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REVIEW

Clinical Update

Exercise and the heart: the good, the bad, and the ugly

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The benefits of exercise are irrefutable. Individuals engaging in regular exercise have a favourable cardiovascular risk profile for coronary artery disease and reduce their risk of myocardial infarction by 50%. Exercise promotes longevity of life, reduces the risk of some malignancies, retards the onset of dementia, and is as considered an antidepressant. Most of these benefits are attributable to moderate exercise, whereas athletes perform way beyond the recommended levels of physical activity and constantly push back the frontiers of human endurance. The cardiovascular adaptation for generating a large and sustained increase in cardiac output during prolonged exercise includes a 10–20% increase in cardiac dimensions. In rare instances, these physiological increases in cardiac size overlap with morphologically mild expressions of the primary cardiomyopathies and resolving the diagnostic dilemma can be challenging. Intense exercise may infrequently trigger arrhythmogenic sudden cardiac death in an athlete harbouring asymptomatic cardiac disease. In parallel with the extraordinary athletic milieu of physical performances previously considered unachievable, there is emerging data indicating that long-standing vigorous exercise may be associated with adverse electrical and structural remodelling in otherwise normal hearts. Finally, in the current era of celebrity athletes and lucrative sport contracts, several athletes have succumbed to using performance enhancing agents for success which are detrimental to cardiac health. This article discusses the issues above-mentioned, which can be broadly classified as the good, bad, and ugly aspects of sports cardiology.

Keywords Arrhythmias • Athletes • Athlete's heart • Cardiomyopathy • Exercise • Sudden death

The beneficial effects of exercise

The cardiovascular benefits of regular exercise are well established. Exercise aids blood pressure control,[1] improves the blood lipid profile,[2] and increases insulin sensitivity.[3] Through promotion of a favourable cardiac risk profile, exercise is associated with a significant reduction in cardiac events in the middle age. In the 1950s, Morris *et al.* reported that active bus workers and postmen demonstrated a 50% lower event rate from coronary artery disease (CAD) compared with less active bus drivers and clerical workers in the post rooms.[4] In a more recent study of over 44 000 professional males with a follow-up period of 475 755 person-years, regular exercise reduced coronary event rates by a similar magnitude.[5] The amount of exercise required to achieve such benefits is relatively modest and amounts to 2 h of exercise per week at an intensity of 6–10 metabolic equivalent of tasks (METS) divided over three bouts of exercise. Examples include a brisk walk, a gentle jog at a pace of 6.4–8 km/h or cycling at a pace of 15–20 km/h.[6,7] Even lower intensities of exercise have a beneficial prognostic impact compared with a completely sedentary lifestyle. Indeed, for every MET of exercise achieved >4 METS, there is a 12–20% reduction in cardiovascular mortality.[8]

Among patients with established CAD, there is evidence that exercise attenuates the disease process and is the cornerstone of cardiac rehabilitation. A systematic review and meta-analysis of 34 randomized control trials assessing the efficacy of exercise-based cardiac rehabilitation following myocardial infarction demonstrated a lower risk of re-infarction, cardiac mortality, and all-cause mortality in patients randomized to exercise-based cardiac rehabilitation.[9] These benefits are thought to be secondary to modulation of signalling pathways involved in cardiac remodelling as well the beneficial effects of exercise on conventional risk factors for coronary atherosclerosis. In patients with heart failure, regular physical activity is associated with better functional capacity and contributes modestly to a reduction in hospitalization and all-cause mortality.[10]

The implementation and promotion of regular exercise in the population as a whole cannot be considered more prudent than in the current climate of rising obesity rates to almost epidemic levels in some Western regions.[11] Apart from the cardiovascular benefits,

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exercise reduces the risk of prostate and breast cancer,[12] prevents osteoporosis and may retard the onset of dementia.[13] Exercise also improves stamina, promotes self-confidence, and is considered an anti-depressant by many.[14] In terms of longevity of life, individuals who engage in regular exercise live at least 3 years longer than sedentary counterparts,[15] therefore, exercise may be considered the most effective, accessible, and cheapest therapy a physician can prescribe (Figure 1) .

The Athlete's heart

The current European[16] and American[17] guidelines recommend a minimum of 150 min of moderate intensity exercise per week for an adult. Competitive (and some recreational) athletes perform way above these recommendations and regularly engage in over 20 h of intense exercise (15 MET) per week. Such intense levels of exercise require a sustained 5- to 6-fold increase in cardiac output for prolonged periods which are met by a plethora of unique electrical, structural, and functional cardiac adaptations that are collectively termed the 'athletes heart' (*Figure 2*).

The Athlete's electrocardiogram

The electrical manifestations of athletic training are broadly categorized into those due to high vagal tone and those reflecting increased cardiac chamber size. Common ECG patterns in athletes include sinus bradycardia, sinus arrhythmia, J-point elevation with ascending ST segments, first degree atrioventricular block (AV), voltage criteria for left and right ventricular hypertrophy, and incomplete right bundle branch block.[18] Some athletes demonstrate a nodal rhythm or Mobitz type 1 second degree AV block at rest which resolves with mild exertion.[19]

