STATE-OF-THE-ART PAPER

Sudden Cardiac Death in Young Athletes

Practical Challenges and Diagnostic Dilemmas

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Sudden cardiac death (SCD) in an athlete is a rare yet highly visible tragedy that generates significant media attention and discussion among medical personnel, sports communities, and laypersons alike. The incidence of SCD is greater in athletes compared with their nonathletic counterparts due to the increased risk associated with strenuous exercise in the context of a quiescent cardiac abnormality. Numerous structural, electrical, and acquired cardiovascular abnormalities are capable of causing SCD, many of which can be identified during life and managed by lifestyle modifications, pharmacotherapy, and device therapy. Strategies for the prevention of SCD, including pre-participation cardiovascular screening, are endorsed by sports governing bodies, but mandatory pre-participation cardiovascular screening remains rare. Evaluation of athletes poses diagnostic difficulties, particularly differentiating between physiological adaptation to exercise, known as athlete's heart, and cardiomyopathic processes capable of causing SCD. This paper provides a detailed review regarding the etiology of SCD in young athletes and provides insight into the challenges and dilemmas faced when evaluating athletes for underlying pathological conditions.   (J Am Coll Cardiol 2013;61:1027–40) © 2013 by the American College of Cardiology Foundation

The beneficial effects of regular exercise for primary and secondary prevention of cardiovascular disease are well documented (1). Paradoxically, athletes harboring quiescent cardiovascular abnormalities are at greater risk of exercise-related sudden cardiac death (SCD). Data from Italy have shown a 2.8-fold greater risk of SCD among competitive athletes compared with their nonathletic counterparts. SCD results from intense physical exercise in the context of an underlying cardiovascular abnormality (2). The mechanism is typically ventricular arrhythmia, probably due to exercise-induced catecholamine surges acting on an arrhythmogenic substrate. Postulated contributory mechanisms also include dehydration, hyperpyrexia, electrolyte imbalances, and increased platelet aggregation associated with exercise (3).

The precise definition of an athlete is complex; however, for the purposes of this review, we define an athlete as an individual engaged in regular physical training and participating in official sports competition with an emphasis on excellence and achievement (4). SCD in a young athlete is often difficult for the public to comprehend because athletes are perceived as the healthiest segment of society. Most nontraumatic deaths are attributed to cardiovascular abnormalities that can be identified during life and managed with lifestyle modifications including abstinence from exercise of high or moderate intensity, pharmacotherapy, and implantable cardioverter-defibrillators (ICDs) (5). Prevention of such catastrophes by pre-participation cardiovascular screening (PPS) is recommended by learned organizations and sports governing bodies including the European Society of Cardiology (ESC), American Heart Association, and the International Olympic Committee (6–8).

This paper provides a detailed review regarding the etiology of SCD in young athletes and provides insight into the challenges and dilemmas faced when evaluating athletes for underlying pathological conditions.

Epidemiology of SCD in Athletes

The incidence of SCD among young athletes is a source of debate, particularly as studies differ in their methodology. Data compiled retrospectively from media reports, insurance claims, and electronic databases are likely to represent a significant underestimate. The most robust data are derived from prospective, observational studies in Italy using regional registry data with mandatory reporting systems, which report incidence rates of 3.6/100,000 per year in the pre-screening era. More recent cross-sectional studies from the United States have demonstrated relatively similar

figures with incidence rates ranging from 2.3 to 4.4/100,000 per year (9–11).

There is a significant male predominance of SCD among athletes. Data from the National Center for Catastrophic Sports Injury Research on high school and college athletes reported a 5-fold higher incidence of SCD in male compared with female athletes (12). In the Veneto region of northern Italy, where >110,000 athletes were evaluated over a 21-year follow-up period, the incidence rates of SCD were 2.6/100,000 person-years in male athletes and 1.1/100,000 person-years in their female counterparts (2). Several factors are implicated in this sex difference including lower participation rates among female athletes at the elite level, although this trend is changing, and lower prevalence of cardiac abnormalities capable of causing SCD in females (13).

Over the past 3 decades, there has been an explosion in the number of African/Afro-Caribbean (black) athletes competing at the elite level (14). SCD appears to be more common in this ethnic group, with a reported incidence rate of 5.6/100,000 per year in the United States (11). Cardiomyopathy has been consistently demonstrated as the most common cause of exercise-related SCD in young athletes. Data from U.S. autopsy series have reported higher death rates from hypertrophic cardiomyopathy (HCM) in black compared with white athletes (20% vs. 10%, respectively), raising concern that this condition may exhibit a more malignant phenotype in black individuals (15).

Sudden death occurs more frequently in certain sports. In the United States, basketball and football have the greatest incidence, whereas in Europe, soccer predominates (16). Extrapolation of this observation suggests that individuals participating in sports of high dynamic and low isometric intensity are at higher risk of death. However, there is the potential for data bias due to higher participation rates in these sports.
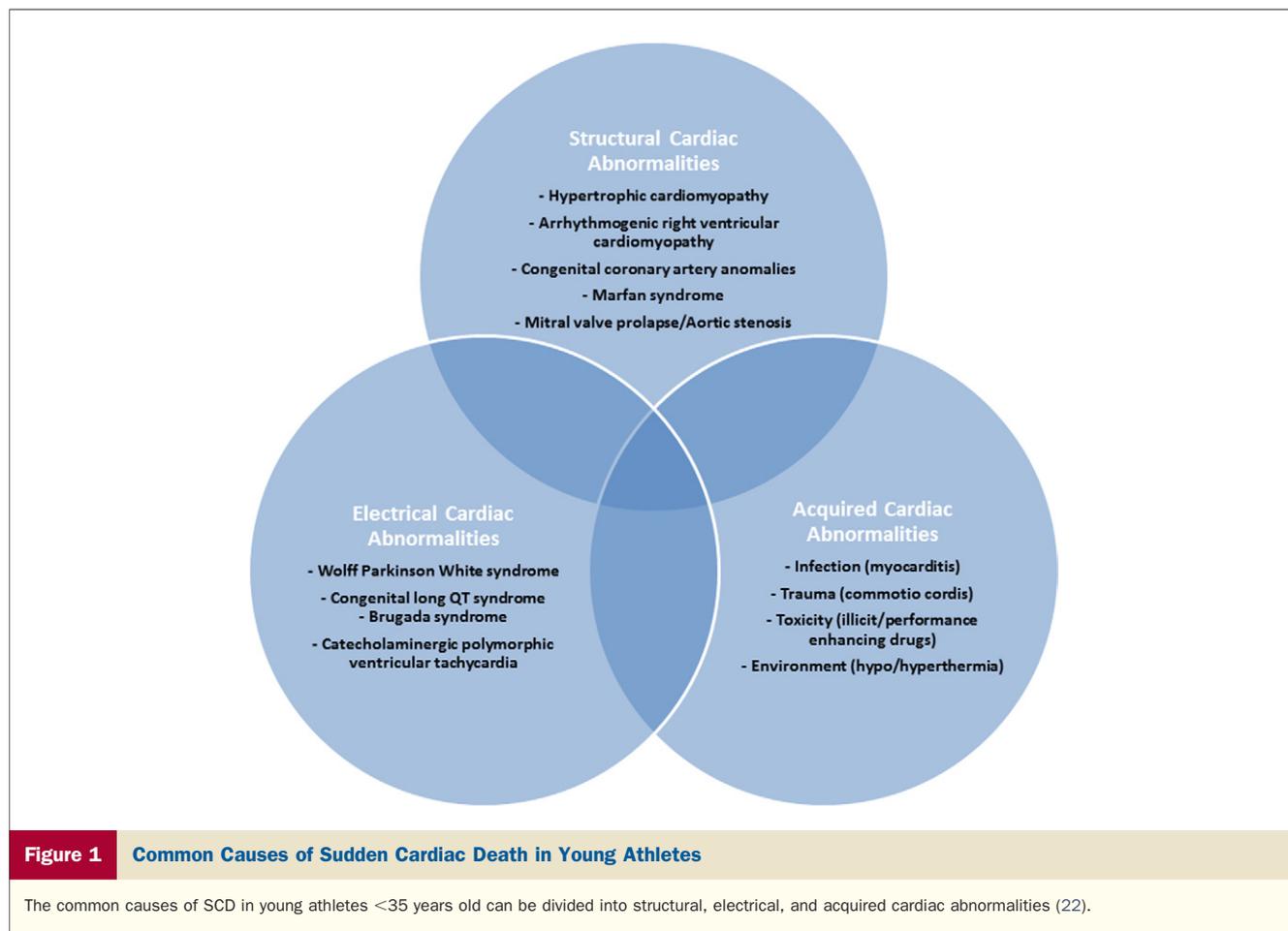
Etiology of SCD in Athletes

