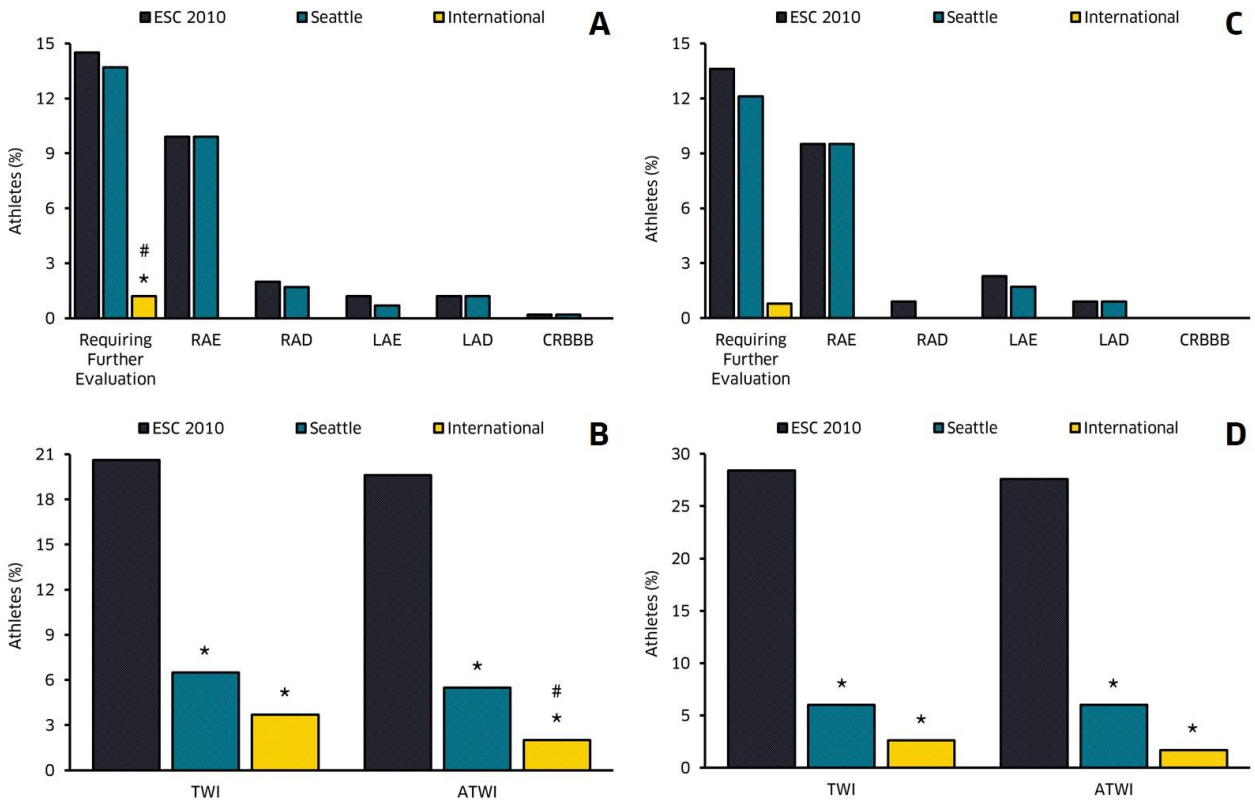

Figure 5. 5 Bar chart shows specific ECG false positives rates with reference to to 3 ECG interpretation criteria, within athletes aged 13-14 years (A and B) and aged 11-12 years (C and D).

Key: ATWI, anterior T-wave-invserion; CRBBB, Complete rigby bundle branch block; LAD, left axis deviation; LAE, left atrial enlargment; RAD, right axis deviation RAE, right atrial enlargement.

5.3.6 IMPACT OF CHRONOLOGICAL AGE ON FALSE POSITIVE RATES PER CRITIERA

New international ECG recommendations significantly (p<0.0001) reduced the false positive rate for pathology that may predispose to SCA/D compared to the Seattle Criteria and 2010 ESC recommendations in athletes aged ≤16 years (6.9% vs. 23.4% vs. 45.6%), ≤14 years (8.7% vs. 27.9% vs 52.7%), and ≤12 years (8.6% vs 29.3% vs 68.1%), respectively (Figure 5.6).

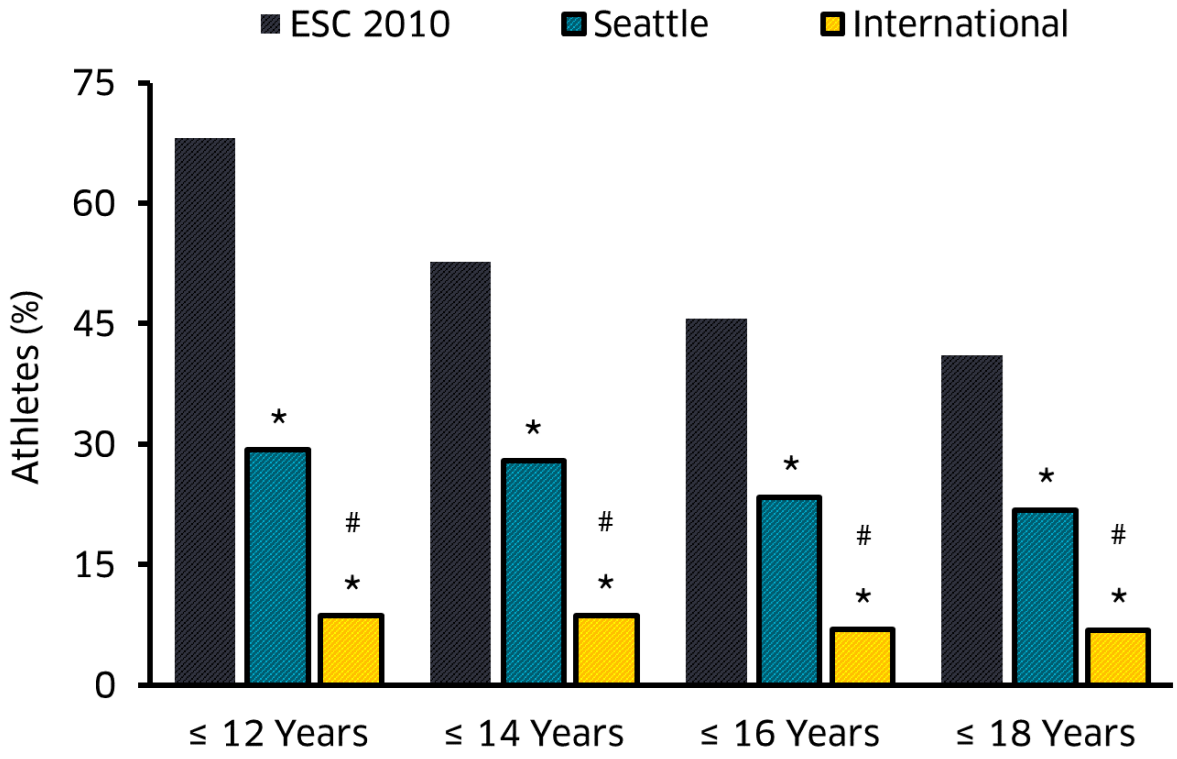

Figure 5. 6 Bar chart shows percentage of false positive ECG findings according to the 3 ECG interpretation criteria by chronological age.

*P <0.05, Significantly reduced prevalence to ESC 2010 recommendations.

# P <0.05, Significantly reduced prevalence to Seattle Criteria.

5.3.7 DIAGNOSTIC ACCURACY PER CRITIERA

For pathology that may predispose to SCA/D, diagnostic accuracy was poor [0.64, 95% CI 0.47-0.81] for health questionnaire and/or physical examination, poor [0.68, 95% CI 0.54-0.82] for the 2010 ESC recommendations, fair [0.70, 95% CI 0.54-0.85] for the Seattle criteria and fair [0.77, 95% CI 0.61-0.93] for new international recommendations (Figure 5.7, Table 5.3).

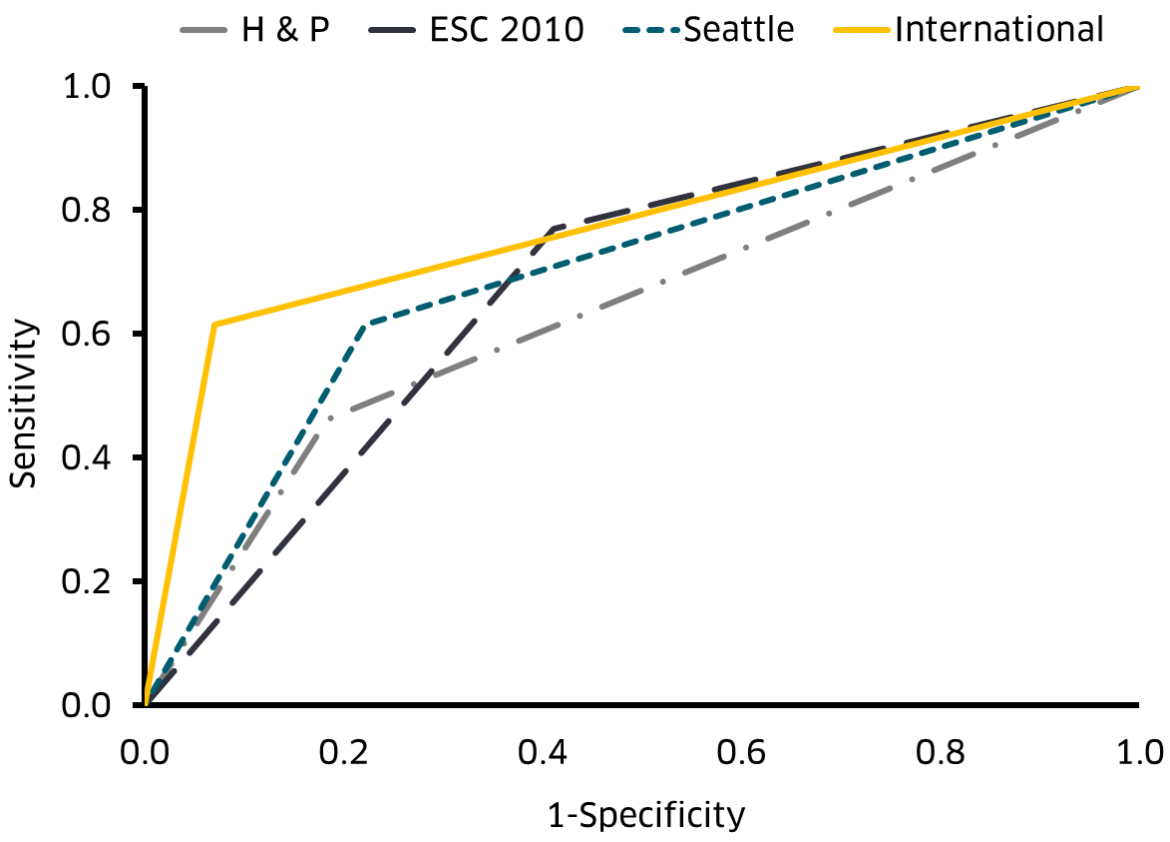

Figure 5. 7 Receiver-operating curves according to health questionnaire and/or physical examination and the 3 ECG interpretation criteria to detect cardiac pathology that may predispose to sudden cardiac death/arrest. Echocardiography was used as the gold-standard test for the detection or exclusion of cardiac pathology **that may predispose to SCA/D**.

Table 5. 3 Positive and Negative Likelihood Ratios of Three ECG Interpretation Criteria to Detect Cardiac Pathology that may Predispose to Sudden Cardiac Death/Arrest only

	Combined Athletes (n=1304)			Arab Athletes (n=876)			Black Athletes (n=428)		
	ESC 2010	Seattle Criteria	International Criteria	ESC 2010	Seattle Criteria	International Criteria	ESC 2010	Seattle Criteria	International Criteria
Sensitivity,%	76.9 (46.2-95.0)	61.5 (31.6-86.1)	61.5 (31.6-86.1)	75.0 (34.9-96.8)	50.0 (15.7-84.3)	50.0 (15.7-84.3)	80.0 (28.4- 99.5)	80.0 (28.4-99.5)	80.0 (28.4-99.5)
Specificity, %	59.0 (56.3-61.7)	78.2 (75.9-80.5)	93.2 (91.7-94.5)	62.4 (59.1-65.7)	79.7 (76.9-82.4)	94.5 (92.7-95.9)	52.0 (47.1-58.9)	75.2 (70.8-79.2)	90.5 (87.4-93.2)
AUC	0.68 (0.54-0.82)	0.70 (0.54-0.85)	0.77 (0.61-0.93)	0.69 (0.51-0.86)	0.65 (0.44-0.86)	0.72 (0.50-0.94)	0.66 (0.44-0.88)	0.77 (0.57-0.98)	0.85 (0.65-1.00)
+ve Likelihood Ratio	1.9 (1.2-2.3)	2.7 (1.6-3.9)	9.0 (5.1-13.1)	2.0 (1.1- 2.5)	2.5 (1.1-4.0)	9.0 (3.8-15.8)	1.7 (0.8-2.1)	3.2 (1.5-4.3	8.5 (3.8-12.5)
-ve Likelihood Ratio	0.4 (0.1-0.9)	0.5 (0.2-0.8)	0.4 (0.2-0.7)	0.4 (0.1- 0.9)	0.6 (0.3-1.0)	0.5 (0.2-0.8)	0.4 (0.07-1.2)	0.3 (0.05-0.8)	0.2 (0.04-0.7)

+ve Post-Test Chance of Pathology, %	1.9 (0.9-3.4)	2.7 (1.2-5.3)	8.3 (3.3-14.3)	1.8 (0.7- 3.9)	2.3 (0.6-5.6)	7.7 (2.1-18.2)	2.0 (0.5-4.8)	3.8 (1.0-8.8)	8.1 (2.1-18.2)
-ve Post-Test Chance of Pathology , %	0.4 (0.08-1.2)	0.5 (0.2-1.2)	0.4 (0.1-1.0)	0.4 (0.04-1.3)	0.5 (0.2-1.5)	0.5 (0.1-1.2)	0.5 (0.01-2.5)	0.4 (0.0-1.8)	0.2 (0.0-1.5)

Data are presented as % (95 % CI)

AUC, area under the curve; +ve, positive; -ve, negative.

5.3.8 CLINICAL IMPLICATION OF USING THE NEW INTERNATIONAL RECCOMENDATIONS

New international recommendations provided an overall +ve and -ve LR of 9.0 (95% CI 5.1-13.1) and 0.4 (95% CI 0.2-0.7), respectively. When split by ethnicity, 9.0 (95% CI 3.8-15.8) and 0.5 (95% CI 0.2-0.8) for Arab, and 8.5 (95% CI 3.8-12.5) and 0.2 (95% CI 0.04-0.7) for black athletes, respectively.

5.4 DISCUSSION

The correct differentiation of physiological cardiac adaptation owing to sustained and intensive exercise from an inherited cardiac pathology is paramount to correctly identify athletes at risk of SCA/D. In this study of 876 Arab and 428 black male paediatric athletes, it was observed that new international ECG recommendations significantly reduce false positive rates by 83.4% and 68.7% respectively when compared to the Seattle criteria and 2010 ESC recommendations, irrespective of chronological age, whilst yielding a 'fair' diagnostic accuracy for conditions that may predispose to SCA/D. To place new international recommendations into clinical context, the 'chance' of detecting cardiac pathology that predispose to SCA/D within a paediatric male athlete is approximately 1%. A positive ECG (+LR=9.0) as per new international recommendations, means that the same athlete now has an 8.3% 'chance' of pathology, whereas a negative ECG (-LR=0.4) has a 0.4% 'chance'.

5.4.1 DIAGNOSTIC ACCURACY OF NEW INTERNATIONAL RECCOMENDATIONS IN PAEDIATRIC ARAB AND BLACK ATHLETES

When applying the 2010 ESC recommendations to our athletes, almost 1 in 3 Arab and 1 in 2 black athletes would warrant further evaluation, demonstrating a poor (0.68) AUC (diagnostic accuracy). The Seattle criteria improved these rates to 1 in 5 Arab and 1 in 4 black athletes, with a fair (0.70) overall diagnostic accuracy. While the 2010 ESC recommendations are based upon consensus rather than scientific evidence, the Seattle Criteria modified its interpretation criteria by applying evidence that 1) accounted for black ethnicity (J-point elevation and convex ['domed'] ST-segment elevation followed by TWI in leads V_1–V_4), a false positive in 6.9% of our black paediatric athletes and 2), by adjusting ventricular pre-excitation criteria to require a concomitant delta wave (slurred upstroke in the QRS complex) and wide QRS (>120ms) in addition to a short PR (<120ms), a false positive in 7.0% of our paediatric athletes. However, we acknowledge, upper limits of QRS duration defined within the paediatric non-athlete (Rijnbeek et al., 2008), are 103 ms and 111 ms among males aged 8-12 and 12-16 years, respectively. It is therefore possible that we may have missed cases of ventricular pre-excitation in the paediatriac athlete ≤16 years who presented with a slurred upstroke in the QRS complex in addition to a short PR (<120ms), but in the absence of a QRS duration meeting criteria defined by 95th centile in adults.

To further reduce false positive ECG rates and improve diagnostic accuracy, new international recommendations now categorize the presence of atrial enlargement (8.9% in our athletes), axis deviation (1.9% in our athletes), and CRBBB (0.4% in our athletes),

as ‘borderline’ findings when observed in isolation or in association with a recognized training-related ECG change, as they correlate poorly with cardiac pathology predisposing to SCA/D in sport (Gati et al., 2013; Zaidi et al., 2013b) (Figure 5.1). Our data supports these recommendations, by observing 112 athletes (8.6%) with isolated borderline ECG findings, and just 9 athletes (0.7%) with ≥2 borderline ECG findings that would trigger additional investigation; with none found to have pathology predisposing to SCA/D in sports (Figure 5.2 and 5.3). False positive rates were again further reduced by deeming the juvenile T-wave pattern to be physiological, a false positive in 121 (17.3%) athletes aged <16 years compared to 36 (6.1%) athletes ≥16 years. In real terms, when new international recommendations are applied to our athletes, 1 in 17 Arab and 1 in 10 black athletes would warrant further evaluation, with a fair (0.77) overall diagnostic accuracy [specifically, a fair (0.72) diagnostic accuracy for Arab but importantly, a good (0.85) diagnostic accuracy for black athletes]. In application, when presented with an asymptomatic paediatric athlete with no family history of inherited cardiac disease or SCD and a normal ECG as per new international recommendations, a need for further diagnostic evaluation owing to a sensitivity of 61.5%, is subject to the available resources of the attending clinician and/or cardiac screening requirements of the sporting team or institutional standard/league policy.

5.4.2 CLINICAL APPLICATION OF NEW INTERNATIONAL RECOMMENDATIONS IN PAEDIATRIC ARAB AND BLACK ATHLETES

Our data confirm that like their adult counterparts (4.9%) (Riding et al., 2014b), a comparable proportion of paediatric athletes demonstrate a false positive ECG (6.9%) when utilizing similar ECG criteria; a result observed irrespective of chronological age

(≤16 years [7.6%] vs. ≤14 years [9.6%] vs. ≤12 years [8.6%]. This finding is important as the ESC state that ECG screening should start at the beginning of competitive athletic activity, which for the majority of sporting disciplines corresponds to an age of 12–14 years (Corrado et al., 2005a). Whilst this low false positive rate is reassuring, care is warranted however, if considering the sensitivity of ECG screening. Dhutia et al. (2017) diagnosed 15 athletes (from 4,925 screened; 0.3%) with cardiac pathology that may predispose to SCA/D, all of whom presented with an abnormal ECG according to new international recommendations (i.e. 100% sensitivity). We diagnosed 13 athletes with cardiac pathology that may predispose to SCA/D, of which just 8 (61.5% sensitivity) had an abnormal ECG according to new international recommendations (Table 5.2). However, the ECG is unable to detect anomalous coronary arteries (n=1), aortopathies (n=2) and valvular disease (=1) (Drezner et al., 2017; Sharma et al., 2017b, 2018), and thus helps explain the reduced sensitivity observed. In line with previous literature (Harmon et al., 2015b), we confirm that medical questionnaires and/or physical examinations were associated with poor sensitivity (46.2%) for conditions predisposing to SCA/D.

Bayesian analysis allows for the quantification of 'chance' that a patient with an abnormal or normal ECG will have a cardiac pathology that may predispose them to SCA/D (Whiteley, 2016). As the first study to apply Bayesian analysis in any young athletic population, our data demonstrates that baseline 'chance' of having cardiac pathology predisposing to SCA/D was 1% for the entire cohort. The findings presented here show that a positive ECG has a +LR=9.0 meaning that the same athlete with a positive test has an 8.3% 'chance' of cardiac pathology. Conversely, an athlete with a negative ECG (-

LR=0.4) would have an 0.4% chance. Our analysis also demonstrate that the new international recommendations provide a greater positive likelihood (+LR=9.0) compared to the 2010 ESC recommendations (+LR=1.9) and the Seattle Criteria (+LR=2.7), respectively (Table 5.3).

5.4.3 LIMITATIONS

Our results are based on observational cross-sectional data, and thus we may have underestimated prevalence of cardiac pathology that may predispose to SCA/D in sport, since it is recognized that gene carriers of inherited cardiac pathology may not exhibit phenotype evidence until early adulthood. Secondly, our population were exclusively Arab and black male athletes, limiting application to other ethnicities and the female paediatric athlete. Finally, whilst we only recruited athletes who were registered with the Qatar Olympic Committee exercising ≥6 hours/week, we did not define fitness (such as aerobic capacity).

5.4.4 CONCLUSION

In conclusion, new international ECG interpretation recommendations for athletes outperform both the Seattle criteria and 2010 ESC recommendations by reducing false positive rates in Arab and black paediatric male athletes, whilst yielding a ‘fair’ diagnostic accuracy for conditions that may predispose to SCA/D in sports Interpretation of the paediatric athletes ECG by new international recommendations provides the best likelihood of triggering further evaluation in the attempt to detect cardiac pathology

CHAPTER 6:

PREVALENCE AND SIGNIFICANCE OF T-WAVE-INVERSION IN ARAB AND BLACK PAEDIATRIC ATHLETES; SHOULD ANTERIOR T-WAVE INVERSION INTERPRETATION BE GOVERNED BY BIOLOGICAL OR CHRONOLOGICAL AGE?

McClean, G., Riding, N.R., Pieles, G., Sharma, S., Watt, V., Adamuz, C., Johnson, A., Tramullas, A., George, K.P., Oxborough, D. and Wilson, M.G., (2019) Prevalence and significance of T-wave inversion in Arab and Black paediatric athletes: Should anterior T-wave inversion interpretation be governed by biological or chronological age? European Journal of Preventive Cardiology, [online] 266, pp.641–652. Available at: http://journals.sagepub.com/doi/10.1177/2047487318811956.

6.1 INTRODUCTION

TWI may represent the only sign of cardiac pathology predisposing to SCD/A without phenotypic manifestation on secondary investigation (Wilson *et al.*, 2012). Whilst lateral, inferolateral and inferior TWI are universally recognised as abnormal, new international recommendations for ECG interpretation in athletes regard anterior TWI (ATWI) in V_1–V_4

when preceded by J termination (Jt) and/or ST-segment elevation in black athletes, in V_1–V_3 when chronological aged <16 years, and biphasic in V_3 only, to be normal and does not require further evaluation in the absence of other clinical or ECG features suggestive of cardiomyopathy (Sharma et al., 2018).

Prior work within white athletes recognizes ATWI extending beyond V_2 to be rare in those aged ≥16 years (0.1%) (Papadakis et al., 2009) and beyond V_3 with complete pubertal development (1.6%) (Migliore et al., 2012). Subsequently, 16 years marks the cut off (TWI in V_1–V_3) for new international ECG interpretation recommendations. Additional work within white and black adult athletes demonstrates that detailed assessment of Jt and/or ST-segment amplitude preceding ATWI can accurately discriminate physiological adaptation from cardiomyopathy, independent of ethnicity (Calore et al., 2016). Yet, the appropriateness of such assessments in Arab and black paediatric athletes is unknown. Unlike chronological age, maturation status is not linear; varying in extreme cases by six years between two 9-year-old males (Johnson et al., 2009). Previous investigators have considered maturational status when interpreting an ECG (Migliore et al., 2012) but used Tanner staging assessment (Marshall and Tanner, 1970), now regarded as inappropriate due to child protection concerns. Furthermore, self-assessment yields poor validity (27%) (Schmitz, 2004). Alternatively, skeletal age (biological age) assessment via radiological hand-wrist X-ray examination is recognised by the IOC as the ‘gold standard’ estimate of maturity status (Engebretsen et al., 2010). To interpret presentation of ATWI in clinical context, especially when there is no ‘gold standard’ test to identify cardiac pathology, Bayesian analysis allows for the quantification of ‘chance’ of pathology as per

examination methodology (in this case, ECG interpretation), based upon *pre-* and *post-test odds* (Whiteley, 2016).

Accordingly, our primary aim was to identify the prevalence, distribution, and determinants of TWI by ethnicity, chronological and biological age within a large cohort of Arab and black paediatric athletes. Secondarily, we aimed to establish diagnostic accuracy of new international ECG recommendations against refinement in paediatric athletes who present ECG variants isolated to ATWI (V_1-V_4,) by ROC analysis. Clinical context was calculated using Bayesian analysis.

6.2 METHODS

6.2.1 ETHICAL APPROVAL

Ethical approval was provided by Anti-Doping Laboratory Qatar (IRB #E2013000003 and #E20140000012), with all parents/guardians providing informed consent, as detailed in chapter 3.

6.2.2 PARTICIPANTS

Between 2009-2017, 418 Arab and 314 black male paediatric athletes registered with the Qatar Olympic Committee [exercising ≥6 hours/week, aged 11-18 years.] presented at our institution for ECG screening. Ethnicity was self-determined by the athlete (or guardian) in accordance to definitions offset by the UK government's statistical service (Harmonised concepts and questions for social data sources, GSS Harmonised Principle:

Ethnic group). Based on 2-year chronological age categories participants' demographic distribution is described in Table 6.1. Whilst we acknowledge ECG interpretation criteria were developed for athletes aged 12-35 years (Sharma et al., 2018), a minority of athletes <12 years presented at the request of the Qatar Olympic Committee.

6.2.3 PRELIMINARY INVESTGATIONS

6.2.3.1 Health questionnaire and physical examination

Athletes completed a health questionnaire (with primary guardians) regarding family history of cardiovascular disease and personal symptoms, together with anthropometric (height and body mass; BSA (Haycock et al., 1978)) and left brachial artery blood pressure assessment in collaboration with an Arabic, French, and/or English-speaking nurse. Precordial auscultation in supine and standing positions and assessment for underlying congenital or syndromal disorders were undertaken by a sports medicine physician.

6.2.3.2 Resting 12-lead ECG

ECG was recorded with standard 12-lead positions using a GE Mac 5500 (New York, USA). All 732 ECGs were retrospectively interpreted by GMC applying new international recommendations (Sharma et al., 2018), whilst blinded to pathology. ECG variants isolated to ATWI (V_1-V_4), were secondarily interpreted by: Jt and/or ST-segment elevation irrespective of ethnicity and biological age <16 years when confined to V_1-V_3.

The amplitude of the J *termination* (Jt) (Macfarlane et al., 2015) was measured at the end of the QRS complex (the onset of the ST-segment) with reference to the onset of the QRS complex and was considered elevated if Jt ≥0.1mV or depressed if Jt ≤-0.1 mV (Figure 6.1). The ST-segment was considered elevated if the amplitude of the ST-segment 100ms after Jt (interval M) were greater than the amplitude at Jt, depressed if below and isoelectric if in line with the Jt.

