Exercise, the Athlete's Heart, and Sudden Cardiac Death

DOI: 10.3810/psm.2014.05.2062

Andrew D'Silva, BSc (Hons), MBBS, MRCP (UK)
Sanjay Sharma, BSc (Hons), MD, FRCP (UK), FESC

Department of Cardiovascular Sciences, St. George's University of London, London, UK

Abstract: Physical activity is a potent therapy for both the prevention and treatment of cardiovascular disease. Exercise appears to most benefit people who are the least active. There is some evidence to suggest that a curvilinear relationship exists between exercise and survival, whereby beyond an optimal level of fitness, the principle of diminishing returns applies. Indeed, some go further in suggesting that there is evidence that extreme athletic training may be harmful in some individuals. The incidence of sudden cardiac death in athletes is greater than in matched, nonathletic counterparts, and this finding is driven by the provocation of an underlying cardiac abnormality by strenuous exertion. The task of detecting pathological myocardial substrate in athletes is made difficult by physiological adaptations to exercise that can mimic the appearance of cardiomyopathies and ion channelopathies in some individuals. This article details the clinical evaluation of the athlete with reference limits for cardiac physiological remodeling and discusses the diagnostic dilemmas that arise.

Keywords: cardiac physiological remodeling; cardiovascular disease; physical activity; sudden cardiac death

Introduction

It has been well established that regular physical activity yields significant health benefits. Regular exercise reduces cardiovascular mortality by 35% and all-cause mortality by 33%.[1] Additional benefits of exercise include weight reduction, blood pressure reduction,[2] increased insulin sensitivity,[3] improved lipid profile,[4] lower incidence of certain cancers,[5] and improved healthy aging with better physical and cognitive function and improved mental health.[6] Indeed, individuals who exercise regularly live, on average, 7 years longer than their physically inactive counterparts.[7]

What remains unknown is precisely how much exercise is required to produce these beneficial effects and, more controversially, could excessive exercise cause harm? In an observational study of nearly 45 000 professional males, individuals who ran for $\geq$ 1 hour per week had a 42% risk reduction of coronary artery disease compared with inactive individuals. By comparison, individuals who undertook $\geq$ half an hour per day of brisk walking had only an 18% risk reduction.[8] This would suggest that the more intensive the physical activity undertaken, the greater the cardiovascular benefit. Data from other large cohort studies have shown that for every metabolic equivalent (MET) of exercise achieved, there was a risk reduction in mortality of approximately 13%.[9] Interestingly, the largest reduction in mortality was observed between the least-fit category (achieving $<$ 6 METs) and the next least-fit category (6–8 METs). Furthermore, fitness continued to be associated with reductions in mortality risk until

Correspondence: Sanjay Sharma, BSc (Hons), MD, FRCP (UK), FESC, Department of Cardiovascular Sciences, St. George's University of London, Cranmer Terrace, London, SW7 0RE, UK.
Tel: 0208-672-1390.
E-mail: sasharma@sgul.ac.uk

achieving 10 METs, where additional mortality benefit was not seen with higher levels of fitness.[10]

This curvilinear relationship[11] has again been shown in a study from Taiwan, which demonstrated that after 15 minutes a day of exercise, every additional 15 minutes of daily exercise conferred an additional reduction of 4% in all-cause mortality, approaching 100 minutes per day, after which the beneficial effect appeared to plateau.[12] With respect to runners, an observational study with 15 years' follow-up found that those who participated in leisure-time running had a 19% lower risk of all-cause mortality compared with nonrunners. Intriguingly, those who had the greatest survival benefit ran distances of 1 to 20 miles per week, at speeds of 6 to 7 miles per hour at frequencies of 2 to 5 days per week. Higher mileage, faster paces, and more frequent running were not associated with better survival.[13,14]

Controversially, some authors have proposed that a U-shaped curve exists for optimal exercise dosage, and that extreme levels of vigorous physical activity for prolonged periods could be harmful to the heart.[13,15] Although it is speculative, some argue that the higher prevalence of atrial fibrillation seen in veteran endurance athletes[16–18] is evidence of a harmful "overtraining syndrome" resulting in atrial enlargement, inflammation, and fibrosis, which ultimately culminates in an arrhythmogenic substrate.[19]

The American Heart Association[20] and the United Kingdom Department of Health recommend that 150 minutes of moderate-intensity aerobic exercise per week (more simply expressed as 30 minutes of exercise 5 days a week) should be the minimum recommended physical activity level.[11]

Athletes achieve levels of physical activity several magnitudes of scale above the recommended level, and although there is a commonly held preconception that a higher level of fitness is synonymous with good health, there is some emerging evidence that may suggest otherwise.

For the purposes of this review, the term *athlete* is used to describe an individual who engages in regular physical training and participates in official sports competition with an emphasis on excellence and achievement.[21] The term *athlete's heart* describes specific circulatory and cardiac morphological alterations that represent physiological adaptation to systematic training, such as an increase in cardiac mass.[22] These alterations are regarded as benign. However, as a consequence of expanding research, both the clinical entity has been more precisely defined and further uncertainty has been raised regarding the possibility of pathological myocardial changes resulting from prolonged, intensive athletic training.

Cardiac Remodeling

In healthy individuals, the resting cardiac output is approximately 5 L/min. During strenuous aerobic exercise, cardiac output is capable of increasing to 25 to 35 L/min.[13] From a hemodynamic perspective, exercise can be broadly described as either endurance training or strength training.

Typical examples of endurance training (also commonly termed dynamic, isotonic, or aerobic exercise) include long-distance running, swimming, rowing, cycling, and cross-country skiing. This type of physical activity triggers acute changes in cardiovascular physiology by increasing maximum oxygen consumption, cardiac output, stroke volume and systolic blood pressure with an associated fall in peripheral vascular resistance and heart rate. The overall effect is an increase in cardiac preload but a reduction in afterload, resulting in a predominantly volume-loaded left ventricle (LV).[22]

Typical examples of strength training (also termed static, isometric, or anaerobic exercise) include weight lifting, wrestling, and throwing heavy objects. Acute cardiovascular responses in these activities result in only a mild increase in oxygen consumption and cardiac output but substantial increases in blood pressure, peripheral vascular resistance, and heart rate. Here, the overall effect is proportionally higher afterload, resulting in a pressure-loaded LV.[22]

In 1975, the focus of cardiac remodeling was centered on the LV and on forms of adaptation that enabled it to generate such a sustained increase in workload for a prolonged time period. Morganroth et al[23] demonstrated, with echocardiographic assessments of 56 athletes, that those athletes in predominantly endurance training sports had increased LV mass with an increase in LV end-diastolic volume but a normal LV wall thickness, termed eccentric hypertrophy. Athletes in predominantly strength training disciplines had increased LV mass with an increase in LV wall thickness but a normal LV end-diastolic volume, termed concentric hypertrophy.[23,24] Although the Morganroth model has been debated, it serves as a good conceptual model supported by cross-sectional and longitudinal work.[25] However, the issue is more complicated than that, as most athletic disciplines combine endurance and strength modes of physical conditioning, and physiological changes are the resultant effect of integrated structural, metabolic and hormonal changes.[22,26]

During endurance exercise LV diastolic function is enhanced, as assessed by E wave velocity and mitral annular/LV tissue velocities. This ability of the LV to relax briskly at high heart rates is likely to facilitate the preservation of stroke volume during exercise.[25]

Although LV performance has been the initial focus of characterizing the athlete's heart, attention is now being paid to the effect of systematic exercise on the right ventricle (RV). Endurance exercise requires that both ventricles are receiving and pumping large blood volumes. Pulmonary artery pressure rises significantly on exercise but with minimal reduction in pulmonary vascular resistance. As cardiac output and heart rate are equivalent in both ventricles, it follows that the RV has a greater workload burden relative to the LV during exercise.[27] As a structure it is more difficult to make easily reproducible and objective measurements of RV size and function, when compared with the LV, partly due to its crescentic shape and numerous trabeculations. For this reason cardiac magnetic resonance imaging (MRI) is the modality of choice for assessment of the RV. A study comparing male endurance athletes and untrained controls demonstrated that RV enlargement was common among endurance athletes, and that RV enlargement paralleled LV enlargement, giving support to the concept of balanced biventricular enlargement.[28]

However, a theory gaining growing popularity is that endurance training may be associated with pathological, arrhythmogenic remodeling of the RV. An Australian observational study of 40 marathon runners demonstrated that intense endurance exercise was associated with an acute reduction in RV systolic function, as assessed by cardiac MRI, which recovered by 1 week after the athletic event. Left ventricular function in this cohort was preserved and, interestingly, it was observed that RV remodeling and focal gadolinium enhancement were more prevalent in athletes with a longer history of competitive sports.[29] These observations have lent support to the idea that, in susceptible individuals, with sustained increases in cardiac output, the associated repetitive RV chamber dilatation is brought about by myocyte changes and possible slippage of myocytes within cardiac tissue (Figure 1). This in turn could lead to loss of integrity of intracellular junctions and subsequent chronic changes culminating in cardiac fibrosis that could form a substrate for arrhythmic sudden death in marathon runners. This idea is highly controversial, and larger studies are required to investigate the cause and implications of RV changes detected by MRI in extreme athletes.