In athletes older than 35 years of age, 80% of SCD is frequently due to atherosclerotic coronary artery disease, but in younger athletes, inherited and other acquired cardiovascular abnormalities are usually responsible (Fig. 1). Cardiomyopathy, including HCM and arrhythmogenic right ventricular cardiomyopathy (ARVC), is the most common cause of exercise-related SCD (5).

Structural cardiac abnormalities. HYPERTROPHIC CARDIOMYOPATHY. The reported prevalence of HCM is 0.2% in the general population and 0.07% to 0.08% in athletes (17). HCM is a primary myocardial disorder with an autosomal dominant pattern of inheritance, characterized by left ventricular hypertrophy (LVH) in the absence of abnormal loading conditions and myocardial disarray on histology. Sudden death due to ventricular tachycardia (VT)/ventricular fibrillation (VF) is often the first clinical manifestation (18). Deaths caused by HCM are common in start-stop sports, for example, football and basketball, but rare in endurance events such as rowing, long-distance cycling, and running. It is hypothesized that the combination of myocardial hypertrophy, impaired myocardial relaxation, myocardial ischemia, and dynamic left ventricular (LV) outflow obstruction impede augmentation of stroke volume for prolonged periods, and individuals with HCM are therefore usually selected out of endurance sports.

The diagnosis is made using electrocardiography (ECG) and echocardiography. More than 90% of affected individuals have an abnormal resting electrocardiogram (Figs. 2A and 2C) (19). All individuals with previous cardiac arrest or sustained VT are at high risk of SCD and require treatment with an ICD. Other recognized risk factors for SCD include: 1) unheralded syncope; 2) family history of SCD; 3) severe LVH (>30 mm); 4) sustained or nonsustained VT; and 5) attenuated blood pressure response to exercise. These 5 risk factors have low positive predictive value but high negative predictive value. Subjects exhibiting ≥1 of the 5 risk markers should be considered for prophylactic insertion of an ICD (20).

ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY. ARVC has a reported prevalence of 1/1,000 in the general population. It is an inherited myocardial disease caused by mutations in genes encoding cardiac desmosomal proteins (21). The mechanism of SCD is complex and myocardial stretch and myocyte detachment during exercise are thought to result in ventricular arrhythmia and SCD. In survivors, focal myocarditis with subsequent healing leads to progressive fibrofatty replacement of the myocardium and a propensity to VT/VF. Macroscopic appearances include right ventricular (RV) dilation, dysfunction, and aneurysm formation (22). Exercise exacerbates these pathophysiological changes, and a 5-fold higher risk of SCD in ARVC has been demonstrated during competitive sports compared with sedentary activity (2). Diagnosis relies on meeting the 2010 ARVC Task Force criteria, which include symptoms, family history, resting/ambulatory electrocardiographic changes, echocardiographic and cardiac magnetic resonance imaging and myocardial tissue characterization (Figs. 2B and 2D)

Figure 1   **Common Causes of Sudden Cardiac Death in Young Athletes**

The common causes of SCD in young athletes <35 years old can be divided into structural, electrical, and acquired cardiac abnormalities (22).

(23). Previous cardiac arrest, unexplained syncope, VT with hemodynamic compromise and extensive structural disease including LV involvement are risk factors for SCD and should prompt consideration of prophylactic ICD implantation (20,24).

CONGENITAL CORONARY ARTERY ANOMALIES. Congenital coronary artery anomalies (CCAAs) reportedly cause SCD in 12% to 33% of athletes. The most common anomalies implicated are left coronary artery origins in the right sinus of Valsalva and right coronary artery origins in the left sinus of Valsalva (25). SCD results from ventricular arrhythmia triggered by myocardial ischemia during exercise. Coronary blood flow is impaired by the abnormal ostium of the anomalous vessel, compression of the anomalous artery as it courses between the pulmonary artery and ascending aorta, and/or coronary spasm triggered by endothelial dysfunction (26). Victims of SCD due to CCAA are often asymptomatic before presentation, although chest pain associated with syncope should raise suspicion of the disorder.

Diagnosis using ECG, echocardiography, and exercise stress testing is notoriously difficult because affected individuals rarely reveal features of inducible ischemia during exercise stress testing or pharmacological functional tests. Cardiac magnetic resonance angiography and computed

tomography coronary angiography are the gold standard imaging modalities (27). The usual recommended therapy for CCAA is surgical correction; however, there is controversy regarding which specific types of CCAA require surgical correction in an asymptomatic athlete. Although surgery is almost universally recommended for left-sided CCAA, clinical management of a right-sided CCAA is more uncertain. It has been suggested that an intramural course, acute-angled take off, stenosis, or slitlike opening carry higher risk (25).