The normal spectrum of the athlete's ECG is influenced by age, sex, ethnicity, and type of sport. Endurance athletes exhibit the highest prevalence of electrical patterns of athlete's heart. Females demonstrate similar changes to males but to a quantitatively lesser extent. Adolescent athletes aged under 14 years old frequently show a juvenile ECG pattern consisting of T-wave inversion in leads V1–V4; however, persistence of T-wave inversion beyond V2 is uncommon after the age of 16 in Caucasians.[20,21] Athletes of African and Afro-Caribbean origin (black athletes) demonstrate more pronounced repolarization changes compared with white athletes. ST segment elevation is 6-fold greater in black athletes compared with white athletes. T-wave inversion which would be considered abnormal in most adult Caucasian athletes is present in up to 25% of black athletes. Asymmetric deep T-wave inversion preceded by convex ST segment elevation in leads V1–V4 is the most common pattern of T-wave inversion (*Figure 3A*) in these athletes and has not been shown to correlate with cardiac pathology or an adverse outcome.[22] The significance of T-wave inversion in the inferior leads is unknown but is probably a normal variant in black athletes. Axis deviation and voltage criterion for atrial enlargement are considered normal variants in isolation and do not warrant investigation in the absence of symptoms, normal physical examination, or relevant family history (*Figure 4*).[18]

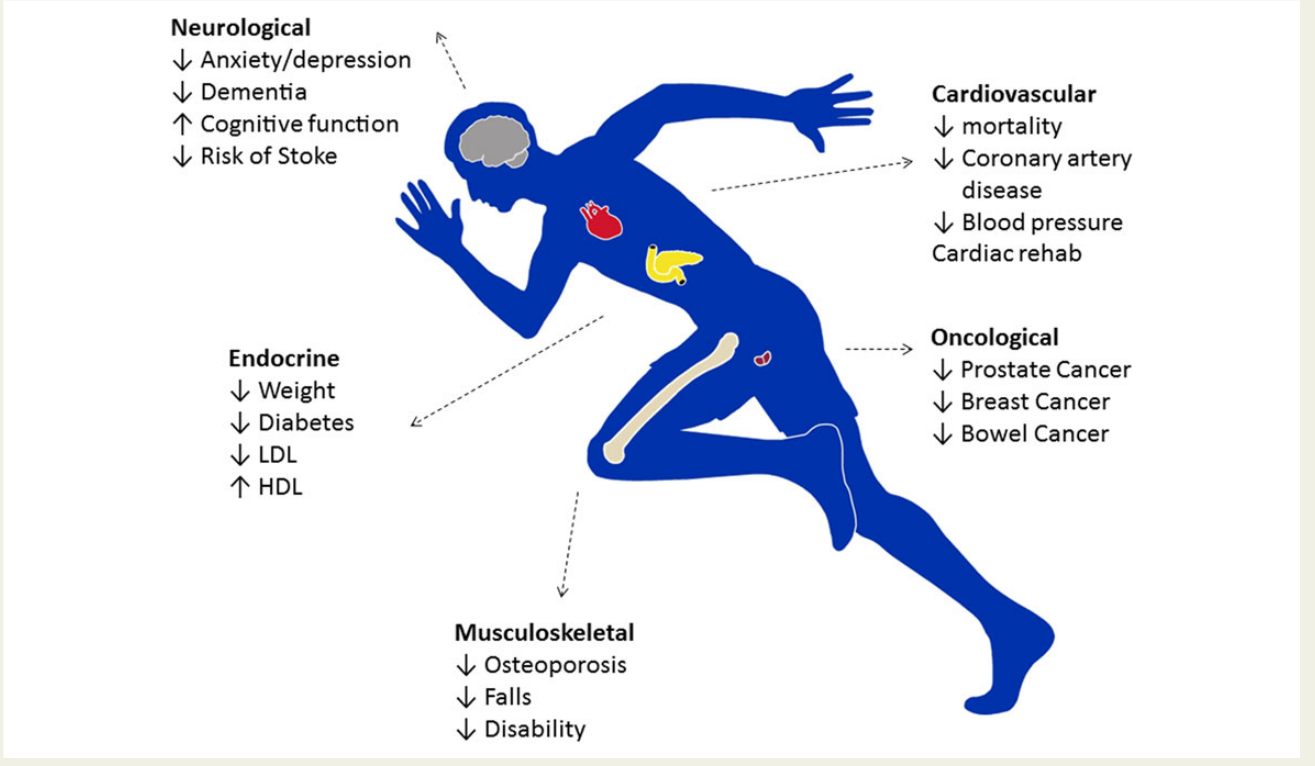

Figure 1 The benefits of exercise: HDL, high-density lipoprotein; LDL, low-density lipoprotein.