Many factors determine the extent to which the heart remodels in response to extreme levels of exercise, including type of sport training, age, sex, ethnicity, and body surface area (Figure 2).[27] In general, large adult male athletes engaged in endurance sports exhibit the largest cardiac dimensions, and black ethnicity is associated with greater LV wall thickness.

Exercise and Sudden Death

If extreme athletic levels of physical activity could result in early death during exercise, why do emergency service calls not reflect this finding? Estimates of the incidence of sudden cardiac death (SCD) in young athletes range from 1 in 25 000 to 1 in 300 000, with the former figure generated from an Italian mandatory registry for SCD. Factors that influence the wide range of estimates reflect differences in the populations studied and variations in methods of identifying deaths in athletes. The most robust data are derived from the Veneto region of Italy, where preparticipation screening is mandatory and there is a systematic registry for SCD in athletes. Therefore, accurate figures are available for the numerator (number of SCDs in athletes) and the denominator (number of competitive athletes).[30,31] It is worth noting that the data from this country might not be widely applicable to other countries.

Age has an important influence on the cause of SCD in athletes. In athletes aged $\geq$ 35 years, the vast majority of SCDs ($>$ 80%) are due to atheromatous coronary artery disease.[32,33] By contrast, SCDs in athletes aged $<$ 35 years are most commonly due to inherited or congenital abnormalities affecting the heart muscle, coronary arteries and conduction system. In a study of 1435 competitive athletes from a United States registry the most common cause of SCD was hypertrophic cardiomyopathy (HCM; 36%) followed by congenital anomalies in coronary arteries (17%; Figure 3). It is noteworthy that completely normal hearts were found in only 3% of those studied.[34]

Interestingly, registry data from the Veneto region in Italy suggest that arrhythmogenic right ventricular cardiomyopathy (ARVC) is the most common cause of SCD in that study,

Figure 1. Schematic representation of cardiomyocytes and the sarcomere.

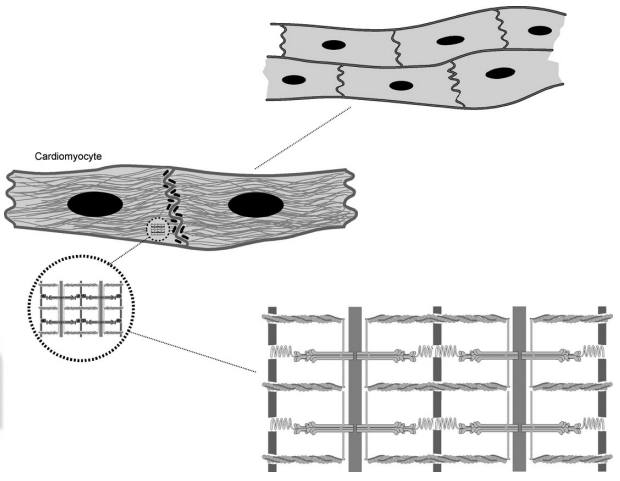
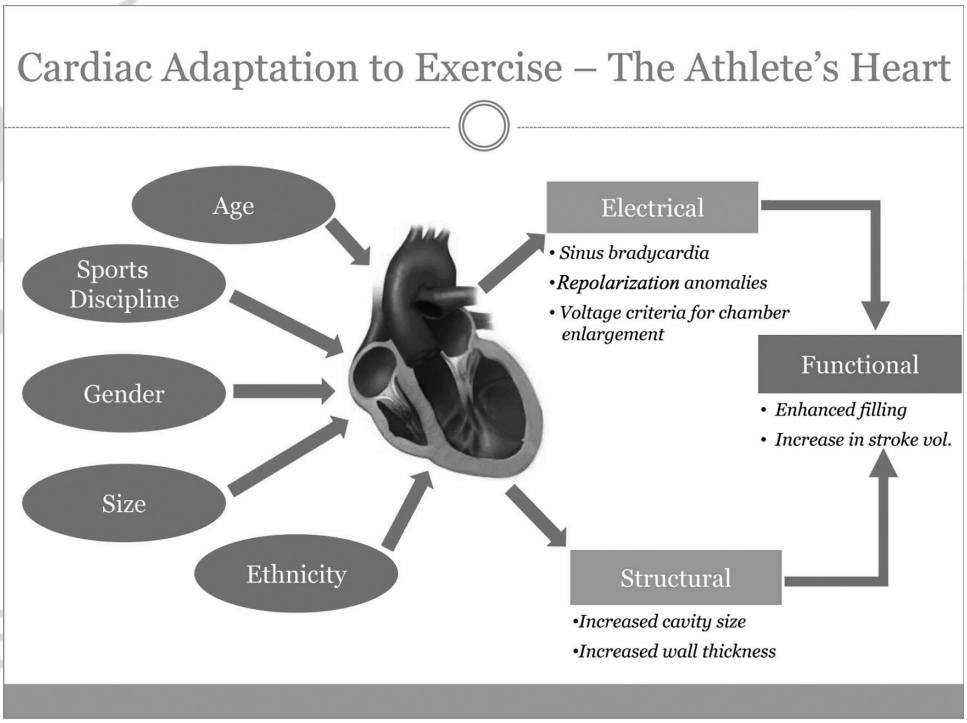


Figure 2. Determinants of cardiac dimensions and physiological adaptation in the athlete's heart.



followed by premature coronary artery disease, and then by coronary artery anomalies.[35] These differences may reflect the fact that Italy's preparticipation cardiovascular screening of all young competitive athletes has been effective in detecting HCM and excluding such individuals from competitive sport. The same group reports a 90% mortality reduction in young athletes since the introduction of preparticipation screening.[31]

Most (90%) SCDs in young athletes occur during or immediately after exercise. Dehydration, hyperpyrexia, electrolyte imbalances, and increased platelet aggregation are exercise-driven mechanisms that may contribute to the timing of SCD, but most fatalities also entail an underlying, undiagnosed arrhythmogenic cardiac substrate.[35]

In a 21-year prospective cohort study, the relative risk of SCD by cardiovascular causes was 2.8 times higher in athletes compared with nonathletes.[35] Certain populations of athletes seem to be at greater risk of SCD. Males appear to outnumber females with relative risks that range from 5:1 to 9:1.[36–38]

In the US National Collegiate Athletic Association registry, male athletes had a 2.3-fold higher risk of SCD than female athletes, and black athletes had a 3-fold greater risk of SCD than white athletes (1:17 000 versus 1:58 000).[39]

Sudden cardiac death is most frequently reported in sports disciplines with an explosive start–stop component such as basketball, football, and soccer.[40] This may be because athletes with HCM may still be able to demonstrate excellence participating in these sports without being overwhelmingly impaired by the inability to augment stroke volume for prolonged periods. Sports requiring sustained periods of endurance activity, such as distance running, would tend to select out these individuals during competition.

Clinical Assessment of an Athletic Individual

History

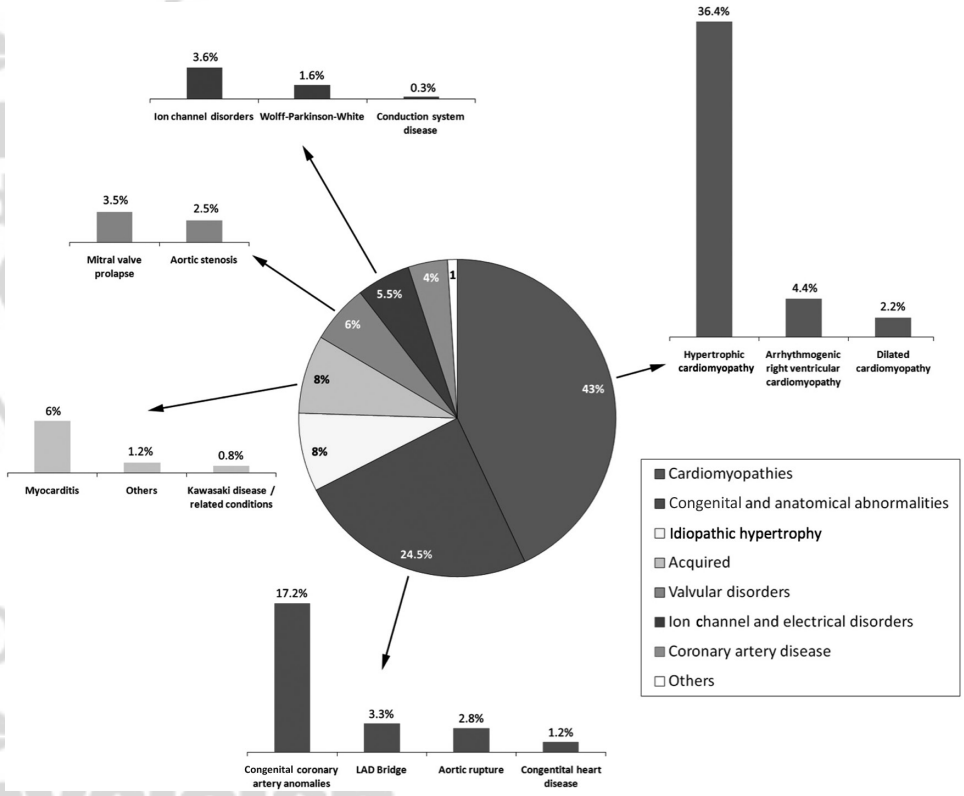
Cardiovascular symptoms in athletic individuals are assessed the same way as in any other population. Symptoms of exertional chest pain, dyspnea out of proportion to effort, palpitation, and syncope should be sought (Table 1).