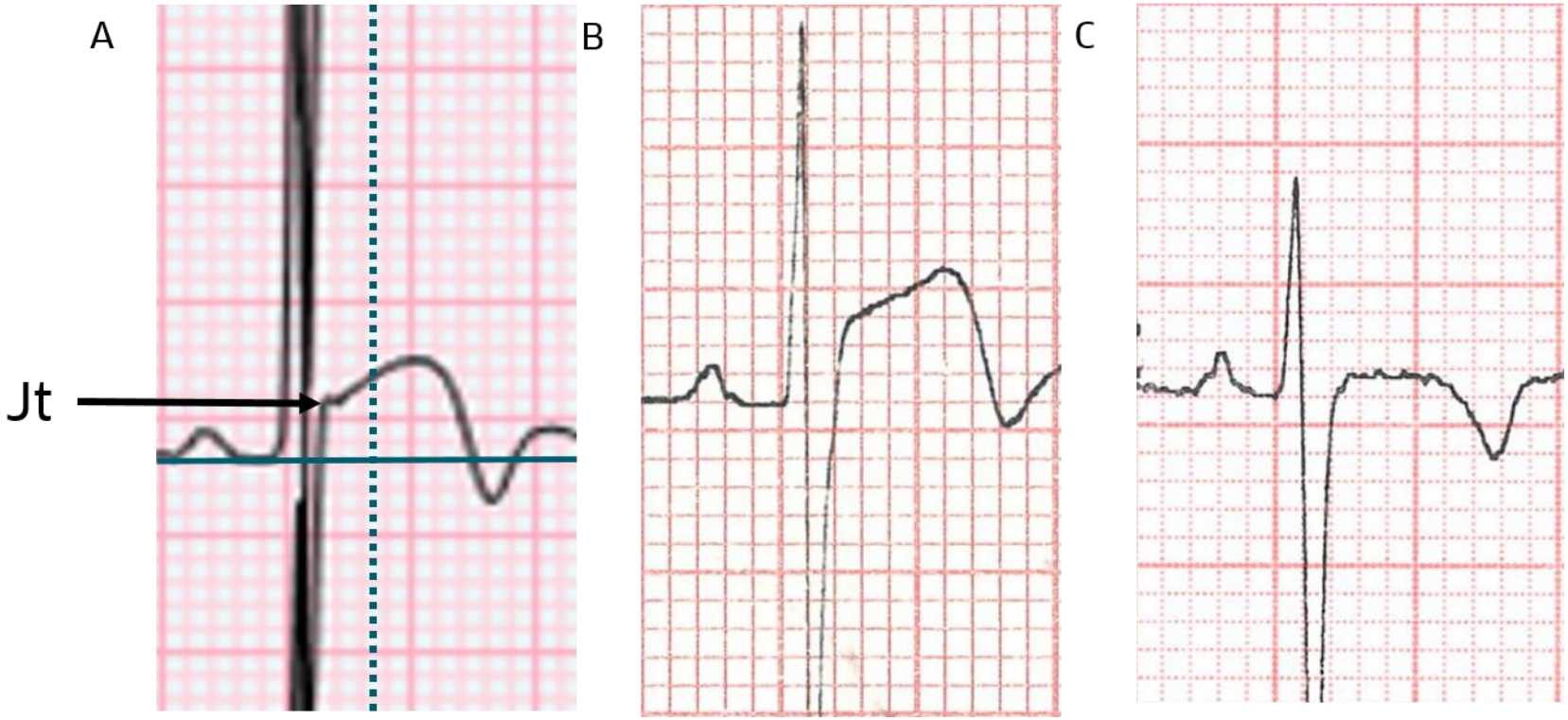

Figure 6. 1 Measurement of J *termination* (Jt) elevation and classification of ST-segment morphology, preceding anterior T wave-inversion. (A) The horizontal dashed line through the onset of the QRS complex, acted as a reference for the measurement of J *termination* (Jt). The vertical dashed line defines the M interval (100ms). ST-segment morphologies are shown as the following: (B) ascending convex, and (C) isoelectric.

6.2.3.3 Echocardiography

2D transthoracic echocardiographic examination was performed using IE33 (Philips, USA) and Artida (Toshiba Medical Systems, Japan) ultrasound systems. Standard views were obtained and analysed for left and right ventricular wall thickness and cavity dimensions as well as the identification of the origins of the left and right coronary arteries in accordance with current guidelines (Lopez et al., 2010b).

6.2.3.4 Chronological and Biological Age Assessment

Chronological age was calculated as the difference between date of birth as per passport and date of examination. Radiological hand-wrist imaging using a Digital Diagnost (Philips, USA) of the left hand-wrist allowed biological age estimation by the Fels method (Roche et al., 1988), by a single examiner with previously demonstrated intra-class correlation coefficient of 0.998 (Johnson et al., 2009). Radiation exposure is considered almost negligible (0.00017 millisievert); corresponding to 1 hour of background radiation from major cities in the UK (Blake, 1998; Huda and Gkanatsios, 1998).

6.2.4 FURTHER INVESTIGATIONS

Athletes presenting with an abnormal health questionnaire, physical examination, ECG or echocardiographic examination suggestive of underlying cardiovascular pathology were invited for further evaluation. Subsequent examinations may have included 24h-ECG or ambulatory blood pressure monitoring, maximal cardiopulmonary exercise testing, electrophysiology study, computerized tomography and cardiac magnetic

resonance imaging. Diagnosis of disease was established and managed in accordance to guidelines (Jenni, 2001; Brothers et al., 2009; Friedrich et al., 2009; Marcus et al., 2010; Cohen et al., 2012b; Elliott et al., 2014; Nishimura et al., 2014).

6.2.5 STATISTICAL ANALYSIS

Data were expressed as mean (±SD) or percentages as appropriate and analysed with SPSS software (Version 21.0, Chicago, IL). Continuous variables were tested for normality using the Shapiro-Wilk test. Comparisons between groups were performed using a student *t*-test for continuous variables by ethnicity (Arab vs. black), and χ^2 test or Fisher's exact tests for categorical variables by ethnicity (Arab vs. black), and biological age (<16 vs. ≥16 years). Z tests, adjusted for Bonferroni (P≤0.05), allowed for multiple comparisons to explain the effect of biological age (10-12 years. vs. 13-14 years. vs. 15-16 years. vs. 17-18 years.), within ethnicity, upon the prevalence of TWI by territory. Univariate and multivariate binomial logistic regression was used to determine which factors (black ethnicity, chronological, or biological age <16 years) were significantly associated with the presence of TWI by territory; calculated from those with no identified cardiac pathology. New international recommendations (Sharma et al., 2018) guided selection of chronological and biological age of <16 years.

ROC curve analysis was used to describe the sensitivity and specificity of ECG interpretation criteria to identify cardiac pathology that may predispose to SCA/D (Finocchiaro et al., 2016b). AUC represented diagnostic accuracy in differentiating

athletes with cardiac pathology; interpreted as excellent (>0.90), good (0.80-0.90), fair (0.70-0.80), poor (0.60-0.70), or fail (<0.60) (Mehdi and Ahmadi, 2011). Positive (+LR) and negative likelihood ratios (-LR) were calculated from the specificity and sensitivity values of ECG interpretation criteria, to allow estimation of 'chance' of cardiac pathology, after application of ECG interpretation criteria. Specifically, base prevalence rate was determined from the *pre-test odds*, and the +LR and –LR was used to compute the *post-test odds* (Whiteley, 2016).

6.3 RESULTS

6.3.1 DEMOGRAPHICS

Arab athletes descended from West-Asia (85.8%), Africa (14.0%), and North America (0.2%). Black athletes descended from Africa (66.2%), West-Asia (30.6%), and Central America (3.2%). Athletes participated in 26 different sports, with football (60.5%) dominating. Whilst chronological age (14.6 ± 2.0 vs. 14.2 ± 1.5, years, $p<0.01$), and BSA (1.63 ± 0.22 vs. 1.59 ± 0.29, m^2, $p<0.05$) were significantly greater in Arab than black athletes, biological age (16.6 ± 1.7 vs. 15.7 ± 2.1, years, $p<0.001$) was significantly greater in black than Arab athletes (Table 6.1).

Table 6. 1 Anthropometric Data of Paediatric athletes

Chronological age group, years	Group	*N*	%	Biological age, years	Height, cm	Body mass, kg	BSA, m^2
11-12	Total	147	20.1	13.4 ± 1.4	151.6 ± 8.8	44.3 ± 10.7	1.36 ± 0.19
	Arab	111		13.2 ± 1.3	150.1 ± 7.8	43.2 ± 9.0	1.34 ± 0.16
	Black	36		13.8 ± 1.6*	156.1 ± 10.1**	47.4 ± 14.4	1.42 ± 0.25*
13-14	Total	355	48.5	16.2 ± 1.6	166.3 ± 9.5	128.8 ± 56.1	1.60 ± 0.21
	Arab	148		15.5 ± 1.5	163.3 ± 10.2	54.6 ± 14.5	1.56 ± 0.24
	Black	207		16.8 ± 1.4***	168.7 ± 8.3***	57.4 ± 10.4	1.63 ± 0.18**
15-16	Total	135	18.4	17.3 ± 1.1	172.3 ± 8.6	64.8 ± 18.6	1.75 ± 0.28
	Arab	92		17.4 ± 0.9	173.2 ± 8.6	66.9 ± 20.0	1.78 ± 0.29
	Black	43		17.2 ± 1.3	170.1 ± 8.1	60.0 ± 13.7	1.67 ± 0.22
17-18	Total	95	13.0	17.8 ± 0.5	174.3 ± 6.8	70.0 ± 10.4	1.8 ± 0.2
	Arab	67		17.9 ± 0.5	174.5 ± 7.1	66.7 ± 9.5	1.79 ± 0.15
	Black	28		17.8 ± 0.5	173.9 ± 6.2	67.7 ± 12.3	1.80 ± 0.18

Values are mean ± standard deviation; BSA, Body surface area.

*p≤0.05, significantly more prevalent or greater in black than Arab athletes

** p≤0.01, significantly more prevalent or greater in black than Arab athletes

*** p≤0.001, significantly more prevalent or greater in black than Arab athletes

6.3.2 ABNORMAL ECG FINDINGS

Abnormal ECGs that required further evaluation were more frequent in black than Arab athletes (12.1% vs. 4.3%, P<0.001) (Figure 6.2). Specifically, 5.1% and 2.2% of black and Arab athletes, presented an abnormal TWI according to new international recommendations, with a diagnostic yield for cardiac pathology of 3.0% and 3.4%, respectively.

6.3.3 HEALTH QUESTIONAIRE AND PHYSICAL EXAMINATION

Overall 77 (10.5%) athletes revealed cardiovascular abnormalities identified by health questionnaire and/or physical examination. Specifically, 56 (7.7%; 7.7% Arab and 7.6% black) athletes self-reported cardiovascular medical issues; syncope (0.7% Arab vs. 0% black), arrhythmia (0.2% Arab vs. 1.0% black), chest pain/tightness (0.2% Arab vs. 0.0% black), palpitations (0.5% Arab vs. 0.3% black), and family history of congenital heart disease/cardiomyopathy (2.6% Arab vs. 0.3% black), and unexplained premature SCD (2.6% Arab vs. 5.7% black).

25 (3.4%; 1.7% Arab and 5.7% black) athletes demonstrated an abnormal physical examination. Specifically, cardiac murmur (1.2% Arab vs. 1.0% black), and elevated blood pressure ≥140/90 mm Hg (0.5% Arab vs. 4.8% black).

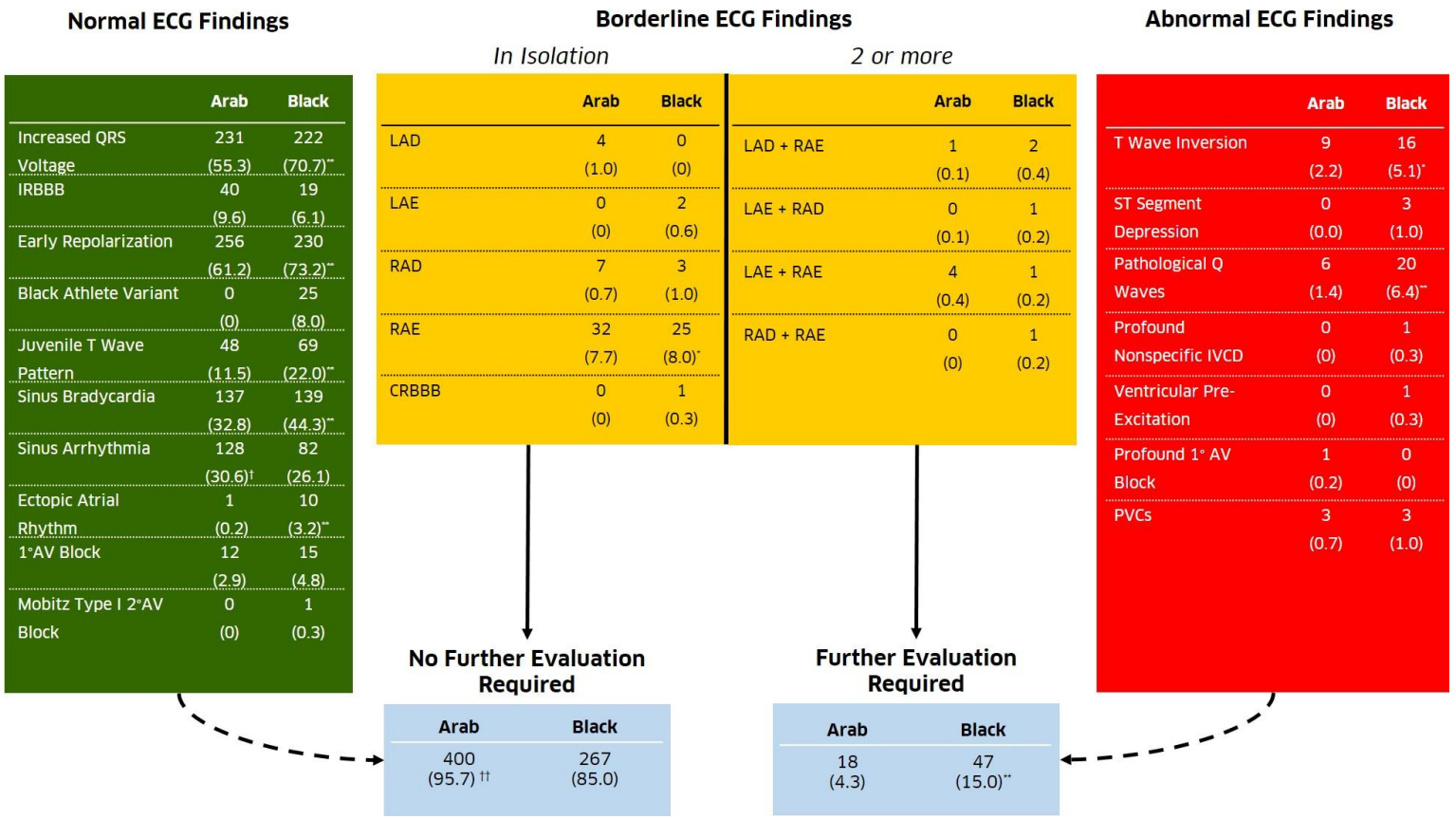

Figure 6. 2 New international recommendations for ECG interpretation in Arab and black paediatric athletes.

Key: data are presented as n (%). AV, atrioventricular; CRBBB, complete right bundle branch block; CLBBB, Complete left bundle branch block; IRBBB, Incomplete right bundle branch block; IVCD, intraventricular conduction delay; LAD, left axis deviation; LAE, left atrial enlargement; RAD, right axis deviation; RAE, right atrial enlargement; PVCs, premature ventricular contractions.

*p≤0.05, significantly more prevalent in black than Arab athletes' ** p≤0.001, significantly more prevalent in black than Arab athletes; † p≤0.05, significantly more prevalent in Arab than black athletes; †† p≤0.001, significantly more prevalent in Arab than black athletes.

6.3.4 PREVALENCE OFATWI (V_1-V_4)

Overall, 116 (15.8%) paediatric athletes presented ATWI (V_1-V_4), of which 96 (82.8%) were observed in the absence of other ECG findings considered to be abnormal as per new international recommendations for ECG interpretation in athletes. Prevalence was more common in athletes biologically aged <16 than ≥16 years (18.8% vs. 13.6%, $p<0.05$), and in black than Arab athletes (23.2% vs. 10.3%, $p<0.0001$).

6.3.5 DISTRIBUTION OF ATWI

Ninety-one (12.4%) athletes presented with ATWI confined to V_1-V_3, constituting 79.3% of all ATWI cases (Figure 6.3). A further 25 (3.4%) athletes exhibited ATWI beyond V_3, with prevalence similar in athletes biologically aged ≥16 and <16 years, but more common in black than Arab athletes (7.0% vs. 0.7%, $p<0.001$). Prevalence was similar across biological age groups for black athletes (10-12 years. [7.1%], 13-14 years. [4.0%], 15-16 years. [5.6%] and 17-18 years. [8.4%]) compared to zero cases in Arab athletes biologically aged >14 years (Table 6.2).

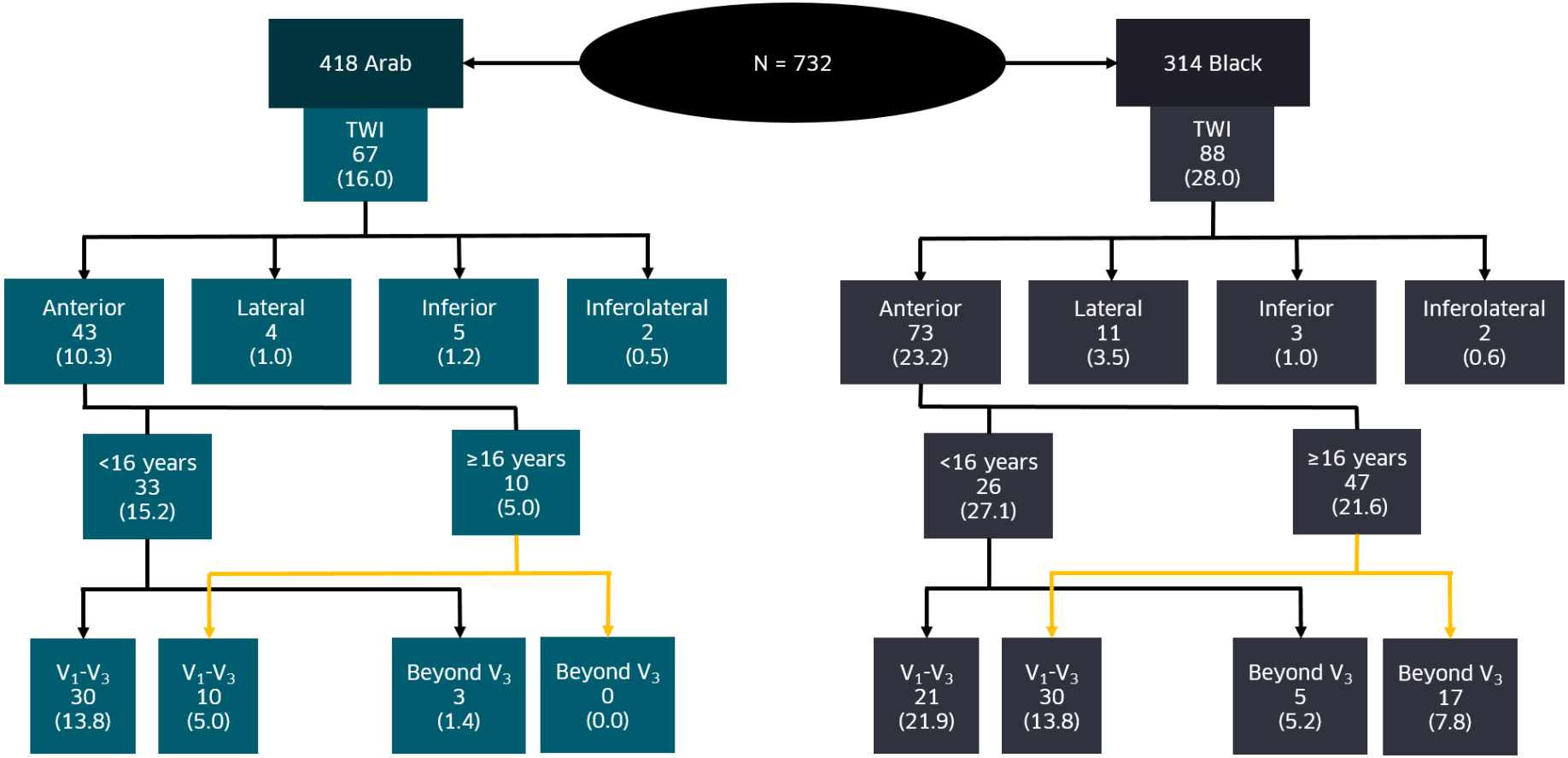

Figure 6. 3 Prevalence and distribution of T-wave inversion in both Arab and black by biological age. Numbers in brackets express percentages (%) of each cohort.

Table 6. 2 Athletes with TWI by Biological Age Group within Ethnicity and by Territory

	Arab	Black	Arab	Black	Arab	Black	Arab	Black
	10-12 years		13-14 years		15-16 years		17-18 years	
	n=52	n=14	n=122	n=50	n=66	n=72	n=178	n=178
Anterior								
V_1-V_3	7 (13.5)	2 (14.3)	20 (16.4)†	13 (26.0)	3 (4.5)	10 (13.9)	10 (5.6)	26 (14.6)*
Beyond V_3	2 (3.8)	1 (7.1)	1 (0.8)	2 (4.0)	0 (0)	4 (5.6)	0 (0)	15 (8.4)*
Lateral	2 (3.8)	0 (0)	0 (0)	1 (2.0)	2 (3.0)	4 (5.6)	0 (0)	6 (3.4)*
Inferolateral	1 (1.9)	0 (0)	0 (0)	0 (0)	1 (1.5)	2 (2.8)	0 (0)	1 (0.6)
Inferior	1 (1.9)	0 (0)	0 (0)	0 (0)	3 (4.5)	1 (1.4)	1 (0.6)	1 (0.6)

Data are presented as number (%) for each column.

Lateral, leads I and AVL, V_5 and/or V_6 (only one lead of TWI required in V_5 or V_6); Inferolateral, leads II and aVF, V_5-V_6, I and AVL; Inferior, leads II and aVF.

*p≤0.05, significantly more prevalent in black than Arab athletes of the same biological age group

†p≤0.05, significantly more prevalent than in Arab athletes biologically aged 17-18 years.

6.3.6 JT ELEVATION AND ST-SEGMENT MORPHOLOGY PRECEDING ATWI CONFINED TO V_1-V_3

ATWI confined to V_1-V_3 was preceded by Jt elevation in 37.4%. Jt elevation was more common in athletes biologically aged ≥16 than <16 years (52.5% vs. 25.5%, $p<0.01$) and in black than Arab athletes (56.9% vs. 12.5%, $p<0.001$).

ATWI in V_1-V_3 was preceded by ST morphology that was isoelectric in 62.6%, and ascending convex in 37.4% (Figure 6.4). Isoelectric ST-segment morphology was more frequent in athletes biologically aged <16 than ≥16 years (74.5% vs. 47.5%, $p<0.01$).

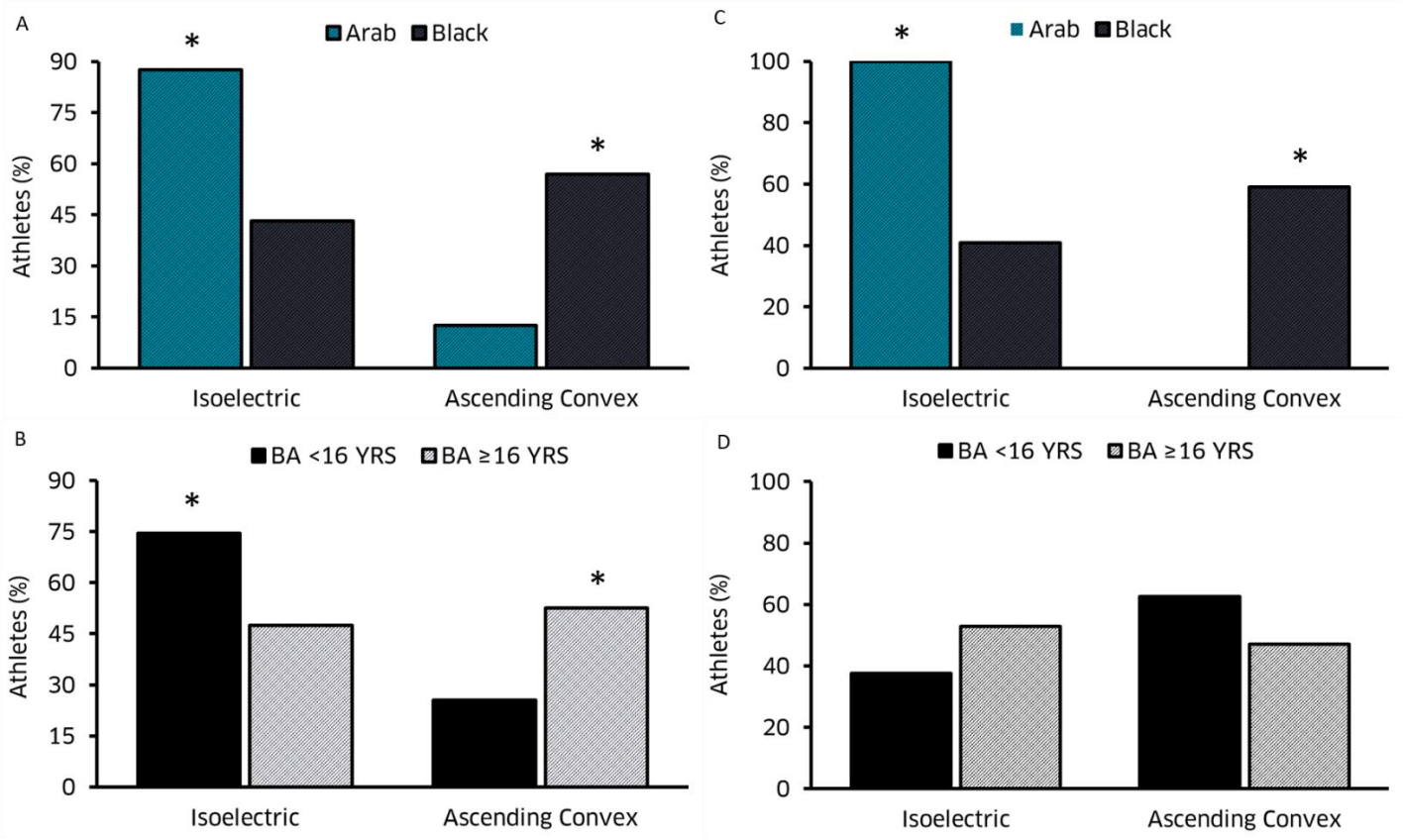

Figure 6. 4 Bar graph shows ST-Segment morphology type preceding anterior T-wave inversion confined to V_1-V_3 by (A) ethnicity, and (B) biological age (BA) and anterior T-wave inversion extending beyond V_3 by (C) ethnicity, and (D) biological age. *P <0.05, significant effect of group.

6.3.7 JT ELEVATION AND ST-SEGMENT MORPHOLOGHY PRECEDING ATWI EXTENDING BEYOND V_3

ATWI extending beyond V_3 was preceded by Jt elevation in 52.0%. Whilst prevalence did not differ by biological age, this observation was confined to black athletes (59.1%). ATWI extending beyond V_3 was frequently preceded by ST morphology that was isoelectric in 48.0%,and ascending convex in 52.0% (Figure 6.4). No healthy athlete with ATWI demonstrated a depressed Jt/ST-segment.