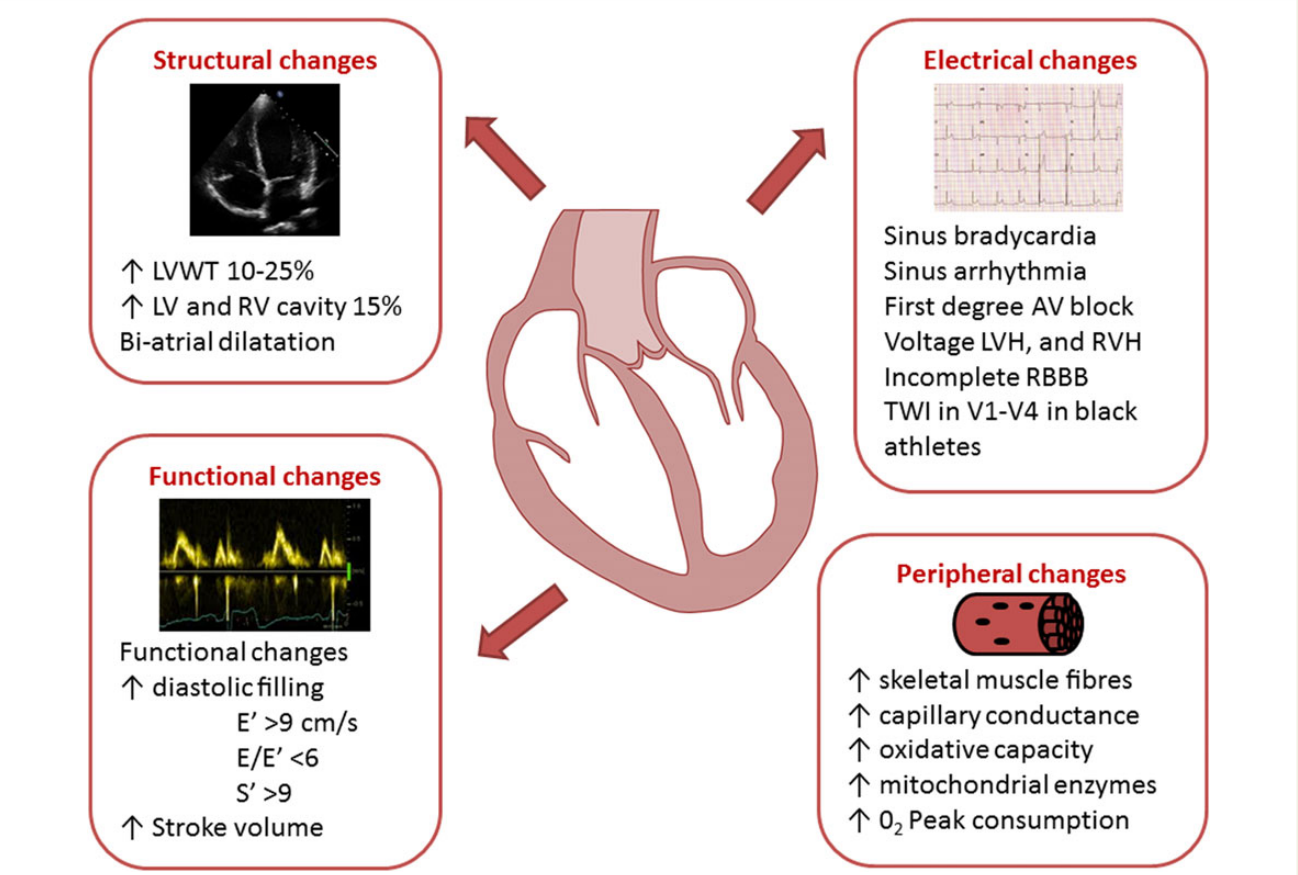

Figure 2 Cardiovascular and peripheral adaptation to exercise in athletes. AV, atrioventricular; LV, left ventricular; LVH, left ventricular hypertrophy; LVWT, left ventricular wall thickness; RV, right ventricle; RVH, right ventricular hypertrophy; TWI, T-wave inversion.

Cardiac dimensions in athletes

The increased cardiac preload and afterload associated with chronic intensive exercise is associated with symmetrical enlargement of all cardiac chambers.[23] In general, athletes show a 10–20% increase in left ventricular (LV) wall thickness and a 10–15% increase in both left and right ventricular cavity size compared with individuals of similar age and size. Additionally, athletes demonstrate enhanced cardiac filling in diastole, augment stroke volume even at very high heart rates, and exhibit increased oxidative capacity and capillary conductance within the skeletal muscle which results in high-peak oxygen consumption during exercise.

Upper limits of cardiac dimensions

The upper limits for cardiac dimensions in athletes are presented in *Table 2*. The magnitude of these adaptations is lower in adolescent athletes who are generally physically less mature and have trained for shorter periods.[24–26] The largest cardiac dimensions are generally observed in male endurance athletes with large body surface areas, particularly rowers and long-distance cyclists.[27] In absolute terms, the LV wall thickness in athletes is usually within the normal accepted ranges for the sedentary population (8–12 mm). Only 2% of Caucasian athletes show an LV wall thickness >12 mm and such dimensions are confined to male athletes.[28] In contrast, LV hypertrophy >12 mm is relatively common in black male athletes and up to 13% of black males and 3% of black female athletes show an LV wall thickness >12 mm. Irrespective of ethnicity, an LV wall thickness >16 mm is most uncommon[29,30] (*Table 1*).

Up to 50% of male athletes show left and right ventricular cavity dimensions exceeding predicted upper limits. A study of over 1300 white Italian Olympic athletes demonstrated that 45% had LV cavity size exceeding predicted upper limits and 14% had a cavity >60 mm which could be consistent with dilated cardiomyopathy.[27] A more recent study of almost 700 nationally ranked black and white athletes revealed that almost 40% of the male athletes exhibited right ventricular enlargement similar to that observed in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC).[31] Although athletes show a slightly increased aortic root diameter compared with sedentary individuals, an aortic root >40 mm is rare and should be considered abnormal.

Differentiating athlete's heart from cardiomyopathy

The aforementioned electrical and structural changes in athletes are considered benign and generally reversible after detraining; however,