The age of the individual should be taken into consideration, given the higher proportion of SCD that is attributable to coronary artery disease in athletes aged ≥ 35 years. The most appropriate additional investigations can be tailored to evaluate the most likely underlying disease process.

Attention should be paid to the nature of the sport and the training undertaken, and to whether an individual undertakes sufficient physical activity to conceivably result in significant cardiovascular remodeling.

Syncope warrants special mention, as it is common in athletes. In a large Italian cohort, 6% of athletes reported syncope. In most cases (86.7%), syncope was unrelated to exercise.

Figure 3. Causes of sudden cardiac death in young athletes.



Data from Maron et al.[34]
Abbreviation: LAD, left anterior descending.

In 12%, syncope occurred in the postexertional period, and a small minority (1.3%) had true exertional syncope.[41] Athletes with true exertional syncope are commonly found to have underlying heart disease. Syncope immediately postexertion is more typical in athletes and is usually attributable to neurocardiogenic mechanisms. The cessation of skeletal muscle contraction and altered sympathetic/parasympathetic balance heralds an abrupt reduction in venous return, with subsequent transient cerebral hypoperfusion. This form of syncope can often be avoided by instituting an active cool-down period after vigorous exercise, with care being taken to maintain adequate hydration and intake of supplemental salt.[25]

A comprehensive family history should include any inherited cardiac disease and premature atherosclerotic disease, as well as more subtle features that might suggest premature cardiac death, such as unexplained drowning, motor vehicle accidents, and suspected seizure.

The medication history is also very important, but given that the use of performance-enhancing drugs is forbidden for professional athletes, such important details may not be disclosed. Anabolic androgenic steroids can induce hypertension and alter lipid metabolism, promoting premature atherosclerosis and subsequent myocardial infarction. Ephedrine and other stimulants have been used to boost training workouts and can also aid weight loss. These agents also induce hypertension, can trigger arrhythmias, and may result in cardiomyopathy. In 2012, a London marathon runner died $<$ 1 mile from the end of the course having taken dimethylamylamine in the form of an energy drink during her run. Her inquest revealed

Table 1. Red-Flag Features in an Athlete's History that Should Prompt Specialist Referral

- Exertional chest pain or discomfort
- Breathlessness disproportionate to the amount of exercise being performed, unexplained breathlessness, or fatigue related to exercise
- Palpitation
- Syncope, or near-syncope, particularly if occurring during exercise
- History of elevated blood pressure
- Prior recognition of a heart murmur
- Personal or family history of unexplained drowning or motor vehicle accidents
- Family history of SCD

Reprinted from *The Physician and Sportsmedicine*, 39, Sheikh N, Sharma S. Overview of sudden cardiac death in young athletes. 22–36, Copyright 2011, with permission from JTE Multimedia.
Abbreviation: SCD, sudden cardiac death.

that this substance played an important contribution to her death. The commercial product is now banned in the United Kingdom.

Although professional athletes differ from recreational runners, in that they are subjected to strict regulations on prohibited substances and drug testing, revelations from the professional cycling community indicate that these issues are still relevant. A history of recreational drug use, such as amphetamines and cocaine, is also important for the reasons stated above. Attention should be paid to the use of medications that can cause QT-interval prolongation, for example specific antibiotics and antidepressants. Toxicology, therefore, is an important part of the postmortem investigation of SCD in an athlete.[42]

Examination

Clinical examination may reveal bradycardia and a soft flow murmur but is generally unremarkable in a normal athlete. However, findings suggesting an underlying cardiac pathology may put an athlete at risk of harm during intense physical activity.

A thorough cardiovascular examination should aim to detect hypertension, valvular heart disease, subvalvular resting outflow tract obstruction, coarctation of the aorta, features of Marfan's syndrome, and stigmata of hypercholesterolemia, such as corneal arcus, xanthelasma, and xanthomata (Table 2).

The 12-Lead Electrocardiogram

Regular physical activity enhances vagal tone and increases cardiac dimensions, both of which may manifest on the surface electrocardiogram (ECG). As a result, abnormal ECGs are common when evaluating athletes. In an Italian study of 1005 athletes, 40% had an abnormal ECG, with only 5% showing any structural cardiac abnormality on echocardiography.[43]

Common ECG findings of athletic individuals are sinus bradycardia and Sokolow-Lyon voltage criteria for left ventricular hypertrophy (LVH). A small minority will exhibit a nodal rhythm or Wenckebach second-degree atrioventricular block. Mild exertion results in a reversion to sinus rhythm and acts as confirmation that these rhythms are part of normal physiological conditioning. The European Society of Cardiology has produced consensus guidelines for the interpretation of the 12-lead ECG in the athlete, which describes 2 groups of ECG changes.[44] Group 1 includes common ECG changes that are training related and, in isolation, require no further investigation. Group 2 comprises uncommon ECG changes that occur in $< 5\%$ of athletes, are unrelated to training, and suggest an underlying cardiac disorder, such as cardiomyopathy or ion channelopathy (Table 3). Athletes with ECG changes in the group 2 category require further evaluation. The resting ECG is an important tool that can assist in differentiating physiological cardiac changes in the athlete and in identifying underlying cardiomyopathies. Cardiomyopathies that warrant special mention due to features that overlap with the remodeling seen in the athlete's heart are HCM and ARVC.

Hypertrophic cardiomyopathy is a primary heart muscle disorder, predominantly caused by gene mutations encoding sarcomeric contractile proteins. It is inherited as an autosomal dominant condition and characterized by LVH and myocyte disarray histologically. Affected individuals can exhibit dynamic outflow tract obstruction due to systolic anterior motion of the mitral valve leaflet against a thickened interventricular septum; 30% demonstrate an outflow tract gradient under resting conditions, but this figure may increase to 70% with exercise.[45,46]

Hypertrophic cardiomyopathy demonstrates wide clinical and morphological heterogeneity. Most affected individuals are unable to augment their stroke volumes for prolonged periods to compete in sports at an elite level. However, some individuals experience no symptoms, and the index presentation may be sudden death, during or immediately after exercise.[47]

Over 95% of individuals with HCM have an abnormal resting ECG, which may include T-wave inversions in leads other than III, aVL, aVR, or V_1, pathological Q waves, ST depression in > 2 contiguous leads, and left bundle branch block.[48] These abnormalities can be present 4 to 5 years before the development of cardiac hypertrophy.[49]

Arrhythmogenic right ventricular cardiomyopathy is an inherited autosomal dominant condition caused by gene mutations encoding cardiac desmosomal proteins. There is a predominance of right ventricular involvement; however, biventricular and isolated left ventricular involvement also has been described.[50] Histologically, ARVC is characterized by myocardial cell loss and replacement with fibrofatty tissue. Clinical manifestations include arrhythmias of RV origin, morphological changes affecting the RV, and sudden death, particularly during exertion. A popular theory suggests that under mechanical stress the inherent weakness of cell–cell junctions, caused by abnormal desmosomal proteins, results in myocyte detachment. This detachment and subsequent fibrofatty replacement form a substrate for ventricular arrhythmias.[51]

Electrocardiogram manifestations of ARVC include T-wave inversions and QRS duration prolongation in the

Table 2. Conditions Associated with Sudden Cardiac Death in an Athlete and the Physical Signs they Produce