OTHER STRUCTURAL CARDIAC ABNORMALITIES. Other structural cardiac abnormalities associated with SCD include aortic dissection/rupture typically in the context of Marfan syndrome, mitral valve prolapse (MVP), and aortic stenosis. Marfan syndrome is a collagen disorder caused by mutations in the gene encoding fibrillin, inherited as an autosomal dominant trait with a prevalence of 1 in 5,000. It accounts for approximately 3% of exercise-related SCD in young athletes and is characterized by skeletal, cardiac, and ocular abnormalities. Cystic medial necrosis in the tunica media of the aorta results in aortic dilation, dissection, or rupture, which may be expedited by the increases in aortic pressure associated with exercise (28,29). Marfan patients should be prohibited from isometric or isotonic exercise of moderate to high intensity. Individuals with an enlarged
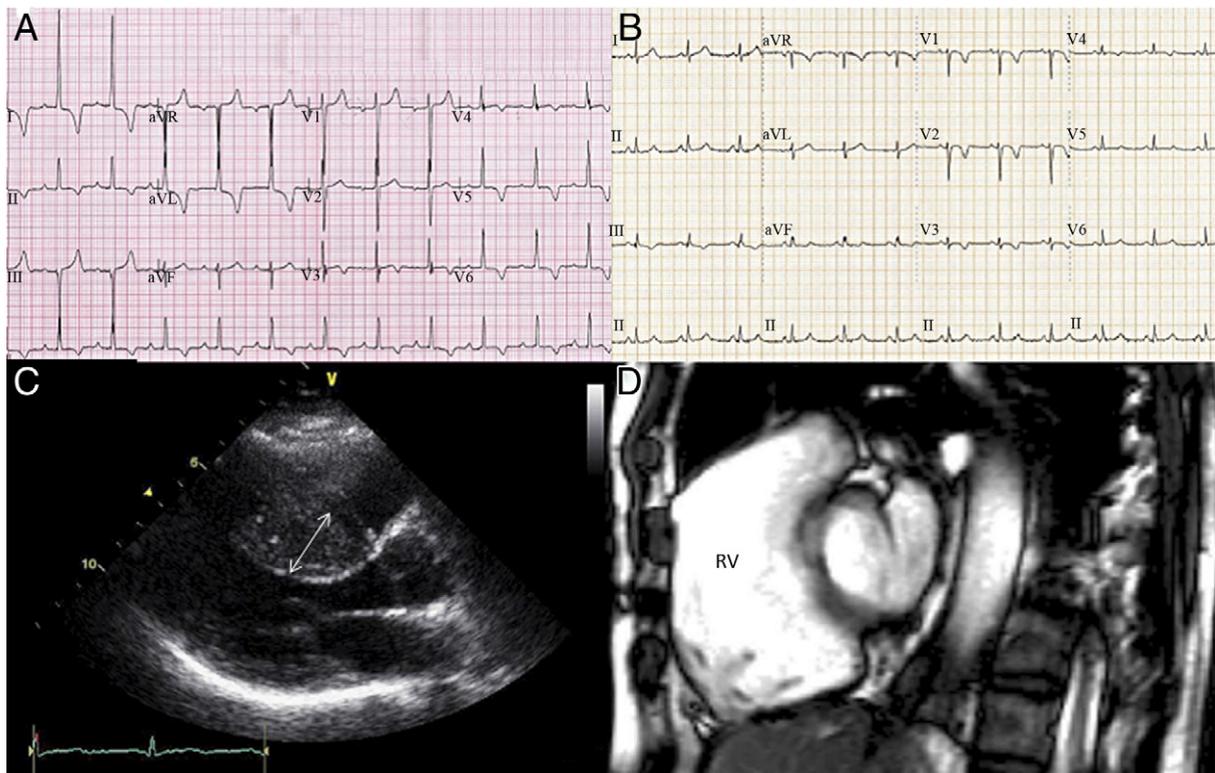
Figure 2   ECG and Imaging Abnormalities Observed in HCM and ARVC

(A) Electrocardiogram (ECG) in hypertrophic cardiomyopathy (HCM) demonstrating left axis deviation, voltage criteria for left atrial enlargement, and left ventricular hypertrophy. There is ST-segment depression with deep T-wave inversion in leads I, aVL, and V_5 and V_6, and T-wave inversion in leads II and V_3 and V_4. **(B)** ECG in arrhythmogenic right ventricular cardiomyopathy (ARVC) demonstrating T-wave inversion in right precordial leads. **(C)** Transthoracic echocardiogram demonstrating HCM with significant asymmetrical septal hypertrophy **(arrow)** measuring 22 mm. **(D)** Cardiac magnetic resonance scan showing ARVC with right ventricular (RV) dilation and wall fibrosis.

aortic root (>40 mm) should receive a beta-blocker to help retard aortic dilation (30).

MVP affects 3% to 5% of the general population; however, <100 cases of SCD have been reported in which MVP was the only abnormality identified, and only 3 occurred during physical exertion. Most individuals are asymptomatic. In rare instances, the condition is associated with VT, although the exact mechanism is unknown. The relatively high-frequency of MVP in the general population raises the question of whether identification of MVP in a victim of SCD is causal or coincidental (31,32). In general, athletes with MVP are allowed to continue to compete; however, competitive sport is precluded when MVP is associated with moderate to severe mitral regurgitation, severe chest pain, exertional syncope, documentation of VT, a long QT interval, or Marfan syndrome (30).

Aortic stenosis due to a congenital bicuspid aortic valve is a rare but recognized cause of SCD in young athletes that can be identified through basic screening efforts involving cardiovascular physical examination. Athletes with mild aortic stenosis may compete in low- to moderate-intensity dynamic or static sports provided that they are asymptomatic

and free of documented arrhythmia, with normal LV function both at rest and during exercise echocardiography (30).

Electrical cardiac abnormalities. WOLFF-PARKINSON-WHITE SYNDROME. Wolff-Parkinson-White syndrome describes ventricular pre-excitation due to anterograde conduction via an accessory atrioventricular pathway with paroxysmal arrhythmias that usually result from atrioventricular re-entrant tachycardia (33). The prevalence of pre-excitation in athletes is similar to that in the general population (0.1% to 0.3%) and may be revealed by a delta wave, short PR interval, and prolonged QRS duration on the electrocardiogram (Fig. 3A). Most affected athletes are asymptomatic, but some report symptoms of palpitations. If atrial fibrillation develops in individuals with Wolff-Parkinson-White syndrome, there is a risk of SCD from VF secondary to rapid anterograde conduction via the accessory pathway (34). Determining the electrical properties of the accessory pathway is therefore crucial for establishing the risk of SCD. Curative catheter ablation of the accessory pathway in adults permits return to competitive sport after 3 months (33). Recent guidance suggests that in adolescents, only high-risk pathways require catheter
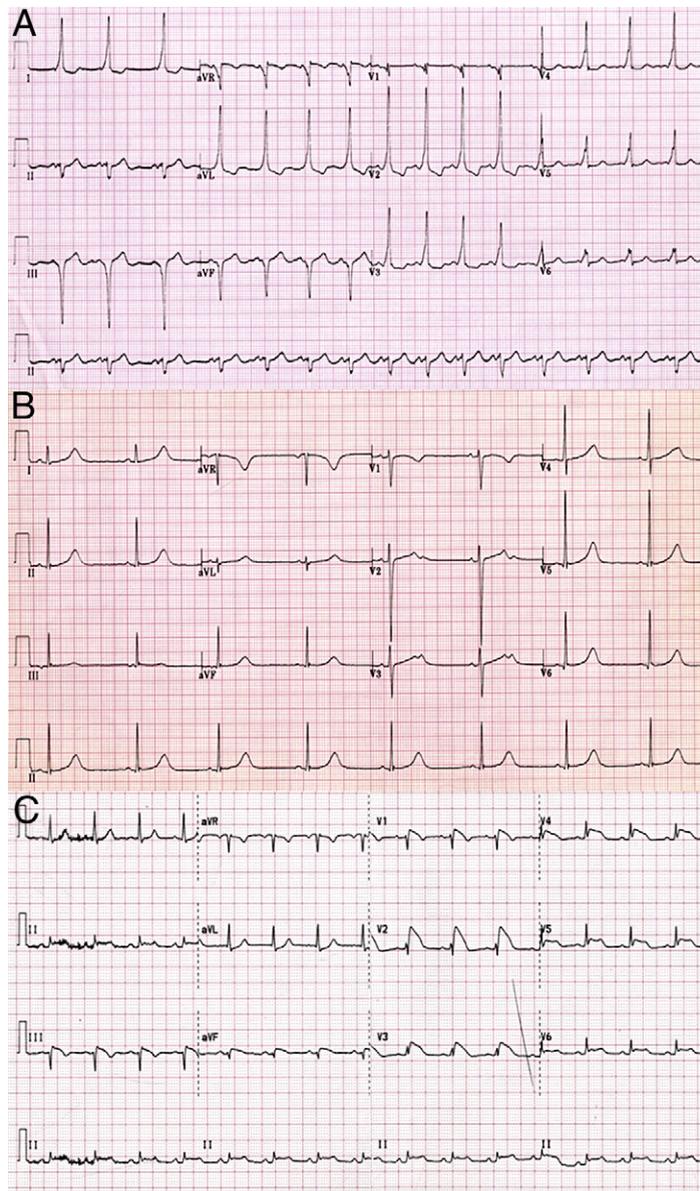
Figure 3   Electrocardiographic Patterns Observed in Electrical Cardiac Abnormalities Associated With Sudden Cardiac Death

(A) Wolff-Parkinson-White syndrome with characteristic short PR interval, delta wave, prolonged QRS interval, and ST-segment depression in leads I, aVL, and V_2 through V_4. (B) Congenital long QT syndrome with QTc interval of >460 ms. (C) Brugada syndrome with characteristic coved-type and down-sloping ST-segment elevation in leads V_1 through V_4 (type 1 electrocardiographic pattern).

ablation; however, referral to an electrophysiologist is recommended (35).