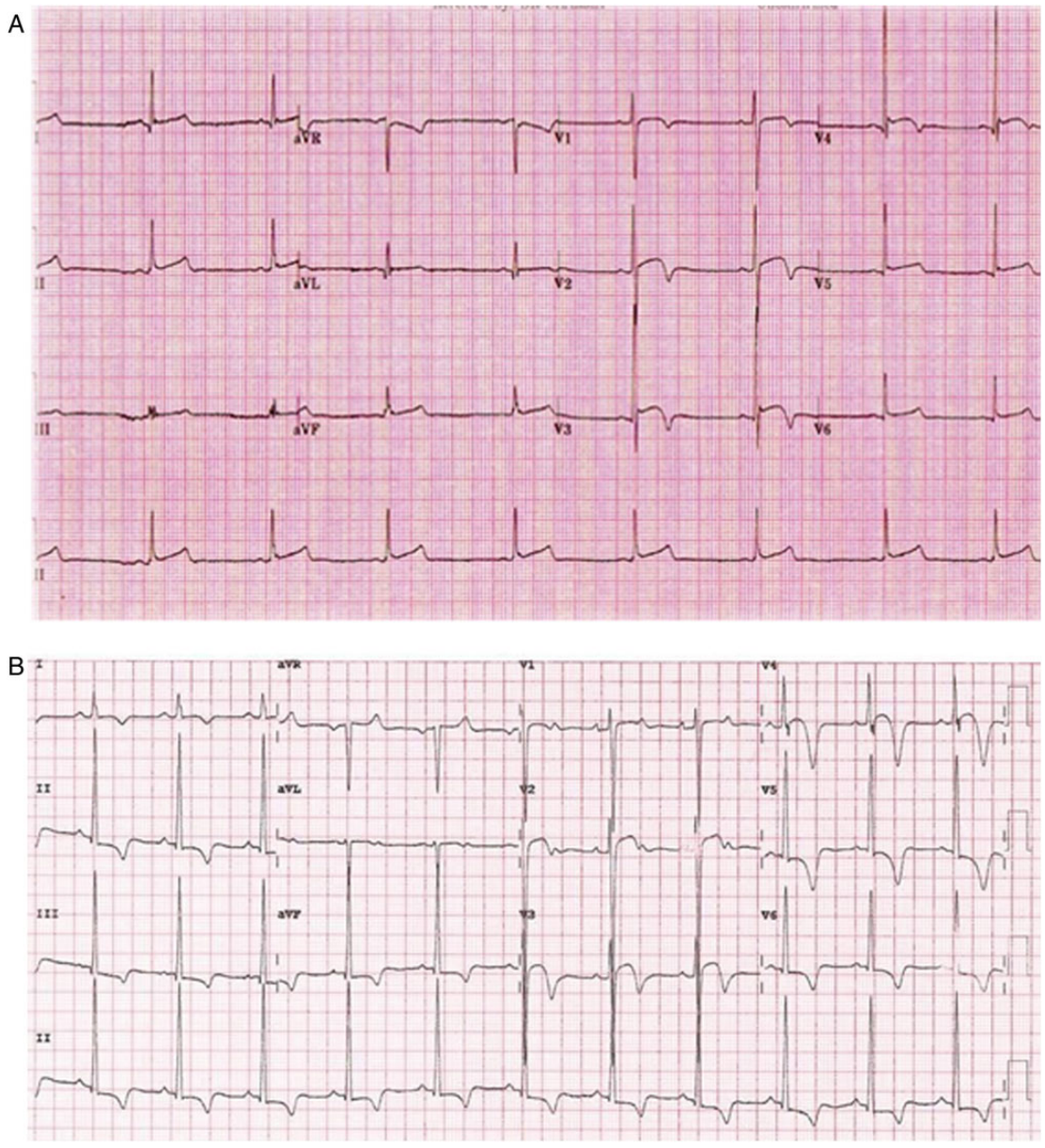

Figure 3 (*A*) A healthy black athlete demonstrating deep asymmetric T-wave inversion preceded by convex ST-segment elevation in leads V1–V4. (*B*) A black athlete with hypertrophic cardiomyopathy showing deep infero-lateral T-wave inversion and ST-segment depression.

the combination of LV hypertrophy with repolarization changes or an increased left or right ventricular cavity size with borderline low ejection fraction may overlap with a cardiomyopathy. The issue is particularly pertinent in black athletes who have a higher prevalence of both LV hypertrophy and repolarization changes and endurance athletes who exhibit very large ventricular cavities with borderline low ejection fractions. In such circumstances, the assessment should be performed by an expert because an erroneous diagnosis of cardiomyopathy may result in disqualification from sport. Conversely, an erroneous diagnosis of athlete's heart in an individual with cardiomyopathy may jeopardise a young life.

The differentiation between physiology and pathology requires the use of multiple modalities of investigations including ECG, echocardiography, cardiopulmonary exercise testing with exercise echocardiography, cardiac magnetic resonance imaging (CMRI), 24 h ECG monitoring and genetic testing. Co-existing symptoms and a relevant family history of a cardiomyopathy favour cardiac pathology. The presence of ST segment depression in any lead, T-wave inversion in the lateral leads (*Figure 3B*), pathological q waves (*Q*/*R* ratio >0.25) or left bundle branch block on the ECG[18,19] is highly suggestive of a cardiomyopathy, as are abnormal indices of diastolic function, reduced longitudinal systolic function, regional wall motion