Condition	Clinical Features
Hypertrophic cardiomyopathy	Ejection systolic murmur, accentuated with standing and Valsalva maneuver, and diminished with squatting. If dynamic outflow obstruction, pulsus bisferiens and double apical impulse may be detected
Mitral valve prolapse	Midsystolic click with late systolic murmur, accentuated with standing, Valsalva maneuver and hand grip, and diminished with squatting
Aortic stenosis	Ejection systolic murmur; in severe cases, narrow pulse pressure, slow rising pulse, and diminished or absent second heart sound
Marfan syndrome	Tall height, arachnodactyly, arm span > height, pectus excavatum or carinatum, high arched palate, joint hypermobility, lens subluxation, mitral or aortic regurgitation
Familial hypercholesterolemia	Eruptive xanthoma, xanthelasma, premature corneal arcus

RV leads (V_1–V_3), epsilon waves (representing delayed repolarization), and ventricular extrasystoles of RV origin (having left bundle branch block morphology). In athletes, the diagnosis can be particularly challenging, as early in the disease process there is a "concealed phase" with a heart that appears morphologically normal. Moreover, in athletes participating in ultra-endurance exercise, training can induce changes in the RV that are identical to ARVC, raising the possibility that in a small proportion of athletes ARVC might be acquired.[52–56]

In the interpretation of the athlete's ECG, race and age also must be taken into consideration. Physiological remodeling of the athlete's heart involves a degree of ethnic variation that is reflected in the ECG. Electrical abnormalities are twice as common in black athletes compared with white athletes.[57] Sokolow-Lyon voltage criteria for LVH is more common in black athletes, at 68%, compared with white athletes, at 40%.[58] Repolarization differences between these 2 ethnic groups are more striking, with 85% of black athletes demonstrating ST segment elevation, compared with 62% of white athletes. In this study, deep T wave inversions (> 0.2 mV) were observed in 12% of black athletes but in none of the white athletes.[58]

In another study, deep T-wave inversions were reported in 16% of black athletes, compared with only 2% of white athletes.[59] The pattern of T-wave inversions in black athletes was largely confined to the anterior (V_1–V_4) precordial leads (Figure 4). After extensive clinical evaluation, this pattern of T-wave inversions was not associated with any underlying cardiac pathology, and, in a subset of athletes, a period of detraining led to resolution of these changes.

Therefore, T-wave inversions in leads V_1 to V_4 are likely to represent a benign finding in black athletes. In contrast, inferior or lateral T-wave inversions were an uncommon finding, and longitudinal follow-up of athletes with these patterns found sudden death events or a subsequent diagnosis of HCM. Therefore, deep T-wave inversions extending to the inferior or lateral leads in athletes warrant further detailed evaluation and follow-up, regardless of the athlete's ethnicity.[59]

Age must also be taken into consideration, as athletes aged < 16 years may demonstrate a normal juvenile pattern of anterior T-wave inversions in leads V_1 to V_4.[60] In contrast, T-wave inversions are identified in only 0.1% to 0.2% of older athletes.

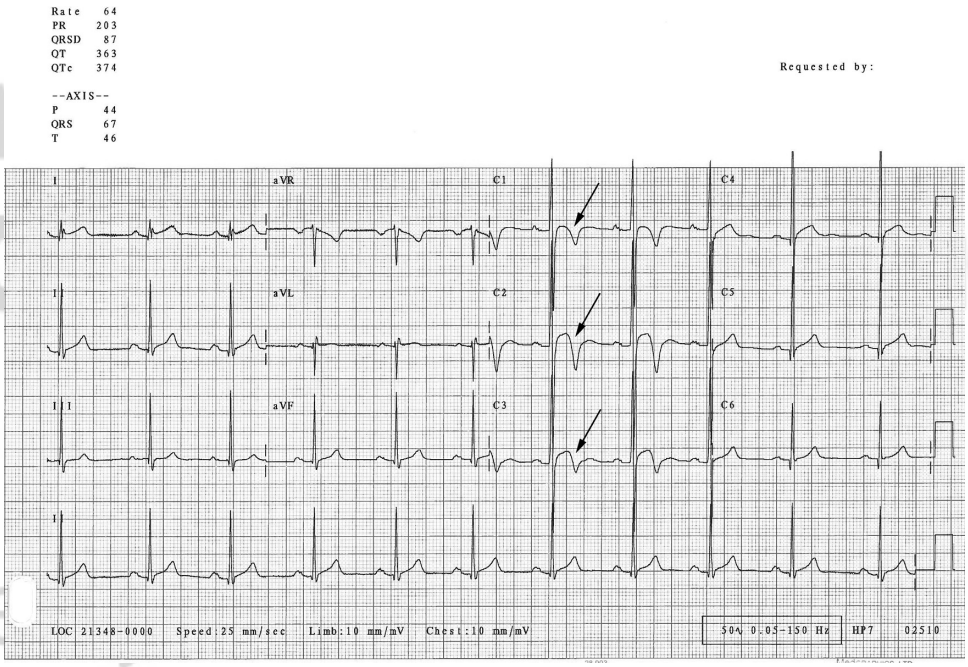
In summary, white adult athletes with deep T-wave inversions in leads other than III, aVL, aVR, or V_1 warrant further evaluation for cardiomyopathy. In athletes aged < 16 years, anterior T-wave inversion can represent a normal juvenile pattern. In black athletes, T-wave inversions confined to V_1 to V_4, particularly in combination with minor concave ST segment elevation in these leads, are likely to represent normal repolarization changes that occur

Table 3. Common and Uncommon ECG Findings in Athletes

Common and Training-Related ECG Changes	Uncommon and Training-Unrelated ECG Changes
Sinus bradycardia	T-wave inversion > 1 mm • in leads other than III, aVR, and V_1 and V_2 in white athletes • in leads other than III, aVR, and $V_{1–4}$ (particularly if preceded by convex ST-segment elevation) in black athletes
First-degree atrioventricular block	
Incomplete RBBB	
Early repolarization	
Isolated QRS voltage criteria for left ventricular hypertrophy	
	ST-segment depression
	Pathological Q waves
	Left atrial enlargement
	Left-axis deviation/left anterior hemiblock
	Right-axis deviation/left posterior hemiblock
	Right ventricular hypertrophy
	Ventricular preexcitation
	Complete LBBB or RBBB
	Long- or short-QT interval
	Brugada-like early repolarization

Adapted from Corrado D, Pelliccia A, Heidbuchel H, et al, Recommendations for interpretation of 12-lead electrocardiogram in the athlete, *European Heart Journal*, 2010, 31, 2, 243–259, by permission of Oxford University Press.
Abbreviations: aVR, augmented voltage right arm; ECG, electrocardiogram; LBBB, left bundle branch block; RBBB, right bundle branch block.

Figure 4. An ECG from a black athlete, showing cardiac adaptive changes in this ethnicity. Convex ST-segment elevation with deep T-wave inversion is evident in leads V_1 to V_3 *(arrows)*.



Abbreviation: ECG, electrocardiogram.

with cardiac remodeling. However, deep T-wave inversions in inferior or lateral leads are not consistent with benign, exercise-related cardiac remodeling in any subgroup of athletes (Figure 5).

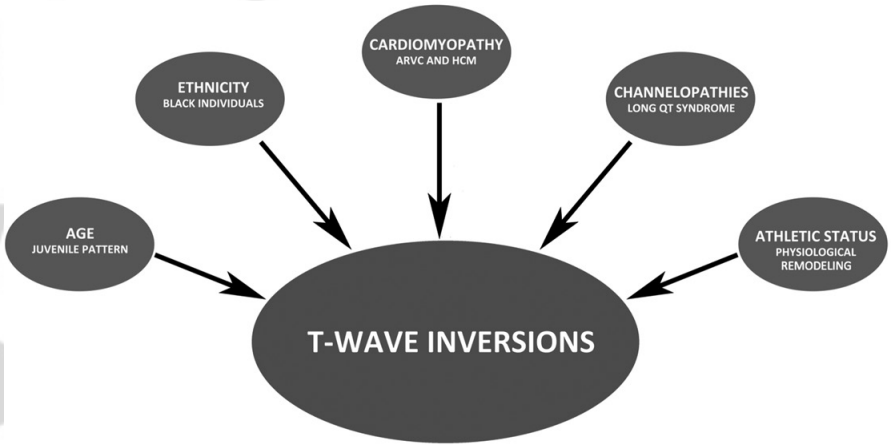
Echocardiography

A study of > 1000 male American athletes demonstrated, by M-mode echocardiography, that in comparison with control subjects, athletes exhibited a 14% to 19% increase in LV wall thickness (LVWT), a 10% increase in LV end-diastolic cavity dimension (LVEDD), a 46% increase in LV mass, and a 24% increase in RV end-diastolic cavity size.[61]

Further large observational studies in mostly white male and female athletes found that ≥ 25% of athletes have LVWT that exceeded reference limits for nonathletes.[62] Echocardiographic upper reference limits for LVWT, LVEDD, and RV dimensions were generated by this and other observational studies according to age, ethnicity, and gender, and are summarized in Table 4.[60]

In predominantly white male athletes, values of LVWT in a range compatible with HCM (> 12 mm) were

Figure 5. Factors influencing T-wave inversions.