CONGENITAL LONG QT SYNDROMES. Long QT syndrome (LQTS) comprises a group of hereditary ion channelopathies with a prevalence of 1 in 2,000 to 5,000 in the general population. The incidence of SCD in athletes due to LQTS was 2% in the U.S. registry data (15). Although 12 different culpable genes have been identified, >70% of cases are due to loss-of-function mutations in *KCNQ1* (encoding potassium channel I_{Ks}; LQT1) and *KCNH2* (encoding potassium channel I_{Kr}; LQT2) and gain-of-function mutations in

SCN5A (encoding sodium channel I_{Na}; LQT3). Abnormal cardiac repolarization predisposes to polymorphic VT/VF. Individuals present with pre-syncope, syncope, palpitations, or SCD. LQTS may be misdiagnosed as epilepsy due to myoclonic movements occurring during syncope. LQT1 is most commonly associated with SCD during exercise, in particular, swimming and diving, likely due to adrenergic surges that occur with sudden immersion in cold water (36).

LQTS should be considered when the QTc interval exceeds 440 ms in males or 460 ms in females, in the

absence of medications capable of causing acquired QT interval prolongation (37). Athletes may exhibit slightly longer QT intervals compared with the general population and 0.4% to 0.7% of highly trained athletes may exhibit values >440 to 460 ms (see the following text). The 36th Bethesda Conference guidelines therefore recommend restriction of athletic individuals with a QTc interval exceeding 470 ms in males and 480 ms in females to improve the positive predictive value (29). The diagnosis of LQTS should be made using probability scoring systems that include symptoms, family history, electrocardiographic changes (Fig. 3B) and evidence of torsade de pointes, as some affected individuals have a QTc interval within the normal range (38). High-risk features include a QTc interval >500 ms and adolescents or females with the *LQT2* genotype. Individuals with a history of aborted SCD, recurrent syncope, and polymorphic VT despite medical therapy with beta-blockers should be considered for prophylactic implantation of an ICD (39).

BRUGADA SYNDROME. Brugada syndrome (BrS) is an autosomal dominant sodium channelopathy with an incidence of 1 in 2,000 to 5,000 (40). The condition is characterized by a partial right bundle branch block pattern on the electrocardiogram with associated coved ST-segment elevation (BrS type 1 electrocardiographic pattern) (Fig. 3C). Individuals present with syncope or SCD due to polymorphic VT/VF. Mixed phenotypic expressions of the disease, ranging from distinct repolarization abnormalities to subclinical cardiac conduction defects, also occur. BrS is not typically associated with exercise-related SCD; however, increased vagal tone induced by chronic athletic conditioning at rest and exercise-induced hyperthermia may enhance the propensity to SCD and may trigger ventricular arrhythmias (41). The only established treatment is ICD insertion. Although deaths from BrS characteristically occur at rest, intensive exercise is generally not advised because it may be associated with profound bradycardia and core temperatures exceeding 40°C, both of which may precipitate fatal arrhythmias in affected individuals.

CATECHOLAMINERGIC POLYMORPHIC VT. Catecholaminergic polymorphic VT is associated with mutations in the ryanodine receptor, calsequestrin, and ankyrin-B proteins, which predispose to adrenergically mediated polymorphic VT and recurrent syncope provoked by physical exercise or emotional stress (42). Typically, the baseline electrocardiogram is unremarkable, but exercise stress testing may provoke multifocal ventricular premature beats or VT with beat to beat 180° alternating QRS axis (bidirectional VT). The disorder commonly presents in adolescence, and affected individuals may have a family history of juvenile sudden death or stress-induced syncope. Prevention of SCD includes medical therapy with beta-blockers and ICD insertion in those who continue to experience symptoms despite medical therapy.

Acquired cardiac abnormalities. COMMOTIO CORDIS. Blunt trauma to the chest can trigger VF and SCD without causing direct injury to the thoracic cage or heart (43). Commotio cordis typically occurs in sports with projectile objects such as ice hockey, lacrosse, and baseball. High-risk contact sports such as martial arts and player collisions in team sports such as soccer have also been implicated. Commotio cordis is more common in children and adolescents due to a thin and compliant thoracic cage that allows greater transmission of energy to the heart. In animal models, a single blow directly over the precordium 10 to 30 ms before the T-wave peak on the electrocardiogram has been demonstrated to induce VF. A rapid increase in LV pressure follows, which appears to activate ion channels via mechano-electric coupling, resulting in the generation of an inward current, augmentation of repolarization, and nonuniform myocardial activation. Subsequent premature ventricular depolarizations trigger VF and SCD (44).

MYOCARDITIS. Myocarditis, typically caused by viral infections (e.g., Coxsackie B) accounts for up to 7% of SCD in athletes (45). The diagnosis of myocarditis should be considered in any healthy young individual with recent viral illness, new exercise intolerance, clinical signs of cardiac failure, electrocardiographic repolarization abnormalities, and/or echocardiographic regional wall motion abnormalities. Active myocarditis can be identified on cardiac magnetic resonance imaging. Acute illness is associated with ventricular arrhythmia. In some cases, myocarditis can lead to a dilated cardiomyopathy with ongoing symptoms of cardiac dysfunction and increased risk of SCD (46). Athletes diagnosed with myocarditis should refrain from sports activity for a 6-month convalescent period to reduce the risk of SCD.

PERFORMANCE-ENHANCING DRUGS. The use of performance-enhancing drugs occurs in athletes, although the true incidence is unknown. Anabolic-androgenic steroids, stimulants such as ephedrine, and nonsteroidal agents such as recombinant human erythropoietin have been associated with SCD, but a causal relationship is difficult to ascertain given that their use is forbidden. Anabolic androgenic steroids have been shown to change lipoprotein metabolism leading to premature atherosclerosis and myocardial infarction. These agents also induce hypertension and both anabolic-androgenic steroid and ephedrine use may result in cardiomyopathy and ventricular arrhythmias. Toxicological investigation is therefore recommended after a SCD event in an athlete (47).

PREMATURE CORONARY ARTERY DISEASE. In large series from Italy and the United States, premature atherosclerotic coronary artery disease accounted for 2% to 3% of SCD in young athletes (9,15). It is most commonly a manifestation of familial hypercholesterolemia. Symptoms are rare, and SCD is often the first presentation; however, peripheral

stigmata including xanthelesma, corneal arcus, and xanthomata are more common and should raise suspicion.

Recommendations for competitive sports participation by athletes diagnosed with potential causes of SCD exist in the United States and Europe and are summarized in Table 1 (4,29).

Evaluation of Athletes and Diagnostic Dilemmas

PPS is supported by sports organizations at the international and national levels (6). However, a potential limitation is the need for highly trained medical personnel with experience evaluating athletes, interpreting their clinical data, and organizing relevant further investigations when required without affecting training regimens and sporting events. An algorithm for the assessment of athletes for conditions capable of causing SCD is presented in Figure 4.