6.3.8 LATERAL, INFEROLATERAL, AND INFERIOR TWI

Fifteen (2.0%) athletes presented lateral TWI with prevalence unaffected by biological age, but more common in black than Arab athletes (3.5% vs. 1.0%, $p<0.02$); prevalence was sustained across all biological age groups in black athletes. Four (0.5%) and eight (1.1%) athletes presented with inferior and inferolateral TWI, respectively, whilst neither form of repolarization demonstrated an association with ethnicity, chronological or biological age.

6.3.9 DETERMINANTS OF TWI

Of the 726 athletes with no detected cardiac pathology, univariate predictors of ATWI confined to V_1-V_3 were black ethnicity (odds ratio (OR) 1.9; 95% CI 1.2-3.0), chronological age <16 (OR 2.6; 95% CI 1.3-5.4), and biological age <16 years (OR 1.9; 95% CI 1.2-3.0). On multivariable analysis only black ethnicity (OR 2.2; 95% CI 1.3-3.5) and biological age <16 years (OR 2.0; 95% CI 1.2-3.3) remained. Black ethnicity was the only univariate

predictor of ATWI extending beyond V_3 (OR 8.9; 95% CI 2.6-30.4), and lateral TWI (OR 4.0; 95% CI 1.1-15.2).

6.3.10 DIAGNOSTIC YIELD AND ACCURACY OF TWI INTERPRETATION

6.3.10.1 Anterior TWI

Four of 116 (3.4%) with ATWI (V_1-V_4) and 1 of 96 (1.0%) with ATWI (V_1-V_4) observed in the absence of other ECG findings considered to be abnormal as per new international recommendations for ECG interpretation in athletes, were diagnosed with pathology (Table 6.3). Of these 96, diagnostic accuracy was 'fail' [0.47 95% CI 0.00-1.00] for new international recommendations, 'fail' [0.48 95% CI 0.00-1.00] for new international recommendations when governed by Jt and/or ST-segment elevation irrespective of ethnicity, and 'excellent' [0.97 95% CI 0.92-1.00] for new international recommendations when governed by biological not chronological age <16 years (Figure 6.5)

Table 6. 3 Clinical Characteristics of Athletes Diagnosed with Cardiac Pathology that may Predispose to Sudden Cardiac Death/Arrest.

Condition	Chronological Age	Biological Age	Ethnicity	International	International governed by Biological Age	TWI	Other
Aneurysm with dilated ascending aorta	12	11.6	Arab	-	-	-	-
HCM	13	18	Black	+	+	AVL, V_2-V_5	Q waves II, III, AVF, V_5, V_6
LVNC	13	17	Black	+	+	II, III, AVF, V_1-V_6	Q waves II, III, AVF, V_4 -V_6
Myocarditis, with anterolateral, lateral and	14	17.7	Arab	-	+	V_1-V_3	-

inferolateral mid-wall fibrosis at basal level.							
Myocarditis, with anterolateral, lateral and inferolateral mid-wall fibrosis at basal and mid ventricular level	13	15.4	Arab	+	+	AVL, V_1, V_4-V_5	-
WPW ECG pattern	13	18	Black	+	+	AVL,V_1-V_4	Short PR interval Delta Wave Wide QRS

Hypertrophic cardiomyopathy; LVNC, left ventricular non-compaction; MVP; Mitral Valve Prolapse; MR; mitral regurgitation; SCA/D, sudden cardiac arrest/death; TWI, T-wave inversion; WPW; Wolf-Parkinson-White syndrome.

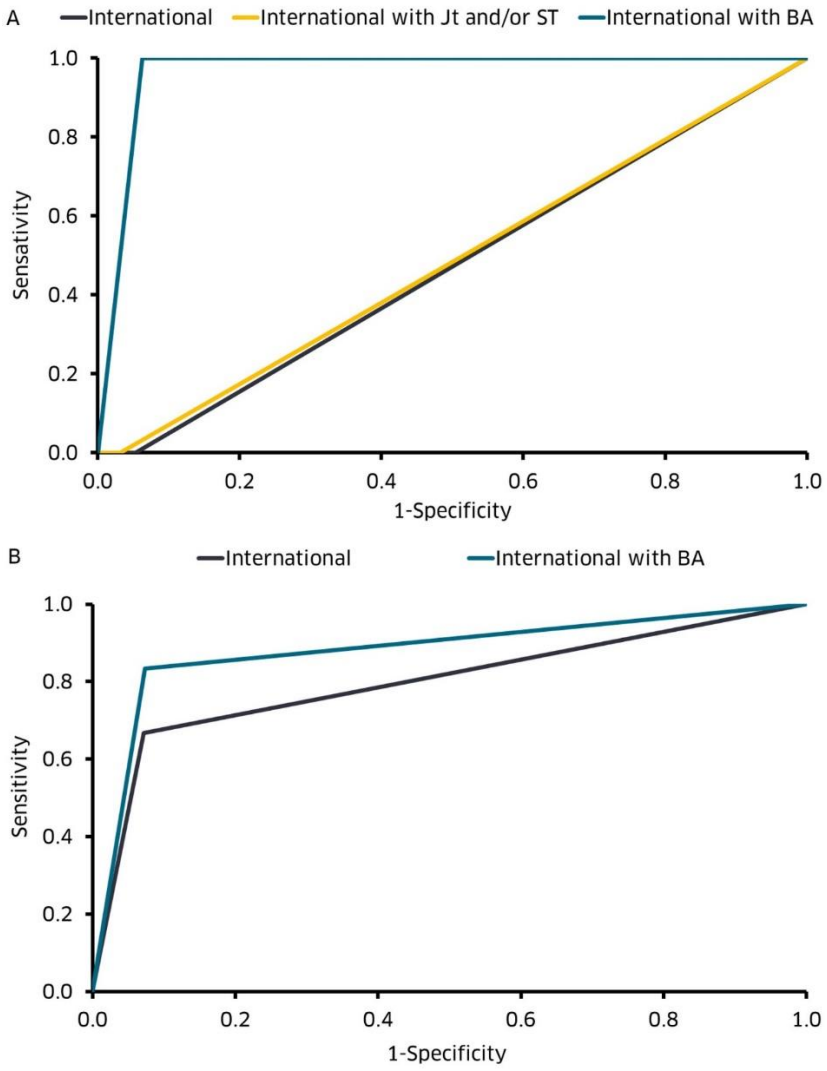

Figure 6. 5 Receiver-operating curves according to ECG interpretation criteria to detect cardiac pathology predisposing to sudden cardiac death/arrest only. Area under curve (AUC) represents test accuracy in differentiating athletes with cardiac pathology predisposing to an increased risk of sudden cardiac death/arrest. (A) Athletes presenting with ECG variants isolated to T-wave-inversion V_1-V_4 by (1) new international recommendations, (2) when governed by Jt and/or ST-segment elevation irrespective of ethnicity and, (3) when governed by biological age (BA) < 16 years. (B) All athletes by (1)

new international recommendations and (2) when governed by biological age < 16 years with anterior T-wave inversion confined to V_1-V_3.

6.3.10.2 Lateral, Inferolateral and Inferior TWI

Three of 15 (20.0%) athletes with lateral TWI were diagnosed with pathology. Of these fifteen, 8 presented ECG abnormalities confined to lateral TWI, with pathology diagnosed in the only Arab athlete. 1 of 4 (20%) and 1 of 8 (12.5%) athletes with inferior and inferolateral TWI, respectively, were diagnosed with pathology. No pathology was diagnosed in athletes with ECG abnormalities confined to inferior (n=3) or inferolateral (n=2) TWI.

6.3.11 DIAGNOSTIC ACCURACY OF NEW INTERNATIONAL RECCOMENDATIONS IN ALL ATHLETES

Diagnostic accuracy of cardiac pathology was 'fair' (0.79 95% CI 0.57-1.00) for international recommendations (specifically, a 'poor' [0.65 95% CI 0.28-1.00] diagnostic accuracy for Arab and an 'excellent' [0.94 95% CI 0.90-99] diagnostic accuracy for black athletes), and 'good' (0.88 95% CI 0.71-1.00) when governed by biological age <16 years (specifically, a 'good' [0.81 95% CI 0.49-1.00] diagnostic accuracy for Arab and an 'excellent' [0.94 95% CI 0.90-99] diagnostic accuracy for black athletes) (Figure 6.5).

6.3.12 CLINICAL IMPLICATIONS WHEN GOVERNING NEW INTERNATIONAL RECCOMENDATIONS BY BIOLOGICAL AGE

Overall, new international recommendations provided a +ve and -ve LR of 9.3 (95% CI 4.0-14.5) and 0.4 (95% CI 0.1-0.8), respectively. When governed by biological age, +ve and -ve LR were 11.4 (95% CI 5.7-16.0) and 0.2 (95% CI 0.03-0.6), respectively. When split by ethnicity, +ve and -ve LR were 15.4 (95% CI 4.5-29.3) and 0.3 (95% CI 0.06-0.8) in Arab and 8.9 (95% CI 3.0-11.2) and 0.0 (95% CI 0.0-0.6) in black athletes, respectively.

Of the 96 with ECG variants isolated to ATWI (V_1-V_4), new international recommendations provided a +ve and -ve LR of 0.0 (95% CI 0.0-22.8) and 1.1 (95% CI 0.1-1.0), respectively. If governing by biological age in this cohort, +ve and -ve LR were 15.8 (95% CI 1.8-28.1) and 0.0 (95% CI 0.0-0.8), respectively.

6.4 DISCUSSION

Differentiating benign from pathological T-wave inversion represents one of sports cardiology greatest conundrums. This study of 418 Arab and 314 black male paediatric athletes demonstrated that: ATWI confined to V_1-V_3 was prevalent among 12.1% of athletes, with prevalence predicted by black ethnicity and biological age, but not chronological age <16 years; whilst ATWI extending beyond V_3 was rare (3.4%), its prevalence was predicted by black ethnicity, and sustained across all biological age groups for this ethnicity; and finally diagnostic accuracy of new international recommendations for cardiac pathology in athletes presenting ECG variants isolated to

ATWI (V_1-V_4), improved from ‘fail’ to ‘excellent’ with biological not chronological age governance. In clinical context, the ‘chance’ of detecting cardiac pathology within a paediatric male athlete presenting ECG variants confined to ATWI (V_1-V_4) is approximately 1%. A positive ECG (+LR=15.8) using biological age governance to new international recommendations means the same athlete now has a 14.4% ‘chance’ of pathology, whereas a negative ECG (-LR=0.0) has a 0% ‘chance’.

6.4.1 PREVALENCE AND DISTRIBUTION OF ATWI

In chapter 4, a relatively high prevalence of ATWI was observed in over 6000 white and 500 black male paediatric athletes (4.2% vs 12.2%, respectively). We observed AWTI confined to V_1-V_3 in 16.2% and 9.6% of black and Arab paediatric athletes, respectively. Although this may represent a ‘juvenile’ ECG when aged <16 years (Sharma et al., 2018); of the 11 articles (Sharma *et al.*, 1999; Papadakis *et al.*, 2009; Schmied *et al.*, 2009; Attisani *et al.*, 2011; Di Paolo *et al.*, 2012; Migliore *et al.*, 2012; Sheikh *et al.*, 2013; Koch *et al.*, 2014; Bessem, de Bruijn and Nieuwland, 2015; Calò *et al.*, 2015; D’Ascenzi, Solari, Anselmi, *et al.*, 2017) whom previously detailed its prevalence and significance, only 4 (Sharma et al., 1999; Papadakis et al., 2009; Migliore et al., 2012; D’Ascenzi et al., 2017d) documented maturity status, of which 3 (Sharma et al., 1999; Migliore et al., 2012; D’Ascenzi et al., 2017d) relied on Tanner Staging. For the first time we considered biological age, recognised by the IOC as the ‘gold standard’ estimate of maturity (Engebretsen et al., 2010). Biological age <16 years and black ethnicity, not chronological age <16 years predicted ATWI confined to V_1-V_3. In extension to Sheikh et al. (2013) who observed ATWI extending beyond V_2 in black athletes (14-18 years) in 74% of cases, we

demonstrated ATWI extending beyond V_3 within black athletes (11-18 years) in 30.0%. Furthermore, prevalence was sustained irrespective of biological age group for this ethnicity, suggesting that this may represent a benign, ethnic manifestation of the athlete's heart, irrespective of biological age.

6.4.2 POTERNTIAL MARKERS OF PATHOLOGY IN PAEDIATRIC ATHLETES WITH ATWI

The prevalence of ATWI confined to V_1-V_3 is increased in male paediatric athletes of younger biological age, with presentation in 15.2% Arab and 27.1% black athletes biologically aged <16 years. Thus, creating considerable overlap in the differential diagnosis of myocarditis, arrhythmogenic right ventricular cardiomyopathy and hypertrophic cardiomyopathy. Accordingly, new international recommendations for ECG interpretation in athletes (Sharma et al., 2018) recognize the 'juvenile ECG pattern' (TWI in V_1-V_3, chronological aged <16 years) to be normal. This assumes, however, an immature heart unlikely to have undergone complete formation of adult ventricular mass, with TWI in V_1–V_3, attributable to right ventricular dominance. In reality, whilst chronological age is a linear factor, growth and maturation are not (Johnson et al., 2009). Subsequently, new international recommendations failed to detect one case of myocarditis, with TWI in V_1-V_3 in an Arab athlete (chronological age 14 years), yielding a 'failed' diagnostic accuracy for ECG variants isolated to ATWI (V_1-V_4). In contrast to observations of adult athletes by Calore et al. (Calore et al., 2016), assessment of the preceding Jt and/or ST-segment amplitude irrespective of ethnicity, yielded a 'failed' diagnostic accuracy. Further, ATWI confined to V_1-V_3, where preceded by a Jt in line with

the onset of the QRS and/or ST-segment that were isoelectric in 62.6%, of which 66.7% were biologically aged <16 years. Finally, new international recommendations governed by biological not chronological age <16 years, yielded an 'excellent' diagnostic accuracy. We believe that when presented with an asymptomatic paediatric athlete with ECG variants isolated to TWI in V_1-V_3, biological age assessment presents an opportunity to reassure the concerned parent/guardian and athlete. TWI in V_1-V_3 in athletes biologically aged <16 years is likely a 'juvenile ECG pattern' not warranting further investigation, but when biologically aged >16 years, further investigation may be warranted.

6.4.3 LATERAL, INFEROLATERAL, AND INFERIOR TWI

In this study of 732 athletes, TWI was detected in lateral leads in 2.0%, inferior leads in 1.1% and, inferolateral leads in 0.5%, with presentation of lateral TWI predicted by black ethnicity. These repolarization patterns are considered abnormal, as confirmed by a recent study (Sheikh et al., 2018) which observed that in black athletes with cardiomyopathy or a genetic mutation of cardiomyopathy, all presented lateral TWI. Whilst ECG abnormalities confined to lateral TWI yielded cardiac pathology in the only Arab athlete, pathology was not detected in any black athlete. Whether this represents the first sign of cardiac pathology, with phenotypic manifestations appearing on secondary investigation in later life or an ethnic manifestation of the athlete's heart remains to be determined. It is universally recognized, however, that these ECG patterns require serial long-term follow-up.

6.4.4 CLINICAL IMPLICATIONS WHEN GOVERNING NEW INTERNATIONAL RECCOMENDATIONS BY BIOLOGICAL AGE

If presented with a paediatric athlete for ECG screening, diagnostic accuracy of new international recommendations improved from 'fair' to 'good', when governed by biological age <16 years. With consideration to Bayesian analysis (Whiteley, 2016), our overall baseline 'chance' of detecting cardiac pathology was 0.8%. A positive ECG (+LR=11.4), means that the same athlete now has an 8.6% 'chance' of cardiac pathology, whereas an athlete with a negative ECG (-LR=0.2), would have a 0.2% 'chance'. We therefore provide further evidence that ECG screening is an effective strategy for detecting cardiac pathology that may predispose to SCD/A in the paediatric athlete (Mont et al., 2015; Grazioli et al., 2017). Whilst new international recommendations represent the current 'gold-standard' for ECG interpretation in the paediatric athlete, as per chapter 5, their governance by biological age, irrespective of cardiac pathology prevalence, increases the likelihood of correctly triggering further evaluation to identify cardiac pathology, whilst reducing the likelihood of incorrectly clearing an athlete to play with potential sinister consequences.

6.4.5 LIMITATIONS

Although no cardiac pathology was detected in paediatric athletes presenting ECG variants isolated to ATWI in V_1-V_3 with a biological age <16 years, we cannot exclude the development of cardiac pathology in later years due to the cross-sectional design. Accordingly, we consider observation to provide only reassurance that this likely represents a 'juvenile ECG pattern', requiring annual follow-up until resolution. Tanner

staging assessment was not conducted in conjunction to biological age assessment due to numerous child protection concerns in addition to a lack of validity for this estimation of maturity when conducted by self-assessment. Finally, our population were exclusively Arab and black male athletes, limiting application of our data to other ethnicities and the female paediatric athlete.

6.4.5 CONCLUSION

Interpretation of ECG variants isolated to ATWI in V_1-V_4 using new international recommendations based on chronological age <16 years, warrants caution, but when governed by biological age <16 years yielded an 'excellent' diagnostic accuracy. Interpretation of the paediatric athletes ECG using biological age governance to new international recommendations provides the best likelihood of triggering further evaluation in the attempt to detect cardiac pathology.

CHAPTER 7:

CARDIAC CHAMBER STRUCTURE AND FUNCTION AND AORTIC ROOT MORPHOLOGY IN ARAB AND BLACK MALE PAEDIATRIC ATHLETES: ALLOMETRIC AND NON-LINEAR MODELLING WITH NOMOGRAMS AND Z-SCORES

7.1 INTRODUCTION

Chapters 5 and 6 of this thesis have both validated and proposed refinement to new international recommendations for ECG interpretation in male Arab and black paediatric athletes. Whilst this may significantly aid and improve ECG-led cardiac screening within the paediatric athlete, the efficacy of any program relies on the diagnostic utility of second-line diagnostic tests, triggered by an abnormal physical examination, health questionnaire and/or ECG, namely an echocardiographic assessment. Furthermore, as per some cardiac screening programs, owing to the inherent limitations of an ECG assessment, an echocardiographic assessment may be considered a mandatory first-line examination.

Chapter 4 of this thesis, determined physiological enlargement and functional alterations of the LV and LA to be established manifestations of the paediatric athlete's heart (Sharma et al., 2002; Makan et al., 2005b; Sheikh et al., 2013). Adaptations which have recently been found to extend to the RV (Popple et al., 2018) and RA (Ascenzi et al., 2016), akin to the adult athlete (Oxborough et al., 2012; D'Ascenzi et al., 2014, 2017b; McClean et al., 2015). In some instances, however, this may overlap with phenotypic expression of hypertrophic cardiomyopathy (Sharma et al., 2002; Makan et al., 2005b; Sheikh et al., 2013), idiopathic LVH (Sharma et al., 2002; Makan et al., 2005b; Sheikh et al., 2013), and ARVC (Popple et al., 2018). Cardiomyopathies which collectively account for 22% of SCDs in athletes aged under 18 years in the UK (Finocchiaro et al., 2016b). Differential diagnosis of physiological adaptation to cardiomyopathy is further challenged during echocardiographic assessment by the impact of maturity status (Valente-Dos-Santos et al., 2013), chronological age (Koch et al., 2014; Cavarretta et al., 2018), ethnicity (Di Paolo *et al.*, 2012; Sheikh *et al.*, 2013), and the allometric relationship of body size to cardiac growth (George et al., 2001) in the paediatric athlete.

The number of Arab and black athletes excelling at an international level is ever increasing. 28 and 79 nations of predominantly Arab and black ethnicity, respectively, competed at the 2018 Youth Summer Olympic Games, winning 94 medals collectively. Whilst data from the UK indicate black paediatric athletes represent one of the highest at-risk populations to SCD (Malhotra et al., 2018), together with more profound LV hypertrophy than their white counterparts (Sheikh et al., 2013), differential diagnosis of physiological remodelling to that indicative of a cardiomyopathy is complex. Accordingly,

ethnic-specific LV upper limits in the paediatric athlete have been defined (Sheikh et al., 2013). Yet no regard was paid to chronological age (Koch et al., 2014; Cavarretta et al., 2018), maturity status (Valente-Dos-Santos et al., 2013) and employed linear (ratiometric) indexing (*y/x*). This scaling approach assumes a constant linear and proportional relationship between cardiac size to BSA, which does not conform to biological associations which often occur in a nonlinear (allometric) manner (Batterham et al., 1999). Current practice for differential diagnosis is therefore dependent upon allometrically normalised structural guidelines from a white paediatric (chronological age 8–18 years) soccer population (Cavarretta et al., 2018), toDoppler and TDI velocity guidelines from a non-athlete paediatric population (Dallaire et al., 2015). Detection of ARVC is further challenged, with guidelines limited to measures of RV size in the white soccer scholar (chronological age 15-18 years) (Popple et al., 2018) and measures of RV size and function by RVFAC only in an ARVC population of predominantly adults (8.8%, chronological aged 12-18 years) (Marcus et al., 2010). In view of RV TDI S' high reproducibility and ability to measure basal RV free wall function, allowing for an improved discriminability to detect normal versus abnormal RV function (Rudski et al., 2010a; D'Ascenzi et al., 2018b), appropriate reference values in the paediatric athlete may increase sensitivity and would be unique. Furthermore, the influence of ethnicity on physiological RV and RA remodelling in the paediatric athlete has never been characterised, despite black paediatric athletes frequently revealing ECG repolarisation anomalies consistent with ARVC (Di Paolo *et al.*, 2012; Sheikh *et al.*, 2013).

Therefore, the primary aims of this study were to determine 1) the allometric relationship of cardiac size to BSA and the impact of biological and chronological age, respectively; 2) the non-linear relationship of cardiac function to chronological age, and the impact of biological age, BSA and HR, respectively; 3) and develop clinically useful nomograms and z-scores and 4) the impact of Arab and black ethnicity to cardiac size and function in paediatric athletes.

7.2 METHODS

7.2.1 ETHICAL APPROVAL

Ethical approval was provided by Anti-Doping Laboratory Qatar (IRB #E2013000003 and #E20140000012), with all parents/guardians providing informed consent, as detailed in chapter 3.

7.2.2 PARTICIPANTS

This study utilised a cross-sectional design to retrospectively analyse 314 Arab and 128 black male paediatric athletes, aged 11-18 years. All athletes were registered with the Qatar Olympic Committee [exercising ≥6 hours/week] and presented at our institution for cardiac screening between 2013-2018. Due to changes in protocol during the screening period sub samples were applied to the left heart and aorta (Arab n = 297 and black n = 120) and the right heart (Arab n = 264 and black n = 84). Based on 2-year chronological age categories participants' demographic distribution is described in Table 7.1 and 7.2.

7.2.3 PRELIMINARY AND FURTHER INVESTIGATIONS

Athletes completed a health questionnaire (with primary guardians), an anthropometric (height and body mass; BSA (Haycock et al., 1978)) and left brachial artery blood pressure assessment, together with a physical assessment undertaken by a sports medicine physician, as described in chapter 3. All ECG and echocardiographic acquisition, and analysis were undertaken as described within chapter 3. Chronological age determination, biological age estimation, and further investigations to exclude or confirm cardiac pathology were also undertaken as described in chapter 3.

7.2.4 STATISTICAL ANALYSIS

Analysis was performed with SPSS software (version 21.0; Chicago, IL, USA). To provide normalised parameters of cardiac chamber and aortic root size and Doppler, TDI, TAPSE, RVFAC. A P value ≤0.05 determined a significant effect, and a P value ≤0.01 determined a significant interaction among effects. Comparisons by ethnicity (Arab vs black), employed a Student's t-test for continuous variables and x^2 test or Fisher's exact tests for categorical variables.

To provide normalised measures of cardiac chamber and aortic root size to BSA, a ratiometric ($y = a * BSA$) model was firstly employed. When a ratiometric model failed to remove the impact of BSA across all parameters, an allometric model ($y = a * BSA^b$), was employed. To ensure size independence, fit plots of the residual values over BSA by linear regression determined the presence of residual association. Preliminary scatter

plots along with lines of best fit and their associated variance (R^2), indicated chronological age to explain the greatest variance (R^2) among parameters of Doppler, TDI, TAPSE, and RVFAC. As per consultation of previously published scatter plots of Doppler and TDI velocities in paediatric non-athletes (Dallaire et al., 2015), second-order polynomial ($y = a * chronological\ age^2 + b * chronological\ age + c$), and third-order polynomial ($y = a * chronological\ age^3 + b * chronological\ age^2 + c * chronological\ age\ + d$) models were employed. To ensure chronological age independence, fit plots of the residual values over chronological age by linear regression determined the presence of residual association.

When the model selection was determined, residual association of ethnicity, chronological and biological age to cardiac chamber and aortic root size parameters, in addition to HR for all parameters of Doppler, TDI, TAPSE, and RVFAC, was determined by multivariable linear regression. If the interaction of chronological and/or biological age were significant, the allometric model $y = a * BSA^{(b+c*age)}$, was employed. If the interaction of ethnicity was significant across all parameters, additional variance (R^2) explained by the determination of ethnic-specific constants and coefficients, were assessed. As per Lopez et al. (2017), an increase of <5% was defined as clinically insignificant.

Preliminary analysis revealed nonconstant variance (heteroscedasticity) of residual values across the entire range of BSA and chronological age, respectively, for most parameters of cardiac chamber and aortic root size, Doppler, and TDI velocities.

Accordingly, regressed SD (RSD), was calculated by linear regression of the scaled absolute value (multiplied by $\sqrt{(2/\pi)}$) (DeVore, 2017). Z-scores were then calculated using equations in Tables 7.5, 7.8, 7.11 and 7.15 with parameters of cardiac chamber and aortic root size, Doppler, TDI, TAPSE, and RVFAC plotted against BSA and chronological age, respectively, with lines depicting the mean, 1Z, and 2Z above and below the mean (Figures 7.1, 7.3, 7.4, 7.7 and 7.9).

We calculated Z-scores of cardiac chambers and aortic root size, Doppler, TDI, TAPSE, RVFAC from our cohort's raw data using established athlete (Cavarretta et al., 2018), and non-athlete (Koestenberger et al., 2012; Cantinotti et al., 2014; Dallaire et al., 2015). Correlation analysis determined the presence of significant interaction ($p \leq 0.01$) to BSA, chronological and biological age, ethnicity and HR. Scatter plots of observations against BSA and chronological age, respectively, with predicted Z-score boundaries, assessed appropriateness of fit. Finally, for those Arab and black athletes where RV assessment was feasible, the ECG and echocardiographic values were compared to published data for an ARVC population (Marcus et al., 2010).

7.3 RESULTS

7.3.1 DEMOGRAPHICS

No participants reported symptoms suggestive of underlying cardiovascular pathology or a family history of premature SCD or an inherited cardiomyopathy. All subjects were healthy and free from known cardiovascular disease and not taking any form of prescribed

medication. Athletes participated in 20 different sports, with football dominating (53.0%). Mean biological age (16.5 ± 1.8 vs. 16.0 ± 2.1 years, P≤0.05) was greater in black than in Arab athletes but mean chronological age (14.9 ± 1.9 vs. 15.0 ± 2.0 years) and BSA (1.6 ± 0.2 vs. 1.6 ± 0.3 m2) did not differ by ethnicity (Table 7.1 and 7.2).

Table 7. 1 Anthropometric Data of Male Arab and Black Paediatric Athletes by Chronological Age Group for Assessment of the Left Heart and Aortic root.