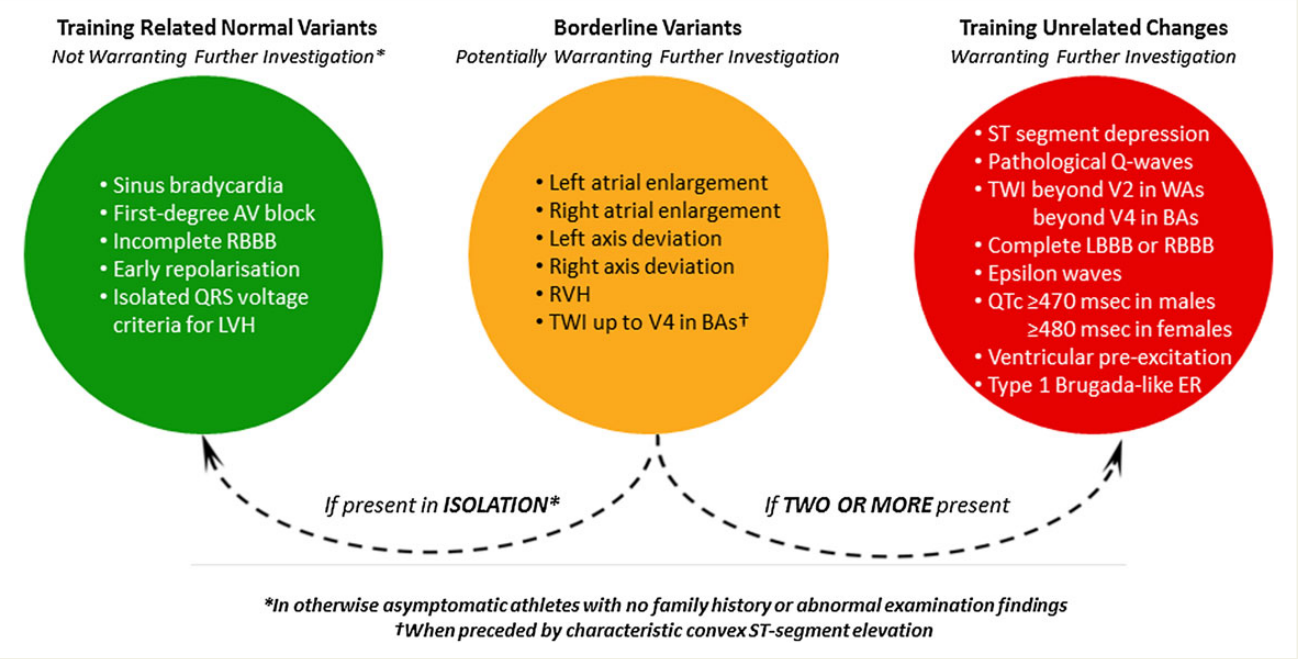

Figure 4 Interpreting the athletes electrocardiogram. Adapted from Sheikh *et al.*[18] Athletes with isolated borderline changes are only investigated in the presence of symptoms, abnormal physical examination, or relevant family history. The presence of >1 borderline changes categorizes the athlete's ECG as abnormal. AV, atrioventricular; BA, black athletes; ER, early repolarization; LBBB, left bundle branch block; LVH, left ventricular hypertrophy; RBBB, right bundle branch block; RVH, right ventricular hypertrophy; TWI, T-wave inversion; WA, white athletes.

Table 1 Upper ranges for cardiac dimensions in athletes[24–31]

		LVEDD (mm)	LVWT (mm)	RVD1 (mm)	RVOT 1 (mm)
Non-athletes	Male	59	10	38	35
	Female	53	9	38	35
Athletes	Caucasian adult				
	Male	63	12	55	43
	Female	56	11	49	40
	Caucasian adolescent (14–18)				
	Male	58	12	–	–
	Female	54	11	–	–
	Black adult				
	Male	62	15	55	43
	Female	56	12	49	40
	Black adolescent (14–18)				
	Male	62	15	–	–
	Female	56	11	–	–

LVEDD, left ventricular end diastolic diameter; LVWT, left ventricular wall thickness; RVD1, basal right ventricular internal diameter; RVOT1, right ventricular outflow tract.

abnormalities, evidence of late gadolinium enhancement (LGE) on CMRI, exercise-induced arrhythmias, complex ventricular arrhythmias on a Holter monitor and a low-peak oxygen consumption (<50 mL/min/kg or <120% predicted value).[32]

Additionally, in athletes with LV hypertrophy (13–16 mm), a relatively small (<50 mm) LV cavity and dynamic LV outflow obstruction during exercise would be consistent with hypertrophic cardiomyopathy. In athletes with a dilated LV with a borderline low ejection fraction, the failure of improvement in LV function or a peak oxygen consumption <50 mL/min/kg (or <120% predicted) would favour dilated cardiomyopathy. In an athlete with a dilated right ventricle, regional wall motion abnormalities or akinetic segments, T-wave inversion in leads V1–V3, preceding isoelectric ST segments or ST segment depression, epsilon waves, low-amplitude QRS complexes in the limb leads, late potentials on a signal averaged ECG and >1000 extra-systoles would all be suggestive of ARVC.

Table 2 Effect of performance enhancing drugs on the heart

Substance	HTN	Arrhythmias	LVH	CAD	MI	HF	SCD
Anabolic androgens	+	+	+	+	+	+	+
Human chorionic gonadotrophin		+	+			+	+
Erythropoietin	+					+	
B2 agonists		+			+	+	+
Diuretics		+					
Amphetamines	+	+			+	+	+
Cocaine	+	+		+	+	+	+
Ephedrine	+	+		+	+		+
Narcotics							+
Cannabinoids		+			+		+
Glucocorticoids	+			+			
Alcohol	+	+			+	+	+

CAD, coronary artery disease; HF, heart failure; HTN, hypertension; LVH, left ventricular hypertrophy; MI, myocardial infarction; SCD, sudden cardiac death.[61]

Left ventricular non-compaction (LVNC) is a relatively novel myocardial disorder characterized by increased LV trabeculation, impaired systolic function, and a predilection to fatal arrhythmias. The diagnosis is based on imaging studies demonstrating a double-layered myocardial structure consisting of an outer (compacted) and inner (trabeculated or non-compacted) layer whereby the ratio of the thickness of the non-compacted to compacted layer is at least 2. Our experience reveals that almost 20% of young athletes show increased LV trabeculation and 8% fulfil diagnostic criteria for LVNC.[33] We propose that in athletes fulfilling echocardiographic criteria for LVNC, a pathological diagnosis is only considered in the presence of reduced LV function, lateral T-wave inversion on ECG, low-peak oxygen consumption, ventricular arrhythmias on an exercise test or Holter monitor or the presence of fibrosis on CMRI (*Figure 5*).