Diagnostic Dilemmas

Athlete's heart. Regular physical exercise can lead to physiological adaptation in cardiac dimensions, including in-

creased LV wall thickness (LVWT) and LV cavity size, which may be reflected on ECG and echocardiography (48). Such remodeling, termed athlete's heart, permits enhanced filling of the left ventricle in diastole and augmentation of stroke volume allowing generation of a large and sustained cardiac output even at rapid heart rates. The magnitude to which this adaptation occurs is influenced by several demographic factors including age, sex, body surface area, sport undertaken, and ethnicity (3). Consequently, a significant diagnostic dilemma can arise when attempting to differentiate physiological adaptation, with associated electrocardiographic and echocardiographic changes, from cardiac pathology. This is particularly important because false-positive diagnoses may lead to erroneous disqualification from a sport with loss of earnings and significant psychological distress to the athlete, whereas false-negative evaluations may result in devastating SCD.

The ESC has devised recommendations for electrocardiographic interpretation in athletes, which have reduced

Table 1	Recommendations for Competitive Sports Participation Among Athletes With Potential Causes of SCD (4,29)	
Condition	**36th Bethesda Conference**	**European Society of Cardiology**
Structural cardiac abnormalities		
HCM	Exclude athletes with a probable or definitive clinical diagnosis from all competitive sports.	Exclude athletes with a probable or definitive clinical diagnosis from all competitive sports.
	Genotype-positive/phenotype-negative athletes may still compete.	Exclude genotype-positive/phenotype-negative individuals from competitive sports.
ARVC	Exclude athletes with a probable or definitive diagnosis from competitive sports.	Exclude athletes with a probable or definitive diagnosis from competitive sports.
CCAA	Exclude from competitive sports.	Not applicable.
	Participation in all sports 3 months after successful surgery would be permitted for an athlete with ischemia, ventricular arrhythmia or tachyarrhythmia, or LV dysfunction during maximal exercise testing.	
Electrical cardiac abnormalities		
WPW	Athletes without structural heart disease, without a history of palpitations, or without tachycardia can participate in all competitive sports.	Athletes without structural heart disease, without a history of palpitations, or without tachycardia can participate in all competitive sports.
	In athletes with symptoms, electrophysiological study and ablation are recommended. Return to competitive sports is allowed after corrective ablation, provided that the ECG has normalized.	In athletes with symptoms, electrophysiological study and ablation are recommended. Return to competitive sport is allowed after corrective ablation, provided that the ECG has normalized.
LQTS	Exclude any athlete with a previous cardiac arrest or syncopal episode from competitive sports.	Exclude any athlete with a clinical or genotype diagnosis from competitive sports.
	Asymptomatic patients restricted to competitive low-intensity sports.	
	Genotype-positive/phenotype-negative athletes may still compete.	
BrS	Exclude from all competitive sports except those of low intensity.	Exclude from all competitive sports.
CPVT	Exclude all patients with a clinical diagnosis from competitive sports.	Exclude all patients with a clinical diagnosis from competitive sports.
	Genotype-positive/phenotype-negative patients may still compete in low-intensity sports.	Genotype-positive/phenotype-negative patients are also excluded.
Acquired cardiac abnormalities		
Commotio cordis	Eligibility for returning to competitive sport in survivors is a matter of individual clinical judgment. Survivors must undergo a thorough cardiovascular workup including 12-lead electrocardiography, ambulatory Holter monitoring, and echocardiography.	Not applicable.
Myocarditis	Exclude from all competitive sports.	Exclude from all competitive sports.
	Convalescent period of 6 months.	Convalescent period of 6 months.
	Athletes may return to competition when test results normalize.	Athletes may return to competition when test results normalize.

ARVC = arrhythmogenic right ventricular cardiomyopathy; BrS = Brugada syndrome; CCAA = congenital coronary artery anomalies; CPVT = catecholaminergic polymorphic ventricular tachycardia; ECG = electrocardiogram; HCM = hypertrophic cardiomyopathy; LQTS = long QT syndrome; LV = left ventricular; WPW = Wolff-Parkinson-White syndrome.
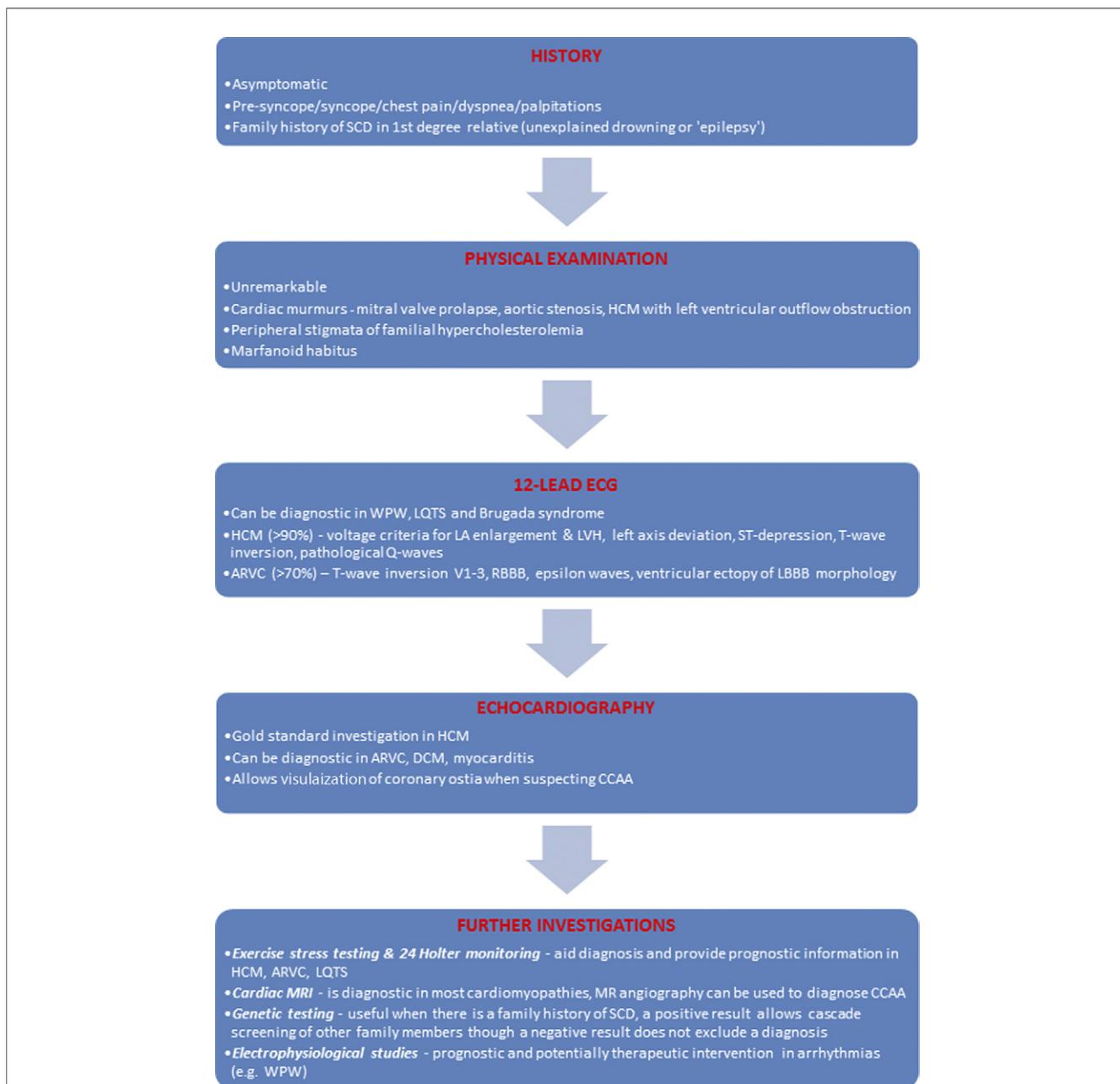
HISTORY