Chronological Age Group, years	Group	*N*	%	Biological Age, years)	BSA, m^2	Systolic BP, mmHg	Diastolic BP, mmHg	Heart Rate, bpm
11-13	Total	*152*	33.8	14.3 ± 1.7	1.44 ± 0.21	113.9 ± 9.8	63.9 ± 9.0	71.5 ± 11.1
	Arab	*100*		13.8 ± 1.5	1.40 ± 0.20	111.8 ± 8.9	62.6 ± 8.1	72.3 ± 10.6
	Black	*52*		15.3 ± 1.7**	1.52 ± 0.21**	117.8 ± 10.4**	66.4 ± 9.9	70.0 ± 12.0
14-15	Total	*126*	36.2	16.3 ± 1.4	1.64 ± 0.20	116.5 ± 9.2	64.9 ± 8.5	65.7 ± 10.5
	Arab	*93*		16.2 ± 1.4	1.63 ± 0.20	115.7 ± 9.2	64.2 ± 8.2	65.6 ± 11.2
	Black	*30*		16.7 ± 1.5	1.66 ± 0.20	118.9 ± 9.0	66.9 ± 9.1	65.7 ± 8.4
16-18	Total	*142*	30.0	17.8 ± 0.5	1.80 ± 0.18	118.8 ± 9.5	65.2 ± 9.4	61.2 ± 10.2
	Arab	*104*		17.8 ± 0.5	1.80 ± 0.19	118.5 ± 9.6	65.5 ± 9.6	61.8 ± 10.4
	Black	*38*		17.9 ± 0.3	1.79 ± 0.17	119.6 ± 9.4	64.5 ± 8.9	59.6 ± 9.6

Values are mean ± standard deviation; BSA, body surface area; BP, blood pressure; bpm, beats per minute; cm, centimetres; kg, kilograms; m^2, $meters^2$; mmHg; millimetre of mercury.

* p≤0.01, significantly more prevalent or greater in black than Arab athletes.

** p≤0.001, significantly more prevalent or greater in black than Arab athletes.

Table 7. 2 Anthropometric Data of Male Arab and Black Paediatric Athletes by Chronological Age Group for Assessment of the Right Heart.

Chronological Age Group, years	Group	*N*	%	Biological Age, years)	BSA, m^2	Systolic BP, mmHg	Diastolic BP, mmHg	Heart Rate, bpm
11-13	Total	*116*	33.3	14.0 ± 1.6	1.41 ± 0.20	111.9 ± 9.4	62.4 ± 8.3	71.8 ± 10.9
	Arab	*89*		13.8 ± 1.6	1.38 ± 0.19	111.2 ± 9.0	62.0 ± 8.3	71.1 ± 10.1
	Black	*27*		14.5 ± 1.6*	1.48 ± 0.24*	114.4 ± 10.6	63.8 ± 8.4	74.1 ± 13.2*
14-15	Total	*108*	31.0	16.3 ± 1.5	1.61 ± 0.15	115.5 ± 9.5	63.9 ± 8.6	65.3 ± 10.0
	Arab	*83*		16.3 ± 1.4	1.61 ± 0.16	115.2 ± 9.3	63.3 ± 8.8	65.0 ± 11.0
	Black	*25*		16.3 ± 1.7	1.62 ± 0.14	116.4 ± 10.1	66.1 ± 7.9	66.0 ± 6.0
16-18	Total	*124*	35.6	17.6 ± 0.9	1.79 ± 0.16	118.2 ± 9.9	64.7 ± 9.9	60.9 ± 10.4
	Arab	*92*		17.6 ± 0.9	1.79 ± 0.16	118.1 ± 10.1	65.1 ± 10.2	61.5 ± 10.6
	Black	*32*		17.6 ± 0.9	1.78 ± 0.18	118.5 ± 9.6	63.4 ± 8.8	59.4 ± 9.6

Values are mean ± standard deviation; BSA, body surface area; BP, blood pressure; bpm, beats per minute; m^2, $meters^2$; mmHg; millimetre of mercury.

* $p \leq 0.01$, significantly greater in black than Arab athletes.

7.3.2 LEFT VENTRICLE, LEFT ATRIAL AND AORTIC ROOT SIZE: MODEL SELECTION

Multivariable regression for IVSd, PWTd, LV Volume during End-Diastole (LV Vol D), and LV mass, by the allometric model $y = a * BSA^b$ revealed residual association to chronological age, only (Table 7.3). The allometric model $y = a * BSA^{(b+c*chronological\ age)}$, revealed no residual association to BSA, ethnicity, chronological and biological age across all parameters of LV, LA and, Aortic Root size (Table 7.4). Allowing for the establishment of the final models (Table 7.5).

Table 7. 3 Residual Association for Parameters of Left Ventricle, Atrial and Aortic Root Size in the Male Arab and Black Paediatric Athlete ($y = a * BSA^b$).

	Residual Association							
	BSA		Chronological Age		Biological Age		Ethnicity	
Parameter	Slope	P Value	Slope	P Value	Slope	P Value	Mean Diff	P Value
LVIDd, mm	-0.020	0.977	0.243	0.072	-0.132	0.316	-0.378	0.309
IVSd, mm	0.008	0.971	0.110	0.010	-0.016	0.704	-0.165	0.166
PWTd, mm	0.012	0.951	0.100	0.007	-0.025	0.480	0.004	0.968
LV Vol D, ml	1.866	0.613	2.234	0.002	-0.249	0.724	0.126	0.950
LVM, g	2.771	0.546	3.395	0.000	-0.864	0.323	-3.211	0.203
Aortic Root, mm	-0.019	0.970	0.082	0.399	0.113	0.232	-0.298	0.266
LAD, mm	0.020	0.977	0.035	0.801	-0.158	0.238	-0.025	0.948
LA Vol, ml	0.149	0.929	0.145	0.666	-0.116	0.725	0.685	0.458

Diff, difference; g, grams; LVIDd, Left Ventricle internal diameter; IVSd, Intraventricular septal wall thickness; PWTd, posterior wall thickness, and; LV Vol D, LV volume during end-diastole; LAD, Left Atrial diameter and; LA Vol, LA volume during end-systole; ml, millilitres, mm, millimetres.

Table 7. 4 Residual Association for Parameters of Left Ventricle, Atrial and Aortic Root Size in the Male Arab and Black Paediatric Athlete ($y = a * BSA^{(b+c*chronological\ age)}$).

	Residual Association							
	BSA		Chronological Age		Biological Age		Ethnicity	
Parameter	Slope	P Value	Slope	P Value	Slope	P Value	Mean Diff	P Value
LVIDd, mm	0.036	0.739	-0.202	0.813	0.007	0.931	-0.461	0.212
IVSd, mm	0.035	0.299	-0.167	0.534	0.040	0.135	-0.217	0.063
PWTd, mm	0.043	0.148	-0.191	0.412	0.031	0.174	-0.033	0.747
LV Vol D, ml	0.527	0.361	-0.924	0.839	0.838	0.060	-0.949	0.630
LVM, g	0.816	0.255	-1.471	0.794	0.936	0.091	-4.565	0.062
Aortic Root, mm	0.063	0.420	-0.331	0.588	0.125	0.037	-0.393	0.139
LAD, mm	-0.051	0.851	0.381	0.858	-0.035	0.868	0.634	0.492
LA Vol, ml	-0.065	0.558	0.332	0.702	-0.113	0.184	0.012	0.975

Diff, difference; g, grams; LVIDd, Left Ventricle internal diameter; IVSd, intraventricular septal wall thickness; PWTd, Posterior wall thickness, and; LV Vol D, LV volume during end-diastole; LAD, Left Atrial diameter and; LA Vol, LA volume during end-systole; ml, millilitres; mm, millimetres.

7.3.3 LEFT VENTRICLE, LEFT ATRIAL AND AORTIC ROOT SIZE: Z-SCORE CALCULATOR

Observations of LV, LA, and Aortic Root size are plotted against BSA with lines representing Z=0, 1, 2, -1, and -2 (Figure 7.1), with RSD accounting for heteroscedasticity. Based on the Allometric model $y = a * BSA^{(b+c*chronological\ age)}$, the Z-score parameters of LV, LA, and Aortic Root size for an athlete with a specific BSA and chronological age can be calculated from Table 7.5 by using the specified *a*, *b*, and *c* mean predicted parameters and *d*, *e*, and *f* RSD for that parameter of LV, LA, and Aortic Root size:

$$z = \frac{obs - (a * BSA^{(b+c*chronological\ age)})}{d + (e * BSA) + (f * chronological\ age)}$$

For example, a 13-year-old male paediatric athlete with a BSA of 1.76 m^2 and a IVSd of 8.5 mm, the Z score is calculated as 1.91 based on the predicted mean parameters for *a* (6.055), *b* (-0.020), *c* (0.031), and regressed SD parameters *d* (1.100), *e* (0.062) and *f* (-0.008).

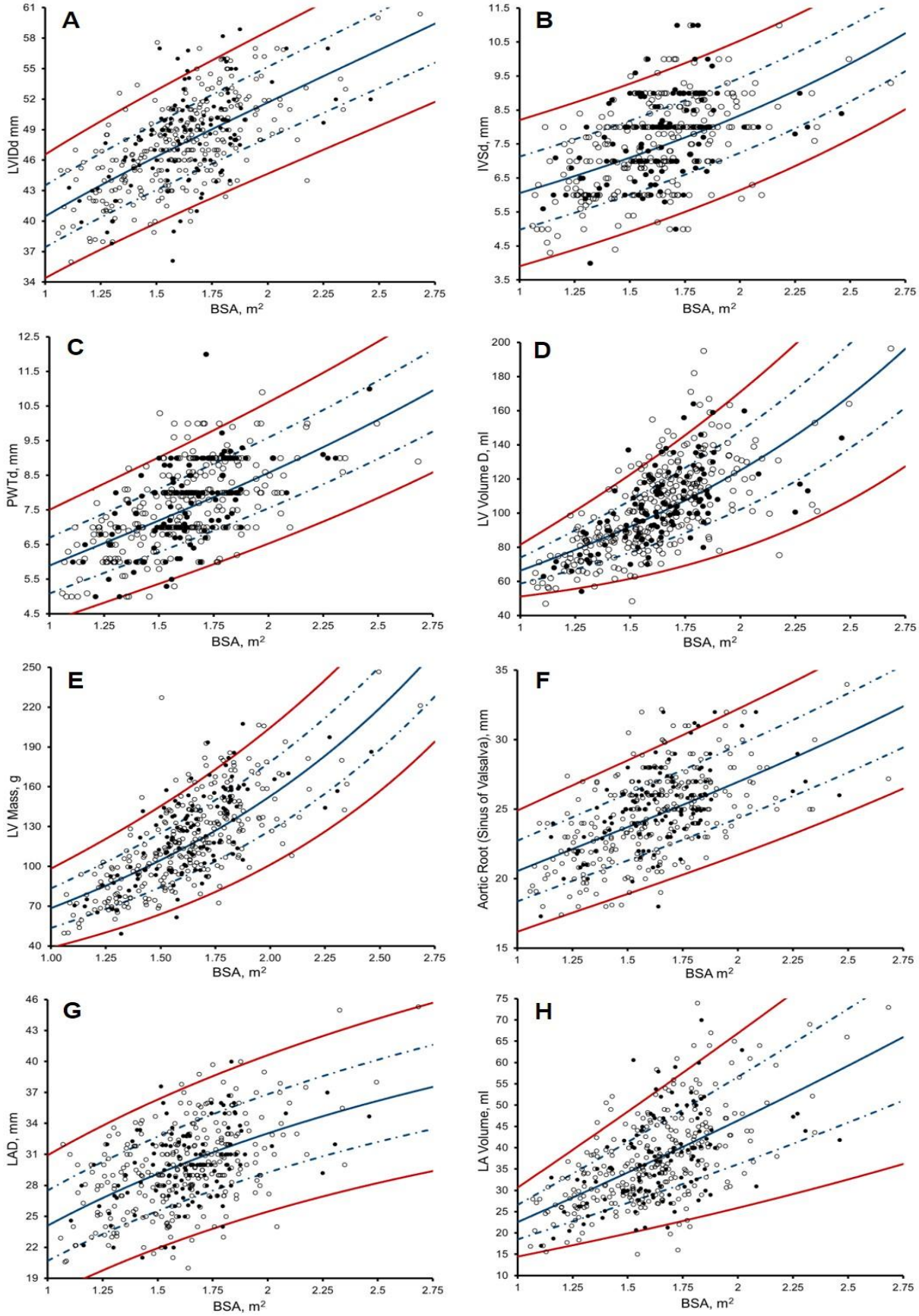
A
LVIDd mm
BSA, m²
B
IVSd, mm
BSA, m²
C
PWTd, mm
BSA, m²
D
LV Volume D, ml
BSA, m²
E
LV Mass, g
BSA, m²
F
Aortic Root (Sinus of Valsalva), mm
BSA m²
G
LAD, mm
BSA, m²
H
LA Volume, ml
BSA, m²

Figure 7. 1 Scatter plots of: A, Left Ventricle Internal Diameter (LVIDd); B, Intraventricular Septal Wall thickness (IVSd); C, Posterior Wall Thickness (PWTd), and; D, LV Volume during end-diastole (LV Vol D); E, LV Mass; F, Atrial Root diameter, at the sinus of Valsalva level during end-diastole; G, Left Atrial Dimension (LAD) and; H, LA Volume during end-systole to BSA in 297 Arab (white dots) and 120 black athletes (black dots), with predicted Z boundaries. Solid blue line, Z=0; dashed blue line, Z=1 and -1; solid red line, Z=2 and -2.

Table 7. 5 Models, Predicted Mean and Regressed Standard Deviation Parameters for Measurements of Left Ventricle, Atrial and Aortic Root Size in the Male Arab and Black Paediatric Athlete.

		Predicted Mean Parameters			Regressed SD Parameters		
Parameter	Model	*a*	*b*	*c*	*d*	*e*	*f*
LVIDd, mm	Allometric	40.469	0.228	0.008	2.276	0.250	0.047
IVSd, mm	Allometric	6.055	-0.020	0.031	1.100	0.062	-0.008
PWTd, mm	Allometric	5.891	0.214	0.021	0.562	0.194	0.005
LV Vol D, mm	Allometric	66.236	0.20	0.046	-10.763	13.239	0.465
LVM, g	Allometric	68.499	0.396	0.049	1.230	8.960	0.429
Aortic Root, mm	Allometric	20.531	0.128	0.017	1.719	0.431	0.003
LAD, mm	Allometric	24.094	0.533	-0.005	3.950	1.035	-0.143
LA Vol, ml	Allometric	22.538	0.948	0.006	-4.254	4.719	0.326

G, grams; LVIDd, Left Ventricle Internal Diameter during diastole; IVSd, Intraventricular Septal Wall Thickness during diastole; PWTd, Posterior Wall Thickness during diastole; LV Vol D, LV Volume during diastole; LAD, Left Atrial Diameter; LA Vol, Left Atrial Volume during systole; ml, millilitres; mm, millimetres; SD, standard deviation.

7.3.4 LEFT VENTRICLE, LEFT ATRIAL AND AORTIC ROOT SIZE: APPLICATION OF ESTABLISHED REFERENCE VALUES

Z-Score boundaries of Cavarretta *et al.* (2018), were visually inadequate for male Arab and black paediatric athletes with a low and high BSA, respectively, across all parameters of LV, LA, and Aortic Root size (Figure 7.2). Significant correlation remained to BSA (*r = 0.135 to 0.220, all P values ≤0.006*) in 50%, to biological age (*r = 0.200 to 0.261, all P values ≤0.001*) in 50%, and to chronological age (*r = 0.100 to 0.278, all P values ≤0.04*) in 66.6% of computed LV, LA, and Aortic Root size Z-score parameters, defined as per Cavarretta *et al.* (2018); indicative of bias (Table 7.6).

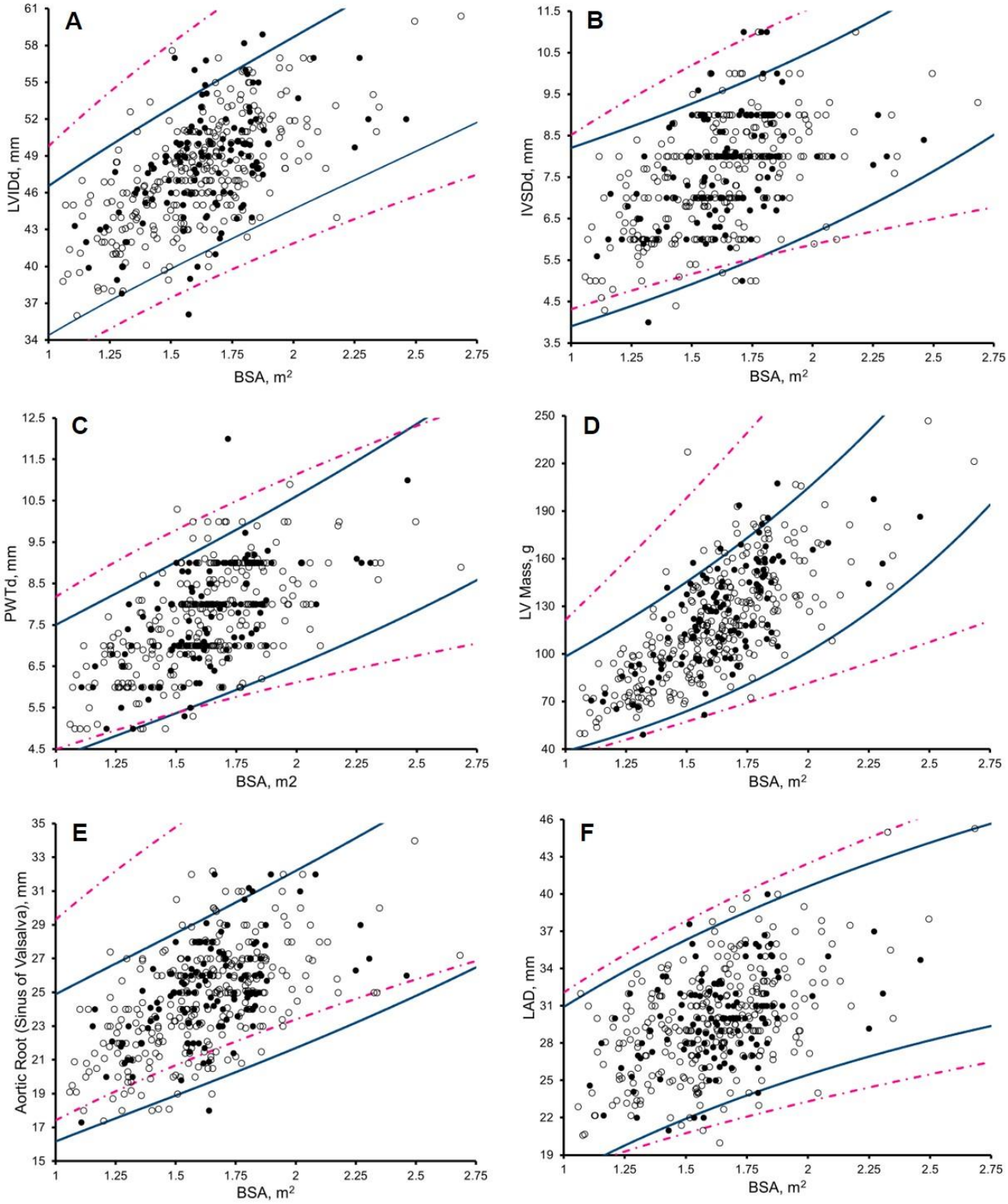
A
LVIDd, mm
BSA, m²
B
IVSDd, mm
BSA, m²
C
PWTd, mm
BSA, m2
D
LV Mass, g
BSA, m²
E
Aortic Root (Sinus of Valsalva), mm
BSA, m²
F
LAD, mm
BSA, m²

Figure 7. 2 Scatter plots of: A, Left Ventricle Internal Diameter (LVIDd); B, Intraventricular Septal Wall thickness (IVSd), and; C, Posterior Wall Thickness during end-diastole (PWTd); D, LV Mass; E, Atrial Root diameter, at the Sinus of Valsalva level during end-diastole; and F, Left Atrial Dimension during end-systole to Body Surface Area (BSA) in 297 Arab (white dots) and 120 black (black dots). Solid blue line, Z=2 and -2 as per proposed reference values, dashed pink line Z=2 and -2 as per Cavarretta *et al.* (2018) proposed reference values.

Table 7. 6 Correlation Analysis for Z-score Parameters of Left Ventricle, Atrial and Aortic Root Size in the Male Arab and Black Paediatric Athlete, Computed as per Caverreta *et al.* (2018).

	Correlation Analysis							
	BSA		Chronological Age		Biological Age		Ethnicity	
Parameter	R	P Value	R	P Value	R	P Value	Mean Diff	P Value
LVIDd, mm	-0.031	0.521	-0.019	0.702	-0.032	0.513	-0.072	0.308
IVSd, mm	0.135	0.006	0.231	<0.0001	0.214	<0.0001	-0.014	0.881
PWTd, mm	0.220	<0.0001	0.278	<0.0001	0.261	<0.0001	-0.151	0.115
LV mass, g	0.146	0.003	0.227	<0.0001	0.200	<0.0001	-0.099	0.136
LAD, mm	0.036	0.463	0.100	0.041	0.141	0.004	-0.112	0.179
Aortic Root, mm	0.034	0.492	-0.001	0.991	-0.029	0.549	-0.017	0.846

Diff, difference; g, grams; LVIDd, left ventricle Internal diameter; IVSd, intraventricular septal wall thickness, and; PWTd, Posterior Wall Thickness during diastole; LAD, Left Atrial Diameter during end-systole; ml, millilitres; mm, millimetres.

7.3.5 LEFT VENTRICLE DOPPLER AND TISSUE DOPPLER IMAGING VELOCITIES: MODEL SELECTION

Visual inspection of biological plausibility, and the additional amount of variance (R^2), explained by a third-order polynomial model (maximal increase of 1%, considered clinically insignificant), contributed to the adoption of a second-order polynomial model across all Doppler and TDI parameters. Multivariable regression revealed residual association between Transmitral A Velocity to biological age, Septal TDI E' to BSA, Transmitral A Velocity, Transmitral E/A, and Septal TDI A' to HR, and Lateral TDI E' to ethnicity (Table 7.7). For example, the residual slope of the Z score for Transmitral E/A versus HR was -0.009, meaning for every increase of 10 bpm, there was a reduction of 0.01 in measured E/A. Determination of ethnic-specific *a* and *b* coefficients and *c* constants across all measures of Doppler and TDI velocity explained only an additional 2% of the variance (R^2), considered clinically insignificant.

Table 7. 7 Residual Association for Parameters of Left Ventricle Doppler and Tissue Doppler Imaging Velocities in the Male Arab and Black Paediatric Athlete ($y = a * chronological\ age^2 + b * chronological\ age + c$).

	Residual Association									
	Chronological Age		Biological Age		BSA		HR		Ethnicity	
Parameter	Slope	P Value	Slope	P Value	Slope	P Value	Slope	P Value	Mean Diff	P Value
Transmitral E Velocity, cm/s	0.000	1.000	0.227	0.731	-9.688	0.055	-0.003	0.968	3.059	0.098
Transmitral A Velocity, cm/s	0.000	1.000	-1.017	0.000	-1.328	0.012	0.045	0.000	2.312	0.043
Transmitral E/A ratio	0.000	1.000	-0.024	0.265	-0.174	0.292	-0.009	0.001	-0.073	0.237
DecT, msec	0.000	1.000	-1.689	0.268	13.438	0.249	-0.450	0.014	-6.107	0.153
Septal E', cm/s	0.000	1.000	0.109	0.153	-1.601	0.006	0.009	0.311	0.304	0.155
Septal A', cm/s	0.000	1.000	0.033	0.501	0.657	0.084	0.017	0.004	-0.221	0.117
Septal S', cm/s	0.000	1.000	-0.004	0.938	0.304	0.424	0.012	0.044	-0.064	0.649

Septal E/E’	0.000	1.000	-0.051	0.339	0.236	0.567	-0.008	0.190	0.029	0.849
Lateral E’, cm/s	0.000	1.000	-0.129	0.267	-0.922	0.298	-0.029	0.036	0.847	0.009
Lateral A’, cm/s	0.000	1.000	0.014	0.819	0.348	0.468	0.013	0.094	0.183	0.298
Lateral S’, cm/s	0.000	1.000	0.196	0.029	-0.986	0.149	0.019	0.075	0.308	0.219
Lateral E/E’	0.000	1.000	0.046	0.240	-0.274	0.358	0.007	0.156	-0.091	0.406
Average E/E’	0.000	1.000	-0.003	0.946	-0.019	0.951	-0.001	0.854	-0.031	0.787

Cm/s, centimetres/second DecT, deceleration time; Diff, difference; msec, milliseconds.

7.3.6 LEFT VENTRICLE DOPPLER AND TISSUE DOPPLER IMAGING VELOCITIES: Z-SCORE CALCULATOR

Observed Doppler and TDI velocities were plotted against chronological age with lines representing Z=0, 1, 2, -1 and -2 (Figures 7.3 and 7.4), with RSD accounting for heteroscedasticity. Based on these models, the Z-score of a functional measurement for an athlete with a specific chronological age can be calculated from Table 7.8 by using the specified *a*, *b*, and *c* mean predicted parameters and d and e RSD for that functional parameter:

$$z = \frac{obs - ((a * chronological\ age^2) + (b * chronological\ age) + c)}{d + (e * chronological\ age)}$$

For example, a 15-year-old male paediatric athlete with an average E/E' of 4.3, the Z score is calculated as -1.87 based on the predicted mean parameters for *a* (0.009), *b* (-0.418), *c* (10.485), and regressed SD parameters *d* (1.413), and *e* (-0.025).

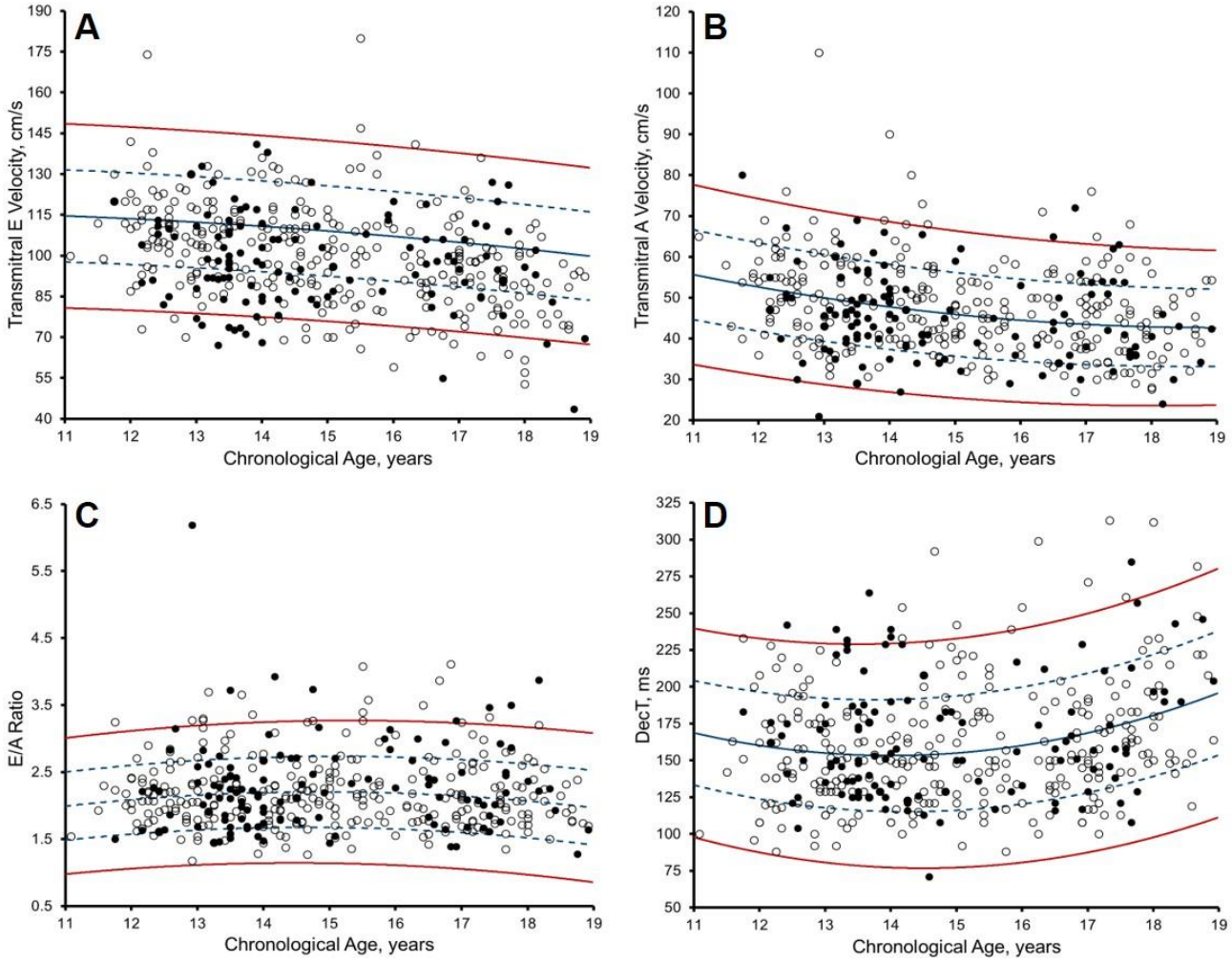

Figure 7. 3 Scatter plots of: A, Transmitral E Velocity; B, Transmitral A Velocity; C, E/A ratio; D, Mitral E wave deceleration time (DecT) to chronological age (years), in 297 Arab (white dots) and 120 black (black dots), with predicted Z boundaries. Solid blue line, Z=0; dashed blue line, Z=1 and -1; solid red line, Z=2 and -2.