In some instances, the diagnostic dilemma is unresolved despite comprehensive investigation and a period of detraining of 6–8 weeks is advised to check for regression of the electrical and structural anomalies in question. Although such an approach seems sensible and pragmatic, convincing competitive athletes to detrain is difficult as it compromises fitness and team selection.

Sudden cardiac death in sport

Occasionally, an athlete may die suddenly during or immediately after competition. Such catastrophes are rare, striking young athletes harbouring cardiomyopathies, CAD, accessory pathways or ion channel disorders, and middle aged athletes with advanced coronary atherosclerosis.[34] The prevalence of sudden cardiac death (SCD) varies according to methods of data collection but the most reliable data reveal a prevalence of ~1 in 50 000 in young competitive athletes[35] and in middle aged marathoners.[36] Ninety per cent of victims are male. Although deaths in competitive athlete afford considerable media attention, over 90% of all exercise-related SCDs occur in recreational athletes.[37,38] Cardiovascular screening to identify athletes predisposed to exercise-related SCD is controversial given the low event rates but data from a large prospective Italian study indicate that evaluation of young athletes with the 12-lead ECG is effective in reducing the risk of SCD.[39] The success of the programme has been attributed to the role of the ECG in detecting ion channel disease and accessory pathways and most patients with a primary cardiomyopathy exhibit an abnormal ECG. In contrast, most middle aged athletes die from CAD which rarely reveals itself on the surface ECG. Current recommendations for identifying middle aged athletes at the highest risk of SCD rely on an exercise stress test;[40] however, it is recognized that most abnormal exercise tests in asymptomatic middle aged athletes represent a false-positive result[41] and have a low-predictive accuracy.[42] Current data suggest that by-stander cardiopulmonary resuscitation and early application of an automated external defibrillator are the most effective methods of preventing SCD in this cohort.[37,38,43]

In most instance of SCD in sport, the reputation of exercise remains unscathed because exercise is considered to be a mere trigger for arrhythmogenesis in predisposed individuals rather than being directly implicated in the development of a pathological substrate.

Can exercise damage a previously normal heart?

The past two decades have witnessed a surge in the number of individuals partaking in gruelling endurance events such as cycling sportive, the marathon, triathlon, and iron man. In parallel, multiple studies have demonstrated raised blood concentrations of biomarkers of cardiac damage in a large number of such athletes.[44] The mechanism and consequences of raised biomarkers of cardiac damage post-exercise is debated; however, it is questionable whether in some individuals with a previously normal heart, repeated bouts of life long endurance exercise is associated with sufficient myocyte necrosis to create an arrhythmogenic substrate through adverse myocardial remodelling and myocardial fibrosis (*Figure 6*). Evidence from animal models tends to support some of this theory. Benito *et al.* exercised rats on a treadmill for 16 weeks, which in human terms is