- Asymptomatic
- Pre-syncope/syncope/chest pain/dyspnea/palpitations
- Family history of SCD in 1st degree relative (unexplained drowning or 'epilepsy')

PHYSICAL EXAMINATION

- Unremarkable
- Cardiac murmurs - mitral valve prolapse, aortic stenosis, HCM with left ventricular outflow obstruction
- Peripheral stigmata of familial hypercholesterolemia
- Marfanoid habitus

12-LEAD ECG

- Can be diagnostic in WPW, LQTS and Brugada syndrome
- HCM (>90%) - voltage criteria for LA enlargement & LVH, left axis deviation, ST-depression, T-wave inversion, pathological Q-waves
- ARVC (>70%) – T-wave inversion V1-3, RBBB, epsilon waves, ventricular ectopy of LBBB morphology

ECHOCARDIOGRAPHY

- Gold standard investigation in HCM
- Can be diagnostic in ARVC, DCM, myocarditis
- Allows visualization of coronary ostia when suspecting CCAA

FURTHER INVESTIGATIONS

- *Exercise stress testing & 24 Holter monitoring* - aid diagnosis and provide prognostic information in HCM, ARVC, LQTS
- *Cardiac MRI* - is diagnostic in most cardiomyopathies, MR angiography can be used to diagnose CCAA
- *Genetic testing* - useful when there is a family history of SCD, a positive result allows cascade screening of other family members though a negative result does not exclude a diagnosis
- *Electrophysiological studies* - prognostic and potentially therapeutic intervention in arrhythmias (e.g. WPW)

Figure 4   **Algorithm for Evaluating Athletes for Conditions Capable of Causing SCD**

The evaluation of athletes for conditions predisposing to SCD must incorporate clinical history, physical examination, 12-lead ECG and trans-thoracic echocardiography with further investigations as required. CCAA = congenital coronary artery anomaly; DCM = dilated cardiomyopathy; LA = left atrium; LBBB = left bundle branch block; LQTS = long QT syndrome; LVH = left ventricular hypertrophy; MRI = magnetic resonance imaging; RBBB = right bundle branch block; SCD = sudden cardiac death; WPW = Wolff-Parkinson-White syndrome.

false-positive rates, in Caucasian athletes at least. Group 1 changes result from physiological adaptation of the cardiac autonomic nervous system and occur in as many as 80% of athletes, but Group 2 changes occur in <5% and are suggestive of underlying cardiovascular disorders, most notably cardiomyopathy and ion channelopathy. When Group 2 electrocardiographic changes are observed, further cardiac evaluation is recommended (Table 2) (37).

Athlete's heart versus HCM. A proportion of male athletes, predominantly those involved in endurance sports, demonstrate extreme physiological adaptation with LVWT measurements of 13 to 15 mm (49). Although the majority of individuals with HCM have a mean LVWT of 18 to 20 mm, ~8% have morphologically mild hypertrophy. Therefore, a male athlete with an LVWT of 13 to 15 mm falls into a 'grey zone', where differentiation between

Table 2	European Society of Cardiology Classification of Abnormalities on the Athlete's 12-Lead Electrocardiogram (37)	
Group 1: Common and Training-Related Electrocardiographic Changes	**Group 2: Uncommon and Training-Unrelated Electrocardiographic Changes**	
Sinus bradycardia	T-wave inversion	
First-degree atrioventricular block	ST-segment depression	
Incomplete right bundle branch block	Pathological Q waves	
Early repolarization	Left atrial enlargement	
Isolated QRS voltage criteria for left ventricular hypertrophy	Right atrial enlargement	
	Left axis deviation	
	Right axis deviation	
	Right ventricular hypertrophy	
	Ventricular pre-excitation	
	Left bundle branch block	
	Right bundle branch block	
	Long QTc interval (>440 ms in males; >460 ms in females)	
	Short QTc interval (<380 ms)	
	Brugada-like early repolarization	

physiological LVH and HCM is crucial. This diagnostic dilemma occurs in 2% to 4% of white male athletes and 12% to 18% black male athletes (Fig. 5) (50,51).

In the majority of athletes, differentiating physiology from pathology is possible using ECG and echocardiography. Isolated QRS voltage criteria for LVH are commonly observed in athletes but occur in only 2% of individuals with HCM. Electrocardiographic changes suggestive of HCM include T-wave inversion, pathological Q waves, ST-segment depression in >2 contiguous leads, and left bundle branch block. Inverted T waves >1 mm in depth in ≥2 contiguous leads except V_1 and V_2 in white athletes and V_1 through V_4 in black athletes should raise suspicion for HCM (52). Physiological LVH is homogeneous and associated with chamber enlargement and normal indexes of diastolic function. In contrast, individuals with HCM often show asymmetrical patterns of LVH, small chamber size, and impaired diastolic function. End-diastolic LV dimensions >55 mm are common in trained athletes but are rare in HCM in which the LV cavity size is usually <45 mm. In addition, HCM is associated with abnormal pulsed and tissue Doppler indexes of LV diastolic filling and impaired relaxation. In selected athletes, cardiac magnetic resonance imaging may offer incremental diagnostic value for detection of segmental LVH in the anterolateral free wall, posterior ventricular septum or apex, and demonstration of delayed gadolinium enhancement indicative of myocardial fibrosis (53). In equivocal cases, the presence of a family history of HCM or SCD and low peak oxygen consumption (peak VO_2max <50 ml/kg/min) on cardiopulmonary exercise testing favor a diagnosis of HCM. Genetic analysis has a high positive predictive value but a low negative predictive value and remains costly and time-consuming (54). In rare cases, re-evaluation with ECG and echocardiography after a period (8 to 12 weeks) of detraining may be the only practical method of differentiating between the 2 entities.

Athlete's heart versus ARVC. The diagnosis of ARVC in athletes is particularly challenging. Early in the disease process, the "concealed phase," the heart may appear morphologically normal (Fig. 5). Minor electrocardiographic abnormalities in RV leads, infrequent ventricular extra systoles of RV origin, and subtle changes in the right
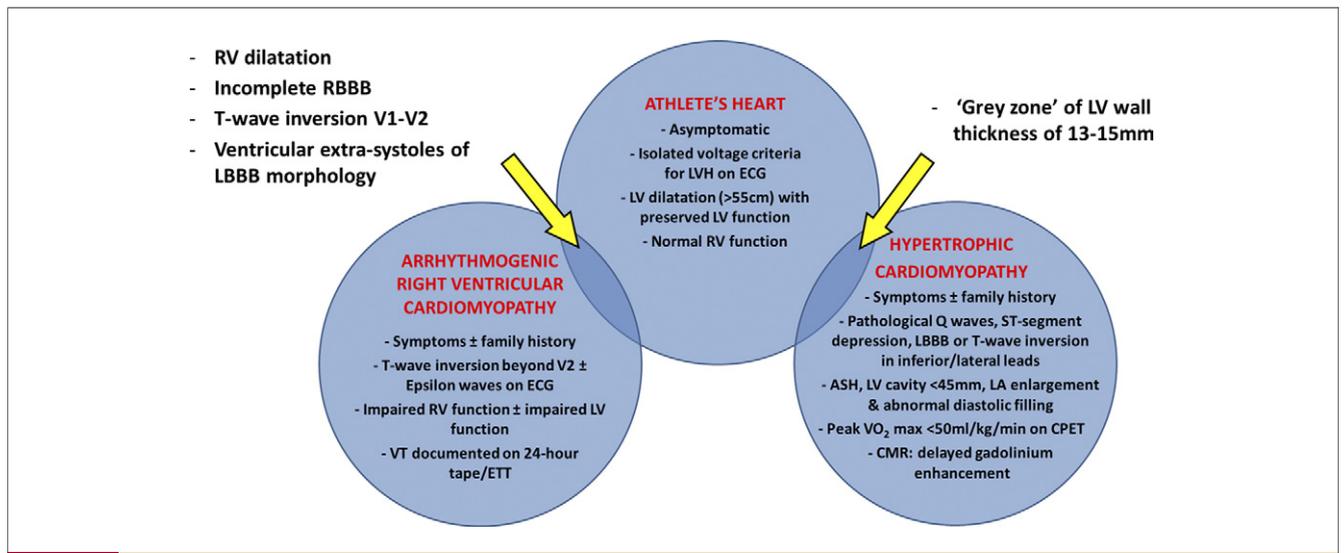