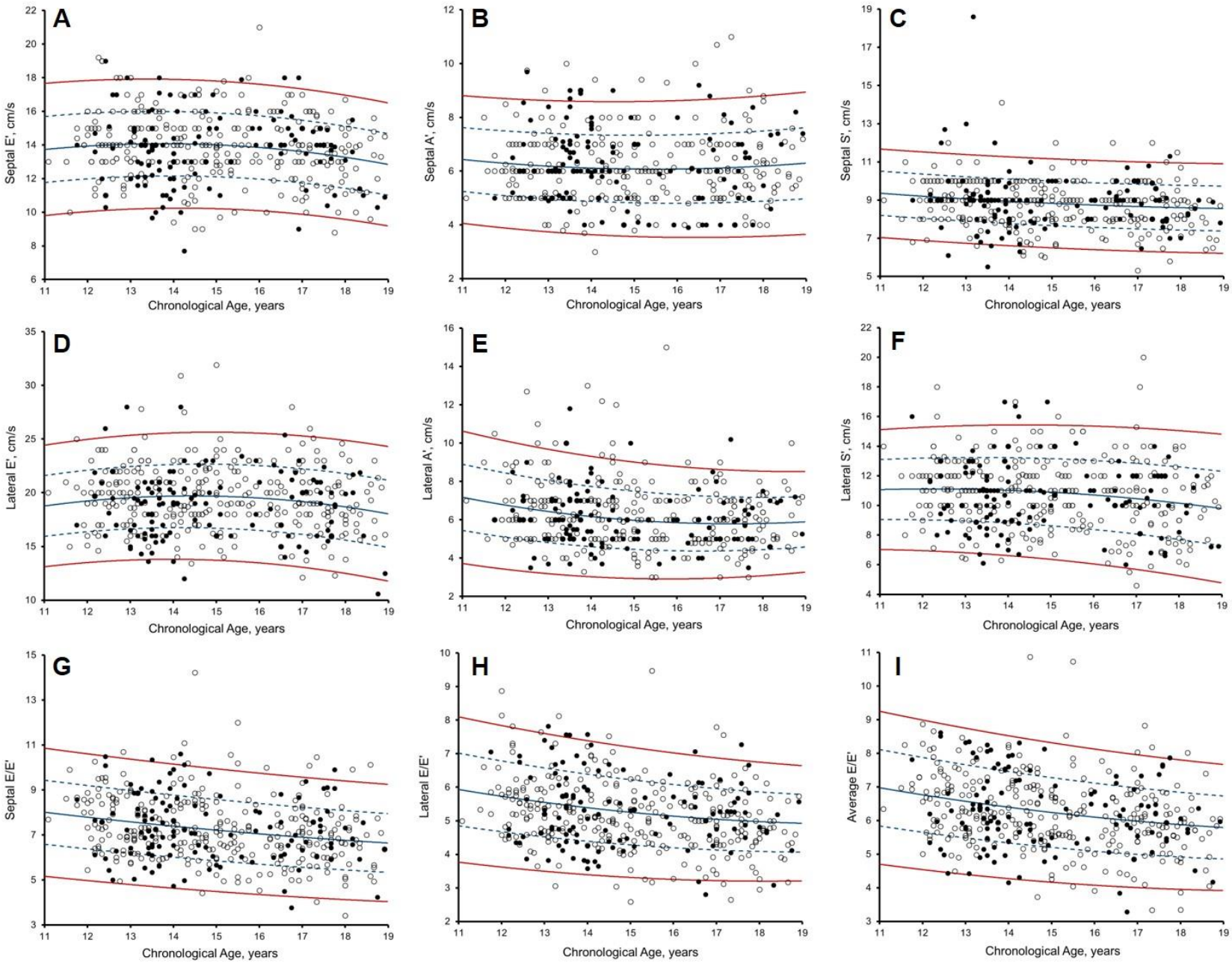
A
Septal E', cm/s
Chronological Age, years
B
Septal A', cm/s
Chronological Age, years
C
Septal S', cm/s
Chronological Age, years
D
Lateral E', cm/s
Chronological Age, years
E
Lateral A', cm/s
Chronological Age, years
F
Lateral S', cm/s
Chronological Age, years
G
Septal E/E'
Chronological Age, years
H
Lateral E/E'
Chronological Age, years
I
Average E/E'
Chronological Age, years

Figure 7. 4 Scatter plots of: A, Septal myocardial velocity in early diastole (Septal E'); B, late diastole (Septal A'); C, and systolic (Septal S'); D, Lateral myocardial velocity in early diastole (Lateral E'); E, late diastole (Lateral A'); F, and systolic (Lateral S'); G, Septal E/E' ratio; H, Lateral E/E' ratio; I, Average E/E' ratio to chronological age (years), in 297 Arab (white dots) and 120 black (black dots), with predicted Z boundaries. Solid blue line, Z=0; dashed blue line, Z=1 and -1; solid red line, Z=2 and -

Table 7. 8 Models, Predicted Mean and Regressed Standard Deviation Parameters of Left Ventricle Doppler and Tissue Doppler Imaging Velocities in the Arab and Black Paediatric Athlete

		Predicted Mean Parameters			Regressed SD Parameters	
Parameter	Model	*a*	*b*	*c*	*d*	*e*
Transmitral E Velocity, cm/s	Polynomial (Second Order)	-0.155	1.597	110.963	17.903	-0.087
Transmitral A Velocity, cm/s	Polynomial (Second Order)	0.202	-7.686	115.752	13.125	-0.193
Transmitral E/A ratio	Polynomial (Second Order)	-0.014	0.417	-0.901	0.442	0.006
DecT, msec	Polynomial (Second Order)	1.710	-47.889	488.577	26.138	0.850
Septal E', cm/s	Polynomial (Second Order)	-0.045	1.239	5.547	2.153	-0.017
Septal A', cm/s	Polynomial (Second Order)	0.018	-0.557	10.382	1.000	0.017

Septal S', cm/s	Polynomial (Second Order)	0.008	-0.340	12.126	1.136	0.002
Septal E/E', cm/s	Polynomial (Second Order)	0.007	-0.381	11.352	1.589	-0.015
Lateral E', cm/s	Polynomial (Second Order)	-0.080	2.308	3.057	2.412	0.038
Lateral A', cm/s	Polynomial (Second Order)	0.035	-1.210	16.250	2.299	-0.052
Lateral S', cm/s	Polynomial (Second Order)	-0.029	0.710	6.767	1.351	0.061
Lateral E/E', cm/s	Polynomial (Second Order)	0.011	-0.456	9.618	1.391	-0.028
Average E/E', cm/s	Polynomial (Second Order)	0.009	-0.418	10.485	1.413	-0.025

Cm/s, centimetres/second; DecT, deceleration time; msec, milliseconds; SD, standard deviation.

7.3.7 LEFT VENTRICLE DOPPLER AND TISSUE DOPPLER IMAGING: APPLICATION OF ESTABLISHED REFERENCE VALUES

Visually the boundaries of Dallaire *et al.* (2015), seemed inadequate across DecT, and most TDI velocities within Arab and black paediatric athletes (Figure 7.5 and 7.6). Upper and lower boundaries of Dallaire *et al.* (2015) were often exceeded for DecT (34.0% and 32.5%), Septal TDI E' (7.4% and 10.8%), A' (4.4% and 0.8%), S' (12.8% and 15.8%), Lateral TDI E' (13.8% and 16.7%), A' (6.1% and 5.8%), S' (14.8% and 16.7%), Septal E/E' (11.1% and 16.7%), and Lateral E/E' (8.4% and 15.8%, $p<0.03$) in Arab and black paediatric athletes, respectively. Significant correlation remained to chronological age (*r = -0.116 to -0.285, all P values ≤0.01*) in 58.3%, to biological age (*r = -0.190 to -0.239, all P values <0.0001*) in 33.3%, to BSA (*r = -0.421 to 0.140, all P values ≤0.004*), in 50.0%, and to HR (*r = -0.162 to 0.233, all P values ≤0.01*) in 58.3% of computed LV Doppler and TDI Z-score velocities, defined as per Dallaire *et al.* (2015). Black paediatric athletes presented significantly larger computed Lateral E' Z scores, than Arab paediatric athletes (mean difference = 0.315, $p<0.04$) (Table 7.9).

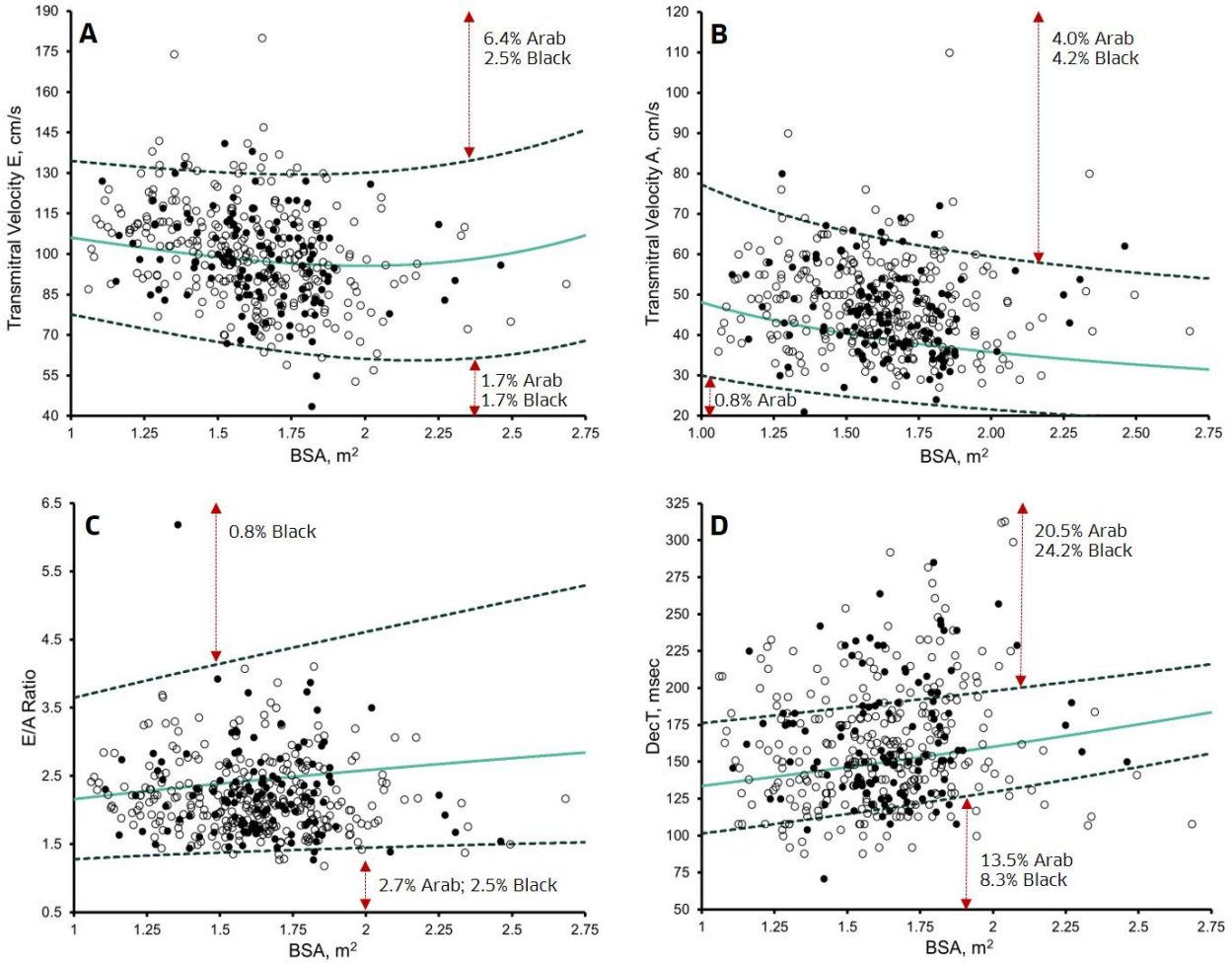

Figure 7. 5 Scatter plots of: A, Transmitral E Velocity; B, Transmitral A Velocity; C, E/A ratio; D, Mitral E wave deceleration time (DecT) to Body Surface Area (BSA) in 297 Arab (white dots) and 120 black (black dots). Solid green line, Z=0; dashed dark green line, Z=2 and -2, as per Dallaire *et al*. (2015) proposed reference values. The percentages of Arab and black athletes exhibiting Z ≥2/≤-2 are demonstrated.

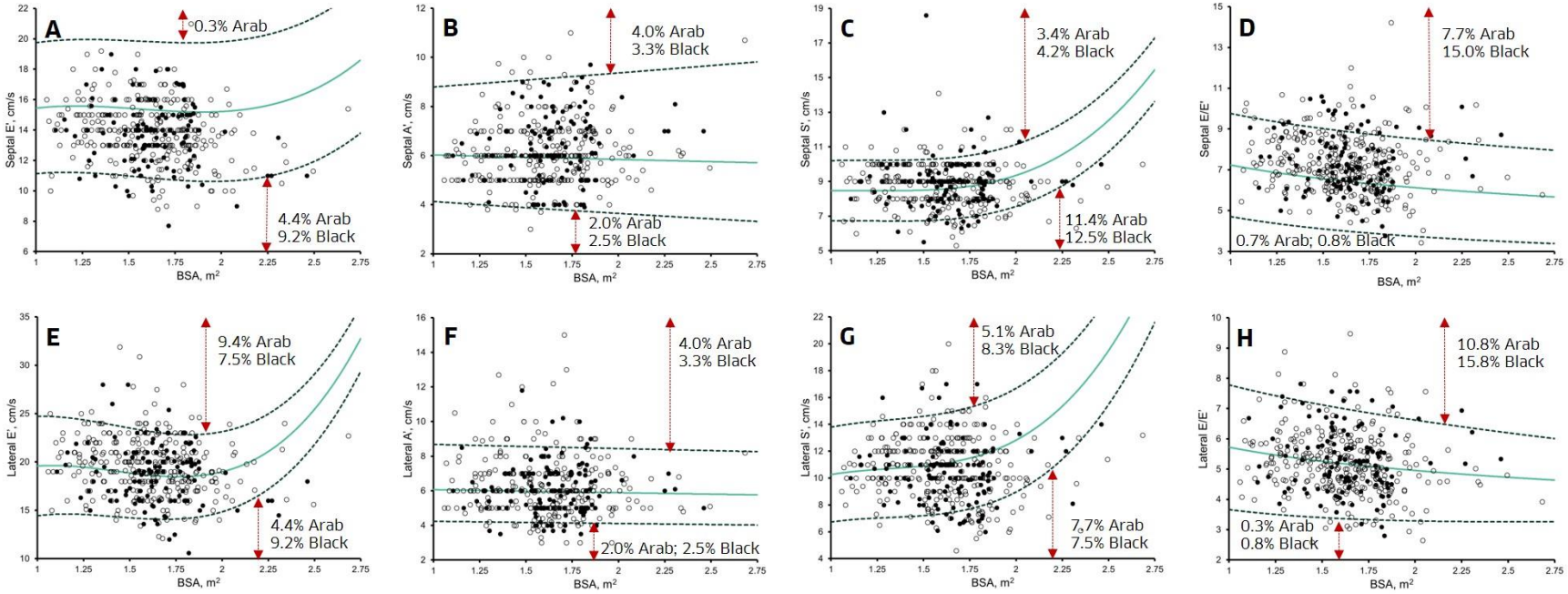

Figure 7. 6 Scatter plots of: A, Septal myocardial velocity in early diastole (Septal E'); B, late diastole (Septal A'); C, and systolic (Septal S'); D, Lateral myocardial velocity in early diastole (Lateral E'); E, late diastole (Lateral A'); F, and systolic (Lateral S'); G, Septal E/E' ratio; H, Lateral E/E' ratio to Body Surface Area (BSA) in 297 Arab (white dots) and 120 black (black dots). Solid green line, Z=0; dashed dark green line, Z=2 and -2, as per Dallaire *et al*. (2015) proposed reference values. The percentages of Arab and black athletes exhibiting Z ≥2/≤-2 are demonstrated.

Table 7. 9 Correlation Analysis for Z-score Parameters of Doppler and Tissue Doppler Imaging Velocities in the Arab and Black Male Paediatric Athlete, Computed as per Dallaire *et al*. (2015).

	Correlation Analysis								Ethnicity	
	Chronological Age		Biological Age		BSA		Heart Rate			
Echo Parameter	R	P Value	R	P Value	R	P Value	R	P Value	Mean Diff	P Value
Transmitral E Velocity, cm/s	-0.267	<0.0001	-0.239	<0.0001	-0.221	<0.0001	0.128	0.009	0.136	0.251
Transmitral A Velocity, cm/s	-0.116	0.017	-0.001	0.985	0.097	0.047	0.233	<0.0001	0.167	0.077
Transmitral E/A ratio	-0.100	0.040	-0.190	<0.0001	-0.260	<0.0001	-0.122	0.013	-0.071	0.454
DecT, ms	0.096	0.051	0.018	0.716	-0.048	0.329	-0.162	0.001	-0.219	0.333
Septal E', cm/s	-0.077	0.116	-0.082	0.094	-0.154	0.002	0.072	0.142	0.110	0.255
Septal A', cm/s	-0.001	0.989	0.087	0.075	0.140	0.004	0.105	0.032	-0.133	0.205
Septal S', cm/s	-0.251	<0.0001	-0.239	<0.0001	-0.336	<0.0001	0.150	0.002	-0.090	0.603
Septal E/E'	-0.116	0.018	-0.058	0.235	0.037	0.456	0.011	0.823	-0.020	0.872

Lateral E', cm/s	-0.040	0.420	-0.087	0.077	-0.211	<0.0001	-0.088	0.071	0.315	0.039
Lateral A', cm/s	-0.144	0.003	-0.111	0.023	-0.033	0.501	0.140	0.004	0.107	0.325
Lateral S', cm/s	-0.285	<0.0001	-0.222	<0.0001	-0.421	<0.0001	0.113	0.022	0.157	0.300
Lateral E/E'	-0.147	0.003	-0.058	0.240	-0.003	0.947	0.125	0.011	-0.145	0.237

Cm/s, centimetres/second; DecT, deceleration time; Diff, difference; msec, milliseconds.

7.3.8 RIGHT VENTRICLE AND RIGHT ATRIAL SIZE: MODEL SELECTION

Multivariable regression across all parameters of RV and RA size, by the allometric model $y = a * BSA^b$, revealed residual association between chronological and biological age to RA area only (Table 7.10). For example, the residual slope for RA area vs. chronological age was 0.333, meaning that an increase of chronological age by 1 year, equated to an increased RA area size by 0.333. The allometric model $y = a * BSA^{(b+c*age)}$, explained only an additional 2% and 0.5% of the variance (R^2) for chronological and biological age, respectively; considered clinically insignificant.

Table 7. 10 Residual Association for Parameters of Right Ventricle and Atrial Size in the Arab and Black Male Paediatric Athlete ($y = a{:}\, BSA^b$).

	Residual Analysis							
	BSA		Chronological Age		Biological Age		Ethnicity	
Parameter	Slope	P Value	Slope	P Value	Slope	P Value	Mean Diff	P value
$RVOT_{PLAX}$, mm	0.022	0.978	0.225	0.120	-0.288	0.038	0.632	0.142
$RVOT_1$, mm	-0.005	0.995	0.070	0.622	-0.108	0.425	0.058	0.890
$RVOT_2$, mm	-0.034	0.950	-0.041	0.686	0.004	0.969	-0.253	0.395
RVD_1, mm	-0.063	0.949	-0.090	0.621	0.188	0.281	-1.146	0.034
RVD_2, mm	-0.003	0.998	0.261	0.123	-0.144	0.374	-0.572	0.254
RVD_3, mm	-0.182	0.913	0.268	0.387	0.013	0.965	-0.529	0.565
RVD_{area}, cm^2	0.034	0.967	0.036	0.818	0.083	0.575	0.034	0.941
RVS_{area}, cm^2	0.059	0.925	-0.010	0.933	0.113	0.315	-0.315	0.365
$RA_{diameter}$, mm	-0.006	0.995	0.199	0.274	-0.128	0.460	-0.675	0.210
RA_{area}, cm^2	-0.016	0.977	0.333	0.001	-0.268	0.005	0.188	0.532

Cm, centimetres; Diff, difference; mm, millimetres; $RVOT_{PLAX}$, Right Ventricular Outflow Tract dimension from a parasternal long axis orientation; $RVOT_1$, proximal RVOT (short axis); $RVOT_2$, distal RVOT dimension (short axis); RVD_1, RV basal dimension; RVD_2, RV mid-ventricular dimension; RVD_3, RV longitudinal dimension; and RVD_{area}, RV area during end-diastole; RVS_{area}, RV area; RA_{area}, Right Atrial area, and; $RA_{diammeter}$, RA diameter during end-systole (minor axis).

7.3.9 RIGHT VENTRICLE AND RIGHT ATRIAL SIZE: Z-SCORE CALCULATOR

Observations of parameters of RV and RA size were then plotted against BSA with lines representing Z=0, 1, 2, -1, and -2 (Figure 7.7), with RSD accounting for heteroscedasticity. Based on the allometric model $y = a * BSA^b$, the Z-score parameters of RV and RA size for an athlete with a specific BSA can be calculated from Table 7.11 by using the specified *a and b* mean predicted parameters and *c and d* RSD for that parameter of RV and RA size:

$$z = \frac{obs - (a * BSA^b)}{c + (d * BSA)}$$

For example, a male paediatric athlete with a BSA of 1.4 m^2 and a $RVOT_{PLAX}$ of 30.5mm, the Z-score is calculated as 1.93 based on the predicted mean parameters for *a* (21.549), and *b* (0.38), and RSD parameters of *c* (2.050), and *d* (0.764).

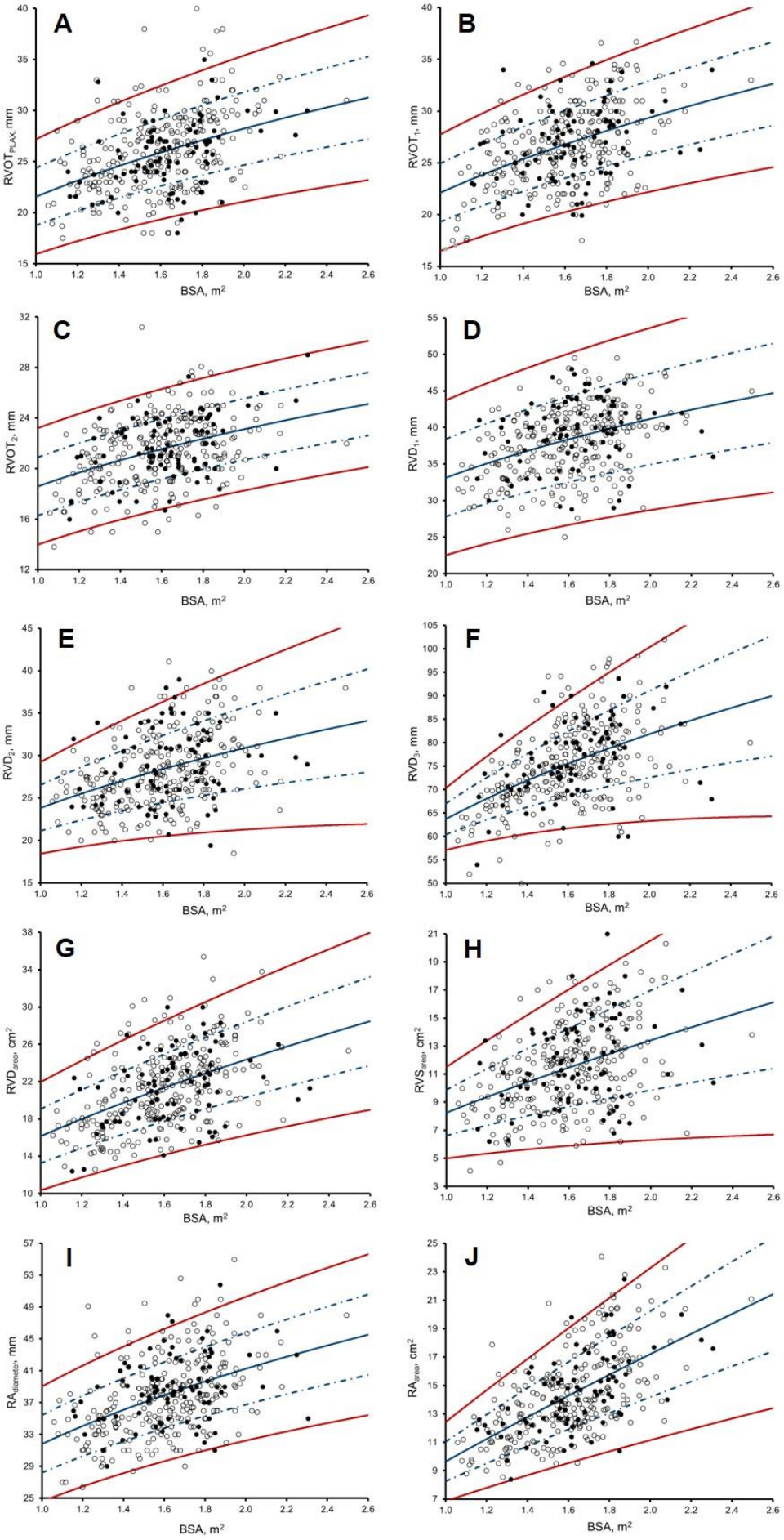
A
RVOT$_{PLAX}$, mm
BSA, m^2
B
RVOT$_1$, mm
BSA, m^2
C
RVOT$_2$, mm
BSA, m^2
D
RVD$_1$, mm
BSA, m^2
E
RVD$_2$, mm
BSA, m^2
F
RVD$_3$, mm
BSA, m^2
G
RVD$_{area}$, cm^2
BSA, m^2
H
RVS$_{area}$, cm^2
BSA, m^2
I
RA$_{diameter}$, mm
BSA, m^2
J
RA$_{area}$, cm^2
BSA, m^2

Figure 7. 7 Scatter plots of: A, Right Ventricular Outflow Tract dimension from a Parasternal Long Axis orientation ($RVOT_{PLAX}$); B, Proximal RVOT dimension, from a parasternal short axis orientation ($RVOT_1$); C, Distal RVOT dimension, from a parasternal short axis orientation ($RVOT_2$); D, RV basal Dimension (RVD_1); E, RV mid-ventricular Dimension (RVD_2); F, RV longitudinal Dimension (RVD_3), and; G, RV area during end-Diastole (RVD_{area}); H, RV area (RVS_{area}); I, Right Atrial diameter during end-systole, minor axis ($RA_{diammeter}$); and; J, RA area during end-systole (RA_{area}) to Body Surface Area (BSA) in 264 Arab (white dots) and 84 black (black dots) with predicted Z boundaries. Solid blue line, Z=0; dashed blue line, Z=1 and -1; solid red line, Z=2 and -2.