Abbreviations: ARVC, arrhythmogenic right ventricular cardiomyopathy; HCM, hypertrophic cardiomyopathy.

Table 4. Echocardiographic Upper Reference Limits for Cardiac Dimensions in Athletes and Non-Athletic Controls, According to Age, Gender, and Ethnicity

	Nonathletes		Athletes					
			White Adults		White Adolescents		Black Adults	
	Male	Female	Male	Female	Male	Female	Male	Female
LVEDD (mm)	≤ 59	≤ 53	≤ 63	≤ 56	≤ 58	≤ 54	≤ 62	≤ 56
LVWT (mm)	≤ 10	≤ 9	≤ 12	≤ 11	≤ 12	≤ 11	≤ 15	≤ 12
RVOT1 (mm)	≤ 35		≤ 38	≤ 37	Not known			
RVD1 (mm)	≤ 42		≤ 45	≤ 42	Not known			

Data taken from references 25, 58, 62–67, 79, and 80.
Reproduced from Zaidi A, Sharma S. Exercise and heart disease: from athletes and arrhythmias to hypertrophic cardiomyopathy and congenital heart disease. *Future Cardiol.* 2013;9(1):119–136, with permission from Future Medicine Ltd.
Abbreviations: LVEDD, left ventricular end-diastolic diameter; LVWT, maximal end-diastolic left ventricular wall thickness; RVOT1, right ventricular outflow tract end-diastolic diameter in parasternal short axis view (above the aortic valve); RVD1, right ventricular end-diastolic basal diameter in apical 4-chamber view.

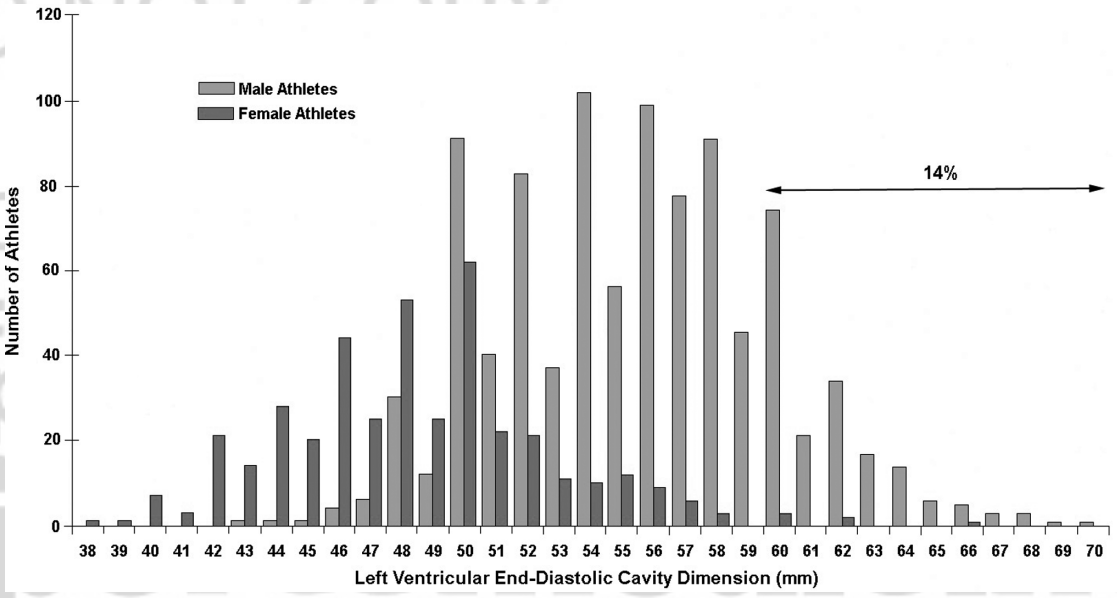
uncommon and present in only 2%. Marked LV cavity dimensions in a range compatible with dilated cardiomyopathy (DCM; LVEDD > 60 mm) were seen in 14% of athletes, although none were > 70 mm (Figure 6).[62,63]

When the same group compared 600 female athletes with matched sedentary female controls and male athletes, it found that although LVWT and LVEDD were greater in female athletes than in sedentary female controls, these dimensions were much greater in male athletes. An LVWT > 12 mm was seen in 2% of male athletes but in none of the female athletes, and an LVEDD > 60 mm was seen in 14% of male athletes but only in < 1% of female athletes.[64]

Adult athletes demonstrate greater cardiac dimensions than adolescent athletes of the same sex and similar sports discipline. This may be related to their greater physical maturity and the duration of intense training as well as other hormonal factors. In studies focusing on the adolescent athlete, only 0.4% had an LVWT > 11 mm,[65] and no athletes had an LVEDD > 60 mm.[66]

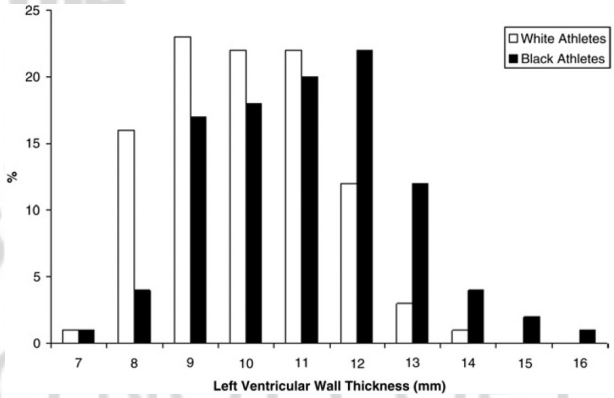
Black athletes display greater LVWTs compared with their white counterparts. In 1 study comparing the cardiac dimensions of 300 black male athletes and 300 white male athletes, matched for age, size, and sports discipline, a LVWT ≥ 13 mm was present in 18% of black athletes compared with 4% of white athletes. An even greater LVWT, ≥ 15 mm, was seen in 3% of black athletes but in none of the white athletes (Figure 7).[58] Another observational study compared black female athletes and white female athletes, and found that 3% of black female athletes had an LVWT ≥ 12 mm in comparison with none of the white female athletes.[67]

Figure 6. Left ventricular end-diastolic diameter in 1309 elite male and female athletes.



Data from Pelliccia et al.[63]

Figure 7. Distribution of LVWT (in mm) in black male and white male athletes, demonstrating a significant proportion of black male athletes with a maximal LVWT between 13 and 16 mm.



Reprinted from *Journal of the American College of Cardiology*, 51(23), Basavarajaiah S, Boraita A, Whyte G, et al, Ethnic differences in left ventricular remodeling in highly-trained athletes relevance to differentiating physiologic left ventricular hypertrophy from hypertrophic cardiomyopathy, 2256–2262, Copyright 2008, with permission from Elsevier.

Abbreviation: LVWT, left ventricular wall thickness.

Therefore, in general, large male athletes participating in endurance sports develop the greatest cardiac dimensions, with black athletes demonstrating a greater magnitude of LVH than matched white athletes.

Diagnostic Dilemmas

A proportion of male athletes demonstrate extreme physiological LVH with LVWTs of 13 to 15 mm. By contrast, individuals with HCM have a mean LVWT of 18 to 20 mm, though approximately 8% will have morphologically mild hypertrophy.[40] Therefore, 4% of white male athletes and 18% of black male athletes fall into a diagnostic gray zone, where differentiation between HCM and athletic remodeling is crucial (Figure 8).[58]

Echocardiography is a powerful tool in identifying key distinguishing features of physiological LVH, such as homogeneous hypertrophy with associated enlargement of chamber size and normal diastolic function. Individuals with HCM tend to show bizarre, often asymmetrical, patterns of LVH, a small chamber size, and impaired diastolic function. Large LV cavity sizes, with LVEDD $>$ 55 mm, are common in highly trained athletes but are rare in HCM where the LVEDD is usually $<$ 45 mm.[68] The presence of systolic anterior motion of the mitral valve and outflow tract obstruction points to a diagnosis of HCM, and these morphological abnormalities of papillary muscles and the mitral valve apparatus are not a feature of the athlete's heart. Diastolic dysfunction is commonly found in HCM, often preceding systolic dysfunction and other structural abnormalities. As a result, left atrial enlargement reaching $>$ 50 mm may be seen. The athlete's heart, by comparison, may demonstrate enhanced relaxation and supranormal diastolic function. Although the heart can symmetrically enlarge, a left atrial size $>$ 50 mm would not be expected.[60]