Figure 5 Differentiating Between Physiology and Pathology: 'Athlete's Heart' Versus HCM and ARVC

Regular exercise can lead to physiological adaptation of cardiac structure and function (athlete's heart) which can be identified by changes on ECG and echocardiography. There is some overlap with HCM and ARVC **(yellow arrows)**. Key features can be used to differentiate between physiology and pathology. ASH = asymmetrical septal hypertrophy; CMR = cardiac magnetic resonance imaging; CPET = cardiopulmonary exercise test; ETT = exercise tolerance test; LV = left ventricular; RV = right ventricular; VT = ventricular tachycardia; other abbreviations as in Figures 2 and 4.

ventricle may be the only objective manifestations of the disorder, and these may overlap with physiological adaptation of the right ventricle to regular exercise (22). The presence of epsilon waves, abnormal late potentials on signal averaged ECG, nonsustained VT of left bundle branch block morphology, and RV regional wall motion abnormalities favor the diagnosis of ARVC (55).

The majority of current data regarding RV size and function are determined on the basis of dimensions derived from small cohorts of normal individuals. Previous imaging studies have demonstrated that athlete's heart represents balanced cardiac enlargement with proportional increases in LV and RV mass, LV and RV end-diastolic volumes, and LV and RV stroke volumes compared with sedentary controls (56). The impact of exercise on the right ventricle has not been studied as comprehensively as the left ventricle, probably due to difficulties arising from its complex shape and trabeculated structure. However, studies of endurance athletes have shown that cardiac remodeling is not limited to the left heart. Data from 102 subjects demonstrated chronic RV cavity enlargement with RV outflow tract values greater than the proposed major criteria for ARVC in 28% of endurance athletes (23,57). As-yet unpublished data from our group have demonstrated significantly increased echocardiographic RV dimensions in professional soccer players, greater than the upper reference limits defined by the ESC and American Society of Echocardiography (58). This increases the difficulty in differentiating between physiological adaptation and ARVC, and larger studies are necessary to determine physiological upper limits of RV dimensions in athletes.

QTc interval in athletes. The diagnosis of congenital LQTS is determined on the basis of a triad of a prolonged QTc interval, unheralded syncope or documented polymorphic VT, and family history of SCD or LQTS. Although the prevalence of LQTS is 1 in 2,500 to 10,000 in the general population, in athletes, QTc interval prolongation is reportedly as high as 0.4% to 0.7% (equivalent to 1 in 150 to 250) and therefore higher than the prevalence of cardiomyopathy (59). Current data on SCD in young athletes indicate that death due to ion channel disease occurs in 2% to 4% of cases (15,16). The relatively high prevalence of QTc interval prolongation in athletes and the low death rate of LQTS suggest that the majority of causal mutations may be relatively benign and/or that most athletes with an isolated long QTc interval do not actually have LQTS. Isolated QTc interval prolongation in an athlete may represent delayed repolarization as a result of increased LV mass, autonomic adaptation, or the fact that Bazett's formula undercorrects the QTc interval at low heart rates (59). However, as many as 34% of SCDs in athletes from the U.S. registry data remain unexplained and undiagnosed ion channel disease may therefore also account for a proportion of this group (15). Our own data, which was determined on the basis of 118 consecutive SCD referred to a tertiary cardiac pathology center, failed to identify an abnormality in 23% of cases. However, it could be argued that the high incidence of normal hearts may represent a referral bias because deaths associated with structurally normal hearts were more likely to be referred to a tertiary cardiac pathology center for more detailed assessment (60).

Black athletes. Studies have demonstrated that black individuals exhibit more marked electrocardiographic repolarization changes and a greater magnitude of LVH on echocardiography compared with white individuals (14). It can be extrapolated that exercise-associated increases in preload and afterload may result in greater physiological cardiac adaptation in black compared with white athletes, leading to greater overlap with disease phenotypes, in particular HCM.

Data from the United Kingdom have demonstrated significantly greater LVH by voltage criteria (68% vs. 40%, respectively; p < 0.001), repolarization abnormalities including ST-segment elevation (85% vs. 62%, respectively; p < 0.001), and deep T-wave inversion (12% vs. 0%, respectively; p < 0.001) in black athletes compared with their white counterparts (51). T-wave inversion occurs predominantly in electrocardiographic leads V_1 through V_4. Further comprehensive clinical evaluation and follow-up data has shown no evidence of underlying cardiomyopathy in black athletes with anterior T-wave inversion in leads V_1 through V_4, suggesting that this is likely to represent a benign finding in this ethnic group (Figs. 6A and 6B).

Echocardiographic data from athletes matched for age, body surface area, and sport showed significantly greater LVWT in black than white athletes (11.3 mm vs. 10.0 mm, respectively; p < 0.001) (Fig. 6C) (51). Among black athletes, 18% exhibited an LVWT ≥13 mm, and 3% had an LVWT ≥15 mm, in the range consistent with morphologically mild HCM. In contrast, only 4% of white athletes had an LVWT ≥13 mm, and none had an LVWT ≥15 mm. None of the black athletes with LVH exhibited other phenotypic features of HCM on echocardiography, cardiac magnetic resonance imaging, exercise stress testing, or 24-h electrocardiographic monitoring. In black male athletes, an LVWT ≥13 mm warrants further investigation but may represent physiological adaptation, whereas an LVWT ≥16 mm is suggestive of underlying pathology. The greater prevalence of repolarization changes on ECG and increased LVWT on echocardiography have also been demonstrated to a lesser extent in female (Fig. 6D) and adolescent black athletes (61,62).