Table 7. 11 Models, Predicted Mean and Regressed Standard Deviation Parameters for Measurements of Right Ventricle and Atrial Size in the Arab and Black Paediatric Athlete.

		Predicted Mean Parameters		Regressed SD Parameters	
Parameter	Model	*a*	*b*	*c*	*d*
$RVOT_{PLAX}$, mm	Allometric	21.549	0.389	2.050	0.764
$RVOT_1$, mm	Allometric	22.102	0.408	2.064	0.775
$RVOT_2$, mm	Allometric	18.853	0.315	2.184	0.121
RVD_1, mm	Allometric	33.114	0.314	4.363	-0.064
RVD_2, mm	Allometric	23.828	0.375	0.592	2.109
RVD_3, mm	Allometric	63.711	0.361	-2.648	5.953
$RVD_{area,}$ cm^2	Allometric	16.142	0.594	1.743	1.157
$RVS_{area,}$ cm^2	Allometric	8.246	0.702	-0.299	1.930
$RA_{area,}$ cm^2	Allometric	9.644	0.835	-0.244	1.636
$RA_{diameter}$, mm	Allometric	31.814	0.375	2.714	0.899

Cm, centimetres; mm, millimetres; $RVOT_{PLAX}$, Right Ventricular Outflow Tract dimension from a parasternal long axis orientation; $RVOT_1$, proximal RVOT (short axis); $RVOT_2$, distal RVOT dimension (short axis); RVD_1, RV basal dimension; RVD_2, RV mid-ventricular dimension; RVD_3, RV longitudinal dimension; and RVD_{area}, RV area during end-diastole; RVS_{area}, RV area; RA_{area}, Right Atrial area, and; $RA_{diammeter}$, RA diameter during end-systole (minor axis).

7.3.10 RIGHT VENTRICLE AND RIGHT ATRIAL SIZE: APPLICATION OF ESTABLISHED REFERENCEVALUES

RV and RA size allometric relationship to BSA was accounted for by the Z-score boundaries of Cantinotti *et al.* (2014) (Figure 7.8). Upper boundaries of Cantinotti *et al.* (2014), for RVD_2 (7.2% vs. 13.1%), RVD_3 (33.7% vs. 38.1%), RVD_{area} (11.0% vs. 13.1%), and $RVS_{area,}$ (41.3% vs. 41.7%), were often exceeded in male Arab and black paediatric athletes, respectively. Correlation remained to BSA (*r =-0.135 to -0.287, all P values ≤0.01*) in 71.4%, to chronological age (*r = -0.136 to -0.150, all P values ≤0.02)* in 28.6%, and to biological age (r = -0.128 to -0.173*, all P values ≤0.01*) in 28.6% of computed RV and RA size Z-score parameters, defined as per Cantinotti et al. (2014) (Table 7.12**)** $RVOT_{PLAX}$ and $RVOT_1$, often met minor (36.0% and 39.3% for $RVOT_{PLAX}$ and 26.9% and 28.6% for $RVOT_1$ in Arab and black athletes, respectively) and major (16.7% and 7.1% for $RVOT_{PLAX}$ and 7.2% and 7.1% for $RVOT_1$ in Arab and black athletes, respectively) indexed structural criteria for arrhythmogenic RV cardiomyopathy. Concomitant minor structural echocardiography and ECG criteria were met by 4.8% Arab and 2.3% black athletes respectively, compatible with two minor diagnostic criteria for ARVC. No RV wall motion abnormalities, including akinesia, dyskinesia, and aneurysm were found in either group.

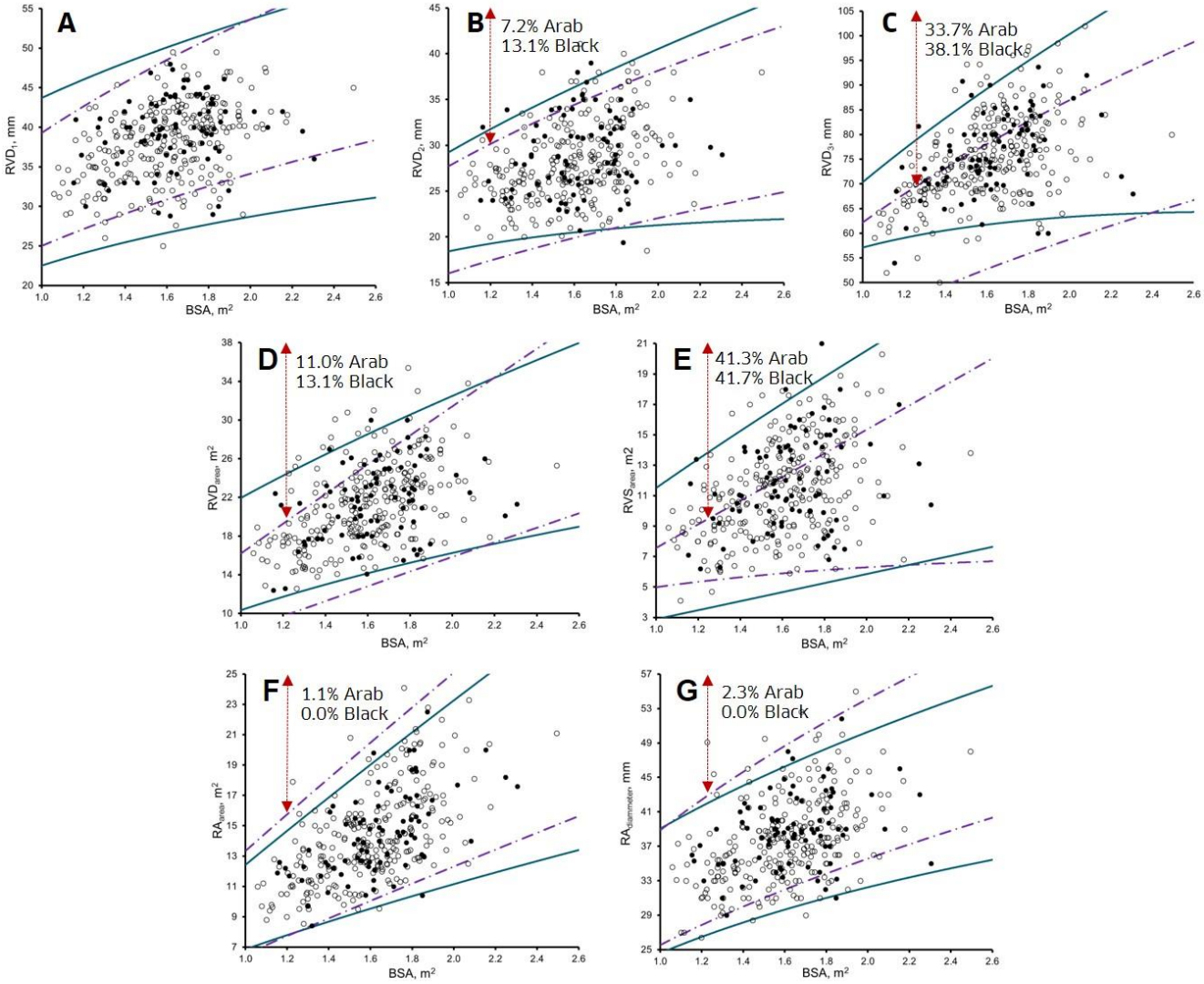

Figure 7. 8 Scatter plots of: A, Right Ventricular basal dimension (RVD_1); B, RV mid-ventricular dimension (RVD_2); C, RV longitudinal dimension (RVD_3), AND; D, RV area during end-diastole (RVD_{area}); E, RV area (RVS_{area}); F, Right Atrial diameter during end-systole, minor axis ($RA_{diammeter}$); and G, RA area during end-systole (RA_{area}) to Body Surface Area (BSA) in 264 Arab (white dots) and 84 black (black dots). Solid blue line, Z=2 and -2 as per proposed reference values, dashed purple line Z=2 and -2 as per Cantinotti *et al.* (2014) proposed reference values. The percentages of Arab and black athletes exhibiting Z ≥2/≤-2 are demonstrate

Table 7. 12 Correlation Analysis for Z-score Parameters of Right Ventricle and Atrial size in the Arab and Black Paediatric Athlete, Computed as per Cantinotti *et al*.(2014)

	Correlation Analysis							
	BSA		Chronological Age		Biological Age		Ethnicity	
Parameter	R	P Value	R	P Value	R	P Value	Mean Diff	P Value
RVD_1, mm	-0.230	<0.0001	-0.136	0.011	-0.128	0.0172	-0.223	0.091
RVD_2, mm	-0.101	0.059	-0.007	0.901	-0.062	0.250	-0.129	0.315
RVD_3, mm	-0.188	0.000	-0.059	0.274	-0.091	0.090	-0.045	0.718
$RVD_{area,}$ cm^2	-0.287	<0.0001	-0.150	0.005	-0.173	0.001	0.056	0.666
$RVS_{area,}$ cm^2	-0.174	0.001	-0.076	0.155	-0.066	0.218	-0.092	0.486
$RA_{diammeter}$, mm	-0.135	0.012	-0.055	0.307	-0.097	0.072	-0.163	0.224
$RA_{area,}$ cm^2	-0.081	0.132	0.030	0.583	-0.090	0.095	0.070	0.543

Cm, centimetres; Diff, difference; mm, millimetres; $RVOT_{PLAX}$, Right Ventricular Outflow Tract dimension from a parasternal long axis orientation; $RVOT_1$, proximal RVOT (short axis); $RVOT_2$, distal RVOT dimension (short axis); RVD_1, RV basal dimension; RVD_2, RV mid-ventricular dimension; RVD_3, RV longitudinal dimension; and RVD_{area}, RV area during end-diastole; RVS_{area}, RV area; RA_{area}, Right Atrial area, and; $RA_{diammeter}$, RA diameter during end-systole (minor axis).

7.3.11 RIGHT VENTRICLE TDI, TAPSE, RVFAC: MODEL SELECTION

Visual inspection of biological plausibility, and the additional amount of variance (R^2), explained by a third-order polynomial model (maximal increase of 1%, considered clinically insignificant), contributed to the adoption of a second-order polynomial model across all RV TDI parameters. No residual association to chronological and biological age, BSA, ethnicity and, HR was observed across all RV TDI parameters (Table 7.13). TAPSE and RVFAC revealed no residual association to chronological age, but between RVFAC to biological age and BSA (Table 7.14). Adoption of a second-order polynomial model to TAPSE and RVFAC was considered clinically insignificant.

Table 7. 13 Residual Association for Parameters of Right Ventricle Tissue Doppler Imaging Velocities in the Arab and Black Paediatric Athlete ($y = a * chronological\ age^2 + b * chronlogical\ age + c$).

	Residual Analysis									
	Chronological Age		Biological Age		BSA		Heart Rate		Ethnicity	
Parameter	Slope	P Value	Slope	P Value	Slope	P Value	Slope	P Value	Mean Diff	P value
RV TDI S', cm/s	0.000	1.000	0.203	0.021	-1.393	0.065	0.015	0.153	0.311	0.242
RV TDI E', cm/s	0.000	1.000	0.240	0.037	-2.196	0.027	0.012	0.392	0.002	0.995
RV TDI A', cm/s	0.000	1.000	-0.026	0.780	0.520	0.510	0.020	0.067	0.323	0.245

Cm/sec, centimetres/second; Diff, difference; mm, millimetres; RV TDI, right ventricle Tissue Doppler Imaging.

Table 7. 14 Correlation Analysis for TAPSE and RVFAC in the Arab and Black Paediatric Athlete

	Correlation Analysis								Ethnicity	
	Chronological Age		Biological Age		BSA		Heart Rate			
Parameter	R	P Value	R	P Value	R	P Value	R	P Value	Mean Diff	P Value
TAPSE, mm	0.085	0.122	0.089	0.098	0.090	0.094	-0.028	0.599	-0.083	0.506
RVFAC, %	-0.099	0.065	-0.150	0.005	-0.155	0.032	-0.031	0.570	0.209	0.095

Diff, difference; mm, millimetres; RVFAC, Right ventricular fractional area change; TAPSE, tricuspid annular plane systolic excursion.

7.3.12 RIGHT VENTRICULAR TDI, TAPSE, AND RVFAC: Z-SCORE CALCULATOR

Observed RV TDI velocities, TAPSE and RVFAC were plotted against chronological with lines representing Z=0, 1, 2, -1 and -2 (Figure 7.9), with RSD accounting for heteroscedasticity. Based on these models, the Z-score of a TDI velocity for an athlete with a specific chronological age can be calculated from Table 7.15 by using the specified *a*,*b*, and *c* mean predicted parameters and *d* and *e* RSD for that TDI velocity:

$$z = \frac{obs - ((a * chronological\ age^2) + (b * chronological\ age) + c)}{d + (e * chronological\ age)}$$

For example, a 12-year-old male paediatric athlete with a TDI S' velocity of 10.0, cm/sec, the Z-score is calculated as -1.98 based on the predicted mean parameters for *a* (0.051), *b* (-1.631), *c* (26.370), and RSD parameters *d* (2.095), and *e* (0.000).

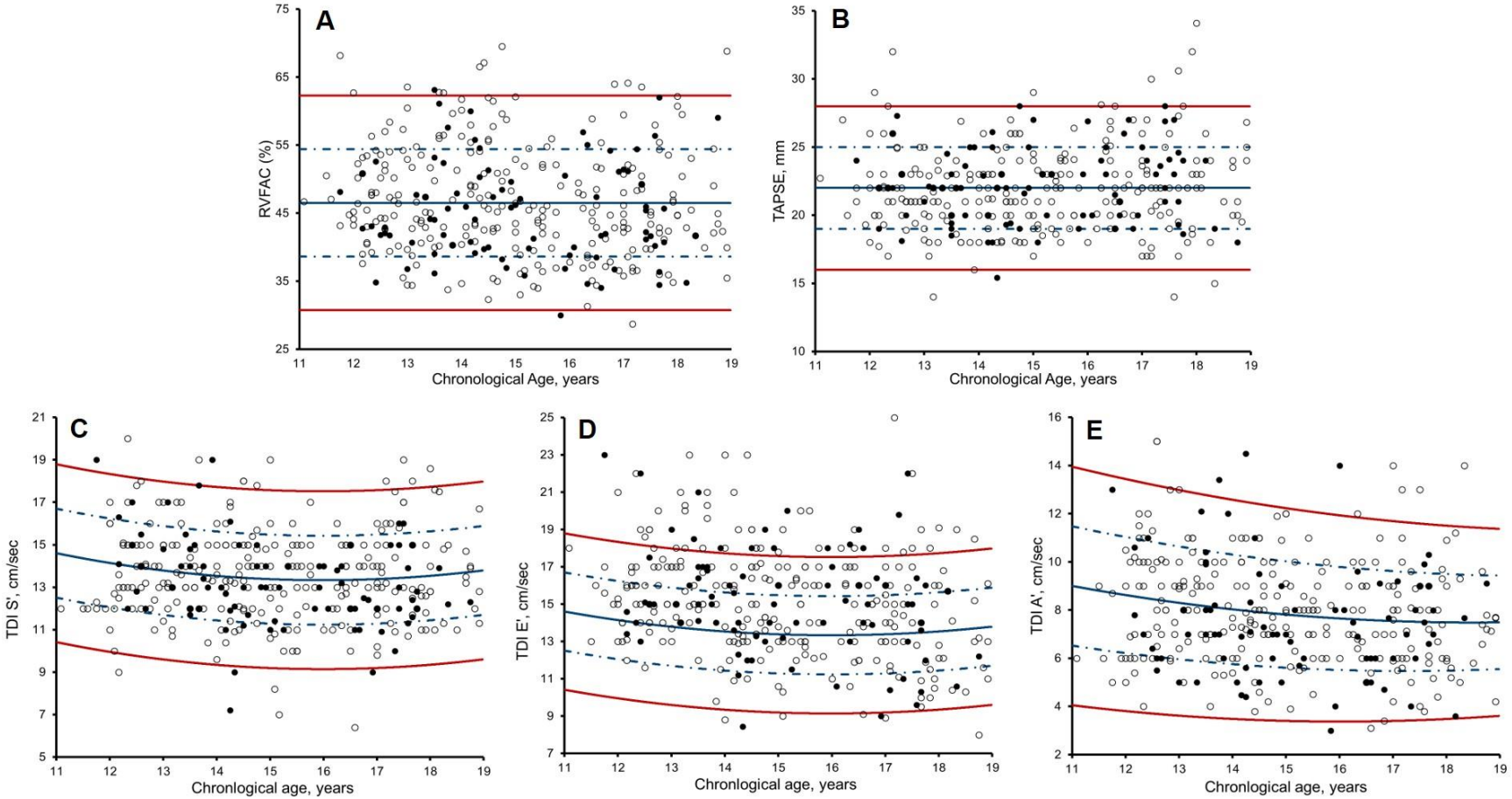

Figure 7. 9 Scatter plots of: A, Right Ventricular Fractional Area Change (RVFAC); B, Tricuspid Annular Plane Systolic Excursion (TAPSE); C, Right Ventricular Systolic velocity (RV TDI S'); D, in early diastole (RV TDI E'); and E, late diastole (RV TDI A') to chronological age in 264 Arab (white dots) and 84 black (black dots) with proposed Z boundaries. Solid blue line, Z=0; dashed blue line, Z=1 and -1; solid red line, Z=2 and -2.

Table 7. 15 Models, Predicted Mean and Regressed Standard Deviation Parameters for Measurements Right Ventricle Tissue Doppler Imaging Velocities, TAPSE and RVFAC in the Arab and Black Paediatric Athlete.

		Predicted Mean Parameters			Regressed SD Parameters	
Parameter	Model	*a*	*B*	*c*	*d*	*e*
RVFAC, %	-	46.507	-	-	7.900	-
TAPSE, mm	-	21.986	-	-	2.994	-
TDI S', cm/sec	Polynomial (Second Order)	0.051	-1.631	26.370	2.095	-
TDI E', cm/sec	Polynomial (Second Order)	-0.023	0.336	15.434	1.201	0.104
TDI A', cm/sec	Polynomial (Second Order)	0.027	-0.999	16.724	3.212	-0.067

Cm/sec, centimetres/second; mm, millimetres; RVFAC, right ventricular fractional area change; TAPSE, tricuspid annular plane systolic excursion.

7.3.13 RIGHT VENTRICULAR TDI: APPLICATION OF ESTABLISHED REFERENCE VALUES

TDI S' non-linear relationship to chronological age, was visually not accounted for by the Z-score boundaries of Koestenberger *et al*. (2012) (Figure 7.10). 6.1% and 4.8% of Arab and black athletes, respectively, were regarded to have reduced (≥-2Z) TDI S' velocities, with 14.4% observed velocities outside the predicted Z-score boundaries. Significant correlation remained to BSA (*r = -0.144*, p=0.034) and HR (*r = 0.117*, p=0.029). RVFAC often met minor (19.3% vs. 25.0%) and in some major (1.1% vs 1.2%) functional criteria for ARVC in Arab and black athletes, respectively. Concomitant minor RVFAC and ECG criteria were observed in 1.1% Arab and 2.4% and black athletes, respectively, compatible with two minor diagnostic criteria for ARVC.

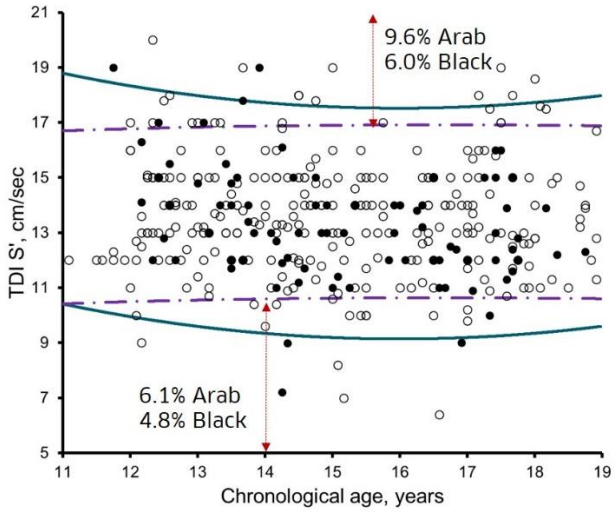

Figure 7. 10 Scatter plot of Right Ventricular Tissue Doppler Imaging in Systole (RV TDI S') to chronological age in 264 Arab (white dots) and 84 black (black dots). Solid blue line, Z=2 and -2 as per proposed reference values, dashed purple line Z=2 and -2 as per Koestenberger *et al.* (2012) proposed reference values. The percentages of Arab and black athletes exhibiting Z ≥2/≤-2 are demonstrated.

7.4 DISCUSSION

The correct differentiation of physiological cardiac enlargement or functional adaptations owing to regular and sustained exercise to cardiac pathology is paramount to the detection of athletes at risk of SCD/A. For the first time, we present BSA, ethnicity, chronological, and biological age independent measures of cardiac chamber and aortic root morphology in male Arab and black paediatric athletes. Secondly, we present chronological age independent LV and RV measures of Doppler and TDI velocities, RVFAC and TAPSE in male Arab and black paediatric athletes. To place into clinical context, we propose a new tool for differential diagnosis of physiological remodelling to an indicator of cardiac pathology, by the establishment of male paediatric athlete specific nomograms and Z-scores, obviating the need for ethnic-specific normative ranges.

7.4.1 LEFT VENTRICLE, LEFT ATRIAL AND AORTIC ROOT MORPHOLOGY

Investigations in the UK, France (Sheikh et al., 2013), and Italy (Di Paolo *et al.*, 2012; Pelà *et al.*, 2014), indicate that black paediatric athletes present with disproportionately increased LV wall thickness and LAD to white paediatric athletes, irrespective of chronological age. Indeed, in the investigations of Sheikh *et al.* (2013), almost 25% of black athletes who presented LVH (>12 mm), were chronologically aged < 16 years old. Leading to proposals that upper limits of LVH, established in the black adult athlete (>15mm), may also be applied to the black paediatric athlete. Paediatric athletes, however, undergo significant changes in anthropometry during maturation, acting as important determinants of cardiac size (George et al., 2001). Indeed, our data questions proposals that upper limits of LVH not adjusted to body size, and chronological age are

appropriate for application in the Arab and black paediatric athlete. Until now, our understanding of ethnic-specific LA physiological remodelling in the paediatric athlete has been limited to the assessment of LAD (Di Paolo *et al.*, 2012; Sheikh *et al.*, 2013). The LA, however, is a non-symmetrically shaped three-dimensional structure, therefore, differential diagnosis of physiological to pathological dilatation determined solely by LAD increases the risk of a false-negative diagnosis (Lester et al., 1999; Vyas et al., 2011). We, therefore, determine the impact of ethnicity to physiological LA enlargement by assessment of LA volume. Evaluation of volume, accounts for dilatation of the LA in all directions, providing a powerful prognostic value to a variety of inherited cardiomyopathies (Rossi et al., 2002; Losi et al., 2004). For the first time, we provide references values of LV, LA, and aortic root size allometrically normalised to BSA and chronological age in the male Arab and black paediatric athlete. References values were independent of biological age, whilst obviating the need for ethnic-specific normative ranges, therefore, simplifying clinical interpretation.

7.4.2 LEFT VENTRICLE, LEFT ATRIAL AND AORTIC ROOT MORPHOLOGY: APPLICATION OF ESTABLISHED REFERENCE VALUES

Until recently, investigations defining upper limits of physiological remodelling within the paediatric athlete were defined by chronological age (Sharma et al., 2002; Makan et al., 2005b; Koch et al., 2014). Cavarretta *et al.* (2018), now provide reference values in white Italian paediatric (chronological age 8-18 years) soccer players, which account for both chronological age and BSA, whilst enabling Z-score calculation. Although Cavarretta *et al.* (2018) considered heteroscedasticity, employing logarithmic transportations of both

BSA and cardiac measurements, testing for the absence of residual heteroscedasticity is not mentioned. Furthermore, mathematical transformations are artificial, often introducing distortion of the data and obeys statistical models that behave very differently than those in the arithmetic scale (Packard and Boardman, 2008). Reflected in exceedingly high boundaries for Aortic Root size, and notably wide boundaries for LVIDd and LV mass when applied to male Arab and black paediatric athletes. Of additional concern, computed Z-scores of IVSd, PWTd, and LV mass were not chronological or biological age independent, whilst IVSd was not BSA independent; indicative of bias. Subsequently, upper limits (≥2Z) of normality for PWTd in an 11-year-old athlete with a BSA of 1.2 m^2, were considered to be 7.2 mm as per our proposed reference values, but 8.9 mm as per Cavarretta *et al.* (2018). It is, therefore, possible, application of Cavarretta *et al.* (2018) proposed reference values to the male Arab and black paediatric athlete may lack adequate sensitivity.

7.4.3 LEFT VENTRICLE DOPPLER AND TDI VELOCITIES

Enhanced LV diastolic function owing to regular and sustained exercise in some cases may represent supernormal diastolic function (Claessens et al., 2001; D'Ascenzi et al., 2011). Although adult athlete specific cut-offs have been appropriately defined (Finocchiaro et al., 2018), chronological age is a strong determinant of myocardial relaxation, leading to calls for paediatric athlete specific thresholds of normality (Finocchiaro et al., 2018). Indeed, we observed an inverse relationship between chronological age to TDI velocity, necessitating non-linear modelling for the establishment of appropriate cut-offs. LV function in the paediatric athlete is understood to be

independent of ethnicity, however, investigations are limited to Doppler velocity assessment (Di Paolo *et al.*, 2012; Sheikh *et al.*, 2013), precluding an understanding of regional relaxation and contractile function. Despite adjustment for chronological age, Lateral TDI E' velocity was dependent to ethnicity. Although, considered clinically insignificant with the determination of ethnic-specific *a* and *b* coefficients and *c* constants, explaining only an additional 2% of the variance (R^2).

Secondary to supernormal diastolic function, the paediatric athletes echocardiogram is typically characterised by a 'reduced' LVEF, observed to be as low as 50% [41,132,262], creating an illusion of an abnormal pump function. The limitations of this parameter are highlighted by recent studies of pathological hypertension, in patients diagnosed with heart failure, but with normal EF (MacIver and Townsend, 2008). Accordingly, we provide reference values for the assessment of systolic function at the mitral annular tissue level (TDI S'), within the Arab and black paediatric athlete, which may allow for superior differential diagnosis by the detection of reduced subendocardial fibre function (Kitaoka et al., 2013).

Finally, a significant residual association was present to HR for parameters of Transmitral A Velocity, Transmitral E/A, and Septal TDI A'. Owing to the complex relationship of HR on Doppler and TDI velocity, we did not attempt to normalise to HR. With this in mind, normalised measures with HR dependency should be interpreted with caution, especially in athletes with a resting HR unusually low or high for their respective chronological age.