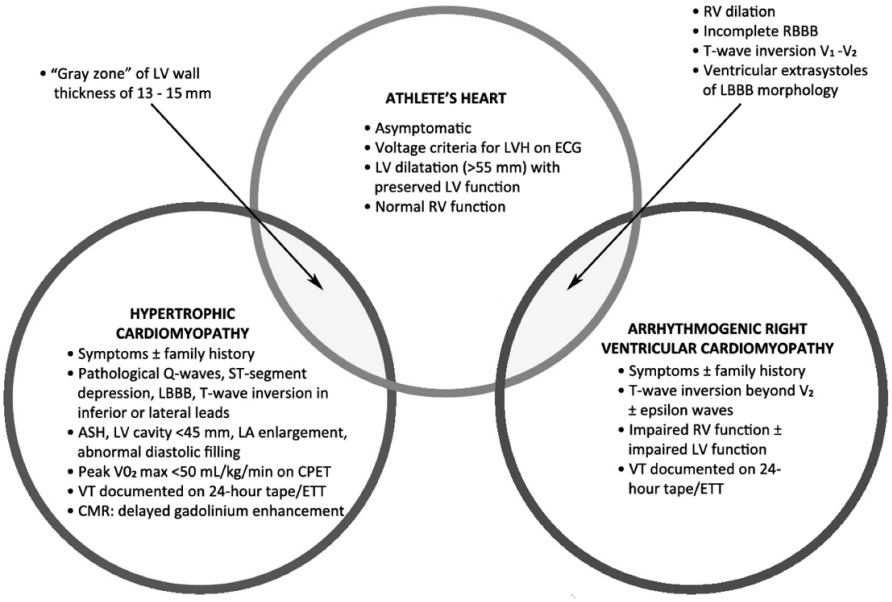
Cardiac MRI is of value in detecting segmental LVH in the anterolateral free wall, posterior ventricular septum, or apex, and in demonstrating delayed gadolinium enhancement, as an indicator of pathological myocardial fibrosis.[69] Cardiopulmonary exercise testing can also be useful, as individuals achieving a peak volume of oxygen consumption per unit of time (Vo_2) $>$ 50 mL/kg/min or $>$ 120% predicted for age, gender, and size are more likely to have athlete's heart than HCM.[70] Occasionally, an 8- to 12-week period of detraining, with reevaluation of ECG and echocardiography, may be the only remaining practical method of differentiating between HCM and the athlete's heart. This method is a powerful discriminator of disease, as only physiological LVH of the athlete's heart will regress.[71] However, this is undesirable for competitive athletes and creates an obstacle to maintaining peak performance, albeit temporary.

Given that HCM is predominantly caused by gene mutations in sarcomeric contractile proteins, one might suspect that genetic testing plays an important role in identifying affected individuals. However, there is substantial genetic heterogeneity underlying inherited cardiac diseases, with poor correlations between genotype and phenotype. Individuals who test positive with an abnormal gene may never go on to develop the phenotype. Furthermore, the total extent of disease-causing mutations is not yet known, such that genetic testing may be negative in up to 50% of HCM, 60% of ARVC, and 70% of DCM patients exhibiting the disease phenotype.[72] In families where a genetic mutation has already been identified, genetic testing of a new suspected case can often be used to confirm the diagnosis. Even in these cases, genetic testing is limited by its availability, it is expensive and the results may be unavailable for some time.

Arrhythmogenic right ventricular cardiomyopathy can also be particularly difficult to distinguish from remodeling changes induced by endurance exercise. The ECG patterns that may arise from ARVC have been described above. Those patterns that particularly favor the diagnosis are epsilon waves, late potentials on signal averaged ECG, and nonsustained VT of left bundle branch block morphology. However, the only demonstrable abnormalities in some affected individuals may be minor ECG abnormalities in RV leads and infrequent ventricular extrasystoles of RV origin.

Assessment of the right ventricle by echocardiography is challenging as it is incompletely visualized in any

Figure 8. A practical guide for differentiating between physiological changes seen in the athlete's heart from hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy.



Reprinted from *The Physician and Sportsmedicine*, 39, Sheikh N, Sharma S. Overview of sudden cardiac death in young athletes. 22–36, Copyright 2011, with permission from JTE Multimedia.

Abbreviations: ASH, asymmetric septal hypertrophy; CPET, cardiopulmonary exercise test; CMR, cardiac magnetic resonance imaging; ECG, electrocardiogram; ETT, exercise treadmill test; LA, left atrium; LBBB, left bundle branch block; LV, left ventricle; LVH, left ventricular hypertrophy; RBBB, right bundle branch block; RV, right ventricle; VO_2max, maximum oxygen consumption; VT, ventricular tachycardia.

2-dimensional window. Moreover, data regarding normal limits of RV size and function are derived from few small studies of normal populations. In ARVC, subtle changes of the RV may be seen on imaging, and regional wall motion abnormalities are even more suggestive of underlying pathology. A study of 102 endurance athletes demonstrated the presence of RV cavity enlargement with RV outflow tract dimensions that were greater than the proposed major criteria for ARVC in 28% of athletes.[73] Where there is a high index of suspicion, cardiac MRI provides more comprehensive imaging of the RV and may also indicate areas of myocardial fibrosis. Genetic testing has the same limitations as described above for HCM. Progress in this area will depend on large studies aiming to define normal limits of RV size and function in athletes.

Cardiac remodeling in athletes can produce echocardiographic appearances that one sees in other cardiomyopathies. Crucially, the absence of other key pathological findings distinguishes the athlete's heart from these cardiomyopathies. Dilated cardiomyopathy is a disorder characterized by its morphological appearance; it has a variety of etiologies including genetic and acquired. Affected individuals have marked impairment of ventricular systolic function accompanied by low exercise capacity, usually prohibiting athletic competition. Marked LV cavity dilatation in the DCM range (LVEDD $\geq$ 60 mm) has been seen in 14% of athletes and almost entirely in males.[62–64]

Left ventricular noncompaction is a cardiomyopathy characterized by increased left ventricular trabeculation and intertrabecular recesses communicating with the LV cavity. This condition manifests with progressive LV dilatation, systolic impairment, fatal arrhythmias, and thromboembolic events. Data from 1146 athletes has shown a higher degree of LV trabeculation (18%) compared with controls (7%). In addition, 8.1% of athletes fulfilled Chin and Jenni criteria for left ventricular noncompaction. The data also suggested that ethnicity may play a role, as increased trabeculation was more common in black athletes (28%) than in white athletes (16%).[74]

Marathon Runners

The modern marathon is derived from Greek legend, commemorating the run of Pheidippides, a soldier who ran from the battlefield in the town of Marathon to Athens, to deliver

the news of a momentous victory over the invading Persians. Legend has it that after running this distance of approximately 26 miles and delivering his message, he suddenly died.

Despite this legend, sudden cardiac death during marathon running is a rare event, occurring with an incidence of 0.54 per 100 000 participants.[75]

Most marathon runners do not satisfy the definition of "athlete" given above and form a more heterogeneous population, with a tendency to be older and harboring more underlying medical conditions, including cardiovascular risk factors. Data from 10.9 million US marathon runners, collected over a 10-year period, found that the most cardiac arrests were due to hypertrophic cardiomyopathy or atherosclerotic coronary disease; 86% of cardiac arrest sufferers were men and the mean age was 42 ± 13 years. Those that survived cardiac arrest were, on average, older than the non-survivors.[75] A possible explanation for this finding is that younger cardiac arrest sufferers had underlying HCM, a condition in which resuscitation after cardiac arrest is reported to be less successful than in other conditions.[76] Older cardiac arrest suffers were more likely to have ischemic heart disease, and this cause of cardiac arrest was the most common in the group of survivors.[75]

In studying the heart for evidence of injury caused by marathon running, interest had originally been focused on the left ventricle. As biomarker elevations had no significant correlation with any changes in LV systolic or diastolic function,[77] their significance is still debated.[78] A more recent small study of 40 marathon runners has shown a correlation in post-race cardiac troponin rise, with reduction in RV ejection fraction, as assessed by MRI. The relevance of delayed gadolinium enhancement, seen in 12.8% of subjects, is not clear, and whether marathon running can have long-term, harmful effects on the myocardium is debatable and warrants further study in larger trials.[29]

Conclusion

Regular physical exercise confers a variety of health benefits, including mortality reduction, with incremental exercise dose being associated with increasing benefit, possibly rising to a plateau in a curvilinear relationship. Frequent and vigorous exertion can induce morphological, functional, and electrical cardiac changes in susceptible individuals that may promote ventricular arrhythmia and sudden death. The majority of sudden deaths in young athletes occur in those with underlying inherited or congenital cardiac disorders, particularly cardiomyopathies. However, a concept gaining popularity, though currently lacking large observational evidence, is that healthy individuals may develop pathological cardiac remodeling and arrhythmias following chronic endurance exercise.