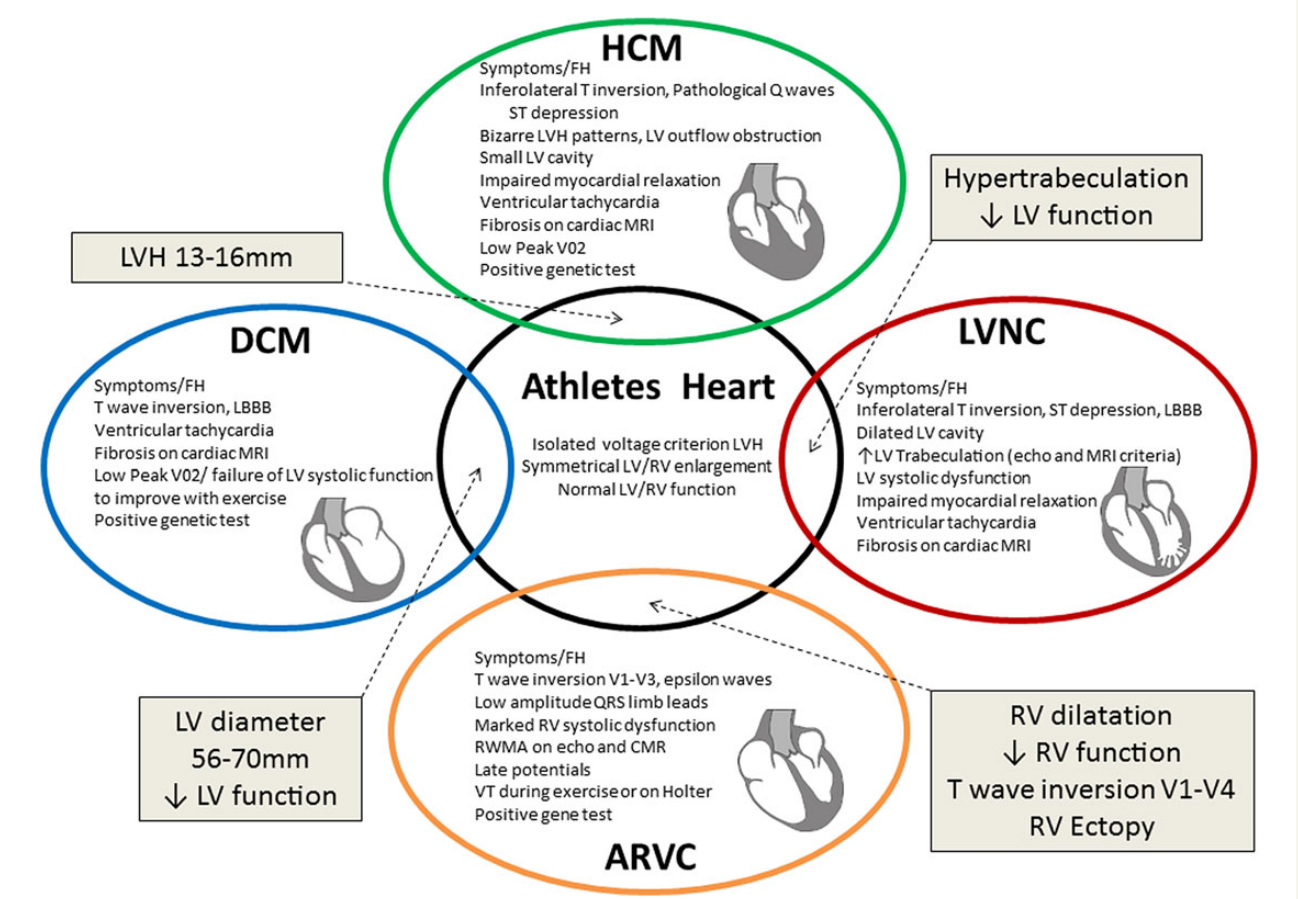

Figure 5 Differentiating features between physiological cardiac changes and cardiomyopathy in athletes. ARVC, arrhythmogenic right ventricular cardiomyopathy; CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; FH, family history; HCM, hypertrophic cardiomyopathy; LV, left ventricle; LVH, left ventricular hypertrophy; LVNC, left ventricular non-compaction; RV, right ventricle; RWMA, regional wall motion abnormalities; VT, ventricular tachycardia.

equivalent to 10 years.[45] At 16 weeks, exercising rats developed eccentric LV hypertrophy, diastolic dysfunction, and diffuse fibrosis in the atria and right ventricle. More importantly, ventricular tachycardia during electrophysiological studies was inducible in 42% of these rats compared with only 6% in sedentary rats.

The role of chronic endurance exercise in myocardial fibrosis has been explored in cross-sectional studies in humans. Breuckmann *et al.* undertook CMRI in 102 men aged $\geq$50 years old who had completed at least five marathons during the past 3 years and had no history of heart disease or diabetes.[46] Veteran marathon runners exhibited a 3-fold greater prevalence of LGE, an indicator of myocardial fibrosis, compared with sedentary controls (12 vs. 4%). Mohlenkamp *et al.* assessed coronary artery calcium scores in the same cohort and found that a larger proportion of marathon runners had coronary artery calcium scores >100 Agatston Units compared with controls matched for age and Framingham risk factors (36 vs. 21%).[47] Shearing forces within coronary arteries during high heart rates, circulating interleukins due to inflammation and the production of free radicals were implicated as possible factors.

Atrial fibrillation and sinus node disease in athletes

Perhaps the most persuasive data to suggest that excessive endurance exercise could prove detrimental for some athletes is the higher than expected prevalence of atrial fibrillation (AF) in middle aged endurance athletes; a meta-analysis of 6 studies, involving 655 athletes engaged in chronic exercise reported a 5-fold risk of AF compared with the sedentary population.[48] In a recent large study of 52 000 long-distance cross-country skiers, the risk of AF was related to the number of races competed and faster finishing times.[49] Some studies have assigned exercise risk thresholds for developing AF. It has been reported that a lifetime sports practice >1500 hours[50] and >5 h of intensive exercise per week at the age of 30 years old and onwards increases the risk of AF.[51]

The precise pathophysiology of AF in athletes is not fully understood but vagally mediated shortening of the atrial refractory period, atrial stretch, atrial inflammation, and scarring have been implicated.[52] Animal models support the theory that AF in athletes is a consequence of adverse atrial remodelling. A recent study