7.4.4 LEFT VENTRICLE DOPPLER AND TDI VELOCITIES: APPLICATION OF ESTABLISHED REFERENCE VALUES

Preliminary investigations of Unnithan et al. (2018) revealed that despite systematic training in the Premier League academy soccer player, diastolic (Lat E') and systolic (Lat S') function is not modulated in the paediatric athlete at rest. We were, therefore, surprised Dallaire *et al*. (2015) reference values, derived from the paediatric non-athlete, indicated supernormal diastolic function (lateral TDI E' velocity) in 9.4% Arab and 7.5% black paediatric athletes. Furthermore, raised LA filling pressure were indicated in 11.1% Arab and 16.7% black paediatric athletes, respectively. Secondary to supernormal diastolic function was the indication of reduced systolic function (lateral TDI S' velocity) in 7.7% Arab and 7.5% black paediatric athletes. It is, therefore, apparent, established reference values of Doppler and TDI derived from the paediatric non-athlete are not appropriate for application in male Arab and black paediatric athletes in view of false positive rates for possible impaired cardiac function in these apparently healthy paediatric athletes. Whilst indicative of a relative load dependency to Doppler and TDI velocity. We, therefore, propose the application of paediatric athlete specific reference values to be necessary, to evade a high burden of false positives.

7.4.5 RIGHT VENTRICLE AND RIGHT ATRIA MORPHOLOGY

For the first time, we demonstrate balanced physiological RV and RA enlargement, in the paediatric Arab and black (chronological age 11-18 years) athlete, extending observations in the white soccer scholar (chronological age 15-17 years) player (Popple

et al., 2018). Adaptations likely attributable to significant volumetric challenges imposed from regular and sustained high-intensity exercise, required to augment cardiac stroke volume, in addition to a disproportionate increase in RV to LV wall stress during exercise (La Gerche et al., 2011). Challenges likely acting as acute stimuli for chronic adaptation (Oxborough et al., 2014a), irrespective of a still maturing heart. In contrast to Zaidi *et al*. (2013), however, RVOT size; an essential component of ARVC criteria, was not dissimilar by ethnicity. An observation which may in part be explained by the dominance of football participation irrespective of ethnicity (Arab 53% vs. black 44%) in our cohort, in contrast to a disproportionate participation in high dynamic-high static sports in white to black athletes (6.0% vs. 27.2%) of Zaidi *et al*. (2013). We believe our data obviates the need for ethnicity-specific RV and RA references values in the male Arab and black paediatric athlete.

7.4.6 RIGHT VENTRICLE AND RIGHT ATRIA MORPHOLOGY: APPLICATION OF ESTABLISHED REFERENCE VALUES.

Physiological RV remodelling may, however, mimic phenotypic expression of ARVC (Oxborough et al., 2012; Zaidi et al., 2013a; Popple et al., 2018). Differential diagnosis further challenged by the presentation of anterior TWI, which is pertinent to ARVC criteria, in a significant proportion of Arab (major: 0.4%; minor 2.7%) and black (major: 2.4% minor: 7.1%) paediatric athletes. Creating a true diagnostic challenge in 4.8% Arab and 2.3% black athletes, respectively. Although no athlete presented with RV wall motion abnormalities and therefore full imaging criteria for ARVC was met in none, identification is difficult (Lindstrom, 2001; Sievers et al., 2004). Physiological remodelling of RV length

and area may pose diagnostic challenges, exceeding upper limits of Cantinotti *et al.* (2014) in many Arab (RVD_3: 33.7%; RVD_{area}: 11.0%) and black (RVD_3: 38.1; RVD_{area}: 13.1%) paediatric athletes. Dilatation of RV inflow (RVD_1) diameter, a recognised manifestation of the endurance (Oxborough et al., 2012) and soccer scholar's (Popple et al., 2018) athletes heart, however, was considered prevalent in none, as per the reference values of Cantinotti *et al.* (2014). Indicative of non-symmetric RV remodelling in the male Arab and black paediatric athlete. Findings of relative surprise, as considerable care was taken to ensure that RV size was maximized in the apical views, that RVD_1 was measured at the widest point of the basal third of the ventricle, and that trabeculations were included within the cavity measurement, in accordance with current ASE guidelines (Rudski et al., 2010a). Yet upon careful evaluation, as per the reference values of Cantinotti *et al.* (2014), upper limits of normality ranged from 44.4 mm in the paediatric with a BSA of 1.05 m^2 to 57.6 mm in the paediatric with a BSA of 2.5 m^2. Upper limits which exceed those of the ASE for adults (>42 mm), applied to the soccer scholar player (Popple et al., 2018), and those of the adult endurance athlete (>54mm) (Oxborough et al., 2012). Application of paediatric athlete specific reference values, therefore, appears necessary for accurate differential diagnosis of physiological to pathological RV and RA remodelling in Arab and black male paediatric athletes.

7.4.7 RIGHT VENTRICLE TDI VELOCITIES, TAPSE AND RVFAC

Conventional assessment of RV function is challenging owing to its complex structure, location and thin myocardial walls (Rudski et al., 2010b). Factors which may in part explain the scant available data in the paediatric athlete (D'Ascenzi et al., 2017c; Popple

et al., 2018). Thereby significantly impairing differential diagnosis as measures of RV systolic function, namely RV TDI S', are guided by cut-offs derived from the adult athlete (D'Ascenzi et al., 2018b), which do not account for chronological age or BSA. Whilst just 5 months of endurance training in the paediatric is understood to induce significant RV functional alterations (D'Ascenzi et al., 2017c), therefore, reference values derived from the paediatric non-athlete (Koestenberger et al., 2012), are likely, not appropriate. Accordingly, we define paediatric athlete specific RV TDI velocity lower-limits, normalised to chronological age, owing to its inverse relationship. Clinical importance is illustrated by lower limits indicative of impaired RV systolic function (RV TDI S'), ranging from 9.1 cm/s in the 13-year-old athlete, to 10.4 cm/s in the 11-year-old athlete.

7.4.8 RIGHT VENTRICLE TDI VELOCITIES, TAPSE, AND RVFAC: APPLICATION OF ESTABLISHED REFERENCE VALUES.

Physiological RV functional alterations may result in diagnostic overlap with impaired systolic function. Specifically, TDI S' velocity, was regarded to be impaired among 6.1% and 4.8% of Arab and black athletes, respectively, as per reference values of Koestenberger *et al*. (2012). Functional alterations that may extend to reduced RVFAC, indicative of ARVC in Arab (minor: 19.3%; major: 1.1%) and black (minor: 25.0%; major: 1.2%) athletes as per the Task Force Criteria (Marcus et al., 2010), respectively. Differential diagnosis further challenged in the presence of concomitant TWI in V_1-V_2 in athletes chronologically aged >14 years old (in the absence of CRBBB), or in V_4, V_5, or V_6, prevalent in 1.1% Arab and 2.4% black athletes, respectively. We, therefore, believe our proposed reference values, which account for functional adaptations and

chronological age, may support the accurate detection of cardiac pathology in the male Arab and black paediatric athlete.

7.4.9 CLINICAL IMPLICATIONS

The differential diagnosis between physiological remodelling to that indicate of an inherited cardiomyopathy within the male Arab and black paediatric athlete may be aided by the determination of Z-scores for a variety of cardiac measures. Calculated visually by nomograms or more accurately by application of Z-score equations, publicly available on http://www.echocalc.org/arab-and-black-paediatric-athlete-calculator/ (password = bse). A website designed to be usable on devices of any size, ranging from small smartphones to laptops/desktop computers. We believe the Z-scores provided will significantly aid clinical interpretation, owing to their BSA, ethnicity, chronological and biological age independence. Whilst serving particularly useful in tracking allometric growth over time in the paediatric athlete necessitating annual follow-up.

7.4.10 LIMITATIONS

Our population were exclusively Arab and black male athletes, limiting application to other ethnicities and the female paediatric athlete. Secondly, ethnicity was self-determined, without consideration to the impact of geographical origin (Riding et al., 2019), owing to insufficient sample size. However, the relative impact of ethnicity was considered clinically insignificant, when cardiac size was allometrically normalised. Thirdly, while we recruited only athletes who were registered with the Qatar Olympic Committee exercising ≥6

hours/week, we did not define fitness (such as aerobic capacity). Finally, measures of speckle tracking echocardiography were not included, as parameters were limited to standard echocardiographic assessment.

7.4.11 CONCLUSION

For the first time, we present BSA, ethnicity, chronological, and biological age independent measures of cardiac chamber and aortic root morphology in male Arab and black paediatric athletes. Secondly, we present chronological age independent LV and RV measures of Doppler and TDI velocities, RVFAC and TAPSE in male Arab and black paediatric athletes. This data may prove useful to differential diagnosis in cardiac screening of the paediatric athlete, with upper limits of physiological remodelling and lower limits of function defined by Z-scores to ease clinical interpretation, whilst assisting in the tracking of allometric growth in the paediatric athlete necessitating annual follow-up.

CHAPTER 8:

GENERAL DISCUSSION

8.1 AIMS OF THESIS

The work in this thesis facilitated the completion of a number of objectives in Arab and black male paediatric athletes, which were: 1) Systematically reviewed the available literature with qualitative and quantitative analysis, describing the ECG, structural and functional manifestations of the paediatric athlete's heart compared with that of age-matched non-athletes; 2) Established the diagnostic accuracy of new international recommendations for ECG interpretation in athletes (Drezner et al., 2017; Sharma et al., 2017b, 2018) against the Seattle criteria (Drezner et al., 2013a) and 2010 ESC recommendations (Corrado et al., 2010), in paediatric athletes; 3) Determined the prevalence, determinants, and significance of TWI by ethnicity, chronological and biological age within Arab and black male paediatric athletes; and 4) Determined the allometric relationship of cardiac size to BSA and the impact of biological and chronological age in paediatric athletes. In addition, the non-linear relationship of cardiac function to chronological age, and the impact of biological age, BSA and HR were also assessed. Further, the impact of Arab and black ethnicity to cardiac size and function in paediatric athletes was explored.

8.2 OVERARCHING ISSUES AND IMPLICATIONS FOR PRE-PARTICIPATION CARDIAC SCREENING IN THE PAEDIATRIC ATHLETE

8.2.1 WHICH RECOMMENDATIONS FOR ECG INTERPRETATION ARE APPLICABLE TO THE PAEDIATRIC ATHLETE?

The ESC state that 12-lead ECG screening should start at the beginning of competitive athletic activity, which for the majority of sporting disciplines corresponds to a chronological age of 12-14 years. The application of this recommendation is considered the law in Italy and Greece, leading to cardiac screening in the athlete as young as 8 years. As demonstrated in Chapter 4, regular and prolonged physical training is associated with a high prevalence of bradycardia, repolarisation changes, atrial enlargement and ventricular hypertrophy in paediatric athletes, thus making the application of criteria derived from the non-athlete (Davignon et al., 1980; Rijnbeek et al., 2001; Molinari et al., 2016; Saarel et al., 2018a) likely inappropriate. Until recently, recommendations for ECG interpretation in athletes did not consider the paediatric athlete (Corrado et al., 2010; Drezner et al., 2013a), leaving the attending physician in a conundrum of which criteria to use.

For the first time in Chapter 5, we demonstrated that in Arab athletes, new international recommendations for ECG interpretation in athletes significantly reduce false positive rates compared to the ESC 2010 recommendations and Seattle criteria by 85% and 72.2% respectively, and in black male paediatric athletes by 80% and 62.4% respectively.

An acceptable false-positive rate was maintained irrespective across chronological ages in Arabs [≤16 years (5.0%) vs ≤14 years (5.4%) vs ≤12 years (5.5%)], but was variable in black paediatric athletes [≤16 years (12.5%) vs ≤14 years (15.5%) vs ≤12 years (19.2%)]. Furthermore, diagnostic accuracy for the detection of cardiac pathology that may cause SCD/A was 'fair' (0.72, 95% CI 0.50 to 0.94) in Arab and 'good' (0.85, 95% CI 0.65 to 1.00) in black male paediatric athletes, and poor (0.64, 95% CI 0.47 to 0.81) when undertaking cardiac screening by physical examination and health questionnaire alone. It is, therefore, apparent that cardiac screening within the paediatric athlete should be led by the 12-Lead ECG, with interpretation governed by new international recommendations (Drezner et al., 2017; Sharma et al., 2017b, 2018).

New International recommendations may trigger further diagnostic tests in 7.5%, but it's statistically improbable for 1 in 14 paediatric athletes (who present for first time cardiac screening) to have a cardiac pathology that may cause SCD/A. For example, if 100 paediatric athletes attended for first time cardiac assessment, we understand that before undertaking any diagnostic test, inclusive of a medical questionnaire and/or physical examination, the 'chance' of detecting a cardiac pathology that may cause SCD/A within the male paediatric athlete is 1 in 100. With the addition of the ECG and application of the new international recommendations for interpretation, in the paediatric athlete with a positive ECG (+LR=9.0), the 'chance' of detection increases to 8 in 100. In the paediatric athlete with a negative ECG (−LR=0.4), the 'chance' of detection decreases to 0.4 in 100, an observation which did not significantly differ by ethnicity (Figure 8.1).

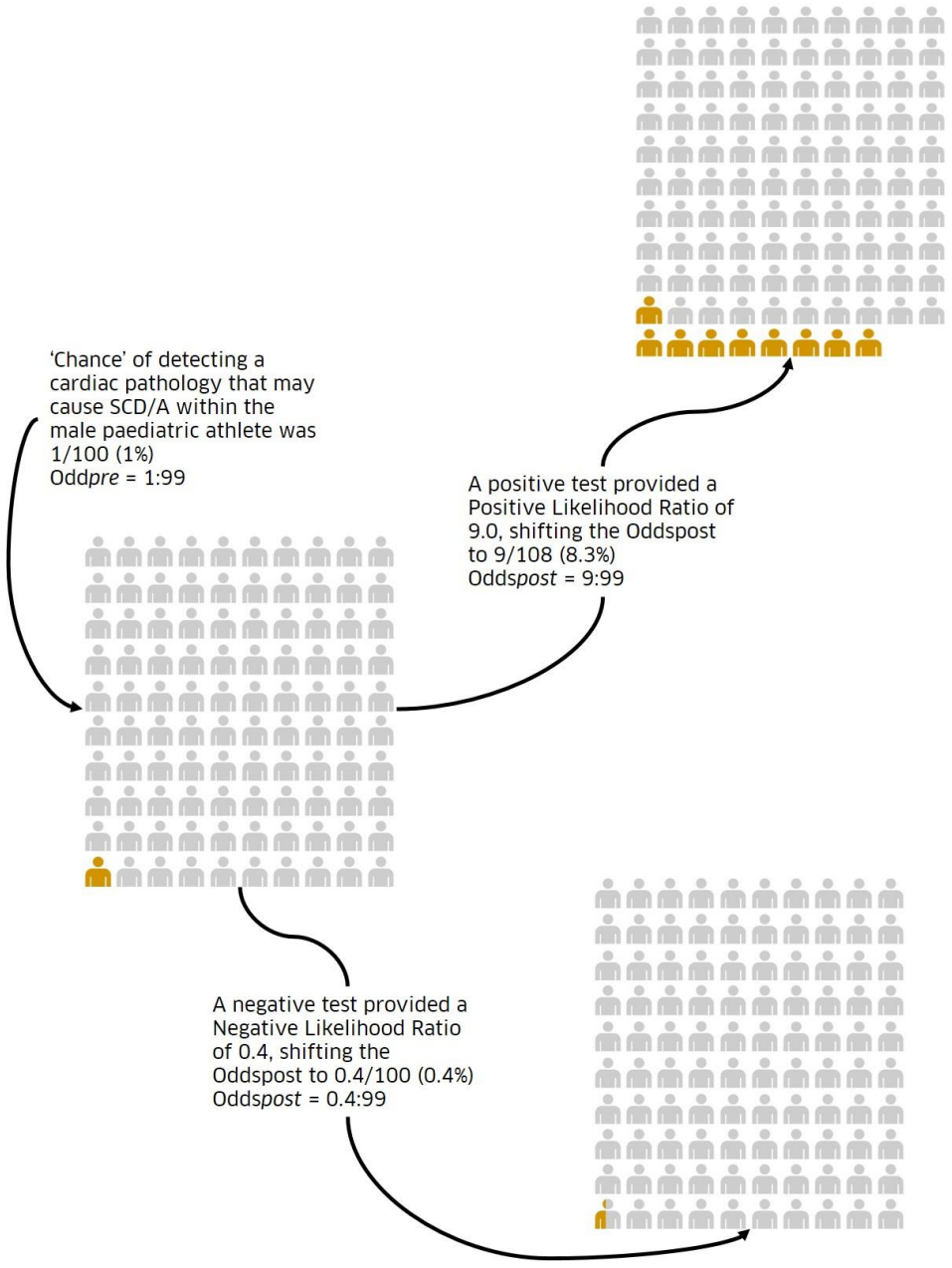

Figure 8. 1 Chance of detecting cardiac pathology in the male paediatric athlete that may cause Sudden Cardiac Death/Arrest before undertaking any diagnostic test and using a medical questionnaire and/or physical examination (Odds*pre*), and after a positive or negative ECG (Odds*post*) as per new international recommendations.

8.2.2 ANTERIOR TWI IN THE PAEDIATRIC ATHLETE: GOVERNED BY BIOLOGICAL OR CHRONOLOGICAL AGE?

In Chapter 5, we demonstrated that new international recommendations for ECG interpretation in male Arab and black paediatric athletes provide a 'fair' (AUC 0.77) diagnostic accuracy. Whilst specificity was remarkably high (93.2%), sensitivity was comparatively low, missing 38.5% of cardiac pathologies that may predispose to SCD/A in sports. However, the ECG is unable to detect anomalous coronary arteries (n=1), aortopathies (n=2) and valvular disease (=1), (Drezner et al., 2017; Sharma et al., 2017b, 2018) and thus helps explain the sensitivity of 61.5% observed. Nevertheless, precision medicine is, '*an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person'* (https://ghr.nlm.nih.gov/primer/precisionmedicine/initiative, 2018). In Chapter 6, we, therefore, proposed the question, can we do better? And therefore, further refine recommendations for ECG interpretation in the paediatric athlete?

TWI may represent the first and only sign of cardiac pathology predisposing to an increased risk of SCD/A, and, therefore, its presentation on an ECG creates considerable concern (Schnell et al., 2014; Wilson and Carre, 2015; Sheikh et al., 2018). Yet, TWI in V_1-V_4 preceded by Jt and/or ST-segment elevation in the black athlete and TWI in V_1-V_3 in the athlete with a chronological age <16 years is considered normal as per new international recommendations for ECG interpretation in athletes (Drezner et al., 2017; Sharma et al., 2017b, 2018). Interpretation directed by chronological age is simple, but limitations must be considered in application.

Chronological age is a linear factor, yet maturity status, which is believed to underpin presentation of TWI in V_1–V_3, owing to an incomplete formation of adult ventricular mass (Park and Guntheroth, Warren, 2006) and thus probable displacement of the RV towards the left axila, is not. In extreme cases, biological age can vary by 6 years between two 9-year-old boys (Johnson et al., 2009). Indeed, significant ethnic variations exist in the chronological age of onset of puberty in both boys and girls (Ontell and Barlow, 1996; Kashani et al., 2009). Furthermore, in Chapter 7, we observed biological age, estimated from radiological hand–wrist imaging of the left hand–wrist by the Fels method (Roche et al., 1988), to be significantly greater than the chronological age of our male Arab and black paediatric athletes. Consistent with our observations, football academy selection appears to systematically favour the maturing athlete, with an approximate 10 fold increased chance of selection in the early maturing athlete evidenced across an English Premier League Football Academy (Manchester United) and Middle Eastern Sports Academy (Aspire Academy) (Johnson et al., 2017), wherein ethnicity was heterogeneous. In consideration that maturity status underpins presentation of TWI in V_1–V_3, together with an increased likelihood of being presented with a paediatric academy player who is biologically more mature than their chronological age owing to a selection bias (Johnson et al., 2017), one wonders should biological not chronological age be used to guide interpretation of TWI in V_1–V_3 in the paediatric athlete?

In Chapter 6 we observed that ‘biological’ not ‘chronological’ age predicted the presentation of TWI in V_1-V_3. Of the 96 paediatric athletes presenting with TWI in V_1–V_4, in the absence of other ECG findings considered to be abnormal as per new international recommendations for ECG interpretation in athletes, diagnostic accuracy for was ‘fail’

(AUC 0.47, 95% CI 0.00–1.00) when governed by chronological age <16 years, but ‘excellent’ (AUC 0.97, 95% CI 0.92–1.00) when governed by biological age <16 years. These findings are indicative that interpretation by ‘biological’ rather than ‘chronological’ age may be of greater relevance to this unique population.

Calore et al. (2016) studied white and black adult athletes with TWI and suggested that differential diagnosis may be solved without the need for additional work-up (biological age estimation, transthoracic echocardiography, cardiac magnetic resonance imaging), requiring only detailed assessment of Jt and/or ST-segment amplitude preceding TWI in V_1-V_4. Specifically, Calore et al. (2016) observed such detailed assessment to accurately discriminate physiological adaptation from cardiomyopathy, independent of ethnicity. We evidenced TWI in V_1–V_3 to be preceded by a Jt in line with the onset of the QRS and/or ST-segment that were isoelectric in 62.6% of cases, of which 66.7% were biologically aged under 16 years. Indeed, among the 96 paediatric athletes presenting with TWI in V_1–V_4 in the absence of other ECG findings considered to be abnormal, as per new international recommendations for ECG interpretation in athletes, the diagnostic accuracy was ‘fail’ (AUC 0.48, 95% CI 0.00–1.00) when governed by Jt and/or ST-segment elevation irrespective of ethnicity.

The diagnostic accuracy and thus power of our findings are limited to one major outcome in our study. This is reflective of a real-life ECG screening scenario in paediatric athletes, wherein the prevalence of cardiac pathology predisposing to SCD/A is considered to be

low. TWI in V_1–V_3 in the athlete with a chronological age <16 years is likely to be a 'juvenile T wave pattern',but warrants caution. Additional work-up by biological and echocardiographic assessment presents an opportunity to reassure the concerned parent/guardian and athlete, that this is likely a 'juvenile T wave pattern', when biological age <16 years, but warrants concern when biological age ≥ 16 years. In figure 8.2**,** we propose a new algorithm for the role of biological age assessment in ECG interpretation within the paediatric athlete.

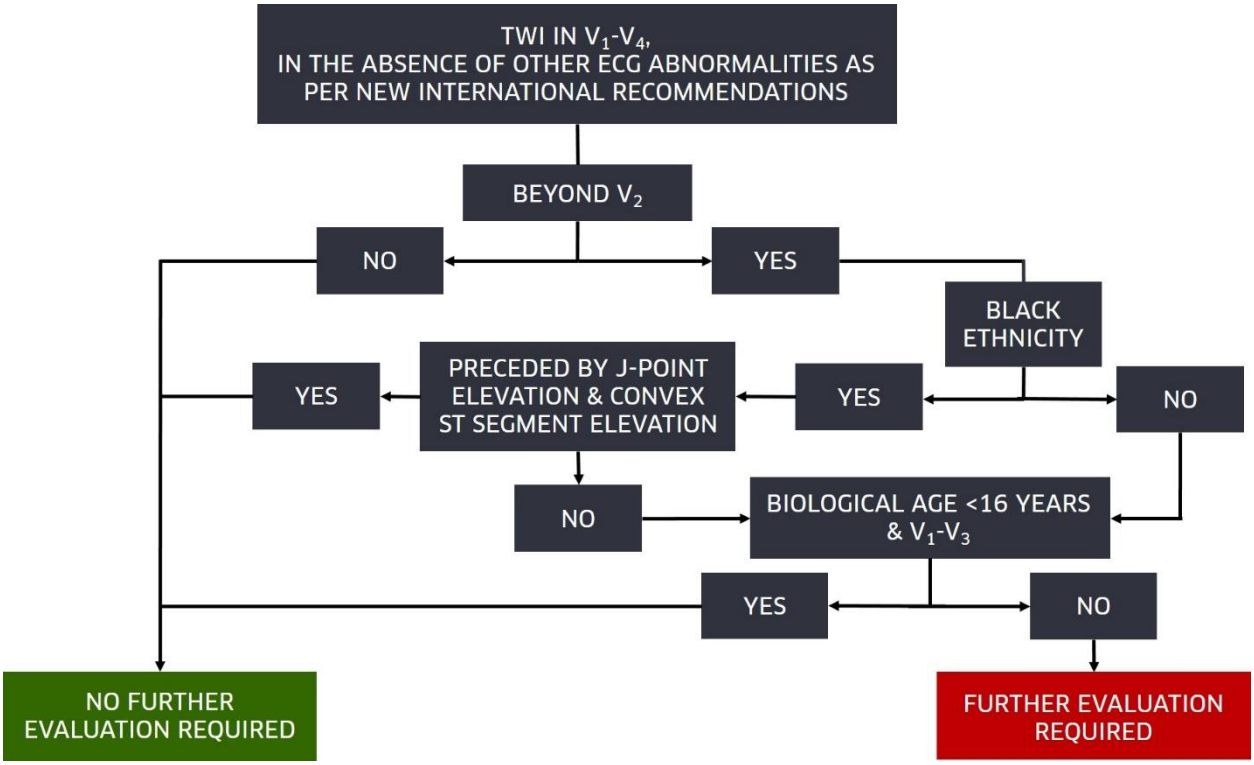

Figure 8. 2 Suggested algorithm for the differentiation of 'benign' to ''abnormal' TWI in V_1-V_4, in the absence of other ECG abnormalities as per new international recommendations for ECG interpretation in athletes (Drezner et al., 2017; Sharma et al.,

2017b, 2018) in the asymptomatic male paediatric athlete with no family history of cardiac disease or SCD, .

8.3.3 THE PAEDIATRIC ATHLETE ECHOCARDIOGRAM: ALLOMETRIC AND NON-LINEAR MODELLING WITH Z-SCORES

Aside from abnormal hemodynamics, BSA represents the most powerful determinant of cardiac size (Gutgesell and Rembold, 1990; de Simone et al., 1995). Unfortunately, as per our observations in Chapter 3, the most commonly applied methodology for adjusting to BSA within the paediatric athlete has been the linear division of cardiac size to BSA (y/x), to calculate a new 'indexed' value (Shi and Selig, 2005; Di Paolo *et al.*, 2012; Koch *et al.*, 2014; Calò *et al.*, 2015). The limitations of which are easy to demonstrate; namely, dimensions, area, and volumes have non-linear relationships to one another. It is therefore impossible for all cardiac dimensions (e.g. wall thickness, chamber area, LV mass) to have a linear relationship to BSA. Investigations within adult athletes have successfully overcome such limitations by allometric indexing, raising BSA to cardiac measure specific b exponents (y/x^b), creating BSA independent measures of cardiac size. Translation, to the paediatric athlete, is limited by the observation of significant heteroscedasticity, in the presence of increased BSA and/or chronological age.

In Chapter 7, it was necessary to model, not index, with significant heteroscedasticity present. Accordingly, cardiac parameter specific RSD was calculated by linear regression of the scaled absolute value (multiplied by $\sqrt{(2/\pi)}$). Subsequently, serving as the divider

of the sum of the measured parameter minus the predicted population mean, permitting calculation of the Z-score. In practice, a measurement 2 SDs above the mean (the 97.7th percentile) has a Z-score of 2, whereas a measurement that is 2 SDs below the mean (the 2.3rd percentile) has a Z-score of -2. One of the most useful applications of our Z-scores is in tracking growth over time. As an exemplar, if a male paediatric athlete presents with a wall thickness at the very upper limits of normality, falling within what may be considered the 'grey zone' of differential diagnosis owing to regular and sustained exercise and that indicative of an inherited cardiomyopathy. If this same individual undergoes rapid growth at the chronological age of 13 years, detection of disproportionate growth of a single measure is made difficult. IVSd, however, grows at an even faster rate within this individual, disproportionate to that expected within a pediatric male athlete. This is succinctly and clearly indicated by a significant increase in the Z-score, thereby altering the clinician, as illustrated in Table 8.1.