Given that physiological cardiac remodeling in athletes is determined by a variety of factors including age, sex, body size, and ethnicity, athletes form a challenging population for evaluating individuals at risk of SCD. Distinguishing between adaptive physiology and pathology can be lifesaving and should be undertaken by physicians with expertise and experience in dealing with athletes.

Conflict of Interest Statement

Andrew D'Silva, BSc (Hons), MBBS, MRCP (UK), and Sanjay Sharma, BSc (Hons), MD, FRCP (UK), FESC, have no conflicts of interest to declare.

References

1. Nocon M, Hiemann T, Muller-Riemenschneider F, Thalau F, Roll S, Willich SN. Association of physical activity with all-cause and cardiovascular mortality: a systematic review and meta-analysis. *Eur J Cardiovasc Prevent Rehabil*. 2008;15(3):239–246.
2. Rowland TW. The role of physical activity and fitness in children in the prevention of adult cardiovascular disease. *Progr Pediatr Cardiol*. 2001;12(2):199–203.
3. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346(6):393–403.
4. Kelley GA, Kelley KS, Tran ZV. Walking, lipids, and lipoproteins: a meta-analysis of randomized controlled trials. *Prev Med*. 2004;38(5):651–661.
5. McTiernan A, Kooperberg C, White E, et al. Recreational physical activity and the risk of breast cancer in postmenopausal women: the Women's Health Initiative Cohort Study. *JAMA*. 2003;290(10):1331–1336.
6. Hamer M, Lavoie KL, Bacon SL. Taking up physical activity in later life and healthy ageing: the English longitudinal study of ageing. *Br J Sports Med*. 2014;48(3):239–243.
7. Chakravarty EF, Hubert HB, Lingala VB, Fries JF. Reduced disability and mortality among aging runners: a 21-year longitudinal study. *Arch Intern Med*. 2008;168(15):1638–1646.
8. Tanasescu M, Leitzmann MF, Rimm EB, Willett WC, Stampfer MJ, Hu FB. Exercise type and intensity in relation to coronary heart disease in men. *JAMA*. 2002;288(16):1994–2000.
9. Kokkinos P, Myers J, Kokkinos JP, et al. Exercise capacity and mortality in black and white men. *Circulation*. 2008;117(5):614–622.
10. Kokkinos P, Myers J. Exercise and physical activity: clinical outcomes and applications. *Circulation*. 2010;122(16):1637–1648.
11. Pate RR, Pratt M, Blair SN, et al. Physical activity and public health. A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *JAMA*. 1995;273(5):402–407.
12. Wen CP, Wai JP, Tsai MK, et al. Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study. *Lancet*. 2011;378(9798):1244–1253.
13. O'Keefe JH, Lavie CJ. Run for your life ... at a comfortable speed and not too far. *Heart*. 2013;99(8):516–519.
14. Lee DP, Pate RR, Lavie CJ, Blair SN. Running and all-cause mortality risk—is more better? *Med Sci Sports Exerc*. 2012;44(5):S699.
15. Schnohr P, Marott JL, Lange P, Jensen GB. Longevity in male and female joggers: the Copenhagen City Heart Study. *Am J Epidemiol*. 2013;177(7):683–689.

16. Karjalainen J, Kujala UM, Kaprio J, Sarna S, Viitasalo M. Lone atrial fibrillation in vigorously exercising middle aged men: case-control study. *BMJ*. 1998;316(7147):1784–1785.
17. Sorokin AV, Araujo CG, Zweibel S, Thompson PD. Atrial fibrillation in endurance-trained athletes. *Br J Sports Med*. 2011;45(3): 185–188.
18. Molina L, Mont L, Marrugat J, et al. Long-term endurance sport practice increases the incidence of lone atrial fibrillation in men: a follow-up study. *Europace*. 2008;10(5):618–623.
19. Turagam MK, Velagapudi P, Kocheril AG. Atrial fibrillation in athletes. *Am J Cardiol*. 2012;109(2):296–302.
20. Haskell WL, Lee IM, Pate RR, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation*. 2007;116(9):1081–1093.
21. Pelliccia A, Fagard R, Bjornstad HH, et al. Recommendations for competitive sports participation in athletes with cardiovascular disease: a consensus document from the Study Group of Sports Cardiology of the Working Group of Cardiac Rehabilitation and Exercise Physiology and the Working Group of Myocardial and Pericardial Diseases of the European Society of Cardiology. *Eur Heart J*. 2005;26(14): 1422–1445.
22. Maron BJ, Pelliccia A. The heart of trained athletes: cardiac remodeling and the risks of sports, including sudden death. *Circulation*. 2006;114(15):1633–1644.
23. Morganroth J, Maron BJ, Henry WL, Epstein SE. Comparative left ventricular dimensions in trained athletes. *Ann Intern Med*. 1975;82(4):521–524.
24. Rodriguez CJ, Diez-Roux AV, Moran A, et al. Left ventricular mass and ventricular remodeling among Hispanic subgroups compared with non-Hispanic blacks and whites: MESA (Multi-ethnic Study of Atherosclerosis). *J Am Coll Cardiol*. 2010;55(3):234–242.
25. Baggish AL, Wood MJ. Athlete's heart and cardiovascular care of the athlete: scientific and clinical update. *Circulation*. 2011;123(23): 2723–2735.
26. Mitchell JH, Haskell WL, Raven PB. Classification of sports. *J Am Coll Cardiol*. 1994;24(4):864–866.
27. Zaidi A, Sharma S. The athlete's heart. *Br J Hosp Med*. 2011;72(5): 275–281.
28. Scharhag J, Schneider G, Urhausen A, Rochette V, Kramann B, Kindermann W. Athlete's heart: right and left ventricular mass and function in male endurance athletes and untrained individuals determined by magnetic resonance imaging. *J Am Coll Cardiol*. 2002;40(10):1856–1863.
29. La Gerche A, Burns AT, Mooney DJ, et al. Exercise-induced right ventricular dysfunction and structural remodelling in endurance athletes. *Eur Heart J*. 2012;33(8):998–1006.
30. Sheikh N, Sharma S. Overview of sudden cardiac death in young athletes. *Phys Sportsmed*. 2011;39(4):22–36.
31. Corrado D, Basso C, Pavei A, Michieli P, Schiavon M, Thiene G. Trends in sudden cardiovascular death in young competitive athletes after implementation of a preparticipation screening program. *JAMA*. 2006;296(13):1593–1601.
32. Thompson PD, Funk EJ, Carleton RA, Sturner WQ. Incidence of death during jogging in Rhode Island from 1975 through 1980. *JAMA*. 1982;247(18):2535–2538.
33. Maron BJ, Epstein SE, Roberts WC. Causes of sudden death in competitive athletes. *J Am Coll Cardiol*. 1986;7(1):204–214.
34. Maron BJ, Thompson PD, Ackerman MJ, et al. Recommendations and considerations related to preparticipation screening for cardiovascular abnormalities in competitive athletes: 2007 update: a scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism: endorsed by the American College of Cardiology Foundation. *Circulation*. 2007;115(12):1643–1455.
35. Corrado D, Basso C, Rizzoli G, Schiavon M, Thiene G. Does sports activity enhance the risk of sudden death in adolescents and young adults? *J Am Coll Cardiol*. 2003;42(11):1959–1963.
36. Maron BJ, Doerer JJ, Haas TS, Tierney DM, Mueller FO. Sudden deaths in young competitive athletes: analysis of 1866 deaths in the United States, 1980–2006. *Circulation*. 2009;119(8):1085–1092.
37. Maron BJ. Sudden death in young athletes. *N Engl J Med*. 2003;349(11): 1064–1075.
38. Drezner JA, Rao AL, Heistand J, Bloomingdale MK, Harmon KG. Effectiveness of emergency response planning for sudden cardiac arrest in United States high schools with automated external defibrillators. *Circulation*. 2009;120(6):518–525.
39. Harmon KG, Asif IM, Klossner D, Drezner JA. Incidence of sudden cardiac death in national collegiate athletic association athletes. *Circulation*. 2011;123(15):1594–1600.
40. Chandra N, Bastiaenen R, Papadakis M, Sharma S. Sudden cardiac death in young athletes: practical challenges and diagnostic dilemmas. *J Am Coll Cardiol*. 2013;61(10):1027–1040.
41. Colivicchi F, Ammirati F, Santini M. Epidemiology and prognostic implications of syncope in young competing athletes. *Eur Heart J*. 2004;25(19):1749–1753.
42. Dhar R, Stout CW, Link MS, Homoud MK, Weinstock J, Estes NA 3rd. Cardiovascular toxicities of performance-enhancing substances in sports. *Mayo Clin Proc*. 2005;80(10):1307–1315.
43. Pelliccia A, Maron BJ, Culasso F, et al. Clinical significance of abnormal electrocardiographic patterns in trained athletes. *Circulation*. 2000;102(3):278–284.
44. Corrado D, Pelliccia A, Heidbuchel H, et al. Recommendations for interpretation of 12-lead electrocardiogram in the athlete. *Eur Heart J*. 2010;31(2):243–259.
45. Williams LK, Frenneaux MP, Steeds RP. Echocardiography in hypertrophic cardiomyopathy diagnosis, prognosis, and role in management. *Eur J Echocardiogr*. 2009;10(8):iii9–14.
46. Maron BJ, Maron MS, Wigle ED, Braunwald E. The 50-year history, controversy, and clinical implications of left ventricular outflow tract obstruction in hypertrophic cardiomyopathy from idiopathic hypertrophic subaortic stenosis to hypertrophic cardiomyopathy: from idiopathic hypertrophic subaortic stenosis to hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2009;54(3):191–200.
47. Maron BJ, Shirani J, Poliac LC, Mathenge R, Roberts WC, Mueller FO. Sudden death in young competitive athletes. Clinical, demographic, and pathological profiles. *JAMA*. 1996;276(3):199–204.
48. Corrado D, Pelliccia A, Bjornstad HH, et al; Study Group of Sport Cardiology of the Working Group of Cardiac Rehabilitation and Exercise Physiology and the Working Group of Myocardial and Pericardial Diseases of the European Society of Cardiology. Cardiovascular pre-participation screening of young competitive athletes for prevention of sudden death: proposal for a common European protocol. Consensus Statement of the Study Group of Sport Cardiology of the Working Group of Cardiac Rehabilitation and Exercise Physiology and the Working Group of Myocardial and Pericardial Diseases of the European Society of Cardiology. *Eur Heart J*. 2005;26(5): 516–524.
49. Gregor P, Widimsky P, Cervenka V, Visek V, Hrobonova V. Electrocardiographic changes can precede the development of myocardial hypertrophy in the setting of hypertrophic cardiomyopathy. *Int J Cardiol*. 1989;23(3):335–341.
50. Norman M, Simpson M, Mogensen J, et al. Novel mutation in desmoplakin causes arrhythmogenic left ventricular cardiomyopathy. *Circulation*. 2005;112(5):636–642.
51. Corrado D, Basso C, Pilichou K, Thiene G. Molecular biology and clinical management of arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Heart*. 2011;97(7):530–539.
52. Heidbuchel H, Hoogsteen J, Fagard R, et al. High prevalence of right ventricular involvement in endurance athletes with ventricular arrhythmias. Role of an electrophysiologic study in risk stratification. *Eur Heart J*. 2003;24(16):1473–1480.
53. Ector J, Ganame J, van der Merwe N, et al. Reduced right ventricular ejection fraction in endurance athletes presenting with ventricular arrhythmias: a quantitative angiographic assessment. *Eur Heart J*. 2007;28(3):345–353.