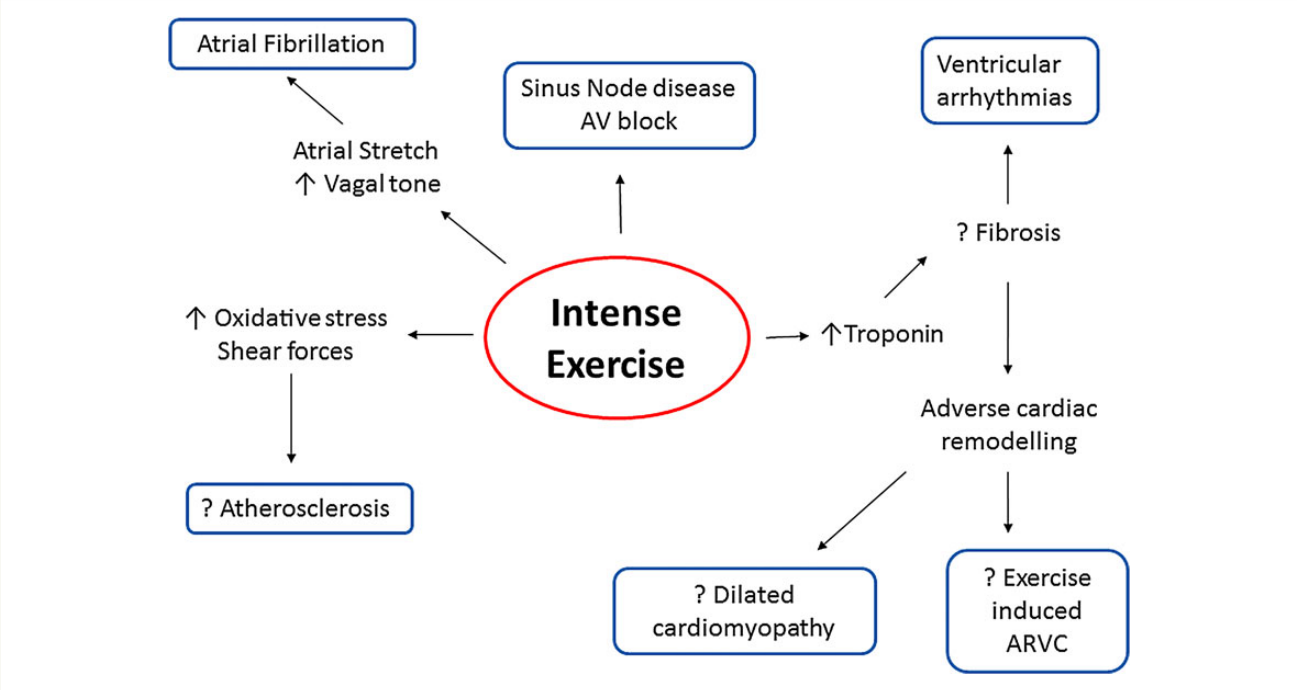

Figure 6 Speculated mechanisms for the detrimental effects of exercise. ARVC, arrhythmogenic right ventricular cardiomyopathy; AV, atrioventricular; DCM, dilated cardiomyopathy.

demonstrated that rats that subjected to intensive exercise for 1 h/day for a total of 16 weeks displayed atrial dilatation and scarring and an enhanced sensitivity to AF induction.[53]

Athletes also reveal a higher prevalence of sinus node dysfunction and second or third degree AV compared with non-athletes.[54]

Adverse cardiac remodelling and ventricular arrhythmias

There is emerging evidence that ventricular arrhythmias in a healthy athlete may have a sinister prognosis. Heidbuchel *et al.* observed a high incidence of major arrhythmic events including SCD (20%) in 46 young athletes presenting with frequent ventricular ectopy or non-sustained ventricular tachycardia over a 5-year follow-up period.[55] Eighty per cent of the ventricular arrhythmias were of right ventricular origin. Subsequent studies from the same group suggest that chronic endurance exercise promotes adverse right ventricle remodelling. Indeed, invasive studies during exercise reveal that pulmonary artery pressures can reach as high as 80 mmHg causing a high afterload on the right ventricle. La Gerche *et al.* studied 40 healthy athletes at baseline and after an endurance race and revealed transient right ventricular enlargement associated with impaired right ventricular function on echocardiography. Cardiac troponin and B-type natriuretic peptides were elevated and corresponded to duration of exercise and magnitude of reduction in right ventricular function. The researchers postulated that repeated insults on the right ventricle of this type following prolonged and intensive endurance exercise may lead to irreversible right ventricular remodelling with a propensity to fatal arrhythmias, which has led to the concept of exercise-induced ARVC.[56] The dose of exercise required for this effect is probably >20 h/week for >20 years.

While there are mounting reports that regular participation in extremely intensive exercise may induce arrhythmogenic cardiac substrates in some athletes, these conclusions are speculative and largely based on observational studies involving a small and select group of symptomatic athletes presenting to the medical profession. If such cases reflected the numerator value for athletes harbouring exercise-induced arrhythmogenic substrates, the percentage of athletes affected would be miniscule when consideration is given to the potential denominator of ~10 million participants in marathons, triathlons and iron man events worldwide each year. A prospective study of 114 Olympic endurance athletes who had competed in 2–5 consecutive Olympic games did not show any deterioration in cardiac function or risk of arrhythmias.[57] Exercise also reduces age-related decreases in compliance and elasticity which may predispose to cardiovascular morbidity in late life.[58] Furthermore, numerous studies have revealed that athletes engaging in the most gruelling endurance events including the Tour de France live longer than inactive individuals.[59] The longevity benefit may be attributed to their generally healthier lifestyle or genetic superiority but should not take away from the fact that years of intensive exercise was not associated with an increased risk of cardiac morbidity.

Current evidence indicates that only a small number of athletes may be at risk of cardiac damage from long-standing intensive exercise and the endorphin-mediated euphoria with such practice in some athletes may be 'cardiotoxic' in only a minority. The large denominator pool available to sports physicians and cardiologists

provides ample opportunity for prospective evaluation of athletes regularly participating in ultra-endurance events with biochemical, genetic, and cardiac imaging tests to draw more accurate conclusions concerning the potentially deleterious effects of exercise.

Performance enhancing agents and the heart

In the modern era of sporting prowess, there are very fine margins between winning and losing, and the rewards of success are substantial. The desire for glorification has seduced some athletes into consuming drugs which can enhance performance. Apart from tarnishing the image of sport, such doping can have multiple cardiac and non-cardiac consequences (*Table 2*). Among the most cardio-toxic doping substances are the androgen-anabolic steroids which are generally used to increase muscle mass and strength and are implicated in adverse lipid and blood pressure profiles, myocardial infarction, arrhythmias, LV dysfunction,[60] and SCD.[61]

Human growth hormone is used to increase skeletal muscle in athletes but can also cause myocardial hypertrophy and fibrosis. Erythropoietin is utilized to increase red cell concentration and improve oxygen delivery to tissues; however, the accompanying rise in haematocrit and dangerous blood viscosity levels may predispose to spontaneous thrombosis and systemic thromboembolism as well as hypertension due to the elevated afterload.[61]

Conclusion

Regular physical activity confers a plethora of health benefits including improved life-expectancy. Athletic training necessitates a constellation of electrical, structural, and functional adaptations within the heart to promote the generation of a large and sustained increase in cardiac output for prolonged periods. Such changes are generally considered benign but may overlap with the phenotypic manifestations of a cardiomyopathy which are the commonest cause of SCD in young competitive athletes. Over the past two decades, there is mounting speculation that long-term vigorous endurance exercise is associated with arrhythmias, myocardial fibrosis, and possibly CAD (*Figure 6*); however, further prospective studies in large cohorts are required to investigate these claims in detail. The impact of performance enhancing agents is difficult to study but is likely implicated in arrhythmogenic substrates in some athletes.

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