Table 8. 1 Increasing Z-score over time of the Intraventricular Wall Thickness, Suggesting Pathological Enlargement.

Chronological age, years	Height, cm	Weight, kg	IVSd, mm	Z-Score
11	140	36	8.4	+1.9
12	145	40	8.8	+2.0
13	150	43	9.4	+2.4
14	160	48	10.1	+2.8
15	170	55	10.9	+3.3

Cm, centimetres; IVSd, intraventricular wall thickness during end-diastole; kg, kilograms; mm, millimetres.

It may be considered impractical for the attending clinician to manually calculate parameter specific Z-scores scores for a number of measures defined as a minimum dataset by the British Society of Echocardiography (Wharton et al., 2015). Accordingly, all of our z-score equations are publicly available on http://echocalc.org/arab-and-black-paediatric-athlete-calculator/, a website designed to be usable on devices of any size, ranging from small smartphones to laptops/desktop computers. This process requires the attending clinician to only enter the patients' age, height, weight, and the respective measured value for an automated Z-score calculation. A screenshot of the website is shown in Figure 8.3.

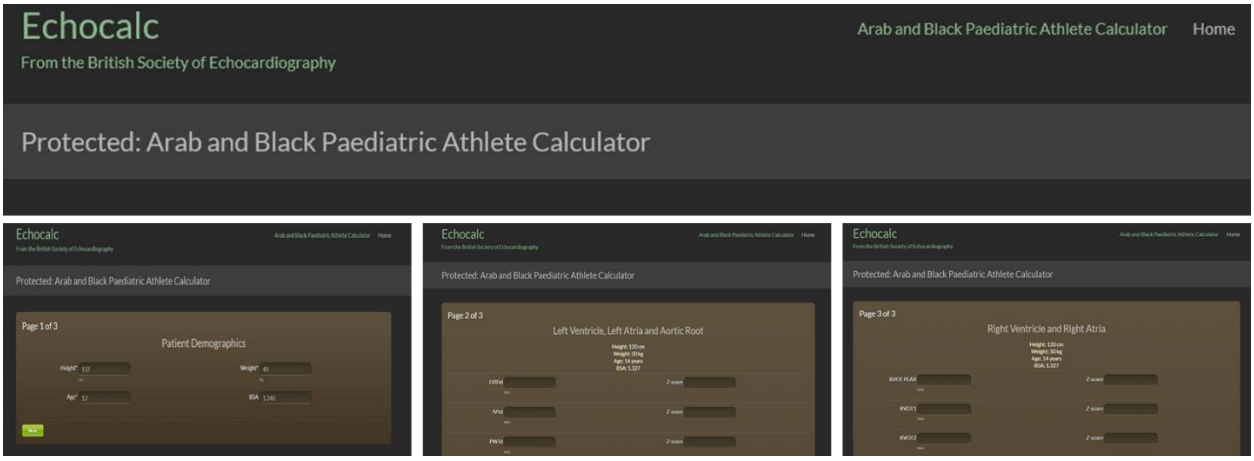

Figure 8. 3 Home page and pages for data entry of patient demographics and measured parameters allowing for automated calculation of Z-score. The data can be stored as a ".pdf" document for emailing or storage on most browsers.

8.3 FUTURE DIRECTIONS

Empirical studies within this thesis were exclusively undertaken with Arab and black male paediatric athletes adopting a cross-sectional design only. Similar rigorous investigations, adopting longitudinal study design are required to validate and substantiate the significance of our findings. Secondly, applicability to other ethnicities and female paediatric athletes requires determination.

Investigations from our research group, running in parallel to this thesis have questioned the clinical utility of a "blanket approach" to the interpretation of the black athlete's ECG and echocardiographic assessment. Remarkably, the number of positive ECGs, as per new international recommendations (Drezner et al., 2017; Sharma et al., 2017b, 2018)

significantly varied by the geographic area of origin of the black athlete. Specifically, positive in as many as 11.9% of Middle African descent, but only in 2.5% of East African descent. More specifically, the prevalence of the black athlete reporlisation variant (Jt and/or ST-segment elevation preceding TWI in V_1-V_4) significantly varied by geographic origin ranging from 12% in the black athlete of Middle African descent to 1.5% of East African descent. How and why the prevalence rate of this and other ECG patterns may differ among black paediatric athletes by geographical origin, and its relative significance to the discrimination of physiology versus that indicative of an inherited cardiomyopathy requires further exploration.

Finally, despite allometrically indexing all parameters of LV size, creating BSA independent measures of cardiac size, posterior and IVSd significantly varied by geographic descent of the black athlete (Riding et al., 2019). Disparity which extends to a small cohort (n=56) investigation within the black paediatric athlete, wherein athletes were approximately classified by tribal origin (Schmied et al., 2009). In Chapter 7 we evidence allometrically normalising of cardiac size indices to refute the need for ethnic-specific normative ranges when comparing Arab and black paediatric athletes. Whether this remains true by geographic descent both within Arab and black paediatric athletes, requires further exploration.

This thesis encompassed a full echocardiographic assessment of cardiac chambers and aortic root size and function. Owing to its non-routine application within our cardiac

screening program, data collected in relation to speckle tracking echocardiography were not reported in the thesis. Speckle tracking echocardiography is an assessment technique that when used in conjunction with standard structural and functional echocardiographic parameters may increase the sensitivity of a transthoracic echocardiographic assessment in the detection of dilated cardiomyopathy (Okada et al., 2012), hypertrophic cardiomyopathy (Butz et al., 2011; Kansal et al., 2011) and ARVC (Teske et al., 2009); inherited cardiomyopathies which collectively account for 12% of SCDs in paediatric athletes (Finocchiaro et al., 2016b). The clinical utility of myocardial speckle tracking is, however, significantly limited by a lack of consistency in vendor methodology and variable reproducibility, together with a lack of appropriate reference within the paediatric athlete accurately defining normality. Until then, the role of this assessment technique in secondary care for differential diagnosis of physiological remodeling owing to regular and sustained exercise to that of a inherited cardiomyopathy within the paediatric athlete is limited and may be considered an important area of further research in the paediatric athlete.

It is pertinent to reflect on the initial hypotheses to determine whether the outcome of the research allows their acceptance or rejection:

Study 1 - H1: Owing to regular and sustained training, paediatric athletes will demonstrate a number of electrophysiological, structural and functional adaptations when compared to non-athletes.

ACCEPT

Study 1 - H2: Electrophysiological, structural and functional adaptations will be dependent on the chronological age, sex, and ethnicity of the paediatric athlete.

ACCEPT

Study 2 - H3: New international recommendations for ECG interpretation in athletes will be appropriate for application in paediatric athletes, outperforming the previous ECS 2010 recommendations and Seattle criteria, irrespective of ethnicity and chronological age.

ACCEPT

Study 3 - H4: Detailed assessment of the preceding Jt and/or ST-segment preceding TWI in V_1-V_4, irrespective of ethnicity and chronological age will significantly aid the detection of cardiac pathology in the paediatric athlete

REJECT

Study 3 - H5: The prevalence and significance of TWI in V_1-V_3 (the juvenile T wave pattern) will be determined by 'biological' not 'chronological' age, irrespective of ethnicity within the paediatric athlete.

ACCEPT

Study 4 - H6: Cardiac growth within the paediatric athlete will conform to the allometric relationship of body size to cardiac growth but will importantly differ by ethnicity.

PARTIALLY ACCEPT

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APPENDIX

APPENDIX 1 - ETHICAL APPROVAL LETTERS

Anti- Doping Lab Qatar Institutional Review Board

Tel: 44132988
Fax: 44132997

IRB MoPH Registration: SCH-ADL-070
MoPH Assurance: MOPH-A-ADL-Q-071

APPROVAL NOTICE
Ethics Approval Renewal & Modification to Approved Protocol

Date	15th Aug, 2018
Lead Principal Investigator	Stephen Targett, Aspetar
Co-PI	Arnhild Bakken, Prof Roald Bahr, Dr Johannes Tol, Jacobus Nicolaas van Dyk
IRB Application #	E2013000003
Sites	Aspetar
Funding Entity	Aspetar
Protocol Title	The benefits of periodic health examination (PHE) in athletes - a prospective cohort study from athlete screening in a Middle Eastern setting
Submission Type	Ethics Approval Renewal & Modification to Approved Protocol
Modification Type	Removal of Co-PI – Karim Khan. Addition of Co-PI- Jacobus Nicolaas van Dyk
Review Type	Expedited Review
Approval Period	22nd Sept, 2018 – 21st Sept, 2019

The Anti-Doping Lab Qatar Institutional Review Board has reviewed and approved the above referenced protocol.

As the Principal Investigator of this research project, you are responsible for:

- Ethical compliance and protection of the rights, safety and welfare of human subjects involved in this research project.
- To follow the policies and procedures as set by ADLQ-IRB in any matters related to the project, following the ADLQ-IRB approval which includes:-
  - Obtaining prior approval of any modifications to the approved protocol including the change of research team members.
  - Reporting deviations and unanticipated events; major deviations within 24 hours.
  - Renewing Ethics annually or every six months if IRB requires it.
  - Submission of progress reports annually
  - Informing the ADLQ-RO of the date of commencement of the research.
- LPI may use the consent of the approved Informed Consent form in their own organizational letter head, if it deems fit for the nature of the project.

ADLQ IRB Chair
Dr. Yorck Olaf Schumacher

مختبر مكافحة المنشطات قطر
Anti Doping Lab Qatar

For Commencement of Research, Protocol Deviation Reporting, Unanticipated Problem Reporting & Research Progress Annual Report, please contact - Education & Research Office, Anti-Doping Lab Qatar.

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Anti- Doping Lab Qatar Institutional Review Board

Tel: 44132988
Fax: 44132997

IRB MoPH Registration: SCH-ADL-070
MoPH Assurance: MOPH-A-ADL-Q-071

APPROVAL NOTICE
[Ethics Approval Renewal]

Date	31st Oct, 2018
Lead Principal Investigator	Marco Cardinale
Co-PI	Tim Cable, Alberto Mendez-Villanueva, Amanda Johnson, Olivier Materne, Cosmin Horobeanu, Philip Graham-Smith, Malcolm Geluk, Jaime Diaz Ocejo, Charalampos Fountoulakis, Conor Kilgallen
IRB Application #	E20140000012
Sites	Aspire Academy
Funding Entity	Aspire Academy
Protocol Title	Assessment and longitudinal monitoring of routine sport science and medical screenings of ASPIRE Academy Student-Athletes
Submission Type	Ethics Approval Renewal
Review Type	Expedited Review
Approval Period	16th Nov, 2018 – 15th Nov, 2019

The Anti-Doping Lab Qatar Institutional Review Board has reviewed and approved the above referenced protocol.

As the Principal Investigator of this research project, you are responsible for:

- Ethical compliance and protection of the rights, safety and welfare of human subjects involved in this research project.
- To follow the policies and procedures as set by ADLQ-IRB in any matters related to the project, following the ADLQ-IRB approval which includes:-
- Obtaining prior approval of any modifications to the approved protocol including the change of research team members.
- Reporting deviations and unanticipated events; major deviations within 24 hours.
- Renewing Ethics annually or every six months if IRB requires it.
- Submission of progress reports annually
- Informing the ADLQ-RO of the date of commencement of the research.
- LPI may use the content of the approved Informed Consent form in their own organizational letter head, if it deems fit for the nature of the project.

ADLQ IRB ORS (Office of Research Support)
Ms. Noor Al Motawa

مختبر مكافحة المنشطات قطر
Anti Doping Lab Qatar

* For Commencement of Research, Protocol Deviation Reporting, Unanticipated Problems Reporting & Research Progress Annual Report, please contact - Education & Research Office, Anti-Doping Lab Qatar.

APPENDIX 2 – HEALTH QUESTIONNAIRE

ASPETAR سبيتار

Pre-participation screening

SPORT/FEDERATION	الرياضة / النادي	
POSITION PLAYED IN SPORT:	موقع اللاعب في الرياضة	
NAME	الإسم	
ID Number	الرقم الشخصي	
DATE OF BIRTH	تاريخ الميلاد	
HOME ADDRESS	العنوان	
EMAIL ADDRESS	عنوان البريد الإلكتروني	
HOME PHONE NUMBER	رقم الهاتف المنزلي	
MOBILE PHONE NUMBER	رقم الجوال	
EMERGENCY CONTACTNAME	إسم الإتصال في حالة الطوارئ	
TELEPHONE NUMBER	رقم الهاتف	
PHYSICIANS NAME	إسم الطبيب	
PHYSICIANS TELEPHONE NUMBER	رقم هاتف الطبيب	
PHYSIOTHERAPIST NAME & NUMBER	إسم ورقم الطبيب الرياضي	
DATE OF BEGINNING PROFESSIONAL ACTIVITY	تاريخ بدء ممارسة الرياضة بإحتراف	
PREVIOUS CLUB(S) POSITION	النوادي السابقة	
How many training sessions do you perform a week?	ما هو عدد التمرينات التي تجريها في الإسبوع؟	
How many hours of training do you perform every session?	ما هي مدة كل تمرين؟	
Name of translator (Language)		
Name of athlete's guardian (if less than 18 years)		
Name of Nurse filling out form		

NAME of ATHLETEالاسم:_____NAME of NURSE: _____

SIGNATURE of ATHLETEالتوقيع:_____ SIGNATURE of NURSE: _____

Parent/Guardian signature if athlete is under the age of 18: _____
توقيع الوالد / الوالي إذا كان سن الرياضي يقل عن 18 سنة
DATE:التاريخ _____ PHYSICIAN SIGNATURE: _____

ASPETAR سبيتار

Pre-participation screening

		YES نعم	NO لا	UNSURE غير متأكد
Any Faintness, dizziness, chest pain, loss of consciousnessduring exercise?	هل سبق لك أن أصبت بغيبوية،دوار أو دوخة، الإحساس بوجع في الصدراثناءالتمرين ؟			
Any Faintness, dizziness, chest pain, loss of consciousness after exercise?	هل سبق لك أن أصبت بغيبوية،دوار أو دوخة، الإحساس بوجع في الصدر بعد التمرين؟			
Have you ever suffered from excessive fatigue or overtraining?	هل سبق لك أن عانيت من إرهاق شديد أو تدريب مفرط؟			
Have you ever had a heart abnormality or murmurdiagnosed by a doctor?	هل سبق أن أصبت بمشاكل في القلب أو مارمر؟			
Have you ever had an abnormal heart rate, palpitations or irregular heart beat?	هل سبق لك أن أصبت بمعدل دقات غير طبيعي في القلب ، خفقان أو عدم انتظام في دقات القلب ؟			
Have you ever had high blood pressure or high cholesterol?	هل سبق لك أن تعرضت لإرتفاع الضغط أو ارتفاع في نسبة الكوليسترول؟			
Has a physician ever denied or restricted you from participating in sports due to heart problems?	هل سبق لأي طبيب أن منعك من المشاركة أو ممارسة الرياضة بسبب مشاكل في القلب؟			
Do you have a chronic illness, or see a physician regularly for any particular problem (e.g. Diabetes, epilepsy, thyroid problems)?	هل لديك أي مرض مزمن أو تزور الطبيب باستمرار بسبب أي مشكل صحي (مرض السكري، الصرع أو مشاكل في الغدة الدرقية)؟			
Do you take any prescribed medication?"Over the counter" supplements/medications/herbal remedies? Please list هل تتناول أية أدوية موصوفة؟ أعشاب أو مكملات غذائية؟ الرجاء ذكرها _____ _____				
Do you wear corrective lenses or glasses?	هل ترتدي العدسات الاصقة أو النظارات؟			
Do you smoke?	هل تدخن؟			
Do you drink alcohol?	هل تتناول الكحول؟			
Have you, or a close relative, ever suffered from depression?	هل سبق لك أو لأي شخص قريب أن عانى من الكآبة؟			
Do you wear orthotics?	هل ترتدي تقويما للأرجل ؟			
Do you wear protective equipment when playing your sport?	هل ترتدي معدات الوقاية أثناء ممارسة رياضتك؟			
Have you ever been tested for HIV? If so, do you have the results?	هل سبق أن أجريت فحص السيدا؟			

NAME of ATHLETE:الاسم _____ NAME of NURSE: _____

SIGNATURE of ATHLETEالتوقيع: _____ SIGNATURE of NURSE: _____

Parent/Guardian signature if athlete is under the age of 18: _____
توقيع الوالد / الوالي إذا كان سن الرياضي يقل عن 18 سنة

DATEالتاريخ: _____ PHYSICIAN SIGNATURE:_____

ASPETAR سبيتار

Pre-participation screening

	YES	NO نعملا	UNSURE غير متأكد
Do you have ever been advised that surgery or medical exam may be required in the future, if yes when and for which reason? هل سبق ان تمت نصيحتك بإجراء عملية جراحية او أي فحص طبي قد يكون مطلوبا في المستقبل إذا كان الجواب بنعم، متى وماهي الأسباب؟ _____			
Have you ever received treatment other than surgery such as plaster, physiotherapy...? هل سبق لك أن تلقيت علاجات غير الجراحية مثل الجبس والعلاج الفيزيائي...؟			
Do you wish to discuss any health or sports medicine issues with the Physician? If yes please list. هل ترغب في مناقشة أية مشكلة صحية مع الطبيب؟اذا كانت الاجابه بنعم يرجى الإشارة. _____ _____			

NUTRITION التغذية

Do you have problems gaining weight for your sport?	هل تعاني من مشكل في زيادة الوزن من أجل رياضتك؟			
Do you follow any special diet (e.g. vegetarian, weight loss, pritikin)?	هل تتبع أي نظام حمية (خضروات، فقدان الوزن، حمية خاصة) ؟			
Have you ever had a nutritional deficiency diagnosed (e.g. iron, vitamin B12)?	هل سبق لك أن عانيت من نقص في التغذية (الحديد، فيتامين ب 12)؟			
FOR FEMALE ATHLETES للرياضيات فقط				
Does your menstruation affect your performance?	هل تؤثر دورتك الشهرية على أدائك الرياضي؟			

NAME of ATHLETE:الاسم _____ NAME of NURSE: _____

SIGNATURE of ATHLETEالتوقيع:_____ SIGNATURE of NURSE: _____

Parent/Guardian signature if athlete is under the age of 18: _____
توقيع الوالد / الوالي إذا كان سن الرياضي يقل عن 18 سنة

DATEالتاريخ: _____ PHYSICIAN SIGNATURE:_____

ASPETAR سبيتار

Pre-participation screening

VACCINATIONS التطعيمات		YES نعم	NO لا	UNSURE غير متأكد
Please enter dates if you have received any of the following:-	الرجاء إعطاء التواريخ في حال أخذت أي من التطعيمات الآتية:			
Tetanus	الكزاز			
Rubella (German Measles)	الحصبة الألمانية			
Influenza	الإنفلونزا			
Typhoid	التيفويد			
Hepatitis A	إلتهاب الكبد - أ			
Hepatitis B	إلتهاب الكبد - ب			
Yellow Fever	الحمى الصفراء			
Chicken Pox	الجدري			
Meningitis C	إلتهاب السحايا ج			
Polio	شلل الأطفال			

NOTE: Hepatitis A and B may be in a combination vaccine, usually a series of three injections over 6 months.
Measles, mumps and rubella is a combination vaccine, part of usual childhood series.

FAMILY MEDICAL HISTORY مرض وراثي		YES نعم	NO لا	UNSURE غير متأكد
Has anyone in your family died suddenly and unexpectedly before the age of 50? If yes specify : Age:	هل حدث موت مفاجئ لأي شخص من العائلة قبل بلوغ سن ال 50 ؟ حدد من؟ عن أي عمر ؟			
Is there any one in your family who suffers from::	هل هناك أي شخص في الأسرة يعاني من			
Heart disease	القلب			
Name of the disease:				
Cancer	السرطان			
Arthritis	الروماتيزم			
Diabetes	مرض السكري			
Stroke, high blood pressure	السكتة، ارتفاع ضغط الدم			
Marfan's syndrome (Genetic Heart Disease)	متلازمة مارفان (أمراض القلب الوراثيه)			
Glaucoma or other eye disease	الزرق أو غيرها من أمراض العيون			
Specific details::تفاصيل محددة _____ _____				

NAME of ATHLETE الاسم: _____ NAME of NURSE: _____

SIGNATURE of ATHLETE التوقيع: _____ SIGNATURE of NURSE: _____

Parent/Guardian signature if athlete is under the age of 18: _____
توقيع الوالد / الوالي إذا كان سن الرياضي يقل عن 18 سنة
DATE: التاريخ _____ PHYSICIAN SIGNATURE: _____

SPECIALIST EXAMINATIONS PERFORMED	YES	NO	UNSURE

ASPETAR سبيتار

Pre-participation screening

فحوصات الأخصائيين		نعم	لا	غير متأكد
Have you ever undertaken an examination of the following specialities in your life?	هل سبق لك أن اجريت طيلة حياتك أي فحص عن التخصصات التالية؟			
Cardiology	القلب			
Neurology	الأعصاب			
Hematology (Blood Test)	الدم			
Ophthalmology	العيون			
Ear, Nose and Throat specialist	أنف، أذن، حنجرة			
Orthopaedicspecialist	العظام			
Internal medicine	باطنية			
Others: (CT, MRI,RADIOLOGY)				

NAME of ATHLETEالاسم: _____ NAME of NURSE: _____

SIGNATURE of ATHLETEالتوقيع:_____ SIGNATURE of NURSE: _____

Parent/Guardian signature if athlete is under the age of 18: _____
توقيع الوالد / الوالى إذا كان سن الرياضى يقل عن 18 سنة

DATEالتاريخ: _____ PHYSICIAN SIGNATURE:_____

The proposed must precisely answer the following questions and give the additional requested documents.

ASPETAR سبيتار

Pre-participation screening

A	Have you ever injured or suffered pain or discomfort, or had surgery to any of the following			هل سبق لك أن تعرضت لإصابة, وجع, إنزعاج أو عملية جراحية للتالي؟
If YES please give details including dates		Yes نعم	No لا	إن كان الجواب نعم, الرجاء ذكر التفاصيل مع التواريخ
a)	Head الرأس			
b)	Neck (cervical spine) الر قبة(العمود الفقري)			
c)	Right shoulder الكتف الأيمن			
d)	Left shoulder الكتف الأيسر			
e)	Chest (including ribs) الصدر (بما فيها الاضلاع)			
f)	Upper back (thoracic spine) العمو د العلوي(القفص الصدري)			
g)	Lower back (lumbar spine including coccyx and sacrum) ا سفل الظهر			
h)	Pelvis / hips (including groin) الورك\ الحوا			
i)	Abdomen (including stomach) البطن			
j)	Right arm (including elbow) الذراع الأيمن			
k)	Left arm (including elbow) الذراع الأيسر			
l)	Right hand (including wrist, fingers and thumb) اليد اليمنى			
m)	Left hand (including wrist, fingers and thumb) اليد اليسرى			
n)	Right thigh (including hamstring) الفخذ الأيمن			
o)	Left thigh (including hamstring) الفخذ الأيسر			
p)	Right knee الركبة اليمنى			
q)	Left knee الركبى اليسرى			
r)	Right lower leg (including ankle and Achilles) الساق السفلي اليمنى			
s)	Left lower leg (including ankle and Achilles) الساق السفلي اليسرى			
t)	Right foot (including toes) القدم الأيمن			
u)	Left foot (including toes) القدم اليسرى			

NAME of ATHLETE الاسم: _____ NAME of NURSE: _____

SIGNATURE of ATHLETE التوقيع: _____ SIGNATURE of NURSE: _____

Parent/Guardian signature if athlete is under the age of 18: _____
توقيع الوالد / الوالي إذا كان سن الرياضي يقل عن 18 سنة
DATE: التاريخ _____ PHYSICIAN SIGNATURE: _____

ASPETAR سبيتار

Pre-participation screening

INJURIES الإصابات				
Have you ever had any injuries/medical illness? For each injury/condition please list	هل سبق أن تعرضت لأية إصابة / مرض؟ الرجاء الإشارة لكل إصابة على حدة:	YES نعم	NO لا	UNSURE غير متأكد

Nature of Injury/ Medical illness/Hospitalization	نوع الإصابة /المرض	Date of injury	تاريخ الإصابة	Residual Problem	مشاكل متبقية

OPERATIONS العمليات				
Have you ever had any surgical operations? For each surgical operations please state:	هل اجريت لك أية عملية جراحية من قبل؟ الرجاء الإشارة لكل عملية على حدة:	YES نعم	NO لا	UNSURE غير متأكد

Nature of Surgery	نوع الجراحة	Date of Surgery	تاريخ الجراحة	Residual Problem	مشاكل متبقية

NAME of ATHLETE الاسم: _____ NAME of NURSE: _____

SIGNATURE of ATHLETE التوقيع: _____ SIGNATURE of NURSE: _____

Parent/Guardian signature if athlete is under the age of 18: _____
توقيع الوالد / الوالي إذا كان سن الرياضي يقل عن 18 سنة

DATE: التاريخ _____ PHYSICIAN SIGNATURE: _____

ASPETAR سبيتار

Pre-participation screening

NURSE TO COMPLETE

ALLERGIES and ADVERSE DRUG REACTIONS (ADR)			
No Known allergies or adverse drug reaction □			
Allergy / ADR	Name of Substance	Reaction	Severity Code
Allergy □ ADR □			
Allergy □ ADR □			
S - SEVERE (rash, hives, anaphylaxis, urticaria) I – MODERATE (pruritis) M - MILD (GI upset, nausea, vomiting, diarrhea) U – UNKNOWN (unknown)			

VITAL SIGNS										
Date & Time	Temp	Pulse	Resp	O2 Sat	Blood pressure	Height	Weight	BMI	Eye test	
									Right eye 20/	Left eye 20/

PAIN ASSESSMENT	
Do you have any pain? □ Yes□ No	Location of pain:
Is it acute pain?□ Yes□ No	Quality of pain:
Is it chronic pain? □ Yes□ No	Duration of pain:
Pain score 0 to 10 (0=no pain 10= the worst pain ever)	
What makes the pain worse?	What makes the pain better?

PAST MEDICAL/ SURGICAL HISTORY					
CARDIOVASCULAR	YES	NO	**NEUROLOGICAL**	YES	NO
Hypertension			Epilepsy / seizure		
Blood clots			Headaches/ Migraine		
Palpitations / arrhythmia			Peripheral neurological signs		
Heart murmur			Cranial trauma		
Dyspnea			sense organ problems		
CVA (stroke)			Other		
MI (heart attack)			**No significant findings** □		
Angina			**GASTROINTESTINAL**		
Rheumatic fever			Ulcer/ gastritis/ Gastric reflex		
Pace maker / Internal defibrillator			Hemorroids		
Artificial heart valve			Bowel problems		
Known ECG abnormal			Liver problems		
Known Echo abnormal			Other		
Description of the abnormalities:			**No significant findings** □		
Other.....			**RENAL DISEASE**		
No significant findings □			Kidney Disease		
RESPIRATORY			UTI recurrent (bladder infection)		
Chronic airway limitation			Other.....		
Diseased lung/ tuberculosis			**No significant findings** □		
Asthma / bronchitis			**HEAMATOLOGICAL**		
Cough / cold			Blood disorder		
Sinusitis			Blood clots		
Other			Bleeding problems		
No significant findings □			Anaemia		
MUSCULOSKELETAL			Other		
Arthritis			**No significant findings** □		
Neck / Back pain			***Diabetes***		
Surgery			Ever had high fever		
Other.....			Others:		
No significant findings □			Others:		

NAME of NURSE:_____ SIGNATURE of NURSE:_____