54. La Gerche A, Connelly KA, Mooney DJ, MacIsaac AI, Prior DL. Biochemical and functional abnormalities of left and right ventricular function after ultra-endurance exercise. *Heart*. 2008;94(7):860–866.
55. La Gerche A, Robberecht C, Kuiperi C, et al. Lower than expected desmosomal gene mutation prevalence in endurance athletes with complex ventricular arrhythmias of right ventricular origin. *Heart*. 2010;96(16):1268–1274.
56. Sharma S, Papadakis M, Whyte G. Chronic ultra-endurance exercise: implications in arrhythmogenic substrates in previously normal hearts. *Heart*. 2010;96(16):1255–1256.
57. Magalski A, Maron BJ, Main ML, et al. Relation of race to electrocardiographic patterns in elite American football players. *J Am Coll Cardiol*. 2008;51(23):2250–2255.
58. Basavarajaiah S, Boraita A, Whyte G, et al. Ethnic differences in left ventricular remodeling in highly-trained athletes relevance to differentiating physiologic left ventricular hypertrophy from hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2008;51(23):2256–2262.
59. Papadakis M, Carre F, Kervio G, et al. The prevalence, distribution, and clinical outcomes of electrocardiographic repolarization patterns in male athletes of African/Afro-Caribbean origin. *Eur Heart J*. 2011;32(18):2304–2313.
60. Zaidi A, Sharma S. Exercise and heart disease: from athletes and arrhythmias to hypertrophic cardiomyopathy and congenital heart disease. *Future Cardiol*. 2013;9(1):119–136.
61. Maron BJ. Structural features of the athlete heart as defined by echocardiography. *J Am Coll Cardiol*. 1986;7(1):190–203.
62. Pelliccia A, Maron BJ, Spataro A, Proschan MA, Spirito P. The upper limit of physiologic cardiac hypertrophy in highly trained elite athletes. *N Engl J Med*. 1991;324(5):295–301.
63. Pelliccia A, Culasso F, Di Paolo FM, Maron BJ. Physiologic left ventricular cavity dilatation in elite athletes. *Ann Intern Med*. 1999;130(1):23–31.
64. Pelliccia A, Maron BJ, Culasso F, Spataro A, Caselli G. Athlete's heart in women. Echocardiographic characterization of highly trained elite female athletes. *JAMA*. 1996;276(3):211–215.
65. Sharma S, Maron BJ, Whyte G, Firoozi S, Elliott PM, McKenna WJ. Physiologic limits of left ventricular hypertrophy in elite junior athletes: relevance to differential diagnosis of athlete's heart and hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2002;40(8):1431–1436.
66. Makan J, Sharma S, Firoozi S, Whyte G, Jackson PG, McKenna WJ. Physiological upper limits of ventricular cavity size in highly trained adolescent athletes. *Heart*. 2005;91(4):495–499.
67. Rawlins J, Carre F, Kervio G, et al. Ethnic differences in physiological cardiac adaptation to intense physical exercise in highly trained female athletes. *Circulation*. 2010;121(9):1078–1085.
68. Rawlins J, Bhan A, Sharma S. Left ventricular hypertrophy in athletes. *Eur J Echocardiogr*. 2009;10(3):350–356.
69. Popovic ZB, Kwon DH, Mishra M, et al. Association between regional ventricular function and myocardial fibrosis in hypertrophic cardiomyopathy assessed by speckle tracking echocardiography and delayed hyperenhancement magnetic resonance imaging. *J Am Soc Echocardiogr*. 2008;21(12):1299–1305.
70. Sharma S, Elliott PM, Whyte G, et al. Utility of metabolic exercise testing in distinguishing hypertrophic cardiomyopathy from physiologic left ventricular hypertrophy in athletes. *J Am Coll Cardiol*. 2000;36(3):864–870.
71. Basavarajaiah S, Wilson M, Junagde S, et al. Physiological left ventricular hypertrophy or hypertrophic cardiomyopathy in an elite adolescent athlete: role of detraining in resolving the clinical dilemma. *Br J Sports Med*. 2006;40(8):727–729, discussion 729.
72. Hershberger RE, Lindenfeld J, Mestroni L, Seidman CE, Taylor MR, Towbin JA. Genetic evaluation of cardiomyopathy—a Heart Failure Society of America practice guideline. *J Cardiac Fail*. 2009;15(2):83–97.
73. Oxborough D, Sharma S, Shave R, et al. The right ventricle of the endurance athlete: the relationship between morphology and deformation. *J Am Soc Echocardiogr*. 2012;25(3):263–271.
74. Gati S, Chandra N, Bennett RL, et al. Increased left ventricular trabeculation in highly trained athletes: do we need more stringent criteria for the diagnosis of left ventricular non-compaction in athletes? *Heart*. 2013;99(6):401–408.
75. Kim JH, Malhotra R, Chiampas G, et al. Cardiac arrest during long-distance running races. *N Engl J Med*. 2012;366(2):130–140.
76. Elliott PM, Sharma S, Varnava A, Poloniecki J, Rowland E, McKenna WJ. Survival after cardiac arrest or sustained ventricular tachycardia in patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 1999;33(6):1596–1601.
77. Shave R, Baggish A, George K, et al. Exercise-induced cardiac troponin elevation: evidence, mechanisms, and implications. *J Am Coll Cardiol*. 2010;56(3):169–176.
78. Whyte GP. Clinical significance of cardiac damage and changes in function after exercise. *Med Sci Sports Exerc*. 2008;40(8):1416–1423.
79. D'Andrea A, Riegler L, Golia E, et al. Range of right heart measurements in top-level athletes: the training impact. *Int J Cardiol*. 2013;164(1):48–57.
80. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr*. 2010;23(7):685–713, quiz 786–788.