Early repolarization in athletes. Early repolarization (ER) was historically considered a benign electrocardiographic variant but has emerged as a risk marker for SCD. Inferior/inferolateral ER with a horizontal/descending ST-segment is associated with idiopathic VF in the general population (63). The prevalence of ER is higher in athletes, ranging from 22% to 43% and is more common in male black athletes with lower heart rates and greater training duration (64). It is typically observed in the lateral electrocardiographic territory with rapidly up-sloping ST-segment mor-
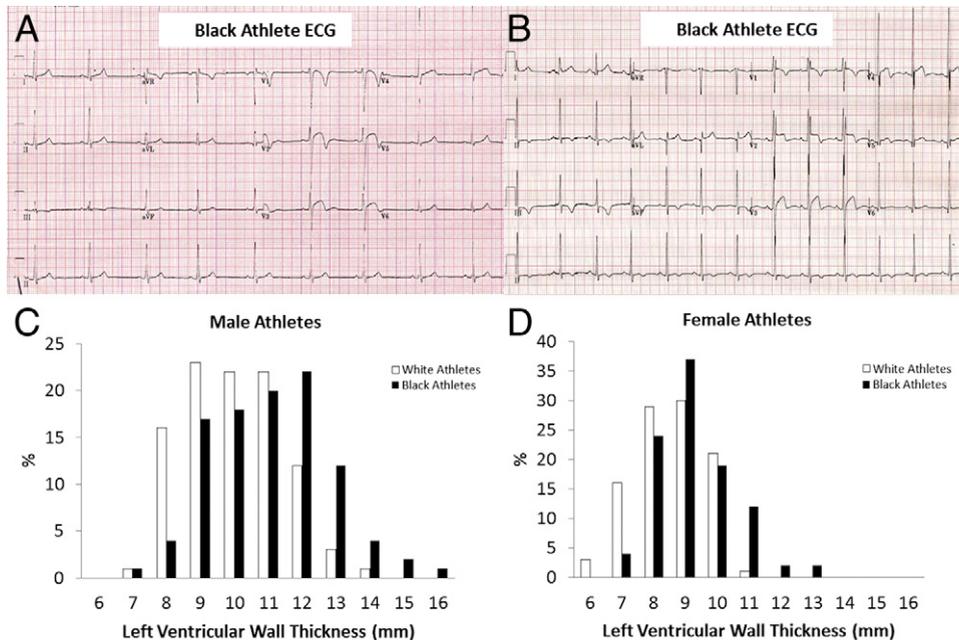
Figure 6 | **Patterns of Repolarization Changes and Distribution of LVWT in Black Male and Female Athletes and Their White Counterparts**

(A) Electrocardiogram (ECG) of a black male marathon runner demonstrating ST-segment elevation in leads V_1 through V_3 with deep T-wave inversion consistent with physiological adaptation to exercise in this ethnic group. **(B)** ECG of a black male boxer demonstrating ST-segment elevation in leads V_1 through V_4 but associated left ventricular hypertrophy and deep T-wave inversion in leads II, III, and aVF, suggestive of cardiac pathology. **(C)** Distribution of left ventricular wall thickness (LVWT) (in millimeters) in black male and white male athletes demonstrating a significant proportion of black male athletes with a maximal LVWT between 13 and 16 mm, compatible with morphologically mild hypertrophic cardiomyopathy (HCM). **(D)** Distribution of LVWT in black female and white female athletes also demonstrating a significant proportion of black female athletes with a maximal LVWT ≥12 mm, compatible with morphologically mild HCM.

phology. The majority of evidence suggests that ER in athletes is benign, although 1 study has shown an increased prevalence of inferior/inferolateral ER with a horizontal/descending ST-segment in athletic survivors of cardiac arrest (65). At present, there is insufficient evidence to make recommendations for competitive sports participation.

Primary and Secondary Prevention of SCD in Athletes

Pre-participation cardiovascular screening. PPS of athletes is recommended by both the American Heart Association and ESC. In the United States, a 12-point screening protocol encompassing symptoms, family history, and physical examination is recommended, whereas in Italy, a mandatory state-sponsored screening program incorporating 12-lead ECG, symptoms, family history, and physical examination exists for all competitive athletes (5). The Italian PPS protocol has been in place for >25 years, and on the basis of the data generated from this experience, the ESC recommends PPS including ECG in a consensus document endorsed by the International Olympic Committee (6,37).

Incorporating ECG into a screening protocol improves efficacy in identifying conditions capable of causing SCD. It is the gold-standard investigation for detection of electrical abnormalities such as Wolff-Parkinson-White syndrome,

and ion channelopathies, including LQTS and BrS. ECG is also effective in identifying cardiomyopathy, and its findings are abnormal in >90% of individuals with HCM and >75% of individuals with ARVC (18,66). The most compelling evidence in support of the Italian PPS model comes from a prospective study with 25 years of follow-up that compared the incidence of SCD in the pre-screening (1979 to 1982) and post-screening eras. This demonstrated a significant reduction in the incidence of SCD from 3.6/100,000 person-years to 0.4/100,000 person-years (p < 0.001), representing a 90% reduction in mortality (9). The predominant reason for this reduction was decreased SCD due to cardiomyopathy, in particular, ARVC, which was a relatively novel entity during the pre-screening era.

Despite such strong evidence for incorporating ECG in PPS, controversy remains, and the American Heart Association does not support routine use of ECG. The primary arguments against electrocardiographic screening include concerns regarding false-positive results, cost-effectiveness, and psychological implications for athletes and their families (5). Sudden death in the sports arena remains rare, and ECG cannot identify all conditions associated with SCD. Due to overlap between the physiological electrocardiographic changes seen in athlete's heart and similar changes seen in pathological states, it is important that evaluation is

performed by highly trained cardiologists and sports physicians with expertise and experience in dealing with athletes and the complex phenotypic expressions of inherited cardiac diseases. The diversity in age, sex, ethnicity, and sport among the modern athletic population further complicates matters, particularly as the majority of published data originate from adult white males. Applying established guidelines for electrocardiographic abnormalities to athletes has been shown to generate false-positive rates between 4% and 7%, which has important implications for both the athlete and physician (67). However, the majority of SCD occurs in individuals without antecedent symptoms and with unremarkable cardiovascular examination, thus highlighting the advantages of evaluation incorporating ECG.

Studies comparing the cost-effectiveness of the U.S. and Italian screening models find in favor of the Italian protocol (68). However, the national screening program in Italy is already well organized and established. It may not be possible to reproduce these results in other countries with limited infrastructure to run a nationwide screening program and fewer trained medical personnel to implement it. An important question is where the financial burden of large-scale screening should fall; should it be paid for by sporting bodies and teams or regional and national governments? There are limited data evaluating the psychological implications of screening on athletes. A study of Norwegian soccer players showed the majority of individuals were satisfied having completed the screening and felt more confident. Less than 3% were distressed by it, and all the players involved would recommend screening to others (69). Data from other established screening programs, including prostate and breast cancer, demonstrate considerable anxiety generated by false-positive results until further investigations provide reassurance, highlighting the importance of prompt evaluation and referral to specialist centers (70). With athletes, there are significant social and financial losses to consider, as well as the long-term implications regarding family screening and insurance policies.

Automated external defibrillators. In the event of cardiac arrest in an athlete, survival is improved by prompt recognition, the presence of trained medical personnel to initiate cardiopulmonary resuscitation, and early access to an automated external defibrillator. Creation of emergency response plans at sports and athletic venues may improve the outcome of SCD events in athletes. A recent analysis of 1,710 U.S. high schools with on-site automated external defibrillators reported 36 cases of cardiac arrest. Of the 36 cases of cardiac arrest, a total of 23 individuals (64%) survived to hospital discharge, demonstrating that early defibrillation provides a survival benefit to young athletic victims of cardiac arrest (71).

Conclusions

SCD in the sports arena is rare but devastating. Preventive strategies, such as large-scale PPS of competitive athletes

and increasing availability of automated external defibrillators are challenges requiring significant infrastructure and expertise but should be considered achievable aims rather than impossible goals. Victims of SCD are often entirely asymptomatic before their initial presentation and demonstrate only subtle abnormalities on investigation. It is therefore recommended that cardiac evaluation of an athlete is performed by trained cardiologists and sports physicians familiar with the conditions capable of causing SCD and the impact of demographic factors associated with the individual athlete.

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